Hormonal Physiology of Childbearing: Evidence and Implications for Women, Babies, and Maternity Care

Sarah J. Buckley

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CHILDBIRTH CONNECTION
a program of the
national partnership for women & families

Childbirth Connection

A Program of the National Partnership for Women & Families

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Founded in 1918 as Maternity Center Association, Childbirth Connection became a core program of the National Partnership for Women & Families in 2014. Throughout its history, Childbirth Connection pioneered strategies to promote safe, effective evidence-based maternity care, improve maternity care policy and quality, and help women navigate the complex health care system and make informed decisions about their care. Childbirth Connection Programs serve as a voice for the needs and interests of childbearing women and families, and work to improve the quality and value of maternity care through consumer engagement and health system transformation.

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Abstract

Hormonal Physiology of Childbearing: Evidence and Implications for Women, Babies, and Maternity Care

This report synthesizes evidence about innate hormonally-mediated physiologic processes in women and fetuses/newborns during childbearing, and possible impacts of common maternity care practices and interventions on these processes, focusing on four hormone systems that are consequential for childbearing. Core hormonal physiology principles reveal profound interconnections between mothers and babies, among hormone systems, and from pregnancy through to the postpartum and newborn periods. Overall, consistent and coherent evidence from physiologic understandings and human and animal studies finds that the innate hormonal physiology of childbearing has significant benefits for mothers and babies. Such hormonally-mediated benefits may extend into the future through optimization of breastfeeding and maternal-infant attachment. A growing body of research finds that common maternity care interventions may disturb hormonal processes, reduce their benefits, and create new challenges. Developmental and epigenetic effects are biologically plausible but poorly studied. The perspective of hormonal physiology adds new considerations for benefit-harm assessments in maternity care, and suggests new research priorities, including consistently measuring crucial hormonally-mediated outcomes that are frequently overlooked. Current understanding suggests that safely avoiding unneeded maternity care interventions would be wise, as supported by the Precautionary Principle. Promoting, supporting, and protecting physiologic childbearing, as far as safely possible in each situation, is a low-technology health and wellness approach to the care of childbearing women and their fetuses/newborns that is applicable in almost all maternity care settings.

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Message from Debra L. Ness

It is with great pride that we release *Hormonal Physiology of Childbearing: Evidence and Implications for Women, Babies, and Maternity Care.* We issue this report at a moment when there is growing recognition that patterns of maternity care in the United States are contributing to unnecessarily high rates of maternal and newborn morbidity and mortality and excess costs. The past year has brought important progress, including position statements from clinical professional societies that call for better alignment of practice with the best evidence and with the needs and interests of women and families. With this report, Childbirth Connection programs at the National Partnership for Women & Families adds strength and urgency to the case to improve the quality and value of maternity care in the United States.

Founded in 1918 as the Maternity Center Association, Childbirth Connection has worked for nearly a century to improve the quality of maternity care on behalf of women and families. A year ago, Childbirth Connection joined forces with and became a core program of the National Partnership, which has a powerful, long-term commitment to quality, affordable health care. Together, we have become a stronger and even more effective force advocating for the needs and interests of childbearing women and families and for maternity care system reform.

For Childbirth Connection programs at the National Partnership, the release of this report is the first step in our work to ensure that its key messages reach diverse audiences and that its recommendations are promoted and adopted by the policy, practice, education, consumer engagement and research communities. Much of this dissemination is being done in partnership with key organizations, agencies, and leaders. We invite all who are committed to the highest standard for maternity care to join us in this work.

I am enormously grateful to all who contributed to this report. Dr. Sarah Buckley's synthesis of the vast literature compels us to move forward to transform maternity services. The five clinical leaders from the most relevant disciplines who wrote the Foreword are invaluable allies as we release the report and take the next steps. Carol Sakala, director of Childbirth Connection programs, and Maureen Corry, senior advisor for Childbirth Connection programs, have shepherded this project every step of the way and made great strides in integrating Childbirth Connection within the National Partnership. Together, we thank the many leaders who provided wise counsel through interviews and who will help us bring the report to essential audiences. And without question, this project would not have been possible without generous funding and support from the Transforming Birth Fund, Lamaze International, and DONA International.

We look forward to working with both established and new allies to reach the day when all women in this country can count on safe and effective maternity services that foster optimal maternal health and give babies the best start in life.

Debra L. Ness, President
National Partnership for Women & Families

Foreword

This report, prepared by Dr. Sarah Buckley in collaboration with Childbirth Connection Programs at the National Partnership for Women & Families, will be retrospectively evaluated as one of the most revolutionary and influential publications on maternity and newborn care ever issued. What is remarkable is that it is not about a new technology or drug. Rather, it compiles scientific evidence that "less is more" and if we get it right in the beginning there are potentially profound impacts on learning, brain development, and well-being in the child.

As leaders from family medicine, midwifery, nursing, obstetrics, and pediatrics, we applaud the stellar compilation of scientific evidence on the hormonal physiology of childbearing. Buckley carefully weaves the hormonal lattice of oxytocin, beta-endorphins, epinephrine and norepinephrine and their related stress hormones, and prolactin to help the reader absorb the exquisite complexity of spontaneous labor, birth, maternal-infant attachment, and lactation. Physiologic preparation for birth is beautifully choreographed in pregnancy with critical hormonal and physical changes unfolding in the weeks, days, and (to date, only in animal studies) hours that lead to labor. The prelabor hormonal changes are neuroprotective in animal studies. The catecholamine surge in late labor is neuroprotective in humans. The critical message is to protect those processes for the health of the mother, the baby, and the future health of the child.

Our maternity care system works from a premise that "more technology is better." Buckley dispels this myth by exposing how the hormonal balances of childbearing, bonding with parents, and lactation may suffer from cascades of interventions. Evidence is becoming clear that the body recognizes medications and procedures intended to artificially simulate labor and birth processes as counterfeits. Tools such as induction and epidurals are used at the cost of disrupting delicate interconnections that are biologically designed to optimally prepare baby and mother for birth. Mothers and babies are well designed for birth; interfering with the process when mother and baby are healthy is not supported by evidence and may cause unintended harm. That harm is expressed in the short term through prolonged labors and unnecessary surgical births. Findings from animal models suggest short-, medium-, and long-term implications including, but not limited to, impaired lactation, diminished maternal attachment, effects on infant brain development and learning, and lifelong health. If overtreatment is defined as instances in which an individual may have fared as well or better with less or perhaps no intervention, then modern obstetric care has landed in a deep quagmire. Navigating out of that territory will be challenging.

The guidepost for the journey must steer us steadfastly down the path of "first, do no harm" in which we have been carefully schooled, but have not necessarily heeded. The "Precautionary Principle," which requires demonstration of safety *before* introducing interventions that may adversely affect labor, birth, and the newborn, must become the mantra in maternity care practice. Every setting providing maternity and newborn care must critically evaluate its common maternity care routines and practices against the evidence presented in this report. Policies at every level must change to afford women the opportunity to achieve a healthy physiologic birth.

Buckley provides us with an opportunity to connect with a growing broad audience of stakeholders, including providers, academicians, researchers, administrators, and consumers, about resetting the trajectories for health and well-being over the life course. Of these, the most crucial to reach are women and their families who want the very best for their child. We are aiming to achieve an era in which health care decisions are shared between the provider and client. Yet, most women and sadly, many providers do not know the information featured in this report.

Systems can be changed. The *National Institutes for Health and Care Excellence* (NICE), which holds Department of Health responsibility for developing guidance and quality standards in England and Wales, released a groundbreaking *2014 Intrapartum Guideline* just weeks before this publication. They recommended that at least 45 percent of low risk women should give birth outside of the hospital in birth centers or at home to avoid unnecessary interventions and harm. They have acted on the evidence within an integrated and responsive health care system. Our challenge is to consider how to best move forward with the findings from this report. Minimally, we would recommend the following**:**

1. This monograph needs to be shared with all physicians, midwives, and nurse providers of maternity and newborn care and administrative leadership of our maternity care units.

2. Basic and advanced curricula for physicians, nurses, and midwives should be interprofessional and founded on this evidence.

3. High-level opinion leaders and decision makers within health care systems and policy making bodies must understand how crucial it is to act on these findings to achieve our triple aim of a) improving the patient experience of care (including quality and satisfaction), b) improving the health of populations, and c) reducing the per capita cost of health care.

4. Strategies must be implemented to help women and their families understand how crucial it is to trust the capability of their body and the fetus in pregnancy and childbearing processes. However, this is not enough if maternity care settings do not provide the environments that support hormonal physiology.

5. Research to further our understanding of the evidence presented in this report is important. However, it should not preclude adoption of what is clearly understood – that supporting physiologic childbearing processes is good for the mother and baby. What will be as important is to understand what helps maternity care practices and units successfully implement the findings from this report.

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Preface

Preparing *Hormonal Physiology of Childbearing* has been an exciting opportunity for me, as a physician and writer on childbearing, to deepen my understanding of this topic and synthesize the current state of knowledge.

The synthesis contributes to our current efforts to clarify how best to care for childbearing women and their babies. First, the hormonal physiology of childbearing is a relatively new and evolving area, with limited content in the education of health professionals and no current and readily available overview. The original research findings discussed here may also be less available to clinicians and others, with many significant and clinically relevant findings published outside of medical, midwifery, or nursing journals.

Second, maternity care services have changed in recent decades. A medically-intensive style of practice is now the norm, so that healthy childbearing women and their newborns generally experience many tests and interventions. While beneficial and even lifesaving in some situations, common or routine maternity care interventions may not be necessary or beneficial for the healthy majority. Their widespread use may result in unintended consequences, including known short- and longer-term impacts, and others that are currently less well researched. In clarifying what is both known and unknown about the possible impacts of widely used maternity care interventions on important hormone systems for childbearing, this report brings crucial knowledge and important questions to light.

Third, there is an urgent need to incorporate the hormonal physiology of childbearing into important newer frameworks and understandings that recognize the perinatal period as a window of heightened sensitivity, with potential longer-term impacts from early life experiences. These frameworks include developmental origins of health and disease (DOHaD), lifecourse health development (LCHD), and epigenetic models. While the possibility of enduring impacts from experiences during the prenatal and postpartum periods are well recognized within these frameworks, the potential consequences for offspring of perinatal experiences are relatively unexplored Longer-term outcomes in women may also be influenced by perinatal events, as detailed here. The hormonal physiology of childbearing can enrich these frameworks and their significance for maternity care policy, practice, education, and research.

This report can contribute to the work of organizations, agencies, and individuals with responsibilities for childbearing women and their babies. With its focus on physiologic processes and maternity practices, it is highly relevant to clinicians, and particularly those working with women and their babies from pregnancy through the early postpartum period. It includes essential knowledge for health professional educators and students in all disciplines of maternity care, and important foundational knowledge for other educators and students. This report can also expand the understanding of childbirth educators, doulas, and lactation and other personnel who support childbearing families.

For administrators, policy makers, health plans and systems, and employers, this synthesis suggests low-cost opportunities to improve the quality, safety, outcomes, and value of maternal-newborn care. Priority research gaps, as highlighted, point researchers and funders of research to needed studies that are potentially of great consequence. Childbirth advocates and childbearing women themselves will gain in-depth knowledge about the physiologic processes of childbearing and ways to foster healthy childbearing. This information will also be of interest to members of the general public who want to better understand mothers and babies, and their optimal care. Various related products will make key findings available to childbearing women and other groups.

This report describes the physiologic roles of four important hormone systems and their impacts on maternal-newborn adaptation around the time of birth, as well as evidence of impacts of widely used interventions on these physiologic processes. It also examines the synchronized maternal-fetal preparations that lead to the physiologic (spontaneous) onset of labor at term, and possible effects of foreshortening gestation by scheduled birth. There are many gaps in our current knowledge, some of which may have major implications for the health and wellness of mothers and offspring.

Despite research gaps, a consistent and coherent mosaic is coming into view of a finely tuned hormonal physiology of childbearing, active from pregnancy to lactation and beyond, which supports health, connection, and well-being of mother and baby, in the short term and even lifelong. When promoted with enabling policies, settings, and knowledge and skill sets; supported by appropriate care practices; and protected from environments and practices that can interfere, hormonal physiologic processes foster not only optimal transitions and outcomes at birth, but also optimal breastfeeding and mother-baby attachment, with substantial positive long-term impacts for mothers and babies, according to the evidence presented in this report. This evidence also suggests that, even when intervention is needed, mothers and babies can benefit by also experiencing hormonal physiology processes as far as safely possible.

Recommendations in the concluding chapter provide further details, and identify implications for policy, practice, education, and research.

I intend *Hormonal Physiology of Childbearing* to be illuminating, to add value to present knowledge, and to practically inform current understandings and endeavors on behalf of mothers, babies, and maternity care.

Acknowledgments

I am deeply grateful for the support received during the preparation of this report.

It is an honor to have leading clinicians from obstetrics, family medicine, pediatrics, midwifery, and nursing join together in a united voice to contribute the Foreword. I am also honored by the supportive message from Debra L. Ness, President, on behalf of the National Partnership for Women & Families.

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Additional opportunities to strengthen this report arose from much-appreciated feedback on recent presentations about this work and during key informant interviews that Childbirth Connection Programs recently conducted.

Thanks to Childbirth Connection for initiating, commissioning, and funding this report, and for additional financial support from the National Partnership for Women & Families, the Transforming Birth Fund, Lamaze International, and DONA International. Thanks to Ellen Papciak (Rose) for the design of this report.

Lastly, I extend heartfelt thanks to Carol Sakala, PhD, MSPH, director of Childbirth Connection Programs at the National Partnership for Women & Families, for her guidance and expertise at every step of the way, including on the conceptualization, framing, and presentation of the report. It is gratifying to know that Childbirth Connection Programs at the National Partnership for Women & Families is committed to raising awareness about the report's results and fostering integration of its implications into maternity care policy, practice, education, and research, on behalf of women and babies.

Executive Summary

Introduction

This report examines current understandings of the hormonal physiology of childbearing, first in relation to the physiologic onset of labor at term and scheduled birth, and then through chapters addressing four impactful hormonal systems: oxytocin; beta-endorphins; epinephrine-norepinephrine (adrenaline-noradrenaline) and related stress hormone systems; and prolactin. Each chapter addresses physiologic hormonal processes followed by the possible impacts of common maternity care practices and interventions. The final chapter presents conclusions, a summary table, and recommendations.

The "hormonal physiology of childbearing" here refers to reproduction-related biologic processes from pregnancy through the postpartum and newborn periods in relation to innate, endogenous hormone systems. "Physiologic childbearing" refers to childbearing conforming to healthy biologic processes. Consistent and coherent evidence finds that physiologic childbearing facilitates beneficial (salutogenic) outcomes in women and babies by promoting fetal readiness for birth and safety during labor, enhancing labor effectiveness, providing physiologic help with labor stress and pain, promoting maternal and newborn transitions and maternal adaptations, and optimizing breastfeeding and maternal-infant attachment, among many processes.

The perinatal period is highly sensitive for mother and baby in relation to hormonal and other biologic processes. Practices that promote (through favorable policies and system capacities), support (with direct facilitating practices), and protect (from disturbance) physiologic childbearing may have amplified, ongoing benefits—for example, through supporting breastfeeding.

Contemporary childbearing has benefitted from many medical advances, and from highly skilled and committed maternity care providers, especially for mothers and babies who require special care. However, current high rates of maternity care interventions may be disadvantageous for the healthy majority. Common maternity care practices and interventions can impact the hormonal physiology of mother and baby, according to physiologic understandings and human and animal studies. Impacts on hormonal physiology and consequences for mother and/or baby may occur in the perinatal period or beyond. For example, prelabor cesareans are associated with reduced fetal/newborn epinephrine-norepinephrine due to loss of the "catecholamine surge," which may contribute to increased respiratory and other morbidities. Longer-term impacts from perinatal hormonal disruptions are possible in women and babies, according to provisional human findings and solid animal research.

Core hormonal physiology themes and principles recur throughout results synthesized in this report, revealing profound interconnections at many levels and over time, as follows:

Evolutionary origins. The hormonal physiology of childbearing has evolved over millions of years to optimize reproductive success. Maternal and infant survival at birth is obviously critical for reproductive success, but equally important for long-term survival are successful lactation and maternal-infant attachment immediately following birth. These hormonally-mediated processes are intertwined and continuous with the biologic processes of parturition. Disruption of perinatal hormonal physiology may thus impact not only labor and birth, but also breastfeeding and maternal-infant attachment. As humans share many reproductive processes with other mammals, animal research helps illuminate human hormonal physiology, especially where human research is currently limited.

Mother-baby dyad. Hormonal physiology is interrelated, coordinated, and mutually regulated between mother and baby to optimize outcomes for both. For example, maternal and fetal readiness for labor is precisely aligned at the physiologic onset of term labor to optimize labor efficiency and maternal and newborn transitions. Similarly, skin-to-skin contact after birth mutually regulates maternal and newborn oxytocin systems. As a general principle, effects on maternal hormonal physiology impact fetal/newborn hormonal physiology, and vice versa.

Beneficial hormonal physiology pathway. From pregnancy through labor and birth, breastfeeding, and maternal-infant attachment, hormonal processes of physiologic childbearing anticipate and prepare for upcoming processes and biological needs. For example, prelabor upregulation of maternal uterine oxytocin receptors promotes labor efficiency, and prelabor epinephrine-norepinephrine receptor upregulation optimizes fetal adaptations to labor hypoxia and newborn transitions via the fetal catecholamine surge.

Interorchestration among hormone systems. The hormone systems described here have complex interactions in the perinatal period, including promoting or inhibiting one another's activity. This can amplify hormonal effects, leading to the peaks that characterize physiologic birth. For example, late-labor oxytocin peaks, promoted by high levels of prolactin and oxytocin itself, assist with the pushing stage. Similarly, excessive stress and stress hormones may disrupt labor progress via hormonal interorchestration.

Cascade of intervention. Hormonal disruptions can be amplified when one intervention necessitates and leads to another that is used to monitor, prevent, or treat its side effects. This escalation of technology can further disrupt hormonal physiology and introduce extra risks for mother and baby. For example, the reduction in maternal oxytocin that generally follows administration of epidural analgesia may lead to use of synthetic oxytocin to compensate. Prolonged use of synthetic oxytocin may desensitize the oxytocin receptor system and increase the risk of postpartum hemorrhage.

Concern about long-term impacts. Non-physiologic exposures during the sensitive perinatal period may disrupt offspring hormone systems, with amplified and/or enduring biological, developmental, and/or behavioral impacts, as found in animal offspring, likely via epigenetic programming effects. High-quality, long-term human studies following fetal/newborn exposure to perinatal drugs and interventions are very limited. Thus, the current evidence-based approach to identifying safe and effective care, based on short-term follow-up and limited examination of hormonally-mediated outcomes such as breastfeeding, may not provide adequate safeguards for mothers and babies. Similarly, conventional shorter-term pharmacologic considerations of fetal/newborn drug exposure (e.g., dose, duration, metabolism) may not adequately safeguard the baby. Current levels of uncertainty about long-term impacts suggest research priorities and support avoiding unneeded interventions.

Physiologic Onset of Labor at Term

The physiologic (spontaneous) onset of term labor is a complex and incompletely understood process. Critical for survival, its timing is thought to be essentially determined by the baby's maturity, via fetal cortisol production, coordinated with the mother's readiness for parturition, via estrogen production and other processes. Timing of the physiologic onset of term labor is difficult to predict due to normal variation in the length of human gestation.

With the physiologic onset of labor at term, maternal and fetal systems are fully primed and precisely aligned for safe, effective, labor and birth, and for optimal postpartum physiologic transitions, including breastfeeding initiation and maternal-newborn attachment, according to physiologic understandings,

and human and animal studies. Physiologic prelabor preparations occur in the weeks, days, and (in animal studies) hours before the onset of labor. Maternal preparations include:

- rising estrogen levels, activating the uterus for an efficient labor
- cervical ripening due to increases in oxytocin and prostaglandin activity (receptors, levels)
- increasing inflammation, which also activates the cervix and uterus
- increasing uterine oxytocin receptors, giving effective contractions during labor, and after birth to reduce bleeding
- increasing brain-based (central) receptors for beta-endorphins (animal studies), contributing to endogenous analgesia in labor
- elevations in mammary and central oxytocin and prolactin receptors (animal studies), which promote breastfeeding and maternal-infant attachment after birth

Similarly, processes before and during labor foster the baby's adaptations for labor and peak readiness for the critical transition to life outside the womb. These include:

- prelabor maturing of the lungs and other organ systems, and of the processes that clear lung fluid in labor
- prelabor development of oxytocin neuroprotective processes (animal studies)
- prelabor increase in epinephrine-norepinephrine receptors, giving protection from labor hypoxia via the late-labor epinephrine-norepinephrine (catecholamine) surge
- in-labor preservation of blood supply to heart and brain, via the catecholamine surge, with neuroprotective effects
- in-labor catecholamine-mediated preparations that will promote newborn breathing, energy and glucose production, and heat regulation

Possible Impacts of Scheduled Birth

Scheduled birth—whether by labor induction or prelabor cesarean section—benefits mother and/or baby in selected circumstances. However, it may also significantly disrupt the processes discussed above.

Possible maternal impacts of scheduled birth include:

- reduced contraction efficiency leading to risks of failed induction, instrumental birth (induction), and postpartum hemorrhage (induction, prelabor cesarean)
- reduction in prelabor oxytocin and prolactin receptor peaks in the breasts and brain (animal studies) with potential impacts on breastfeeding, maternal adaptations, and maternal-infant attachment (induction, prelabor cesarean)

Possible impacts of scheduled birth on the baby include:

- immature protective processes, including the catecholamine surge, with increased vulnerability to labor hypoxia and "fetal distress" (induction)
- increased risks of postpartum breathing difficulties, hypoglycemia, and hypothermia due to lack of exposure to catecholamine surge (prelabor cesarean)
- reduced maturity of brain, brain-hormone, and other organ systems (induction, prelabor cesarean)
- long-term offspring impacts (animal studies), likely via epigenetic programming effects (cesarean section, plausibly relevant to induction)

These are crucial knowledge gaps given the high incidence of scheduled birth.

Oxytocin: Normal Physiology

Oxytocin is a powerful reproductive hormone with widespread effects on the brain and body of all mammals, for example, by mediating sperm ejection, labor contractions, and milk ejection. Oxytocin also reduces stress by centrally activating the parasympathetic nervous system, which promotes calm, connection, healing, and growth; and by reducing activity in the sympathetic nervous system, which reduces fear, stress, and stress hormones, and increases sociability. Oxytocin has a short half-life, but its effects can be prolonged because it modulates other brain-hormone systems (neuromodulation).

In the perinatal period, oxytocin optimizes labor, birth, and postpartum transitions of mother and baby through:

- central oxytocin release into the maternal bloodstream, causing rhythmic uterine contractions, including the late-labor oxytocin surge that benefits pushing (Ferguson reflex)
- central calming and analgesic effects in mothers and babies in labor through the postpartum period
- positive feedback of central oxytocin on itself, especially in multiparous mothers, augmenting and accelerating in-labor effects (animal studies)
- postpartum maternal adaptations that reduce stress, increase sociability, and prime reward centers, imprinting pleasure with infant contact and care, therefore promoting longer-term infant survival

Prelabor increases in uterine oxytocin receptors (human studies) and oxytocin receptors in brain and mammary glands (animal studies) maximize these effects.

The hour or so after physiologic birth is a sensitive period, when skin-to-skin maternal-newborn interactions foster peak oxytocin activity. Benefits may include:

- stronger contractions, likely reducing postpartum hemorrhage risk
- natural warming for the newborn through vasodilation of mothers' chest
- activation of hormonally-mediated maternal-infant biologic bonding
- facilitation of breastfeeding initiation, including by reducing maternal and newborn stress

Common Maternity Care Practices That May Impact Oxytocin Physiology

Common maternity care practices may disrupt these and other beneficial oxytocin effects, with short- and longer-term impacts in mothers and babies. High-quality research is lacking.

While the administration of synthetic oxytocin for induction or augmentation is beneficial in selected circumstances, adverse impacts have been found in women and babies. Synthetic oxytocin administered in labor is not thought to cross into the maternal brain in biologically significant amounts, and so may lack calming and analgesic effects. However, when synthetic oxytocin stimulates contractions, positive feedback cycles may lead to central oxytocin release, promoting further contractions, labor progress, and continued central release.

Synthetic oxytocin may impact maternal oxytocin and physiology. Possible effects include:

- uterine hyperstimulation with potential fetal hypoxia, requiring monitoring
- stronger contractions and increased pain without central oxytocin analgesia
- synthetic oxytocin overexposure causing desensitization of oxytocin receptors, contributing to reduced contractility, prolonged pushing, instrumental birth, and/or postpartum hemorrhage
- disruption of newborn breastfeeding behaviors, reduced maternal oxytocin release with breastfeeding, and possible reduced breastfeeding duration

Physiologic principles, animal studies, and evolving human evidence suggest that perinatal synthetic oxytocin exposure may have longer-term impacts on offspring. While high-quality research is lacking, potential mechanisms include:

- direct fetal brain-hormone effects from synthetic oxytocin transfer through placenta
- indirect signaling of maternal oxytocin to fetal brain
- indirect effects from subclinical hypoxia
- interference with fetal neuroprotective mechanisms (animal studies)
- fetal/newborn impacts from synthetic oxytocin co-interventions such as epidural
- long-term programming of offspring hormonal systems, likely via epigenetic effects (animal studies)
- indirect effects via disruptions to maternal oxytocin systems that impact attachment, reward, breastfeeding, and/or mutual regulation

Epidural analgesia reduces maternal oxytocin in labor, likely due to numbing of the sensory feedback that promotes central oxytocin release. Possible impacts include:

- slowed labor with increased need for synthetic oxytocin
- prolonged pushing stage with increased use of assisted vaginal birth
- disruption of maternal adaptations and attachment

These can also adversely affect the newborn. High-quality research is lacking.

With prelabor cesarean section, mothers and babies miss their complete prelabor physiologic oxytocin preparations; and with any cesarean section, the full oxytocin processes, including the maternal late-labor oxytocin surge and postpartum oxytocin peaks, may be reduced or absent. Impacts on breastfeeding, maternal adaptations, and postpartum hemorrhage have been found. Scheduled cesarean carried out after the physiologic onset of labor may have fewer adverse oxytocin impacts than prelabor cesarean section.

Postpartum separation of healthy mothers and newborns may have detrimental short-and longer-term impacts on the oxytocin system, including:

- reduced oxytocin due to lack of skin-to-skin contact, with increased newborn stress and stress hormones, hypoglycemia, and hypothermia
- disruptions to breastfeeding initiation and long-term success
- deficits in maternal hormones and adaptations, with longer-term impacts on maternal-infant attachment

In animal studies, variations in maternal caregiving in the newborn period lead to epigenetic programming of offspring oxytocin systems, with enduring effects on offspring stress reactivity, and on the maternal care given by female offspring.

Beta-Endorphins: Normal Physiology

Beta-endorphins are endogenous opioids that give analgesic and adaptive responses to stress and pain. Beta-endorphins also activate brain reward and pleasure centers, motivating and rewarding reproductive and social behaviors, and support immune function, physical activity, and psychological well-being.

From labor through the postpartum period, beta-endorphins promote:

- endogenous analgesia though prelabor increase in central receptors (animal studies) and increases in beta-endorphins as labor progresses
- an altered state of consciousness that may help with labor stress and pain
- fetal neuroprotection from hypoxia (animal studies)
- postpartum peaks of beta-endorphins (along with oxytocin) that may facilitate maternal euphoria and prime reward centers, imprinting pleasure with infant contact and care
- reward and reinforcement of breastfeeding in both mother and baby
- newborn support with the stress of postpartum transition, including via beta-endorphins in colostrum

Excessive maternal stress in labor may lead to excessive (supraphysiologic) beta-endorphins, which may inhibit oxytocin and slow labor (animal studies). Alternatively, too-low levels of beta-endorphins (infraphysiologic) may not give adequate stress and pain reduction, or activate postpartum pleasure and reward. Optimal levels of beta-endorphins to reduce stress and pain and promote labor progress likely vary among women.

Common Maternity Care Practices That May Impact Beta-Endorphins Physiology

Laboring women may experience excessive stress in relation to their maternity care providers and birth environments (e.g., if not familiar, calm, and private), which may increase BEs to supraphysiologic levels and slow labor. (Stress mechanisms in women are not clear but may also involve oxytocin and/or epinephrine-norepinephrine.)

Labor analgesia that effectively reduces pain will reduce maternal beta-endorphins to some degree. This may be beneficial if excessive stress is inhibiting labor. However, reduced beta-endorphins, as found with epidurals, may also reduce postpartum reward center activation and priming, potentially impacting hormonally-mediated maternal adaptations and attachment, also involving oxytocin.

Women experiencing a cesarean section may miss prelabor opioid receptor increases (animal studies), in-labor peaks of beta-endorphins, and/or postpartum reward center activation. Cesarean newborns have lower levels of beta-endorphins at birth than vaginally born babies, but levels may rise after birth with separation stress.

Separation of mother and newborn in the early sensitive period following physiologic birth, when levels of beta-endorphins are elevated, may interfere with reward center activation of both. In animal studies, repeated brief separations in the newborn period leads to detrimental impacts on offspring opioid systems, likely via epigenetic programing, with enduring effects on pain sensitivity and addiction.

Epinephrine-Norepinephrine and Related Stress Hormones: Normal Physiology

Epinephrine (adrenaline) and norepinephrine (noradrenaline) mediate "fight or flight" stress responses. Epinephrine-norepinephrine release with perceived danger has promoted safety for laboring females in the wild through human evolution by:

- slowing or stopping labor, giving time for fight or flight
- redistributing blood to heart, lungs, and major muscle groups, and away from uterus and baby, to maximize fight-or-flight actions

This epinephrine-norepinephrine response, which acts at an instinctive, subcortical level in all laboring mammals, may inhibit labor when women do not feel private, calm, safe, and undisturbed in labor. However, if the laboring female perceives stress or danger in late labor, epinephrine-norepinephrine elevations may paradoxically stimulate contractions via differential receptor effects. This "fetus ejection reflex" may also occur physiologically when labor has been largely undisturbed, creating powerful, effective, and involuntary pushing. High-quality research in relation to this reflex and its implications for birth is lacking.

In addition to maternal epinephrine-norepinephrine elevations with perceived stress or danger, a physiologic rise in epinephrine with advancing labor has been found in women. This may benefit laboring women by promoting alertness and may promote labor progress by increasing prostaglandin production. The healthy stress (eustress) of labor also elevates the medium-term stress hormone cortisol as much as ten-fold. Cortisol may promote contractions, increase central oxytocin effects on maternal adaptations and attachment, and enhance postpartum mood.

For the baby, late-labor epinephrine-norepinephrine elevations (catecholamine surge) provide critical adaptations to labor hypoxia and facilitate newborn transitions, e.g., by:

- preserving blood flow to heart and brain
- promoting respiratory transitions, including clearing of lung fluid
- mobilizing metabolic fuels for the newborn period
- promoting newborn thermoregulation by burning brown fat
- promoting newborn alertness and energy for breastfeeding initiation

After birth, epinephrine-norepinephrine levels drop steeply in mother and baby. These decreases promote uterine contractions, which may limit maternal bleeding, and, for the newborn, reduce energy consumption. Warmth and undisturbed skin-to-skin contact may be important in facilitating maternal and newborn epinephrine-norepinephrine reductions.

Common Maternity Care Practices That May Impact Epinephrine-Norepinephrine and Related Stress Hormones

Aspects of contemporary pregnancy care may have unintended negative (nocebo) effects by increasing maternal stress and anxiety. Stress and anxiety in pregnancy can elevate maternal stress hormones, including epinephrine-norepinephrine and cortisol, with detrimental long-term effects on offspring, including impacts on brain development and stress responsiveness, as established in human and animal studies. Studies suggest that maternal relaxation techniques may reduce pregnancy stress and its detrimental effects, but high-quality research is lacking in this important area.

In labor, anxiety or situations in which the woman does not feel private, safe, and undisturbed may provoke epinephrine-norepinephrine elevations, which may slow or stall labor and reduce fetal blood supply via epinephrine-norepinephrine effects. Stress may also slow labor by reducing pulsatile oxytocin and/or by increasing beta-endorphins.

Attention to emotional well-being may promote labor progress. The reduced need for labor interventions associated with doula and midwifery care may reflect this beneficial focus. Conversely, many common maternity care practices may be stressful for laboring women. High-quality research is lacking in relation to physiologic aspects of labor stress, and methods for ameliorating this.

Epidural analgesia can beneficially reduce maternal pain and epinephrine levels, which may have been inhibiting labor. However, the rapid drop in epinephrine may contribute to hypotension and uterine hyperstimulation. More commonly, contractions reduce over time because oxytocin also decreases. Reductions in both epinephrine-norepinephrine and oxytocin with epidural analgesia may contribute to a prolonged pushing stage and assisted vaginal birth. Epidurals do not assist with, and may increase, fetal hypoxia, stress, and stress hormones in labor, and the risk of cesarean for fetal distress.

With cesarean section, both mothers and babies may miss late-labor epinephrine-norepinephrine elevations, and be less alert after birth for breastfeeding initiation. Lack of the fetal catecholamine surge may significantly contribute to newborn morbidities following cesarean section, including breathing difficulties, hypoglycemia, hypothermia, and drowsiness that may impact interactions and breastfeeding. Cesarean birth may impair newborn and infant stress responses.

Separation of healthy mothers and newborns is more likely following cesarean section, leading to newborn stress and stress hormone elevations. Early separation may also be stressful to the mother, depriving her of the opportunity to reduce epinephrine-norepinephrine for herself and her baby through oxytocin elevations with skin-to-skin contact and mutual interactions. In animal studies, repeated brief separations in the newborn period can lead to detrimental impacts on offspring stress hormone systems, likely via epigenetic programming, with enduring effects including depression-like behaviors in adult offspring and also in separated new mothers.

Prolactin: Normal Physiology

Prolactin is a major hormone of reproduction as well as breast-milk synthesis. Prolactin adapts maternal physiology for pregnancy and breastfeeding, promotes maternal adaptations, and is a caregiving hormone in mammalian mothers and fathers. Outside of reproduction, it is a stress and growth hormone.

Maternal prolactin elevations from early pregnancy may have stress-reducing effects that also benefit the fetus. Late-pregnancy prolactin elevations promote the formation of prolactin receptors in the brain and mammary gland (animal studies). Near term, prolactin production also increases in the uterine lining (decidua), and may be involved in labor processes. Prolactin in amniotic fluid, which fills the fetal lungs, may assist with respiratory preparations. Fetal prolactic production increases close to the physiologic onset of labor, and may promote newborn transitions.

Maternal prolactin paradoxically declines as labor advances (outside of labor, stress triggers prolactin release). Prolactin increases steeply as birth nears, likely due to peaks of beta-endorphins and oxytocin, both of which stimulate prolactin release. In addition, prolactin stimulates oxytocin release, contributing to oxytocin peaks in late labor and birth.

Postpartum prolactin elevations, persisting for several hours after birth, may promote breast-milk production and maternal adaptations. Peaks in prolactin and cortisol, together with early and frequent breastfeeding, may promote prolactin receptor formation, with benefits to ongoing milk production ("prolactin receptor theory"). Prolactin levels released during early breastfeeding have been correlated with maternal adaptations, including: reduced anxiety, aggression, and muscular tension; and increased social desirability (conformity), which may help mothers to prioritize infant care.

Common Maternity Care Practices That May Impact Prolactin Physiology

High-quality research is lacking in relation to possible impacts of maternity care practices on prolactin physiology. Stress in labor may paradoxically reduce prolactin secretion, giving infraphysiologic levels in labor and birth, possibly contributing to the negative impacts of labor stress on breastfeeding. Epidurals may cause in-labor prolactin elevations and postpartum prolactin reductions, with unknown impacts. Induction with synthetic oxytocin may also impact physiologic prolactin release. Prostaglandins may inhibit prolactin with possible impacts on breastfeeding success.

With cesarean section, the expectant mother may miss her pre-labor prolactin elevation, late-labor peak and/or postpartum elevations, which may all impact milk production and maternal adaptations. Following cesarean section, prolactin release with early breastfeeding may be reduced or absent. These and other factors may contribute to reduced breastfeeding success following prelabor cesarean section. Following cesarean section, newborns may have lower prolactin levels, possibly contributing to breathing difficulties and low temperature. Lack of the catecholamine surge may also contribute.

Separation of mothers and their healthy newborns, which typically follows cesarean section, may also impact postpartum maternal prolactin levels. If separation interferes with early breastfeeding initiation and frequency, disruption to prolactin receptor formation may impact ongoing milk production and breastfeeding success.

Conclusions and Recommendations

Overall, consistent and coherent evidence from physiologic understandings and human and animal studies finds that that the innate, hormonal physiology of mothers and babies—when promoted, supported, and protected—has significant benefits for both in childbearing, and likely into the future, by optimizing labor and birth, newborn transitions, breastfeeding, maternal adaptations, and maternal-infant attachment.

There are likely additional benefits from avoiding potential harms of unnecessary interventions, including possible adverse epigenetic programming effects.

From the perspective of hormonal physiology, these are not all-or-nothing benefits, but rather accrue along a continuum. Every mother and baby is likely to benefit from additional support for physiologic childbearing, as far as safely possible, including when interventions are used. The hormonal physiology perspective provides additional considerations for weighing possible benefits and harms of maternity care interventions, and suggests new agendas for research. Research priorities include better understanding of many aspects of hormonal physiology and of impacts of maternity interventions on breastfeeding, maternal adaptations, maternal mood, and other short-, medium-, and longer-term hormonally-mediated and developmental outcomes.

Given the uncertainty and potential for significant harms to women and babies in relation to maternity care interventions, application of the Precautionary Principle would be wise in maternity care. Such a standard would involve**:**

- rigorously verifying the benefits of proposed interventions in individual circumstances before undertaking them
- limiting routine practices to those of proven benefit to healthy mothers and babies
- avoiding the use of interventions for the convenience of women or maternity care providers and systems
- initially using less invasive measures to address challenges, and stepping up to more consequential interventions only as needed

A table in the report summarizes the established and potential effects of the maternity care practices addressed in the report on the four hormone systems.

The following recommendations for education, policy, practice, and research arise from the synthesis presented here. Care practice recommendations below are intended to apply whenever safely possible. To optimize hormonal physiology in childbearing**:**

- Educate all maternity care providers in the hormonal physiology of childbearing.
- Use effective policies and quality improvement strategies to foster consistent access to physiologic childbearing.
- Strengthen and increase access to care models that promote physiologic childbearing and safely limit use of maternity care interventions.
- Use effective consumer engagement strategies to inform women about physiologic childbearing and involve them in related aspects of their care.
- Provide prenatal care that reduces stress and anxiety in pregnant women.
- Foster the physiologic onset of labor at term.
- With hospital birth, encourage admission in active labor.
- Foster privacy and reduce anxiety and stress in labor.
- Make nonpharmacologic comfort measures for pain relief routinely available, and use analgesic medications sparingly.
- Make nonpharmacologic methods of fostering labor progress routinely available, and use pharmacologic methods sparingly.

cont'd

- Promote continuous support during labor.
- Foster spontaneous vaginal birth and avoid unneeded cesareans.
- Support early and unrestricted skin-to-skin contact after birth between mother and newborn.
- Support early, frequent, and ongoing breastfeeding after birth.
- Identify and carry out priority research into hormonal physiology of childbearing, and routinely incorporate this perspective in maternity care research.

The Appendix identifies resources for learning more and improving maternity care, including a booklet that presents essential findings from this report to childbearing women.

1
Introduction: Overarching Themes and Scope

This introduction provides an overview and context for the hormonal physiology of childbearing. Evolutionary perspectives are presented, followed by a discussion of contemporary childbirth practices. Overarching themes, including the Hormonal Physiology Pathway, are identified and discussed. The alignment of the report with other frameworks and understandings, such as developmental origins of health and disease, provides a wider context. Finally, the scope is described.

1.1 Human Childbearing: Evolution and Safety

Human birth has evolved over millions of years to optimize reproductive success for mother and offspring, and for our species as a whole. Critical to reproductive success is offspring survival not only at birth, but also in the postpartum period and beyond, which depends on successful lactation and mother-infant attachment. Processes that promote lactation and maternal-infant attachment have therefore evolved to be intertwined and continuous with the biologic processes of birth.

Modern human birth and the powerful, innate childbearing capacities of twenty-first century women and babies are the result of more than 60 million years of mammalian evolution.[1]

Over these millions of years, complex, orchestrated hormonal systems have evolved for mothers and babies to optimize safety during labor and birth (parturition) and in the critical postpartum transitions of both. Equally critical to offspring survival and reproductive success for our evolutionary ancestors have been successful lactation and maternal-infant attachment, including the maternal adaptations that promote infant survival by motivating and rewarding maternal caregiving. The biologic processes that promote the onset of lactation and maternal-newborn attachment immediately following birth, and the ongoing success of these quintessentially mammalian processes, have therefore evolved to be intertwined and continuous with the biologic processes of parturition.

While breastfeeding and the biologic processes of maternal-infant attachment ("biologic bonding") are no longer essential for our offspring's survival, they continue to promote long-term health and well-being of women and babies.[2-6]

Similarly, parturition in our mammalian cousins also requires successful birth, lactation, and mother-infant attachment, and much of the basic research in hormonal physiology derives from animal studies, as further discussed in 1.4.

1.2 Contemporary Childbirth Practices

Contemporary childbirth has benefitted from medical advances. However, current high rates of maternity care interventions may be disadvantageous for mothers and babies in the short and possibly longer terms.

Women's experiences of childbearing in the United States and other high-income countries are very different from the evolutionary experiences of our foremothers.

Contemporary resources and practices, including access to modern medical care, have advanced survival at birth, with benefits to mothers, babies, and society. Beneficial practices include modern hygiene and nutrition, the use of antibiotics to treat infections, skilled treatment for childbirth emergencies, maternal care for high-risk conditions, and neonatal care for sick and premature babies.

However, high rates of maternity care interventions have become standard practice in US hospitals even as most childbearing women and newborns are healthy. This includes interventions that are used liberally or routinely in healthy women and babies, the use of interventions outside of indications supported by high-quality evidence, and the use of more consequential interventions when less invasive measures could suffice. The use of interventions in these situations exposes women and babies to potential harms, both known and as-yet unknown, as discussed in detail in this report, without commensurate benefit. Accumulating evidence suggests that current rates of cesarean section[7-12] and other interventions[12-14] may have exceeded the threshold for benefit, and may now be causing more harm than good.

Maternity care providers are highly skilled and deeply committed to the welfare of women and babies, and to providing the best possible care. However, complex factors within the broader maternity and health care systems profoundly shape practice norms. These include professional education in settings where high use of technology is the norm and experience with other approaches may be limited, financial and delivery systems that reward consequential maternity care interventions above less invasive and costly alternatives, loss of essential skills and knowledge such as simple non-pharmacologic measures for labor progress and comfort, practice variation reflecting local and regional norms, and lack of systems to track important and longer-term maternal and newborn outcomes, including outcomes related to hormonal physiology.

In addition, because of the episodic nature of maternity care, and the division of care for women and babies among many disciplines, including obstetricians, family physicians, midwives, nurses, pediatricians, and lactation consultants, possible links between the childbearing experience and consequential longer-term outcomes for women, children, and childbearing families, as discussed in detail this report, may not be clear.

Many efforts are now under way to address these challenges and develop high-performing maternity and health care systems with better care, outcomes, and value for investments. This report is aligned with those efforts.

Vital records from 2012 show some of the highest intervention rates on record in the United States, with major departures from our evolutionary and hormonal blueprint in a large proportion of the nation's women and newborns. Data from 86 percent of births, as collected in states using the revised birth certificate form, show that:[15]

- 23 percent of birthing women experienced labor induction
- 21 percent experienced augmentation of established labor
- 72 percent used an epidural or spinal for pain relief
- 33 percent gave birth by cesarean section (CS)
- only 10 percent of women with a history of CS gave birth vaginally

The national *Listening to Mothers III* survey of women who gave birth to single babies in US hospitals from mid-2011 to mid-2012, found that these official figures may significantly underreport some procedures,[16] and that many women and newborns also experienced various maternity care interventions not recorded in vital records. Among all survey participants:[17, 18]

- 30 percent reported medically induced labor
- 50 percent received synthetic oxytocin to start and/or hasten labor
- 83 percent used various types of pain medications,
- 11 percent had vacuum- or forceps-assisted births
- 12 percent had episiotomies
- 26 percent of mothers and babies were separated immediately following birth for routine care

Given the novelty and extremely recent appearance of many of these widely-used interventions from an evolutionary standpoint, it is important to understand their possible impacts on the physiology and well-being of mother and baby. Hormonal physiology is a framework that adds value to, and complements, other frameworks and understandings of the processes and outcomes of childbearing, as addressed elsewhere.

1.3 Current Understandings of the Hormonal Physiology of Childbearing

In this report, the "hormonal physiology of childbearing" refers to reproduction-related biologic processes from pregnancy through the postpartum and newborn periods in relation to innate, endogenous hormone systems.

1.3.1 Benefits for Mothers and Babies

Consistent and coherent evidence suggests that physiologic childbearing (conforming to healthy biologic processes) facilitates beneficial (salutogenic) outcomes in mothers and babies, including by promoting: fetal readiness for birth and safety during labor, labor effectiveness, hormonal support for labor stress and pain; and postpartum breastfeeding success and maternal-infant attachment, among other benefits. Greater conformity to healthy biologic processes in childbearing is likely to promote greater benefit for mothers and babies, compared with lesser conformity.

While the hormonal physiology of childbearing is not fully understood, consistent and coherent evidence from physiologic understandings and human and animal studies, as presented here, suggests that physiologic childbearing (conforming to healthy biologic processes) promotes important beneficial outcomes in mothers and babies from pregnancy through to the postpartum and newborn periods. These include:

- precisely aligning readiness for birth between mother and baby with the physiologic onset of labor at term (2.1.)
- preparing the baby for life outside the womb, including maturing the fetal lungs in preparation for breathing (5.1.2)
- protecting the baby from reduced oxygen (hypoxia) during labor (3.1.3, 5.1.3)
- enhancing labor effectiveness, including during the pushing phase (3.1.3)
- providing the mother with physiologic pain and stress reduction (3.1.3, 4.1.3)
- helping to prevent maternal bleeding after birth (3.1.4)
- preparing mother and baby for breastfeeding (3.1.4)
- promoting postpartum maternal adaptations, including activation of pleasure and reward centers, which maximize maternal satisfaction, supporting maternal-infant attachment and infant survival (3.1.4)

The hormonal physiology of childbearing offers a biologic framework that is essentially "salutogenic"—promoting positive health and well-being[19]—for mother and baby in childbearing. Factors that promote physiologic childbearing (conforming to healthy biologic processes) are likely to move mothers and babies toward better health and wellness. This means that physiologic childbearing is not an all-or-nothing process: any practices that support hormonal physiology are likely to benefit mothers and babies, and greater conformity to healthy biologic processes in childbearing is likely to be more beneficial than less conformity.

In addition, because of the sensitivity of the perinatal period, and the potential for epigenetic programming and amplification effects (discussed below), relatively simple hormonal support, such as facilitating skin-to-skin contact in the hour after birth, may have substantial longer-term effects, for example, fostering longer-term maternal-infant attachment and breastfeeding, with exceptional health benefits for mothers and babies. (See "Skin-to-skin contact" in 3.1.4.)

Maternal-newborn attachment differs to some extent between humans and other mammals, especially given that human parents can form strong attachments to non-biologic children. However, biologic, hormonally-mediated attachment processes are measurable in women, as in other mammals, with benefits in the postpartum period and beyond (3.1.4). These processes involve changes in the limbic system (middle brain) in relation to hormonal activity before, during and after birth, and may contribute to offspring survival by enhancing the reward value (pleasure) of infant contact and care. These processes may be more accurately called "biologic bonding."[20]

Recommendations in the final chapter suggest actions to safely support hormonal physiology of women and babies in childbearing, with expected and possibly long-term benefits to health and well-being, as discussed in this report.

1.3.2 Possible Impacts of Maternity Care interventions

Common maternity care practices can impact the hormonal physiology of mother and baby, as described in detail in this report.

Maternity care practices may disrupt hormone systems. Examples of well-known clinical phenomena that are consistent with hormonal physiology effects include:

- slowing or cessation of labor when a laboring women arrives in the unfamiliar hospital environment, due to stress-related increases in epinephrine-norepinephrine, and/or beta-endorphins, and/or reductions in oxytocin (4.1.3, 4.2.1, 5.1.3, 5.2.1)
- prolonged and less effective pushing stage for women using epidural analgesia due to reductions in late-labor oxytocin and/or epinephrine-norepinephrine peaks (3.1.3)
- disruption to newborn transitions with prelabor cesarean due to lack of the fetal late-labor catecholamine surge (5.1.3)
- increased postpartum hemorrhage risk for women following prolonged synthetic oxytocin administration, due to oxytocin receptor downregulation (3.1.3)

Because research in this area is limited, there may be many as-yet unknown hormonal physiology effects from common maternity care interventions, including medium- and longer-term impacts on mother and baby, as discussed in detail in this report.

Hormonal disruptions may contribute to the "cascade of intervention" where one intervention necessitates and leads to another that is used to monitor, prevent, or treat its side effects, with an escalation of technology that can introduce extra risks for mother and baby. Hormonal disruptions can lead to further hormonal disruptions. For example, the reduction in maternal oxytocin that follows epidural analgesia may lead to the use of synthetic oxytocin to compensate. Prolonged use of synthetic oxytocin can desensitize the oxytocin receptor system and increase the risk of postpartum hemorrhage. Interorchestration among hormone systems, discussed below, may also contribute to cascades of intervention.

1.3.3 The Hormonal Physiology Pathway

The Hormonal Physiology Pathway reflects that physiologic childbearing is a temporal pathway, traversing pregnancy, labor, birth, the postpartum and newborn periods, and into the future, and possibly even to subsequent generations, according to epigenetic principles. Each stage includes preparation for upcoming physiologic processes and tasks. The hormonal physiology of mothers and babies is interconnected and interdependent. In addition, hormonal systems interact and interorchestrate with one another, suggesting that disruptions on one hormonal system may spill over to others. This may contribute to the "cascade of intervention."

Physiologic childbearing can be seen as a temporal biologic pathway to a healthy birth and beyond, evolved over millions of years to enhance reproductive success. Beginning from earliest pregnancy, this pathway traverses pregnancy, labor, birth, and the postpartum and newborn periods, and may continue into the future, even to subsequent generations, according to epigenetic principles. Both maternal and fetal/newborn processes are present and interconnected at each stage of the pathway. Recurring and cohesive themes and principles illuminate important properties of this pathway, as seen through this report.

One major, overarching theme is that episodes on this pathway are both processes in themselves and also preparation for upcoming physiologic processes and tasks. This is well illustrated in chapter 2, which describes the prelabor physiologic preparations that ensure peak readiness for term labor and birth of mother and baby. Following on, the processes of labor then prepare for postpartum transitions, for example, the hormonal peaks in late labor likely facilitate the establishment of breastfeeding and promote the maternal adaptations that optimize maternal-infant attachment (described in 3.1.4 in relation to oxytocin). These stages and preparations also overlap, with some prelabor preparations contributing to postpartum processes. For example, prelabor increases in prolactin receptors, as found in animal studies, promote postpartum breast-milk production.

Another illuminating theme on this pathway is the interdependence of hormone systems between mother and the fetus/baby, who can essentially be seen as one biologic system from pregnancy through the postpartum/newborn period. Prelabor preparations, for example, are extensively coordinated, so that readiness of both woman and fetus for labor are precisely aligned at the physiologic onset of term labor. Similarly, when in skin-to-skin contact after birth, mother and baby mutually regulate and promote oxytocin release, and at the same time reduce epinephrine-norepinephrine for each other, with physiologic and ongoing benefits for both (3.1.4, 5.1.4). This coordination also implies that, as a general principle, effects on maternal hormonal physiology can be expected to impact fetal/newborn hormonal physiology, and vice versa.

In addition, these hormone systems interact and interorchestrate with one another, within the biologic systems of mother and baby. Important perinatal hormonal interorchestrations, as found in the maternal system, according to human and animal studies, include that**:**

- beta-endorphins inhibit oxytocin release in the lead-up to labor, helping to regulate labor onset (3.1.2)
- oxytocin stimulates its own release within the brain, contributing to the establishment and acceleration of labor, with greater effects in multiparous females (3.1.3)
- oxytocin promotes beta-endorphins, giving endogenous analgesia to help with contractions (3.1.3, 4.1.3)
- beta-endorphins promote prolactin release in labor, preparing for breastfeeding (4.1.3, 6.1.3)
- prolactin promotes beta-endorphins (4.1.3, 6.1.3)
- extreme levels of beta-endorphins in labor can inhibit oxytocin, slowing labor in situations of excessive stress (4.1.3)
- excessive levels of epinephrine-norepinephrine may also inhibit oxytocin and slow labor when the laboring women feels unsafe or disturbed (5.1.3, 5.2.1)
- pulsatile oxytocin promotes prolactin release in labor (3.1.3, 6.1.3)
- prolactin also promotes oxytocin, contributing to late labor and postpartum peaks of both (5.1.3, 6.1.3)

These interorchestrations suggest that disruption to one hormone system may spill over to other systems, with additional consequences for processes that involve one or both systems. This may contribute to the cascade of intervention, discussed above. For example, epidural-related disruptions to maternal perinatal oxytocin (3.2.5) could also impact prolactin systems, with potential detrimental effects on breastfeeding (see "Synthetic Oxytocin and Breastfeeding" in 3.2.3). Hormonal interorchestrations, and the complex implications for maternity care practices, are not well studied.

1.4 Alignment with Other Frameworks

The hormonal physiology of childbearing is aligned with other major models and frameworks that share an evolving understanding of the critical nature of early development, and the potentially significant impacts of experiences at this time on future health and well-being. The hormonal physiology of childbearing may help to elucidate and extend current understandings within these frameworks, which include the developmental origins of health and disease, epigenetics, and lifecourse health development. Evidence-based and pharmacologic approaches to identifying safe and effective care for mothers and babies may not currently provide adequate safeguards because medium- and long-term outcomes are not well measured.

Outcomes of maternity care and maternity care interventions have traditionally focused on important short-term outcomes such as perinatal mortality, newborn morbidity (e.g., measured by Apgar score, cord blood analysis, and/or admission to advanced care), and certain maternal outcomes. There is increasing recognition, including from other frameworks, that exposures during the highly sensitive perinatal period may have implications for longer-term health and well-being.

Evidence of impacts over time in relation to maternity care exposures is limited, mainly because of very limited medium- and longer-term follow-up. For example, researchers analyzed the larger and more influential randomized studies of effects of perinatal interventions, as found in Cochrane systematic reviews, and found that only 16 percent (40 studies) made any measurement of offspring outcomes beyond hospital discharge.[21] Markedly missing from current research are high-quality studies of the impact of perinatal interventions on medium-term outcomes such as breastfeeding success and duration, maternal-infant attachment, maternal emotional well-being, and other hormonally-mediated salutogenic outcomes.[19]

The growing body of work on the developmental origins of health and disease (DOHaD) recognizes that ". . . a stimulus or insult at a critical period of development has lasting or lifelong effects."[22(p.115)] While this model has, up until now, been mainly applied to events during gestation that may "program" the fetus for later life, (also called "fetal origins of adult disease", FOAD), there is growing awareness that the baby may be equally vulnerable during the perinatal period which, though relatively brief, is pivotal for the complex newborn transitions that promote offspring survival.[23-31]

The term "fetal programming" is generally used to imply maladaptive changes, but this is essentially a mechanism to optimally adapt the baby to the future environment.[32-34] Programming effects that are associated with optimal hormonal processes are likely to be adaptive. For example, animal studies show that high levels of maternal care program low stress responsiveness in adult offspring.[35]

Fetal programming effects are now recognized to involve epigenetic mechanisms—biochemical processes that switch genes on or off.[32, 33] Epigenetic programming due to early life experiences can have enduring effects, which can also be transmitted across generations, with implications for human health and development.[36] For example, transgenerational effects have been found following gestational exposure to diethylstilbestrol (DES),[37] with epigenetic mechanisms identified in animal studies.[38] In addition, human

studies have linked epigenetic changes found in the placenta, particularly those affecting cortisol metabolism (and therefore the transmission of maternal stress to the fetus), with newborn neurobehavior.[39]

In relation to epigenetic effects following perinatal experiences, several studies have found increased DNA methylation, a marker of epigenetic changes, in human newborn tissues following cesarean compared with vaginal birth.[23-25]

Epigenetic mechanisms may also account for the alterations in adult behavior and brain function found among caesarean- compared with vaginally born animal offspring.[27-31] Other possible changes among cesarean-born compared with vaginally-born human offspring, such as altered stress responses in infancy[26] and the well-recognized increased risks of some adult diseases,[40] may derive from epigenetic mechanisms.[23] (See 5.2.6 for more discussion of possible CS effects on offspring stress systems and adult disease.)

If epigenetic programming in the perinatal period (also called "hormonal imprinting" in relation to hormone and hormone-like exposures) applies to humans, as it does to all other species tested so far,[41] the implications for fetal/newborn exposures to perinatal drugs and procedures are considerable.

These concerns have generated the "epigenetic impact of childbirth" (EPIIC) hypothesis.[42] This suggests that**:**

> Physiological labor and birth have evolved to exert eustress (a healthy positive form of stress) on the fetus, and that this process has an epigenomic effect on particular genes . . . . Reduced or elevated levels of cortisol, adrenalin, and oxytocin produced during labor may lead to fetal epigenomic remodeling anomalies which exert influence on abnormal gene expression. This reprogramming could manifest in a range of non-communicative diseases and biobehavioral problems in the neonate and adulthood.[42(p.657)]

The impacts of perinatal experiences, whether physiologic or altered to some extent by maternity care interventions, may be amplified for offspring in the longer term, according to lifecourse health development (LCHD) perspectives.[43] This sophisticated multi-system model predicts that small deviations in biobehavioral systems in early life can alter the health and development trajectory, with large effects into adulthood. According to the LCHD model, "time-specific pathways" exist during critical sensitive periods when developing systems are most vulnerable to alteration, underscoring the crucial importance of the perinatal period for lifelong well-being.

Such alterations in developmental trajectories may also occur indirectly in offspring, via maternal exposures and behaviors. Animal studies (mentioned above) show that the quality of maternal caregiving can epigenetically program offspring stress responses and also the subsequent mothering behaviors of female offspring.[35] This may be relevant to human mothers and babies, including through the possible impacts of maternity care on maternal adaptations and maternal-infant attachment. (See also "Oxytocin and Maternal Adaptations and Attachment" in 3.1.4, "Synthetic Oxytocin and Maternal Adaptations and Attachment" in 3.2.3, and "Epidural Analgesia and Maternal Adaptations in 3.2.5.)

Other biologic models and frameworks, notably the human microbiome and endocrine disruption, also recognize early sensitive periods that may have significant impacts later in life. Given the burgeoning interest and research in the early origins of health and disease, and the recognition of non-communicable disease as a growing global burden,[44] work to understand the links between sensitive periods and long-term health outcomes is critical for global health.

Congruent with these various frameworks, the hormonal physiology of childbearing, as detailed in this report, takes a longitudinal focus in relation to health and wellness. As discussed in relation to evolution, perinatal hormonal systems support reproductive success, which will be optimized when mother and baby not only survive the birth, but also go on to thrive, and produce more offspring who survive and thrive and so on. Hormonal processes during labor and birth that optimize breastfeeding, maternal-infant attachment, epigenetic programming, and health development trajectories thus are likely to contribute to the broader continuum of long-term health and well-being of mother and offspring. Conversely, perinatal hormonal disruptions could have enduring consequences, with researchers and clinicians expressing concerns and suggesting possible mechanisms, as further detailed in this report.[42, 45-54]

Other models used to assess safety for mother and baby may have shortcomings, from these wider perspectives of hormonal physiology. The use of evidence-based health care, including high-quality studies and rigorous up-to-date systematic reviews, has been beneficial in assessing possible benefits and harms in maternity care, albeit with well-documented lags in bringing practice in line with best evidence. However, this model also has significant limitations, because it is limited to the research evidence as it currently exists, reflecting current perspectives and paradigms, and has been primarily focused on a narrow range of short-term outcomes. Other concerns in relation to evidence-based medicine include**:**

- lack of a physiologic childbearing comparison group experiencing minimal or no interventions in most studies, so that differences may be underestimated
- difficulty of measuring effects of interventions due to the common involvement of co-interventions
- frequent lack of data on critical hormonally-mediated outcomes such as breastfeeding and attachment, which are plausibly impacted by preceding maternity care interventions
- minimal follow up beyond hospital discharge in most studies, including most randomized controlled trials, the preferred study design of evidence-based medicine
- to date, no consideration of possible epigenetic programming effects

Because of these limitations, the use of evidence-based health care may be an insufficient safeguard for maximizing benefits and minimizing harms in mothers and babies in relation to maternity care.

Similarly, in relation to fetal/newborn drug exposure, conventional pharmacologic considerations, such as dose, duration, metabolism and excretion, also do not encompass longer-term and possibly epigenetic effects,[55-58] and so may not adequately safeguard the baby, especially in the sensitive perinatal period. For example, studies are now suggesting possible long-term developmental effects from early exposure to anesthetic drugs. According to animal models, “Most clinically utilized anesthetic drugs have been found to induce neuronal cell death in the developing brain and to potentially cause long-term neurological impairment.”[59(p.944), 60] Impactful drugs in these studies include local anesthetics and, to a lesser extent, opioids,[59] which are very common exposures for babies in the perinatal period, including via epidurals.

Due to the current high levels of exposure of mothers and babies to maternity care interventions, and the biological plausibility of as yet unknown unintended, consequences, research into potential impacts of medications and other perinatal practices, including medium- and longer-term outcomes, is a high priority.

1.5 Scope of This Report

1.5.1 Content and Organization

This report examines current understandings of the hormonal physiology of childbearing. The following chapter considers the physiologic onset of term labor and scheduled birth. The subsequent four chapters address four hormonal systems: *oxytocin, beta-endorphins, epinephrine-norepinephrine (adrenaline-noradrenaline) and related stress hormone systems, and prolactin. Each considers physiologic functioning of the hormone system, followed by possible impacts of common maternity care practices and interventions. The final chapter presents conclusions, a summary table, and recommendations.*

The chapter following this introduction summarizes current knowledge about the physiologic onset of labor at term and the possible effects of birth scheduled before physiologic onset by labor induction or planned prelabor cesarean. The specific hormone systems covered in the subsequent four chapters are first described as they function when promoted (through favorable policies and system capacities), supported (with direct facilitating practices), and protected (from disturbance). Following this, the chapters summarize current knowledge of effects of common maternity care practices. The first of these four chapters, on oxytocin systems, is far longer than the others due to the disproportionate amount of research on oxytocin.

Research was available to begin to clarify impacts on the respective hormonal systems of the following widely used labor and birth practices and interventions**:**

- differing maternity care providers and birth environments
- prostaglandins for cervical ripening and labor induction
- synthetic oxytocin for induction, augmentation, and postpartum care
- opioid drugs for pain relief
- epidural analgesia pain relief
- cesarean section
- the early separation of healthy mothers and newborns

Other maternity care practices and interventions such as electronic fetal monitoring, artificial rupture of membranes, restrictions on oral intake, and restrictions on maternal positioning and mobility could not be included because of lack of research data in relation to hormonal physiology. However, some may have direct hormonal impacts, and indirect hormonal effects are also likely in many of these practices. For example, continuous electronic fetal monitoring[61] and being supine and immobile during the first stage of labor[62] increase risk of cesarean section, which has established hormonal impacts, as discussed in the following chapters.

The final chapter gives overall conclusions, provides a summary table of possible impacts of common maternity care interventions, and presents a series of high-level recommendations for clinicians, policymakers and others. An appendix lists selected related resources.

Because of the extremely broad range of material and the large amount of research that is cited, in-depth critical appraisal of individual studies was beyond the scope of this report. It is hoped that this initial synthesis will inspire others to pursue more focused hormonal physiology topics and questions in depth, including the important process of more detailed evaluations of the relevant studies. In addition, many of the hormonal physiology studies cited here are older, reflecting earlier interest in these topics. This basic research deserves revisting with more recent approaches and understandings.

1.5.2 Inclusion of Animal Studies

Animal studies provide valuable information in relation to reproductive physiology. This report includes such studies to illuminate mammalian reproductive physiology, to consider potential human findings, and/or to explore the possible consequences of interventions, where human research is not currently available or feasible.

Much of the current basic understanding of human reproductive biology, including the hormonal physiology of childbearing, comes from research conducted on other mammals such as rats, mice, and sheep and, less often, non-human primates. These animals are widely used in government-funded and other research as models for human physiology, reproductive physiology, and endocrinology because of the extensively documented commonalities with human physiology, the result of millions of years of shared mammalian evolution.[63, 64] In addition, because of shorter lifespans, animal models can provide important information about possible epigenetic programming and transgenerational effects, as discussed above.

Animal research is cited in this report to illuminate mammalian reproductive physiology, to clarify provisional human findings, and/or to explore the possible consequences of intervention, where research cannot be conducted on women and babies for practical and ethical reasons, or has not been conducted to date.

In this report, the use of animal studies is consistently specified. When no human studies were available to examine a specific question or outcome, restriction of knowledge to animal studies is clearly indicated. This implies that similar processes and impacts are possible in humans, but specific research is needed to answer these questions. Where ethical and feasible, it will be important to conduct human studies in the coming years to fill the significant research gaps.

1.6 Introduction: Summary

This report examines current understandings of the hormonal physiology of childbearing, first in relation to the physiologic onset of labor at term and scheduled birth, and then through chapters addressing four impactful hormonal systems: oxytocin; beta-endorphins; epinephrine-norepinephrine (adrenaline-noradrenaline) and related stress hormone systems; and prolactin. Each chapter addresses physiologic hormonal processes followed by the possible impacts of common maternity care practices and interventions. The final chapter presents conclusions, a summary table, and recommendations.

The “hormonal physiology of childbearing” here refers to reproduction-related biologic processes from pregnancy through the postpartum and newborn periods in relation to innate, endogenous hormone systems. “Physiologic childbearing” refers to childbearing conforming to healthy biologic processes. Consistent and coherent evidence finds that physiologic childbearing facilitates beneficial (salutogenic) outcomes in women and babies by promoting fetal readiness for birth and safety during labor, enhancing labor effectiveness, providing physiologic help with labor stress and pain, promoting maternal and newborn transitions and maternal adaptations, and optimizing breastfeeding and maternal-infant attachment, among many processes.

The perinatal period is highly sensitive for mother and baby in relation to hormonal and other biologic processes. Practices that promote (through favorable policies and system capacities), support (with direct facilitating practices), and protect (from disturbance) physiologic childbearing may have amplified, ongoing benefits—for example, through supporting breastfeeding.

Contemporary childbirth has benefitted from many medical advances, and from highly skilled and committed maternity care providers, especially for mothers and babies who require special care. However, current high rates of maternity care interventions may be disadvantageous for the healthy majority. Common maternity care practices and interventions can impact the hormonal physiology of mother and baby, according to physiologic understandings and human and animal studies. Impacts on hormonal physiology and consequences for mother and/or baby may occur in the perinatal period or beyond. For example, prelabor cesareans are associated with reduced fetal/newborn epinephrine-norepinephrine due to loss of the "catecholamine surge," which may contribute to increased respiratory and other morbidities. Longer-term impacts from perinatal hormonal disruptions are possible in women and babies, according to provisional human findings and solid animal research.

Core hormonal physiology themes and principles recur throughout results synthesized in this report, revealing profound interconnections at many levels and over time, as follows**:**

Evolutionary origins. The hormonal physiology of childbearing has evolved over millions of years to optimize reproductive success. Maternal and infant survival at birth is obviously critical for reproductive success, but equally important for long-term survival are successful lactation and maternal-infant attachment immediately following birth. These hormonally-mediated processes are intertwined and continuous with the biologic processes of parturition. Disruption of perinatal hormonal physiology may thus impact not only labor and birth, but also breastfeeding and maternal-infant attachment. As humans share many reproductive processes with other mammals, animal research helps illuminate human hormonal physiology, especially where human research is currently limited.

Mother-baby dyad. Hormonal physiology is interrelated, coordinated, and mutually regulated between mother and baby to optimize outcomes for both. For example, maternal and fetal readiness for labor is precisely aligned at the physiologic onset of term labor to optimize labor efficiency and maternal and newborn transitions. Similarly, skin-to-skin contact after birth mutually regulates maternal and newborn oxytocin systems. As a general principle, effects on maternal hormonal physiology impact fetal/newborn hormonal physiology, and vice versa.

Beneficial hormonal physiology pathway. From pregnancy through labor and birth, breastfeeding, and maternal-infant attachment, hormonal processes of physiologic childbearing anticipate and prepare for upcoming processes and biological needs. For example, prelabor upregulation of maternal uterine oxytocin receptors promotes labor efficiency, and prelabor epinephrine-norepinephrine receptor upregulation optimizes fetal adaptations to labor hypoxia and newborn transitions via the fetal catecholamine surge.

Interorchestration among hormone systems. The hormone systems described here have complex interactions in the perinatal period, including promoting or inhibiting one another's activity. This can amplify hormonal effects, leading to the peaks that characterize physiologic birth. For example, late-labor oxytocin peaks, promoted by high levels of prolactin and oxytocin itself, assist with the pushing stage. Similarly, excessive stress and stress hormones may disrupt labor progress via hormonal interorchestration.

Cascade of intervention. Hormonal disruptions can be amplified when one intervention necessitates and leads to another that is used to monitor, prevent, or treat its side effects. This escalation of technology can further disrupt hormonal physiology and introduce extra risks for mother and baby. For example, the reduction in maternal oxytocin that generally follows administration of epidural analgesia may lead to use of synthetic oxytocin to compensate. Prolonged use of synthetic oxytocin may desensitize the oxytocin receptor system and increase the risk of postpartum hemorrhage.

Concern about long-term impacts. Non-physiologic exposures during the sensitive perinatal period may disrupt offspring hormone systems, with amplified and/or enduring biological, developmental, and/or behavioral impacts, as found in animal offspring, likely via epigenetic programming effects. High-quality, long-term human studies following fetal/newborn exposure to perinatal drugs and interventions are very limited. Thus, the current evidence-based approach to identifying safe and effective care, based on short-term follow-up and limited examination of hormonally-mediated outcomes such as breastfeeding, may not provide adequate safeguards for mothers and babies. Similarly, conventional shorter-term pharmacologic considerations of fetal/newborn drug exposure (e.g., dose, duration, metabolism) may not adequately safeguard the baby. Current levels of uncertainty about long-term impacts suggest research priorities and support avoiding unneeded interventions.

2
Physiologic Onset of Labor and Scheduled Birth

This chapter summarizes current understandings of the physiologic (spontaneous) onset of labor at term and the hormones and hormonal processes involved. It also considers possible impacts on mother and baby of scheduled birth—by induction or prelabor cesarean section—from the perspective of hormonal physiology.

2.1 Physiologic Onset of Labor at Term

Much remains unknown about mechanisms of the physiologic onset of labor in humans. Processes that lead to readiness for labor, birth, and postpartum transitions are coordinated at term labor between mother and baby, whose maturity ultimately determines timing, according to current understanding. The timing of labor onset makes a critical contribution to long-term outcomes of mother and baby by optimizing not only survival at birth, but also the hormonal physiology that supports longer-term well-being and survival via breastfeeding and attachment.

Despite decades of research, the events that trigger the onset of human labor are poorly understood.[65-67] With this limited understanding, there is also a limited ability to effectively halt premature labor and birth, which causes an enormous burden for affected children and families, and for the maternity care system. Prematurity accounts for an estimated 75 percent of newborn deaths in the US.[68]

This chapter highlights the highly complex, orchestrated events that lead to full readiness for labor, birth, and the critical postpartum transitions of mother and baby. These include upregulation of hormone and receptor systems that will maximize labor efficiency and, after birth, will enhance maternal and newborn transitional physiology, breastfeeding, and maternal adaptations, with longer-term benefits to mother and baby. The full consequences of foreshortening these processes are poorly researched and understood.

In addition, because of the wide range of duration of normal human gestation[69] (discussed further in 2.2), it is not currently possible to predict for individual women the day, or even the week, of the physiologic onset of term labor. Therefore, in relation to scheduled birth (induction or prelabor cesarean, PLCS), the degree of foreshortening of gestation, and the potential deficits in fetal maturation and maternal readiness, are also not fully predictable.

Whatever the final trigger for the onset of labor at term, ". . . some mechanism synchronizes fetal development and maturation with the maternal mechanisms that effect the birth."[70(p.569)] This coordination likely follows weeks of progressive changes and preparations.

Current understanding is that the fetus determines the duration of pregnancy, through the culmination of prelabor physiologic preparations, and signals this readiness to the mother's body.[71] The mother's physiology determines the time of day that labor commences, through day-night (circadian) rhythms.[72]

The physiologic onset of labor at term represents the end of a series of processes that begins as early as midpregnancy. This onset is timed to optimize readiness of the mother, maturity of the fetus, survival at birth, and long-term survival of both. The pregnant woman's uterus goes through several states:[73]

- quiescence: in pregnancy, when the uterus is inactive
- activation: preparing for labor, when the uterus becomes capable of being activated
- stimulation: labor itself, with stimulation of uterine activity
- involution: postpartum return to prepregnancy state (not described here)

2.1.1 Quiescent Phase

Progesterone and relaxant prostaglandins are among factors that maintain uterine quiescence in pregnancy.

Many factors inhibit contractions and maintain uterine quiescence through pregnancy. These include: relaxin; nitric oxide (NO); and the female hormone progesterone, which blocks estrogen receptors, inhibits

cervical softening, and may also block oxytocin (OT) effects by inhibiting OT receptor (OTR) functions,[74] among other "progestation" actions.[66, 71] Prostaglandins (PGs) can also have quiescent effects in pregnancy, through acting on different PG receptors,[75] as described below.

2.1.2 Activation Phase

In the last weeks of term pregnancy, the maturing fetal adrenal glands produce both cortisol, which matures the fetal lungs and other organs, and a chemical precursor for estrogen, which is then produced in the placenta and activates the uterus. This ensures coordination of fetal and maternal readiness. Estrogen, inflammation, prostaglandins, and corticotropin releasing hormone all contribute to uterine activation, including oxytocin receptor upregulation. Prelabor physiologic preparations, as seen in animals, also include increases in: oxytocin receptors in the maternal brain and mammary glands, endogenous analgesic systems, fetal neuroprotective processes, and maternal and fetal prolactin systems. These contribute to maternal adaptations, labor analgesia, maternal and newborn transitions, and breastfeeding success.

The activation phase begins many weeks before term labor actually starts, and lasts until the physiologic onset of labor. This phase is concerned with maternal readiness for an effective, efficient labor. Many of the maternal processes of activation, and of the subsequent stimulation phase, are initiated by rising levels of the activating hormone estrogen, which has opposite effects of progesterone. Fetal preparations that promote maturity and readiness for labor, birth, and life outside the womb—obviously essential for fetal survival—occur in parallel, thus coordinating maternal readiness and fetal maturity.

Maternal estrogen levels rise because the baby's maturing adrenal gland produces increasing amounts of the estrogen precursor dehydroepiandrosterone-sulfate (DHEAS) in the four to six weeks before birth. DHEAS is converted to estrogen in the placenta and then enters the mother's circulation.[71] Changes in the ratios of estrogen to progesterone, of the estrogen subtypes estriol and estrone, and/or of progesterone receptors A and B may all be involved in uterine activation, and possibly in the physiologic onset of labor.[76]

Over the final weeks preceding physiologic onset of labor at term, estrogen begins to prepare the mother's body for labor through**:**

- increasing the number (upregulation) of OTRs
- electrically connecting her uterine muscle cells for coordinated contractions in labor via the substance connexin-43
- promoting cervical ripening
- shifting the balance of prostaglandin (PG) receptors towards those that stimulate contractions[75] (below)
- increasing other uterine activating substances and processes[76]
- activating spinal cord pain-relieving pathways (involving non-beta-endorphin opiates) in preparation for labor and birth[77]

As well as DHEAS, the fetal adrenal also produces increasing amounts of cortisol at this time, which acts to mature all of the baby's organs, especially the lungs. In the days preceding the physiologic onset of term labor, the fluid that has filled the developing lungs begins to reduce in amount, and the physiologic mechanisms that will fully clear this fluid before birth begin to mature.[78, 79]

Other important fetal prelabor physiologic preparations, largely mediated by cortisol, include: upregulation of epinephrine-norepinephrine (E-NE) receptors in the lung and heart, which support fetal adaptations to labor hypoxia via the "catecholamine [CA] surge" (5.1.4); thyroid maturation, which assists with early newborn heat production and lung clearance; increases in lung surfactant to promote newborn respiratory transition; and gut and metabolic preparations to ensure sufficient fuels for the postnatal period[78] 5.1.3). Fetal brain development is also completed in the final weeks of gestation, with likely important contributions to maturation of brain-hormone systems (2.2).

In this way, readiness of the baby (maturing adrenal, maturing effects from cortisol, E-NE receptor upregulation, completion of brain development) is coordinated with preparation of the mother's body for labor, via increasing estrogen and other activating effects. Increasing levels of maternal cortisol may also contribute to uterine activation by blocking the quiescent effects of progesterone.[73]

Prostaglandins, mentioned above, have an important role in maternal preparations for labor and birth. Prostaglandin F2alpha and E2, synthetic versions of which are used medically to "ripen" the pregnant woman's cervix, promote cervical changes in the lead-up to labor, including increases in water and elastin, and decreases in collagen. These lead to increased cervical softening and elasticity in preparation for opening during labor.[71] Cervical changes occur progressively over several weeks, triggered by rising PGs, estrogen, and other factors such as inflammation, described below, which also contributes to uterine activation.

As labor draws closer, PG receptors increase differentially in the uterus. As some of these stimulate, and some relax the uterus, this may contribute to a shift from uterine relaxation to activation, especially in the top of the uterus (fundus). Increased PG production and reduced PG breakdown may also contribute.[75] Prostaglandins are also made in the amnion layer of the fetal membranes, with large amounts detectable in the amniotic fluid as labor draws closer. From the amnion, PGs can act on the cervix, as above, and also reach the uterine lining (decidua) and deeper myometrium, where they stimulate contractions and may also promote OT release.[75] Prostaglandin effects are also increased through local positive feedback cycles with cortisol[80] and oxytocin (3.1.3).

Inflammation is usually associated with tissue damage or infection, and involves an increase in white blood cells and inflammatory substances, including PGs, arachadonic acid, a PG precursor, and interleukin-1 beta. Inflammatory changes in the amnion, cervix, and uterus develop over the weeks before the physiologic onset of labor, and may even precede changes in progesterone, estrogen, and OT, making inflammation a possible early trigger for term labor, as it is for preterm labor.[81] Inflammation in the amnion weakens the membranes in preparation for membrane rupture, which further accelerates inflammatory changes in labor by allowing vaginal bacteria to access the uterus.[82, 83] Under physiologic conditions, membrane rupture predominantly occurs after full dilation.[84] In addition, the inflammatory substance interleukin-1beta promotes OTR formation in the amnion, which promotes the formation of PGs that will stimulate the myometrium, as above.[82, 83 85]

Under the influence of factors including estrogen, PGs, and inflammation, OTRs are upregulated in the uterus close to the physiologic onset of term labor, giving peak sensitivity and labor efficiency, as detailed below (2.1.3). Animal studies also show OTR upregulation in the expectant mother's mammary glands[86, 87] and brain[88] in the days preceding the onset of labor at term, giving important preparations for lactation, maternal adaptations, and postpartum behaviors, all essential for offspring survival (2.1.2).

Rises in corticotropin releasing hormone (CRH) activity have also been implicated in uterine activation, and possibly the physiologic onset of labor (5.1.2, 5.1.3). This brain-based stress hormone has a different role in pregnancy, when it is made by the placenta and contributes to fetal adrenal maturation and subsequent cortisol/estrogen increases (above). The rate of rise of maternal CRH in early to midpregnancy may indicate the length of gestation, earning CRH the name "placental clock."[82, 83]

CRH also enhances the laboring mother's uterine response to OT and PGs,[89, 90] promotes the formation of activating PGs[76] and other inflammatory substances,[91] and participates in several activating positive feedback cycles involving fetal cortisol, and maternal cortisol and prostaglandins.[76]

Animal studies have contributed to understandings of important events in the lead-up to labor.[77, 92-96] For the fetus, neuroprotective mechanisms involving the OT system are activated in the 24 hours before the physiologic onset of term labor, and give maximal protection in late labor[97] (3.1.3). Mechanisms involving E-NE and beta-endorphins (BEs) also protect the fetal brain in labor, as described below. For the mother, brain-based (central) activity of beta-endorphins (levels, receptors) rises in late pregnancy and peaks at the physiologic onset of term labor,[92-94, 96] when other endogenous opioid analgesic systems are also upregulated.[77] Prelabor increases in central connections between OT and BEs make BEs powerful at restraining OT release before labor.[95]

Animal studies also show extensive central prelabor preparations for postpartum maternal behaviors, including in the OT system.[98, 99] Some of the changes that are essential for postpartum maternal behaviors occur only in the few hours before the physiologic onset of term labor, and are completed by the processes of labor and birth.[100, 101] (See also "Maternal Oxytocin in Pregnancy" in 3.1.2 and "Maternal Prolactin in Pregnancy" in 6.1.2.)

In women, prolactin (PRL) levels increase as pregnancy progresses, doubling between 35 and 38 weeks, according to one study.[102] These elevations are likely to stimulate upregulation in mammary prolactin receptors (PRLRs), as demonstrated in animals late in pregnancy.[103-105] For the human fetus, late-gestation PRL elevations may assist with lung maturation and begin to prepare for newborn heat production[106] (6.1.2).

Because all of these changes happen in parallel, cervical changes may approximate uterine changes, including OTR numbers, and temporal proximity to term labor, therefore suggesting responsiveness to induction (3.2.3). Researchers who assessed daily pregnant women's cervical status (Bishop score) and uterine responsiveness to synthetic oxytocin (by cardiotocogram, CTG) in the lead-up to the physiologic onset of labor at term, found parallel increases, with both peaking with the last measurement before physiologic labor onset[107] (see 3.1.4). In addition, the coordination of maternal readiness and fetal maturity suggests that maternal cervical status may also indicate fetal maturity (see also 3.2.6).

2.1.3 Stimulation Phase

Peak maternal sensitivity to oxytocin and prostaglandins occurs at the physiologic onset of labor at term, and both substantially contribute to labor processes, including via positive feedback cycles. Hormonal interorchestrations involving prolactin and endorphins augment labor and postpartum hormonally-mediated processes, including breastfeeding and maternal adaptations. Fetal in-labor processes, upregulated before labor onset, protect against hypoxia and also assist with newborn transitions.

The physiologic onset of term labor involves a shift from the irregular, low-frequency uterine activity of pregnancy (contractures) to the high-frequency, high-intensity uterine contractions of labor. Processes within the fetus and placenta are thought to initiate this shift,[71] which usually begins at night, with nocturnal surges in OT triggering contractions.[72, 108] The sleep hormone melatonin increases uterine sensitivity to OT,[109] making labor more likely to begin at night in humans and other day-living species. Lower nocturnal levels of E-NE, which generally inhibit labor, may also contribute.[110]

With the physiologic onset of labor at term, levels of the substance connexin-43 increase in the uterus, contributing to the formation of gap junctions that electrically connect uterine muscle cells for the coordinated contractions of labor.[71]

The physiologic onset of term labor is also the time of maximum sensitivity to the uterine stimulants OT and PGs, with receptor activity for both OT[111] and PGs[75] peaking at this time. Prostaglandins promote contractions in many ways, including by directly stimulating the myometrium and increasing gap junctions, and may promote further PG production in a positive feedback cycle.[112] Prostaglandins also promote uterine sensitivity to oxytocin in vitro,[113] and in vivo,[114] possibly by promoting the formation of OTRs.[112, 115] By causing contractions, PGs also stimulate central OT release in a positive feedback cycle (3.1.3). Prostaglandins also participate in local positive feedback cycles with cortisol.[80]

Oxytocin reaches the laboring woman's uterus from her pituitary and limbic system and is also made locally in the placenta, decidua, and fetal tissues. Within these local tissues, OT-OTR binding stimulates the production of PGs, and PGs stimulate OT activity directly and/or indirectly, as above, creating a positive feedback cycle that accelerates labor (3.1.3). Oxytocin produced in the amnion crosses to the adjacent decidua and stimulates contractions in the deeper myometrium.[116] (See 3.1.3 for more about OT in labor.)

As term approaches, endogenous opioids such as beta-endorphins, which have been acting to restrain OT release within the maternal brain, begin to decline,[117, 118] according to animal studies, further promoting OT's stimulating effects (4.1.2). The substance surfactant-related protein A (SP-A), made in the fetal lungs, may also contribute to the onset of labor. This is secreted into the amniotic fluid, and may be transmitted through the fetal membranes and into the adjacent uterine lining (endometrium) and deeper myometrium, triggering uterine contractions.[83] Increased maternal levels of fetal ("cell free") DNA may also have stimulating effects close to labor onset.[119]

Increased connections within the brain between the OT, BEs, and PRL systems in the lead up to term labor contribute to a hormonal cascade that promotes physiologic labor, birth, and postpartum adaptations:

- OT promotes release of BEs in labor,[120] assisting with stress and pain.
- Both BEs[121] (2.1.3) and pulsatile OT in labor promote PRL release, preparing for breastfeeding.[122, 123]
- PRL promotes OT release, also important in breastfeeding[124] (3.1.1).
- PRL promotes BEs, giving pleasure and reward after birth and with breastfeeding.[125]

According to animal studies, PRL receptors are further upregulated during term labor,[126] preparing for effective lactation, central maternal adaptations, and the maternal behaviors that optimize infant survival (6.1.3).

For the baby, prelabor and in-labor physiologic preparations and processes confer substantial benefits in labor, with a large investment in neuroprotection, as discussed above. In summary, these include:

- neuroprotective systems involving the OT system, which are activated just prior to the physiologic onset of term labor (animal studies, 2.1.2, 3.1.3)
- upregulation in E-NE receptors, which optimize efficacy of the fetal CA surge (below) (5.1.2)
- the late-labor CA surge, which preserves blood and glucose supply to the fetal heart and brain, giving additional neuroprotective effects, and begins preparations for respiratory, metabolic, and thermoregulatory transitions[78, 127] (5.1.3)
- further neuroprotective effects from BEs released with labor stress and hypoxia[128, 129] (animal studies, 4.1.3)

These overlapping mechanisms for the initiation of labor at term, and the many prelabor hormonal orchestrations and interorchestartions that promote optimal transitions for mother and baby, underline the complexity of perinatal hormonal physiology. The critical importance for species survival of the precise alignment of readiness between mother and baby at the physiologic onset of term labor suggests that multiple systems and processes likely converge, with built-in redundancy and backup systems.[66, 71] (Further details of the role of each hormone in the onset and progress of labor are found in 3.1.3, 4.1.2, 5.1.3, and 6.1.3.)

2.2 Possible Impacts of Scheduled Birth

Induction and prelabor cesarean foreshorten these beneficial preparatory processes of mother and baby, with greater effects following prelabor cesarean, as the hormonal processes of labor are also absent in both. While beneficial in some situations, possible impacts of scheduled birth in relation to hormonal disruption include, for induction, reduced contraction efficiency leading to failed induction, instrumental birth, and postpartum hemorrhage. Possible hormonal impacts from prelabor cesarean include deficits in fetal maturity and adaptations leading to respiratory, thermoregulatory, and metabolic vulnerability. Animal studies suggest possible long-term effects. Deficits in maternal prelabor physiologic preparations, including lack of upregulation in central and mammary oxytocin and prolactin receptors, as shown in animals, could hinder breastfeeding, maternal adaptations, and maternal-infant attachment. High quality-research is lacking in these important areas.

Recent research suggests that fewer than half of US mothers and babies experience the spontaneous, physiologic onset of labor, as described above. In response to a national survey of women who had given birth from mid-2011 to mid-2012, 30 percent reported medically induced labor, 18 percent reported a planned PLCS, and two percent reported a cesarean following an attempted induction that did not bring labor on, with yet other women unsure whether attempted induction had caused their labor to begin.[18]

In some situations, induction or PLCS is medically indicated, with clear benefits for mother and/or baby.[130, 131] However, the expected benefits of scheduled birth in many cases may not outweigh the full range of potential harms, including incomplete prelabor physiologic preparations, with potential compromise to in-labor and/or postpartum outcomes in mothers and babies. From the perspective of hormonal physiology, “elective induction” and “elective cesarean,” with no medical indication or benefit, are particularly concerning as there are no benefits to balance the hormonal impacts and other possible adverse effects, both known and plausible yet inadequately researched, in mother and baby.

Current methods of calculating the estimated date of delivery (EDD) can have wide margins,[132] especially later in pregnancy.[133, 134] Women have a particularly large variation in the normal duration of pregnancy, even compared with other primate species.[69] One recent study using accurate timing of ovulation found a variation in normal gestation of up to five weeks (37 to 42 weeks).[69] These factors increase the possibility that scheduled birth will occur before, and perhaps well before, maternal and fetal readiness is aligned, with increased likelihood of maternal and newborn morbidities.

Recent moves to avoid early elective delivery by limiting induction and PLCS to 39 weeks or beyond[135] will increase average fetal maturity and are consistent with improved outcomes. However, dates may not be accurate (discussed above) and this may still be days, or even weeks before the time when the physiologic onset of labor would otherwise have occurred in some women and babies. Mother and baby may still miss important prelabor physiologic preparations, some of which only occur in the hours before physiologic labor onset according to animal research,[97, 100, 101] also discussed above.

The body of clinical studies of the impact of induction on mothers and/or babies is complex and includes contradictory results. Its assessment is beyond the scope of this report. However, the physiologic processes described here suggest that the foreshortening of gestation may have a wider range of adverse impacts than generally recognized, including impacts on hormonally-mediated outcomes such as breastfeeding and maternal adaptations. The use of synthetic oxytocin (synOT) as an induction agent may have additional impacts on mothers and/or babies (3.2.3, 4.2.3, 5.3.3, 6.2.3), and the possible effects of prostaglandins on hormonal physiology are not well studied (3.2.2, 4.2.2, 5.2.2, 6.2.2).

Babies born by PLCS miss not only the prelabor physiologic preparations described above, but also the beneficial stress (eustress) of labor. As discussed in detail in "Fetal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth" in 5.1.3, and in "Cesarean and the Fetus/Newborn" in 5.2.6, labor eustress activates E-NE and many other hormonal and non-hormonal processes that promote optimal newborn transitions. Alterations in stress responses have been found among newborns[136, 137] and infants[26] born by PLCS compared with vaginal birth. Long-term effects on offspring stress and hormonal systems are biologically plausible,[20] as suggested in animal studies of cesarean offspring [27-31, 138-141] (further described in "Cesarean and the Fetus/Newborn" in 5.2.6).

Mothers experiencing PLCS may miss in-labor processes that promote breastfeeding and maternal adaptations, including increases in OT and PRL receptors, as seen in animal studies (3.1.4, 4.1.4, 5.1.4, 6.1.4, with implications discussed in detail in 3.2.6). Deficits in prelabor uterine OTR upregulation may increase risks of postpartum hemorrhage (PPH) following PLCS. (See also Table 3. Established and plausible oxytocin processes and impacts, by type of cesarean, and discussion in 3.2.6).

Table 1 summarizes possible adverse impacts of induction and prelabor cesarean on the hormonal physiology of mother and baby, according to physiologic understandings and human and animal studies, as detailed in this chapter and report.

Table 1. Established and biologically plausible adverse impacts of labor induction and prelabor cesarean

Deficits that may arise with foreshortened pregnancy/gestation	Possible impacts on mother and/or baby
Deficits in prelabor OTR upregulation in uterus Deficits in other uterine activating factors such as PGs, CRH, inflammation (2.1)	Reduced uterine OT sensitivity and contraction efficiency leading to: • slow labor (IOL) • failed induction (IOL) • delay in pushing stage, increase in forceps/vacuum (IOL) • increased PPH risk (IOL, PLCS) • need for synOT at supra-physiologic levels (IOL for labor progress, IOL, CS to reduce PPH risk) (see also 3.2.3)
Deficits in prelabor OTR upregulation in mammary gland*	Reduced breastfeeding success (IOL, PLCS) (see also "Synthetic Oxytocin and Breastfeeding" in 3.2.3 and "Cesarean and Breastfeeding" in 3.2.6)
Deficits in prelabor OTR upregulation in the maternal brain*	Reduced maternal adaptations (IOL, PLCS), including reduced: • personality adaptations, potentially increasing anxiety and tension (see "Maternal adaptations" in 3.1.4) • reward center activation, potentially impacting maternal mood, and pleasure from her baby • maternal-newborn attachment (see "Maternal-infant attachment and childbearing" in 3.1.4) (see also "Synthetic Oxytocin and Maternal Adaptations" in 3.2.3 and "Cesarean and Maternal Adaptations and Attachment" in 3.2.6)
Deficits in prelabor activation of fetal OT neuroprotection*	Increased neurologic vulnerability in labor (IOL); these deficits have been linked with animal models of autism (see "Fetal neuroprotection" in 3.1.3)
Deficits in prelabor activation of BEs and other opioid analgesic systems in maternal brain and spinal cord*	Increased pain, requirement for analgesia (IOL) (see also 4.1.2)

cont'd

Deficits that may arise with foreshortened pregnancy/gestation	Possible impacts on mother and/or baby
Deficits in fetal prelabor E-NE upregulation and in-labor CA surge that support: • protection against hypoxia by preserving blood flow to heart, brain • respiratory preparations • metabolic transitions • thermoregulatory transitions	Increased risks during labor and with newborn transitions, including (IOL and especially PLCS): • vulnerability to hypoxic effects, especially heart and brain • respiratory morbidity • hypoglycemia • hypothermia (see "Fetal catecholamine surge" in 5.1.3) Animal studies show long-term disruption to brain-hormone systems following PLCS (see "Cesarean and the Fetus/Newborn" in 5.2.6)
Deficits in other late-term respiratory preparations, e.g., PRL-related (6.1.2)	Detrimental impacts on respiratory transition (IOL, and especially PLCS)
Deficits in maternal prelabor PRL preparations, including PRLR upregulation in mammary gland* (6.1.2)	Reduced breastfeeding success (IOL, PLCS) (see also "Synthetic Oxytocin and Breastfeeding" in 3.2.3 and "Cesarean and Breastfeeding" in 3.2.6)

Note: BE = beta-endorphins, CA = catecholamine, CRH = corticotrophin releasing hormone, CS = cesarean section, E-NE = epinephrine-norepinephrine, IOL = induction of labor, OTR = oxytocin receptor, PGs = prostaglandins, PLCS = prelabor cesarean section, PPH = postpartum hemorrhage, PRL = prolactin, PRLR = prolactin receptor, synOT = synthetic oxytocin.

*Results have only been reported in animal studies to date

In addition to these concerns, studies suggest many extra-hormonal implications of induction and/or PLCS that may have long-term impacts. These include foreshortening of the final critical weeks of brain development,[142-146] and long-term cesarean impacts on gut flora[147] and immune function,[148] which are beyond the scope of this report. (See also 3.2.3 and 5.2.6 for discussion of possible programming effects of exposure to synOT and PLCS.)[131]

The salutogenic aspects of prelabor hormonal physiology and the physiologic onset of labor at term, as described in this chapter, along with the current paucity of evidence about possible consequential longer-term impacts of scheduled birth in mothers and babies, raise serious concerns about the current high rates of labor induction and PLCS, particularly in healthy women with healthy babies. Also concerning are recent suggestions that routine labor induction could be implemented to improve outcomes for healthy mothers and babies, including to reduce the chance of cesarean section,[149-152] for which there are many evidence-based practices with fewer known and plausible adverse effects.[131, 153] Clear understandings about the possible impacts of scheduled birth on women and babies, including established and plausible hormonal deficits as summarized in Table 1, are essential before routine elective induction of labor or prelabor cesarean could be safely advocated.

As described in detail in this report, the innate hormonal physiology of mother and baby incorporates many processes that support and protect mother and baby through the major transitions of labor and birth. The hormonal physiology of childbearing also promotes ongoing survival and well-being of mother and baby by optimizing breastfeeding and the maternal adaptations that enhance maternal reward and maternal-infant attachment. Other possible positive, but as yet unstudied, effects—for example, beneficial fetal programming from exposure to physiologic hormonal processes—could give additional long-term benefits to offspring.

Scheduled birth is beneficial for mothers and babies in some circumstances. However, from the perspective of hormonal physiology, the established and plausible consequences of induction and PLCS, as discussed in this and the following chapters, raise further concerns for maternity care providers and women to include in assessing benefit/harm trade-offs.

The full impacts of scheduled birth on mother and baby, including possible impacts on hormonally-mediated processes including breastfeeding, maternal adaptations, and maternal-infant attachment, are critical areas for future research.

2.3 Physiologic Onset of Labor and Scheduled Birth: Summary

2.3.1 Physiologic Onset of Labor

The physiologic (spontaneous) onset of term labor is a complex and incompletely understood process. Critical for survival, its timing is thought to be essentially determined by the baby's maturity, via fetal cortisol production, coordinated with the mother's readiness for parturition, via estrogen production and other processes. Timing of the physiologic onset of term labor is difficult to predict due to normal variation in the length of human gestation.

With the physiologic onset of labor at term, maternal and fetal systems are fully primed and precisely aligned for safe, effective, labor and birth, and for optimal postpartum physiologic transitions, including breastfeeding initiation and maternal-newborn attachment, according to physiologic understandings, and human and animal studies. Physiologic prelabor preparations occur in the weeks, days, and (in animal studies) hours before the onset of labor. Maternal preparations include**:**

- rising estrogen levels, activating the uterus for an efficient labor
- cervical ripening due to increases in oxytocin and prostaglandin activity (receptors, levels)
- increasing inflammation, which also activates the cervix and uterus
- increasing uterine oxytocin receptors, giving effective contractions during labor, and after birth to reduce bleeding
- increasing brain-based (central) receptors for beta-endorphins (animal studies), contributing to endogenous analgesia in labor
- elevations in mammary and central oxytocin and prolactin receptors (animal studies), which promote breastfeeding and maternal-infant attachment after birth

Similarly, processes before and during labor foster the baby's adaptations for labor and peak readiness for the critical transition to life outside the womb. These include:

- prelabor maturing of the lungs and other organ systems, and of the processes that clear lung fluid in labor
- prelabor development of oxytocin neuroprotective processes (animal studies)
- prelabor increase in epinephrine-norepinephrine receptors, giving protection from labor hypoxia via the late-labor epinephrine-norepinephrine (catecholamine) surge
- in-labor preservation of blood supply to heart and brain, via the catecholamine surge, with neuroprotective effects
- in-labor catecholamine-mediated preparations that will promote newborn breathing, energy and glucose production, and heat regulation

2.3.2 Possible Impacts of Scheduled Birth

Scheduled birth—whether by labor induction or prelabor cesarean section—benefits mother and/or baby in selected circumstances. However, it may also significantly disrupt the processes discussed above.

Possible maternal impacts of scheduled birth include:

- reduced contraction efficiency leading to risks of failed induction, instrumental birth (induction), and postpartum hemorrhage (induction, prelabor cesarean)
- reduction in prelabor oxytocin and prolactin receptor peaks in the breasts and brain (animal studies) with potential impacts on breastfeeding, maternal adaptations, and maternal-infant attachment (induction, prelabor cesarean)

Possible impacts of scheduled birth on the baby include:

- immature protective processes, including the catecholamine surge, with increased vulnerability to labor hypoxia and "fetal distress" (induction)
- increased risks of postpartum breathing difficulties, hypoglycemia, and hypothermia due to lack of exposure to catecholamine surge (prelabor cesarean)
- reduced maturity of brain, brain-hormone, and other organ systems (induction, prelabor cesarean)
- long-term offspring impacts (animal studies), likely via epigenetic programming effects (cesarean section, plausibly relevant to induction)

These are crucial knowledge gaps given the high incidence of scheduled birth.

3
Oxytocin

This chapter details oxytocin research as relevant to reproduction, presenting firstly what is known about the oxytocin system in relation to healthy, physiologic, childbearing processes and then the possible impacts of specific maternity care practices and interventions, including administration of synthetic oxytocin, on the oxytocin systems of mothers and babies.

3.1 Oxytocin: Normal Physiology

Oxytocin has been called the "hormone of love," as well as "hormone of trust" and "hormone of calm and connection." Current areas of oxytocin research include brain-based and psychological effects in humans, and behavioral and programming effects in animals, including in relation to early oxytocin manipulations.

Oxytocin (OT) has been the focus of a large amount of research over recent decades, with particular interest in its brain-based (central) and psychologic effects. These have earned it names such as the "hormone of love,"[154] "hormone of calm and connection,"[52] and "hormone of trust,"[155] with a growing interest in its role in human parenting.[156] In parallel with these developments, animal research has been uncovering other important aspects of the OT system, including studies suggesting that the perinatal oxytocin system is very modifiable (plastic) in mother and offspring, with possible epigenetic programming effects in offspring in relation to both endogenous OT (produced within the body) and exogenous or synthetic OT (synOT, administered from outside the body) (see "Oxytocin effects," below, 3.1.3, and 3.2.3).

3.1.1 Oxytocin: Introduction

Oxytocin is a hormone that is released into both the body, with physical effects, and the brain, with powerful and widespread physiologic, psycho-emotional, and behavioral effects that benefit reproduction and social behaviors. Synthetic oxytocin is chemically identical to endogenous oxytocin, but has different effects because it is not released from and within the brain.

Oxytocin was discovered in 1906 as a pituitary extract that causes a fast (*oxy*) birth (*tocin*).[157] The OT molecule comprises a chain of nine amino acids and acts in the body of humans and all other mammals as a hormone, that is, a substance that is produced in one part of the brain or body and has effects on distant areas through passage in the bloodstream.

In the brain, OT is produced in the supraoptic and paraventricular nuclei (SON, PVN) within the hypothalamus. From there, within the middle layer of the brain (limbic system), OT is released into local and distant brain areas, giving widespread brain-based (central) effects, and also into the bloodstream via the posterior pituitary gland, giving bodily (systemic) effects. In the brain, OT acts by transmitting signals between nerve cells (neurotransmitter), and by affecting the function of other hormone and brain systems (neuromodulator),[158, 159] with important roles in interorchestrating hormone systems in childbearing. The OT system is also very modifiable in response to physiologic and environmental stimuli.[160] These properties make OT a powerful regulator of biologic processes, especially in relation to reproduction and social behaviors, both of which make major contributions to mammalian survival.

The chemically similar hormone arginine vasopressin (AVP, vasopressin, previously known as antidiuretic hormone, ADH) is also released from the posterior pituitary and has some OT-like effects, and vice versa, from stimulation of each other's receptors.[158] Arginine vasopressin may be critically involved in fetal adaptations to labor pain,[161] and in postpartum maternal protective behaviors, according to animal studies.[160]

Synthetic oxytocin (Pitocin, Syntocinon) is chemically identical to the naturally released, endogenous OT molecule, and binds to the same receptor (see "Oxytocin Regulation and Receptors," below) but has different effects, largely because it is usually administered into the body, rather than being released from and within the brain (see "Oxytocin Effects" below). In this report, "oxytocin" refers to naturally-released, endogenous oxytocin, and "synthetic oxytocin" refers to synthetic, exogenously-administered oxytocin. (See 3.2.3 for a detailed discussion of the possible impacts of synOT on mothers and offspring.)

Oxytocin Effects

Coordination of brain and body oxytocin release may be critical in coordinating the physical processes of labor, birth, and breastfeeding with the brain-based maternal adaptations that foster maternal-infant attachment and infant survival. Synthetic oxytocin does not generally have central, brain-based effects in adults when injected into the body. However, maternal endogenous oxytocin released during labor (and also synthetic oxytocin) may access the fetal brain via the placenta and more permeable fetal blood-brain barrier, according to animal studies.

Systemic oxytocin, released into the body from the pituitary gland, causes the smooth (involuntary) muscle contractions that characterize: male and female orgasm, the rhythmic contractions of labor, and the let-down (milk ejection) reflex in lactation, among other effects. Oxytocin is usually released within the brain in parallel with systemic release and acts centrally to ensure that biological instincts and behaviors are coordinated with reproductive events. For example, during labor and birth, OT is released systemically from the mother's pituitary, causing the uterine contractions of labor, and at the same time is released centrally into her limbic system, where it activates maternal circuits that foster the rapid and beneficial responses to her offspring after birth that promote infant survival.

Central OT levels, as measured in the cerebrospinal fluid (CSF, which circulates around the brain) are generally five to ten times higher than levels measured in the bloodstream.[159] Oxytocin release from the pituitary is constant in most situations, but pulsatile in parturition and lactation.[162] Pulsatile release may have different effects—for example, stimulating prolactin release (6.1.3)—and may also be important in maintaining tissue sensitivity. (See "Synthetic oxytocin and oxytocin receptor desensitization" in 3.2.3.)

Like other peptide molecules (made of amino acids), OT has minimal passage through the adult blood-brain barrier, a structure that protects the brain by filtering out most substances from entering via the bloodstream. [163] Researchers have suggested that one to two percent of synOT administered systemically may cross the blood-brain barrier, so that, with five- to ten-fold higher central levels, systemic administration needs to be around 1,000 times higher than doses administered directly into the brain for equivalent central effects.[159, 164] In one rat study, just 0.002 percent of synOT injected subcutaneously was measured in the brain, peaking 10 minutes after systemic administration.[163] These findings imply that, while systemically-administered synOT can have effects on the body, it does not cross into the adult brain in biologically significant amounts and so its central effects are regarded as minimal in most circumstances.[158] (See "Psychological and therapeutic roles of oxytocin," below, for intranasal OT effects, and 3.2.3 for full discussion of implications of synOT exposure in labor and birth.)

However, the fetal blood-brain barrier is more permeable. Animal studies have found that, during labor, OT at physiologic levels transfers from the mother to the fetal brain, with beneficial neuroprotective effects. (See "Fetal neuroprotection" and "Fetal Oxytocin in Labor and Birth" in 3.1.3, and "Synthetic Oxytocin and the Baby" in 3.2.3 for implications of fetal synOT exposure.)

As well as being released from and within the brain, OT is also made in local tissues, including the pregnant woman's uterus and uterine lining (decidua) and the baby's amniotic sac and membranes. Local OT production may also be important in the processes of labor and birth (3.1.3).

Oxytocin, whether endogenous or synthetic, has a short half-life (time taken to reduce levels by 50 percent) of between 3 and 20 minutes in the bloodstream and around 28 minutes in the brain.[165, 166] However, OT can have profound and long-lasting effects because, as a neuromodulator, it initiates, reorganizes, and interorchestrates other hormone systems and physiologic systems[167] Oxytocin's effects can therefore persist, even lifelong in some circumstances, according to animal studies. This is particularly relevant during

the perinatal period, when offspring hormonal experiences can cause epigenetic changes, with programming effects through to adulthood and even to subsequent generations.[35, 41, 168, 169] (See "Synthetic Oxytocin and Offspring, Longer Term" in 3.2.3.)

Physiologic roles of oxytocin. *Oxytocin has a large and growing number of recognized effects on the brain and body. Oxytocin especially benefits reproduction and sociality, including by reducing fear and stress responses involving the sympathetic nervous system, and increasing relaxation and receptivity via the parasympathetic nervous system. These effects generally require elevations in central (brain-based) oxytocin.*

Currently recognized oxytocin effects include**:**

- **Sexual behavior and pair bonding:** OT is released during sexual activity, when it increases receptivity and initiates pair bonding among monogamous animals.[170] In humans, OT levels increase during sexual arousal and peak at orgasm, causing the rhythmic contractions of sperm ejection in men, and the pelvic floor contractions of female orgasm.[171]
- **Lactation:** OT, released in pulses, mediates the milk-ejection (let-down) reflex, which makes milk available to the suckling infant. At the same time, pulsatile OT promotes central release of prolactin (PRL), which stimulates breast milk production.[53, 172] Animal studies also show involvement of OT in milk secretion,[173] and OT is present in human breast milk.[174]
- **Maternal adaptations:** OT promotes the species-specific maternal adaptations and behaviors that begin immediately after birth, and also primes brain circuits that support ongoing maternal adaptations and behaviors in animals, with evidence for this in women also (3.1.4).
- **Warming:** OT opens up peripheral blood vessels (vasodilatation), creating a warming effect. Vasodilatation of superficial blood vessels on the new mother's chest, in response to postnatal OT peaks, keeps her newborn in skin-to-skin contact (SSC) warm after birth.[175] (3.1.4).
- **Social-affiliative behavior:** OT is a prosocial hormone, motivating social interactions and increasing sociability in all mammals.[176] In human research, both endogenous OT and exogenous (intranasal) synOT promote trust, empathy, generosity, eye contact, recognition of familiar faces, and discrimination of emotional states.[177] Oxytocin is released during social and physical contact, including social vocalization[178] and massage.[179]
- **Regulation of the autonomic nervous system (ANS):** OT increases activity in the parasympathetic nervous system (PNS) branch of the ANS, which slows the heart, reduces blood pressure and energy expenditure, and promotes rest, digestion, and affiliation, producing a "calm and connection" effect.[52] (The ANS controls the internal organs and other key involuntary body functions.)
- **Social engagement:** OT is an effector of the "social nervous system," a more recent and higher-order branch of the ANS, according to the Polyvagal Theory.[180] This promotes social engagement as a first response to stress among mammals, especially humans.
- **Stress reduction:** Release of OT during times of excessive stress can restore physiologic balance (homeostasis). OT reduces activity in the flight-or-flight, or sympathetic nervous system (SNS) branch of the ANS, reducing levels of the stress hormones epinephrine (E, adrenaline) and norepinephrine (NE, noradrenaline). As well, OT reduces activity in the hypothalamic-pituitary-adrenal pathway (HPA system), reducing medium-term stress response hormones, including corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), beta-endorphins (BEs), and cortisol (5.1.1). These stress-reducing effects also benefit women during labor, birth, and the postpartum period, and with breastfeeding.[52]

cont'd

- **Fear and anxiety reduction:** OT reduces activity in the amygdala, the brain's fear center,[181] which reduces anxiety and promotes social behaviors and interactions.[53] Reduced anxiety may persist long term after repeated exposure to OT, such as during lactation in mother and baby[53] (3.1.4).
- **Tend and befriend:** Moderate levels of stress may provoke an OT-mediated "tend and befriend" response, which promotes gathering together for mutual support.[182-184] Through evolution, a tend-and-befriend response to danger by caretaking women may have been more beneficial to offspring survival than an individual-oriented fight-or-flight response.
- **Pain reduction:** OT has natural pain-relieving properties, which may help both mother and baby during labor,[53, 185] and may also involve AVP[161] (3.1.3).
- **Changes in memory and attention:** OT reduces the memory of aversive experience[186] and may also reduce attention to environmental distractions,[186] benefitting laboring and nursing mothers.
- **Pleasure and reward:** OT released within the brain activates dopamine-associated brain reward pathways, giving pleasure and reinforcing reproductive and survival behaviors, including sexual behavior and mating, attachment between infant and mother, and adult social interactions.[156, 187-189]
- **Olfaction:** In other animals, the OT system is closely related to olfactory (smell) centers in the brain. These primitive connections may also exist for humans, contributing to brain-based responses to odors and also to pheromonal effects (below, in this section).[52]
- **Healing and growth:** In animal studies, OT alleviates cell damage in areas including the skin, stomach, liver, bowel, heart, and brain by reducing oxidation and oxidative damage,[190] and has beneficial anti-inflammatory effects.[191-193] OT also facilitates growth in adult brain cells in the memory center (hippocampus),[194] where dysfunctions have been implicated in anxiety and depression.[195]
- **Regulation of other body systems:** OT is involved with many other physiologic functions, including: kidney function and water balance; food intake, digestion, and satiety; insulin release; temperature control; regulation of bone density; prostate function; and pain tolerance, among other known functions.[196]

Many of these effects—including pain relief, stress and fear reduction, and maternal adaptations—depend on central release. Synthetic oxytocin administered systemically, for example during labor, does not readily cross into the maternal brain ("Oxytocin effects," above) and so may not facilitate the calm, reward, and pain relief, or the maternal adaptations that benefit maternal-newborn attachment, which centrally-released, endogenous oxytocin provides, according to current understandings (see "Synthetic Oxytocin and Maternal Adaptations in 5.2.3 for a detailed discussion of these complexities).

Animal research suggests that oxytocin can act pheromonally, that is, transmitted between individuals through the vomeronasal organ in the nose. Studies show that the cagemate of a rat that has had high-dose synOT injected centrally also experiences OT-type central effects, including pain reduction[197] and reduced energy loss.[198] Similarly, the extreme maternal OT peaks that follow physiologic labor and birth, as described below (3.1.4), could transmit calm, connection, and positive mood states to nearby individuals. Anecdotally, relatives and caregivers can report euphoria after being present at physiologic birth.[199] This could plausibly help to connect those present to the newborn, benefitting offspring protection and survival.

Psychological and therapeutic roles of oxytocin. *Oxytocin has an important role in psychological well-being, according to human research. Conversely, early relational deprivation and trauma has been associated with oxytocin dysregulation. Therapeutic intranasal synthetic oxytocin, which has central effects, has been trialed or used in many conditions, including anxiety, depression, addiction, posttraumatic stress disorder, and autism.*

Human studies show that adults who report anxiety or depression, less closeness to parents, less tendency to express and share emotions, a history of childhood neglect or abuse, severe childhood deprivation or institutionalization, and/or parental loss or separation before age 12, as well as men with a life history of aggression and mothers who report poor attachment from their own childhood, have disruptions in OT systems, with shifts in baseline OT levels and/or lack of expected situational rise.[156, 166, 196, 200, 201] This rapidly expanding area of research strongly suggests that early relational deprivation or trauma can have a lifelong impact on OT systems, correlated with psychological morbidity.[156, 201]

Consistent with OT's powerful and positive psycho-emotional effects, synOT administered via intranasal spray has been suggested or trialed as a treatment for many psychological and psychiatric conditions. (Intranasal delivery gives central effects, possibly via a direct route[164] and may activate a central OT feedforward cycle that elevates levels for many hours.[202]) Conditions that may respond to synOT include: anxiety, depression, drug and alcohol addiction, eating disorders, obesity, obsessive-compulsive disorder, posttraumatic stress disorder, schizophrenia, and autism[203-206] (see "Synthetic oxytocin and offspring, human studies" in 5.2.3 for more about synthetic oxytocin and autism). In healthy subjects, intranasal synOT can reduce anxiety and increase trust, among other effects,[207] although effects may also be complex and unpredictable (see "Oxytocin complexities," below).

Oxytocin Regulation and Receptors

Oxytocin regulation. *Activity in the oxytocin system (levels, receptors, effects) is impacted and regulated by many other hormones and systems, including estrogen, opioids, and prolactin. Oxytocin can increase its own release from the brain by autoregulation, contributing to extreme oxytocin peaks and effects at birth.*

Important regulatory hormones include estrogen, which increases OT activity throughout the brain and body (including leading up to labor), and endogenous opioids such as beta-endorphins and dynorphan, which can reduce OT release from the brain, and may help regulate the physiologic onset of labor, according to animal studies[95, 124] (4.1.1, 4.1.2). Conversely, the pulsatile release of OT in labor and lactation stimulates PRL release, with even greater effects as labor and birth approach due to increased connections between these hormone systems within the brain in the perinatal period.[122] (See also 2.1.2.)

Within the brain, OT can influence its own release (autoregulation). Autoregulatory positive feedback mechanisms can lead to the extreme peaks of OT that characterize the physiologic events of labor, birth, and lactation.[196] Animal studies suggest that the stimulating effect of central OT on its own release develops during pregnancy and peaks during labor.[208, 209] Also developing in late pregnancy, and distinctive at this time, is the ability of OT cells in the hypothalamus to "burst fire" in a coordinated way, producing the large pulses of OT that promote discrete labor contractions. Between pulses, uterine rest allows the fetus to replenish blood and oxygen, and this pause in OT exposure also maintains OTR sensitivity (3.1.3). The same mechanism during lactation delivers milk in intermittent pulses that the suckling infant can comfortably ingest.[95]

Oxytocin receptors. *Oxytocin acts by binding with oxytocin receptors, which vary over time and location, and are upregulated before labor due to rising estrogen levels. Multiparous females may have greater central oxytocin receptors and autoregulation effects, according to animal studies.*

As with other hormones, OT acts by binding with its receptor (oxytocin receptor, OTR) on the surface of the target cell, activating a chemical signaling system within the cell. OT has one specific receptor, according to current understanding, and many OT functions are regulated by dynamic changes in OTRs in the brain and/or body. These changes may include increases or decreases in receptor numbers (up- or downregulation) and/or changes in how easily OT binds with the receptor (binding capacity). These changes determine sensitivity to OT in the local area—brain, uterus, etc.[48] Substances that can affect OTR functions include magnesium and cholesterol, which both increase OT-OTR binding,[210] and prostaglandins (PGs), which may promote the formation of OTRs in the uterus (2.1.3).

The number and distribution of OTRs change through development, and in some specific situations, especially in response to sex hormones. This leads to increases or decreases in sensitivity to OT, and to changes in OT effects in the affected tissue. For example, OTR numbers rise dramatically in the expectant mother's uterus close to the time of labor due to rising estrogen levels,[111] increasing her uterine sensitivity to OT and promoting labor efficiency. (See 3.1.3.)

According to animal studies, reproductively experienced (multiparous) females have higher OTRs in the brain during labor, and especially in brain areas concerned with OT autoregulation.[211] This increases central OT positive feedback, substantially augmenting OT release into brain and body and enhancing the efficacy of labor, birth, lactation, and postpartum maternal behaviors.[212, 213] In women, this is consistent with the shorter duration of labor[214] and reduced need for intervention[215] that is well recognized in multiparous women (see 3.1.3).

Oxytocin complexities. *While oxytocin has generally positive associations and effects, these can vary in complex and unpredictable ways according to the social and psychological context, and can even give negative physiologic or social effects. In addition, levels and effects of endogenous and synthetic oxytocin can be complex and difficult to measure and interpret. Epigenetic changes associated with early life programming, including changes in oxytocin receptors and oxytocin sensitivity, may contribute to this complexity.*

Human studies show large inter-individual variation in baseline OT levels (for example, from 32 to 2230 pcg/ml in one study[216]), and levels also vary with gender, and with psychological and social context.[217, 218] For example, in some human studies, higher OT levels have been correlated with elevated anxiety.[219-221] It is uncertain whether such altered levels reflect the causes or consequences of psychological alterations.[158] For example, OT elevation in anxious individuals could reflect compensation for low OT sensitivity, with reduced central receptor numbers due to early OT disruptions (see "Oxytocin Regulation and Receptors," below) and/or stress-induced OT release to restore homeostasis. In addition, elevated basal OT levels may have different implications than OT elevations in response to challenges or situations, which may more accurately reflect OT system functioning. While stress in general may increase OT release to restore homeostasis, as above, stress during labor, birth, and breastfeeding may disrupt pulsatile release as a mechanism to ensure that these important reproductive events occur in safe environments. (See also 3.2.1 and 5.2.1.)

The effects of synOT can also be unpredictable, possibly because OT can have different effects according to site and tissue, route and frequency of administration, dose, time of observation, and other factors, including species differences.[159] In human studies, effects may also vary with the social context. For example, in one study, administration of intranasal synOT was found to worsen, rather than improve, self-reported mood in women with postpartum depression.[222] In addition, accurate and standardized methods for measuring OT levels in the blood and body remain problematic, especially salivary and urinary measurements,[156, 223, 224] and measurement of OT in the blood may not reflect central levels, in many circumstances.[156, 223]

There has been recent interest in genetic and epigenetic variations in human OT systems. Genetic variations in OTR structure and in the CD38 enzyme, which influences OT secretion, have been linked with differences in OT-related functions, including stress responses, adult attachment security, and parenting sensitivity,[225] although these have been found to account for less than five percent of variance in parenting behaviors, according to one review.[226]

Alterations in OT systems due to epigenetic programming effects, are especially likely to occur during early sensitive periods, including the perinatal period.[227] Epigenetic changes in the OTR have been implicated in autism, callous-unemotional traits, and aspects of social perception.[227] Such epigenetic mechanisms may contribute to the inter-generational transmission of parenting patterns in humans.[226, 227] In animal studies, high levels of early maternal care cause epigenetic changes in the OT and estrogen systems of exposed female offspring, programming them to give high levels of maternal care to their own infants,[228] and also positively impacting stress, fear, and attentional processes; brain and cognitive development; and female reproductive behavior.[229] Animal studies also show offspring epigenetic changes following exposure to perinatal stress.[169] (For relevance to childbearing, see 3.1.4, 3.2.3, and 3.2.7.)

3.1.2 Oxytocin in Pregnancy

Preparations for effective labor, birth, breastfeeding, and newborn care, and for maternal and newborn transitions, are obviously critical for survival among all mammalian species. The oxytocin system is involved in many associated prelabor physiologic preparations in mother and baby, from early pregnancy to the onset of labor.

Maternal oxytocin in pregnancy

Oxytocin levels and activity generally rise through pregnancy due to increased estrogen levels, reducing maternal anxiety and stress responses. Prelabor physiologic preparations include increased uterine oxytocin receptors in preparation for efficient labor contractions and, according to animal studies, increased mammary and brain oxytocin receptors. In pregnant women, high or rising oxytocin levels may predict positive mothering behaviors and longer breastfeeding duration, perhaps reflecting optimal early oxytocin experiences and secure attachment, compared with women with low or decreasing oxytocin.

Studies generally show an increase in maternal blood OT levels as pregnancy progresses.[216, 230-232] This reflects the rising estrogen levels that increase activity in the OT system (blood levels, receptor numbers).[233] In women, pregnancy also involves a physiologic increase in cholesterol levels,[234] which may be important in increasing OTRs and OTR binding.[235] Psychological studies show reductions in anxiety from early pregnancy[236] that may reflect central OT effects.[237] Oxytocin has a diurnal pattern in pregnant women, as measured in the blood, with peak levels around midnight.[238, 239] This may contribute to enhanced nocturnal uterine activity in late pregnancy. (See also 2.1.3.)

In one large study, first-time (primiparous) mothers had higher late-pregnancy OT levels than multiparous women,[216] which may reflect reduced OT sensitivity and fewer OTRs due to reproductive inexperience (3.1.1).[238, 239]

Researchers also found correlations between elevated OT from early pregnancy, and postpartum maternal behaviors such as gaze, vocalization, positive affect, affectionate touch, and frequent checking of the infant.[240] In other studies, elevated OT levels in pregnancy predicted breastfeeding at three months,[241] and reduced risk of early postpartum depression.[242]

These results may reflect more maternal attachment behaviors, including breastfeeding, and better mood among mothers who are more securely attached from their own infancy and childhood, with higher OT levels compared with less securely attached mothers (3.1.4). However, one study found that women with higher OT levels in late pregnancy experienced a longer labor and greater chance of epidural use,[216] which may relate to differences among primiparous women, who have higher OT levels as well as longer labor,[214] and greater epidural use.[243] (See also "Oxytocin complexities" in 3.1.1.)

Animal studies show extensive prelabor physiologic preparations within the maternal brain that promote efficiency in labor and birth (3.1.3), and optimize postpartum maternal behaviors (3.1.4). Oxytocin-producing cells in the hypothalamus reorganize for coordinated pulsatile release in labor and lactation, and pituitary OT stores increase by about 50 percent.[98, 99] In rats, central OTRs have been shown to increase by up to 50 percent in OT-associated areas in the final two days before labor onset,[88] sensitizing the maternal brain for effective OT responses in labor, birth, and the postpartum period. The most important brain changes that switch on maternal behaviors may only occur in the final hours before the physiologic onset of labor.[100, 101] Brain OTRs increase even more during labor in some areas of the brain[88, 244] (3.1.3).

Animal studies also show increases in breast (mammary) OTR numbers as gestation advances, with further increases close to the physiologic onset of labor. In rats, mammary OTRs increase 100-fold from early pregnancy to lactation;[87] and in pigs, mammary OTRs increase four-fold over the few days prior to physiologic onset of labor.[86] While it is not possible to verify these changes in pregnant women by directly sampling the brain or breast, hormone-associated prelabor physiologic preparations are also likely in humans to maximize maternal and offspring survival and well-being by promoting lactation and infant care.

In women, OTRs and receptor binding capacity increase in the uterine muscle (myometrium) in late pregnancy,[111] with increases in women's sensitivity to synOT as the physiologic onset of labor approaches,[107] and a further increase with the onset of labor, also found in other mammals.[111] Both hormonal changes and uterine stretch may contribute to OTR upregulation[111] (2.1). One study found that OTR numbers tripled in women from late pregnancy to early labor,[245] with higher OTRs at the fundus, and lower numbers close to the cervix,[98, 111, 245] in preparation for effective expulsion.

Oxytocin receptors also increase in feto-maternal tissues, likely due to increases in estrogen and also cortisol.[246] Cortisol is elevated in amniotic fluid in late pregnancy[247] and promotes OTR formation, according to animal research.[246] Increased OTRs in the fetal membranes (amnion and chorion) and decidua contribute to feedback cycles that increase PGs, promoting contractions in the adjacent myometrium.[111] Local inflammation also has an increasingly recognized role in labor onset (2.1.2) and the inflammatory substance interleukin 1-beta also promotes OTR upregulation.[82, 83] Increasing OTRs, PGs, and cervical ripening all contribute to labor efficiency and effectiveness following physiologic labor onset (2.1.2).[83] Increased uterine OTRs also promote the effective OT-mediated contractions immediately after birth that reduce postpartum hemorrhage (PPH) (3.1.3).

In the lead up to labor, maternal melatonin, a hormone that is secreted from the pineal gland during sleep periods, enhances myometrial sensitivity to OT and the formation of gap junctions, according to in vitro human studies.[109] Gap junctions connect myometrial cells together, increasing uterine contractility. These effects contribute to nocturnal contractions and to the more common physiologic onset of labor at night in women and other day-living species. (For a fuller account of the prelabor physiologic preparations that precede the physiologic onset of labor, see 2.1.)

Fetal Oxytocin in Pregnancy

Fetal oxytocin production increases as gestation progresses and may contribute to parturition.

The fetus produces increasing amounts of oxytocin during pregnancy, according to both animal[248, 249] and human[250] studies. It has been suggested that fetal oxytocin may contribute to the initiation of labor. (See "Fetal Oxytocin in Labor and Birth" in 3.1.3.)

3.1.3 Oxytocin in Labor and Birth

Oxytocin is involved in the processes of labor and birth among all mammals. The exact role of oxytocin in labor initiation is not fully understood.

Maternal Oxytocin in Labor and Birth

During labor, pulsatile oxytocin release from the laboring mother's pituitary gland promotes rhythmic uterine contractions, and also helps maintain oxytocin receptor sensitivity and the effectiveness of contractions. Oxytocin is involved in several positive feedback cycles that promote and accelerate labor progress, involving feedback from uterine sensations and central oxytocin autoregulation. Peaks of oxytocin in late labor promote expulsion by a positive feedback cycle (Ferguson reflex). Central oxytocin systems are also activated in labor, according to animal studies, assisting with stress and pain, and promoting maternal adaptations that benefit infant survival.

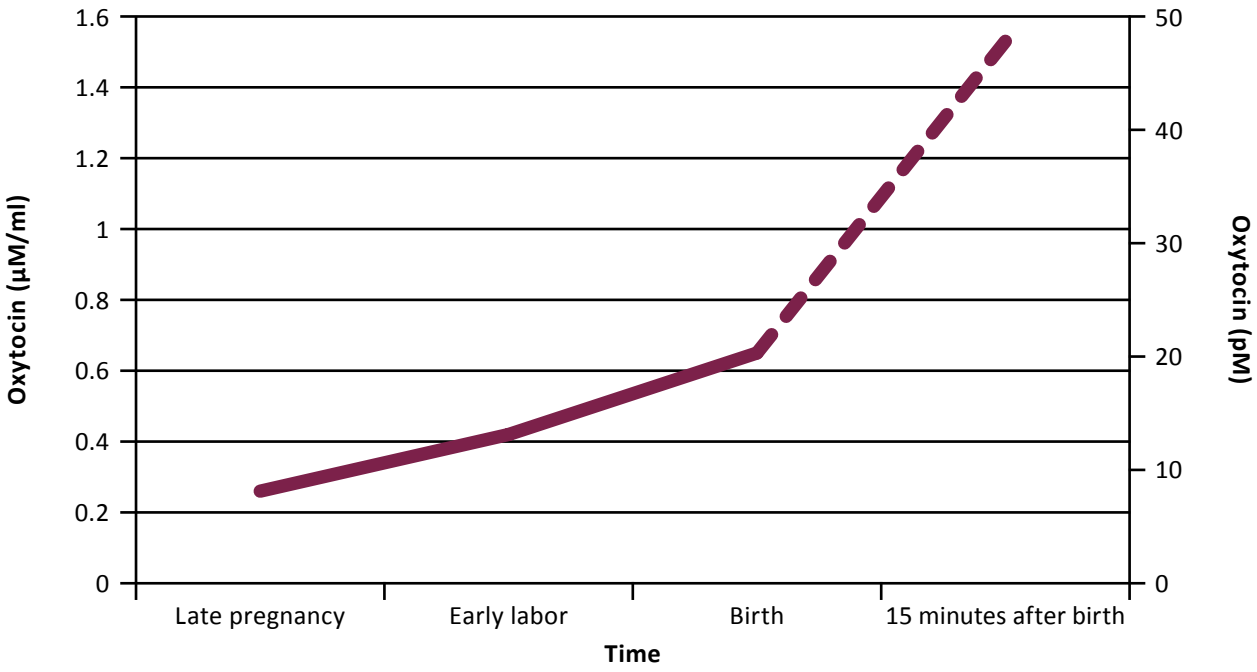
In laboring women, oxytocin is released in pulses from the pituitary into the bloodstream, reaching the uterus and binding with OTRs in the myometrium, where it promotes contractions by increasing calcium and calcium sensitivity.[98] Oxytocin also binds with OTRs in the decidua, stimulating the production of PGs, which promote contractions in the adjacent myometrium.[98] In turn, PGs may sensitize the myometrium to OT by increasing OTRs,[112, 114, 115] and PGs also promote contractions that give sensory feedback and increase central OT release (described below). These mechanisms initiate an important positive feedback cycle, where OT-OTR binding increases PG formation, and PGs promote OT activity. [83] The administration of exogenous PGs (and other methods of labor induction) may initiate labor by activating these mechanisms (3.2.2).

Animal research suggests another positive feedback cycle active on the day of labor. Researchers have found that the sensations from uterine contractions, transmitted via sensory nerves, stimulate brain centers that link to the central oxytocin nuclei (SON and PVN, 3.1.1) and promote the release of central OT, causing further contractions, feedback, and OT release.[251] This positive feedback cycle, operative throughout labor, depends on the sensations of labor and is similar to the late-labor Ferguson reflex (described below). In addition, a central OT positive-feedback cycle involving noradrenergic pathways and maximally active in labor, as found in animals,[208, 209, 252] further promotes OT release into the maternal brain and body and accelerates labor progress (see "Oxytocin regulation" in 3.1.1).

Levels of OT are difficult to measure in the bloodstream of women in labor because of its pulsatile release and because it is rapidly broken down (metabolized) by the enzyme oxytocinase, which the placenta makes during pregnancy and produces in even higher amounts in labor.[98] This rapid metabolism reduces the OT half-life to around three minutes in labor,[253] so that it may almost disappear from the bloodstream between contractions. This ensures that uterine OTRs are exposed to OT intermittently, rather than continuously, which critically maintains receptor sensitivity and contraction efficiency during labor and after birth.[254] As with other hormone systems, exposure to constant high OT levels can lead to receptor reduction (downregulation), with loss of sensitivity and ineffective contractions. (See "Synthetic oxytocin and oxytocin receptor desensitization" in 3.2.3.) Episodic exposure may also benefit the fetus, supporting recovery between contractions.

Blood OT levels, as sampled in spontaneously laboring women, have not been found to increase substantially until the pushing stage of labor,[255-257] although the frequency of OT pulses increases as labor progresses, reaching about six pulses per ten minutes at the end of labor, according to one study.[258] Figure 1[258, 259] illustrates the gradual rise of OT in labor and the large increases from birth through the early postpartum period.

Figure 1. Women's oxytocin levels in late pregnancy, in early labor, at birth, and after birth



Source: adapted from Fuchs[258] (solid, left scale) and Nissen[259] (dashed, right scale)

Oxytocin is also produced locally within the decidua during labor.[111] Local OT release and associated positive feedback cycles (below) may be even more important than centrally-released OT in human labor.[98]

In late labor, strong contractions guide the baby deep into the mother's pelvis, where the baby's presenting part (usually head) stimulates specialized nerves that detect stretch in her lower vagina and cervix. These nerves send a signal to the laboring woman's brain, triggering an outpouring of OT, which further increases contractions and fetal descent, and further stimulates these nerves. This positive feedback cycle, known as the Ferguson reflex,[260] fosters an efficient birth and elevates OT levels into the early postpartum period. Vaginocervical stimulation (VCS) has an analgesic effect in animals and humans, likely via OT,[261] and this may also benefit women during late labor.

Large amounts of OT are also released within the maternal brain during labor and birth, as directly sampled in animal studies.[211, 262, 263] In women, OT levels are elevated in the CSF during labor, also indicating increased central release.[230] The central positive feedback cycle, whereby OT increases its own release from and within the maternal brain (3.1.1), further elevates OT levels, both in the body, contributing to labor efficiency, and in the brain, facilitating beneficial maternal responses after birth. Central OT elevation in labor may also counter maternal fear and pain,[45, 264] and may enhance trust and support-seeking behaviors at this critical time (3.1.1). Central OT may also increase BEs in the brain, according to animal studies,[120] aiding with labor stress and pain. Brain-based OT effects are prolonged because OT has a longer half-life in the brain—around 28 minutes[166]—and because OT activates and reorganizes other hormonal and biologic systems[48] (3.1.1).

These high levels of central OT in labor act on the augmented OTRs in brain areas critical for maternal behavior, according to animal studies.[88] In some brain areas, including the supraoptic and paraventricular nuclei, where oxytocin is produced (3.1.1), OTRs further increase in labor (3.1.3),[88, 244] making parturition ". . . a key time point for full expression of maternal behavior."[244(p.1441)] This major activation of the central OT system in labor fosters the rapid and appropriate maternal postpartum responses that enhance offspring survival.

The transformation in maternal responsiveness toward infants that follows mammalian birth, is "notably conserved" in humans,[156] for whom effective responses to offspring after birth have also promoted species survival.[156]

As discussed in 3.1.1, animal studies show that previous reproductive experience increases OTRs in brain areas involved with OT autoregulation,[211] greatly enhancing the efficiency of labor, birth, and lactation, and the onset of maternal behaviors among experienced mothers of all mammalian species.[212]

Activities that increase endogenous OT release could enhance labor progress in women, and may even trigger the onset of labor when maternal readiness and uterine OTR numbers are maximal, very close to the physiologic onset of labor. Studies have shown mixed results in terms of coitus and labor initiation,[265-270] possibly because few women in these studies were sufficiently close to the physiologic onset of labor, and they therefore had insufficient OTRs to trigger labor initiation with the transient OT elevations from sexual activity.

However, studies using prolonged nipple (breast) stimulation (e.g., for 30 minutes) have found increased OT levels,[271] and a systematic review found enhanced cervical ripening, increased chance of labor onset within 72 hours (among women with a ripe cervix), and a major reduction in PPH.[272] Researchers suggest caution in women with high-risk pregnancies because one study found increased fetal risks.[272] One randomized study found that nipple stimulation using a breast pump was an effective alternative to synOT to enhance labor progress,[273] with benefits in half of the women, likely those with higher OTR numbers. Sexual activity, which also elevates OT levels,[171, 274] could also be effective in augmenting labor,[275] although this has not been specifically researched. The analgesic effect of vaginocervical stimulation[261] could also be beneficial.

Genetic variations (polymorphisms) in OT and its receptor may influence OT-related functions (3.1.1), including labor progress. One study found that labor was 10 percent slower among women with a common OTR variation,[276] although other researchers have not found polymorphisms that explain slow labor or dystocia.[277] It seems unlikely that OT polymorphisms that were significantly detrimental to labor progress would survive evolutionary pressures, given the additional dangers of prolonged labor in the wild (5.1.3).

Other hormonal influences on oxytocin in labor and birth. *Healthy, physiologic levels of stress (eustress) and stress hormones in labor, including cortisol, may be important to promote contractions and labor progress. Excessive stress, or stress hormones, may inhibit labor via oxytocin disruption.*

Other hormones and endogenous substances may influence OT release and/or effects in labor. Excessive levels of stress and stress hormones may inhibit OT release and labor progress (3.2.1). However, expected physiologic stress ("eustress") in labor, with moderate elevations of hormones, may be beneficial.

In animal studies, the stress hormone cortisol upregulates local OTRs and augments the stimulating effects of OTRs on local PGs about 100-fold,[98, 246] as described below. In addition, physiologic increases in the executive stress hormone CRH in women in late pregnancy and labor enhance uterine responsiveness to OT and PGs,[89, 90] and may even be involved in the initiation of labor.[278, 279] (See 5.1.1 and 5.1.3 for discussion of eustress in labor, 5.2.1 for discussion of impacts of excessive stress, and 2.1 for initiation of labor.)

The hormone leptin, which is made in fat tissue and is present in higher amounts in obese individuals, has been found to inhibit contractions and block OT's pro-contraction (uterotonic) effects when directly applied to human myometrial samples. [280] Leptin is also made by the placenta during pregnancy, but levels decline significantly just before birth.[281] Researchers speculate that elevated leptin levels may help to explain the slower labors[282] and lower rates of vaginal birth[280] that obese women experience.

However, other studies have found no correlation between obesity and the contractile ability of uterine muscle,[283] and only modest differences in outcomes for obese women in settings that promote physiologic birth.[284] In animal research, high maternal leptin levels are associated with successfully raising larger litters, which may reflect a greater investment in offspring when maternal nutritional stores are high.[285]

In addition, some studies have shown longer labor and/or increased risks of cesarean [285] and other maternity care interventions in relation to maternal age among nulliparous women,[285-290] while another found increased age was associated with shorter active labor and longer pushing stage, up to 40 years.[291] Reduced myometrial contractility has been found with advancing age in both nulliparous and multiparous women.[289, 290] As with obesity,[292] these potential effects suggest that adjustment of labor expectations and management may be required for older first-time mothers.

Obese and older women and their babies may benefit from promotion of physiologic childbearing, including by minimizing labor stress (5.2.1) and unnecessary maternity care interventions, as discussed in the recommendations.

Positive feedback cycles. *Oxytocin is involved in several positive feedback cycles that are known to promote and accelerate labor progress, producing the hormonal cascade of "active labor." Activation of these cycles is promoted by prelabor physiologic preparations, including receptor upregulation, which is maximal at the physiologic onset of labor. External induction agents may provoke the full activation of these cycles, which is most likely to occur close to the physiologic onset of labor.*

In summary, as described above, positive feedback cycles active in labor that promote and accelerate OT release and establish labor processes include**:**

- OT-OTR binding, which increases PG production in the decidua. PGs increase OT activity indirectly by promoting contractions and possibly also directly. Cortisol may substantially increase PG effects, according to animal research.

cont'd

- The sensations of uterine contractions, transmitted to specific brain areas, give positive feedback to central OT-releasing areas, promoting OT release and creating more contractions and more OT release, according to animal models.
- In late labor, fetal descent stimulates specialized nerves in the laboring woman's lower vagina, which give positive feedback to her pituitary, causing more OT release, stronger contractions, more fetal descent, and more nerve stimulation (Ferguson reflex).
- Central OT release promotes more OT release by positive feedback on central autoregulatory mechanisms, leading to extreme OT peaks in the brain and body during labor and birth. Effects are more pronounced in multiparous mothers, who have more central OTRs. (Found in animal studies.)

These cycles contribute to a hormonal cascade that promotes efficiency in mammalian labor and birth and, through central effects, contributes to the postpartum maternal adaptations that further enhance offspring survival (3.1.4).

Activation of these positive feedback cycles adds momentum to labor, so that the process, when established, is less vulnerable to disruption. This underlies the clinical phenomenon of "active labor." The more effective central mechanisms in multiparous females, likely due to increased central OTRs as above, may give less vulnerability to disruption than in primiparous females. This is consistent with the shorter duration of labor[214] and reduced need for intervention in multiparous women,[215] and in women who are admitted to hospital at later stages of cervical dilation and labor,[215] when these mechanisms are well established.

This cascade may be activated or strengthened in women by exogenous agents that trigger contractions, including synOT, exogenous PGs, and stretch, which may also contribute to the labor induction effects of balloon catheters.[85] These can lead to the full manifestation of labor, including the release of endogenous OT from and within the laboring woman's brain, and its binding to OTRs in her brain and body. The full expression of these cycles, with optimal efficiency of labor, is most likely to occur with the physiologic onset of labor, when OTRs are at maximal levels in the maternal brain and body.

Fetal neuroprotection. *Oxytocin mechanisms may help to protect the fetal brain from labor hypoxia, according to animal studies. This mechanism involves the transfer of maternal oxytocin through the placenta and into the fetal brain, and may be inactive before the physiologic onset of labor. High-dose synthetic oxytocin and oxytocin antagonist drugs (used in women to treat threatened premature labor) inactivate this neuroprotection in animal studies. Deficits in this neuroprotection are associated with animal models of autism.*

Oxytocin may have an important role in protecting the fetal brain (neuroprotection) during labor and birth. According to animal studies, maternal OT crosses into the fetal brain in labor via the placenta and permeable fetal blood-brain barrier where, uniquely, around the time of birth, it activates a switch involving the neurotransmitter gamma-aminobutyric acid (GABA), which reduces fetal brain activity. This effect begins in the 24 hours preceding physiologic labor onset, with maximal effects during late labor that reduce central blood and oxygen requirements, and protect fetal brain cells (neurons) against hypoxia.[97, 293, 294]

In these studies, the neuroprotective effects of OT were reduced, and vulnerability to hypoxic brain damage increased, when high levels of synOT were administered,[293] and with administration of the oxytocin antagonist (OTA) atosiban,[97] which blocks OTRs and effects. Deficits in this neuroprotection mechanism have been found in animal models of autism.[295, 296] (See also "Oxytocin Antagonist Drugs" in 3.2.3.)

These mechanisms are likely to be operative in human babies, who have the same need for neuroprotection in labor and may even produce their own neuroprotective OT, as the human limbic system is more mature than other mammals at birth.[185, 297] These findings imply that fetal neuroprotection may be reduced in the absence of the physiologic onset of labor, with administration of high-dose synOT, and/or with the use of OT antagonists (3.2.3).

Oxytocin-deficient mice. *Mice bred to be deficient in oxytocin or oxytocin receptors have essentially normal labor and birth, but unsuccessful lactation. This suggests that there are overlapping mammalian processes to ensure successful labor and birth.*

Mice that are genetically engineered to produce no OT (OT knock-out, OTKO) have surprisingly been found to labor and birth normally,[298] although OTKO mice mothers have no letdown reflex for lactation and so offspring do not naturally survive. Mice lacking OTRs have similar deficits.[293, 299] These unexpected findings do not negate the role of OT in labor. In animal studies, OT antagonists, which block OTRs, reliably inhibit labor,[300] with modest effects in women,[301] suggesting that the OT system is functionally important for mammalian labor. Because birth is critical to survival, it is likely that there are overlapping mechanisms to ensure success. For example, the related hormone AVP (3.1.1) may cross-react with OTRs at high levels and contribute to uterine contractions in labor.[48]

Fetal Oxytocin in Labor and Birth

The eustress of labor activates important adaptations for the fetus. Fetal oxytocin release with labor may assist with stress and pain, and may even promote contractions by a local effect.

For the baby, the processes of labor and birth involve physical pressures, such as intense squeezing of the body and head,[302, 303] and intermittent loss of blood and oxygen, producing some degree of stress. The eustress of physiologic labor benefits the fetus and newborn by turning on adaptive mechanisms. (See "Fetal catecholamine [CA] surge" in 5.1.3). Researchers have generally found higher newborn OT levels or production (assessed by differences between umbilical artery and vein levels) following labor, compared with prelabor cesarean section (CS).[255, 304-309] Newborn OT elevations may counteract "the stress of being born,"[175] with natural painkiller effects.[161, 185] See also "Newborn and Later Oxytocin," below.)[309]

In rats, fetal oxytocin released by electrical stimulation of the hypothalamus crosses into the maternal circulation and can cause uterine contractions near term.[310] Human studies also suggest that fetal OT may reach the mother's uterus, possibly via amniotic fluid, potentially causing uterine contractions and even contributing to the initiation of labor.[305] It has been suggested that, in response to hypoxic stress, increased fetal OT could beneficially hasten labor.[255, 311] While this would be adaptive for offspring survival, evidence is contradictory.[309] (See "Synthetic Oxytocin and Offspring, Longer Term" in 3.2.3 for discussion of passage of OT from mother to fetus.)

In animal studies, maternal OT peaks at birth benefit the newborn by synchronizing brain-cell activity in the hippocampus, an area involved with learning and memory.[312]

3.1.4 Oxytocin after Birth

Peaks of oxytocin during labor and birth continue into the early postpartum period, with beneficial effects for mothers and newborns.

Maternal Oxytocin After Birth

High maternal oxytocin levels at physiologic birth are further elevated through early skin-to-skin contact and newborn prebreastfeeding behaviors. This elevation promotes contractions that prevent postpartum hemorrhage, and may prime longer-term maternal adaptations through central oxytocin effects, according to human studies.

Maternal OT levels are elevated at physiologic birth due to the oxytocin surge that promotes effective pushing (Ferguson reflex, 3.1.3). Levels increase even further during the first hour after birth, correlated with skin-to-skin contact and newborn prebreastfeeding behaviors, according to studies discussed below. High OT levels are crucial at this time for contracting the new mother's uterus and preventing PPH. Oxytocin also has critical postpartum roles in switching on the central maternal adaptations that promote maternal-infant attachment (biologic bonding) and lactation in all mammals, as detailed below. After birth that follows the physiologic onset of labor, high levels of OTRs in the new mother's uterus, and likely her brain and breasts (as found in animal studies) will assist with these processes (3.1.3).

Oxytocin and maternal-newborn contact and interactions. *One study found correlations between infant breast massage behaviors and maternal oxytocin elevations in the first two hours. Diminishing oxytocin responsiveness over this time suggests a rapid loss of oxytocin sensitivity over the first one to two hours and supports the concept of a "sensitive period" in relation to maternal hormonal physiology.*

Maternal OT release after birth may be stimulated by maternal-newborn contact. One study found around 1.8-fold average elevations of OT at 15 and 45 minutes after spontaneous birth among new mothers who were in immediate SSC with their newborn before breastfeeding initiation, as measured by blood samples.[259]

Newborn OT elevations may contribute to the alert newborn state that follows physiologic birth and persists for two hours or so.[313] At this time, an unmedicated and undisturbed newborn in SSC can enact a series of behaviors that culminate in self-attaching to the mother's breast and suckling. This sequence can take one hour or longer.[314, 315] (See also "Breastfeeding initiation" in 3.1.4.)

One study of SSC mothers and babies found maternal postpartum OT peaks that correlated with their newborns' instinctive hand massage of the breasts (predominantly the areola and nipple) and with early suckling. These interactions elevated maternal OT levels up to ten-fold, as seen from the data of one mother and baby.[316] In these data, the new mother's OT levels peaked at 45 minutes then decreased into the second hour, even though breast stimulation from her infant's breast massage was maximal at 75 minutes, and suckling occurred at 90 minutes.

Similar findings were seen in another study (mentioned above) that measured postpartum maternal OT with SSC.[259] In this study, peaks of maternal OT occurred at 15 and 45 minutes and then subsided, even though first suckling, which might be expected to maximally stimulate OT release, occurred at 87 minutes.

Together, these findings suggest that new mothers may have increased nipple sensitivity, possibly via peaks of central OTRs, which subsides after the first hour. This supports current understanding of the importance of SSC, with newborn access to the mother's breasts, in the first hour after birth to promote

breastfeeding and biologic aspects of maternal-infant attachment. (See "Postpartum sensitive period," below.) In addition, according to these findings, newborn breast contact may be more important than actual breastfeeding for elevating maternal OT levels. (See also 3.2.7.)

Kennell and McGrath comment, "Before the availability of medications such as Pitocin, the newborn's touches were probably crucial for the survival of mothers by raising OT levels to cause strong, repeated uterine contractions, which prevented a fatal hemorrhage."[317(p.20)]

Oxytocin and postpartum hemorrhage. *The postpartum oxytocin elevations that follow physiologic birth and undisturbed postpartum skin-to-skin maternal-newborn contact likely reduce the risk of postpartum hemorrhage. Evolving evidence supports this model.*

The risk of postpartum hemorrhage has not been assessed in relation to maternal postpartum OT levels. Undisturbed SSC provides the necessary context for the newborn's prebreastfeeding behaviors and breast massage, which increase maternal OT levels (see "Oxytocin and maternal-newborn contact and interactions," above).

While the relationships between postpartum OT levels and PPH risk have not been directly researched, studies suggest lower PPH incidence in low-technology settings, where SSC is more likely to be supported. Observational studies of birth at home[318-322] show a reduction in PPH risk compared with routine hospital care, although obviously risks are likely to be reduced among a healthy home birth population. Population[323] and cohort[324, 325] studies have also found lower PPH risk among low-risk women experiencing physiologic (or "holistic psychophysiological") care compared with "active management of the third stage of labor," and a systematic review found equivalent PPH rates (SSC status not stated).[326]

Other researchers have found a reduced time from birth until the mother expelled her baby's placenta among women randomized to SSC,[327] and quicker uterine involution, as well as reduction in bleeding, among SSC mothers compared with controls.[328, 329] (See also "Synthetic oxytocin and postpartum hemorrhage" in 3.2.3.)

Postpartum hemorrhage is a life-threatening complication, especially in low-resource settings. Understanding and fostering physiologic processes to prevent hemorrhage is an important area for high-quality research.

Newborn and Later Oxytocin

Elevated newborn oxytocin levels at birth may have calming and analgesic effects that assist with the baby's postpartum transition, and promote breastfeeding initiation. Maternal-newborn interactions – including through skin-to-skin contact, vocalizations, and maternal odor – may further beneficially elevate newborn oxytocin, reduce stress, and stabilize newborn physiology. Physiologic hormonal experiences in the newborn period may optimally program hormonal systems longer term by epigenetic mechanisms, as found in animal studies.

Following labor and birth, the newborn has high OT levels, as measured in cord blood, and compared with levels in babies born by prelabor cesarean (PLCS) or to non-pregnant adult levels.[305-307] Higher levels in the umbilical artery than vein suggest fetal OT production during labor[174, 305] (3.1.3). Newborn oxytocin levels peak at around 30 minutes after birth,[174] and may give feelings of calm, connection, and pleasure to newborns at this time, consistent with OT effects in adults (3.1.1). One study found pulsatile OT release among newborns in NICU.[330]

Researchers have found a physiologic analgesia among vaginally-born human[302] and animal[185] newborns that declines over several hours and that may reflect the analgesic effects of OT (3.1.1). Beta-endorphins and norepinephrine may also contribute.[302] The closely related hormone AVP, which can occupy the OTR (3.1.1), also peaks following labor and birth and may be an even more powerful analgesic than OT for the fetus and newborn.[161] Breastmilk also has analgesic properties,[331] and postpartum breastfeeding and SSC may have additive analgesic effects.[332]

Newborn blood OT levels were found to decline by more than 50 percent in the hour after birth in one study, but were elevated above adult levels for the first four days.[174] Oxytocin's calming effects likely benefit the newborn through this period of transition.

Newborn OT may be further released through early interactions with the mother,[52, 333] as shown in animal studies.[334] Contributing factors may include**:**

- skin-to-skin and eye-to-eye contact (3.1.1)
- social vocalizations[178]
- maternal and milk odors, which are soothing for the newborn[335]
- suckling, which releases OT (3.1.1)
- food intake and digestion, which releases OT (3.1.1)
- ingestion of breast milk, which contains OT[174]

These newborn OT elevations, and the interactions that promote them, may be important in activating the PNS-related calm and connection system (3.1.1). This reduces the birth-related surge of E-NE, which can be harmful after birth if prolonged, especially in relation to energy consumption (5.1.4). The more stable temperature, heart rate, breathing, and neurobehavioral responses of babies experiencing SSC compared with separated babies[336] are likely due to this OT-mediated shift from the SNS to PNS[333] (3.1.1). This PNS shift also conserves newborn energy stores,[333, 337] contributing to higher blood glucose levels among SSC newborns compared with separated newborns.[336] (See 5.1.4 for more about newborn stress hormone levels.) OT may mediate the analgesic effects of SSC[338] (see "Skin-to-skin contact," below).

Newborn OT elevations in association with SSC and breastfeeding may begin to sculpt the brain for positive social-affiliative behaviors.[339] In humans, elevated OT levels increase gaze to the eyes, the ability to read the emotions of others from facial cues, and interpersonal trust.[340] As with the mother, newborn experiences during this sensitive period may also imprint pleasure and reward in relation to maternal-infant contact, creating brain connections that have longer-term benefits. (See "Pleasure and reward," below.) One study found correlations between newborn OT levels in the cerebrospinal fluid, reflecting brain levels, and prosocial behavior at three and six months.[341]

In addition, the newborn period, including the days that follow birth, may be crucial for setting life-long programs in brain-hormonal systems. In animal studies, maternal and social interactions during the newborn period program subsequent biologic functions and behaviors by altering sensitivity to neuropeptides, including OT and AVP.[342-344] (See Introduction for more about fetal/newborn programming and "Synthetic Oxytocin and Offspring, Longer Term" in 3.2.3 for a detailed discussion of possible epigenetic impacts from perinatal exposures.)

Oxytocin and Breastfeeding

The maternal oxytocin system is involved with important physiologic preparations to optimize lactation. These processes may begin even before the physiologic onset of labor, with late-pregnancy breast oxytocin receptor increases, as found in animals. During lactation, oxytocin is released in pulses and mediates the let-down reflex, which makes milk available to the suckling baby, also promoting prolactin release and possibly directly stimulating milk secretion.

In other animals, upregulation of mammary OTRs occurs before the onset of labor,[86, 345] ensuring effective mammary responses to the early postpartum OT elevations ("Maternal Oxytocin After Birth" in 3.1.4). Direct OTR sampling is not possible in women, but similar preparations are likely because of the evolutionary benefits of successful lactation for reproduction. Oxytocin also promotes PRL secretion[346] (3.1.1), giving even more benefits to prelabor OT and OTR preparations.

Oxytocin mediates the milk ejection ("letdown") reflex by causing rhythmic contractions in the myoepithelial cells that line the milk ducts. This pushes milk through the ducts for a suckling baby to ingest. Blood OT levels rise during a nursing episode, peaking at 5 to 10 minutes, and remaining elevated for 20 to 30 minutes after initiation,[237] with brain levels likely elevated for a longer period because of the longer half-life.[347] The pulsatile release of OT from the pituitary is only present during labor, birth, and lactation;[209] at other times, OT is released in a constant manner (3.1.1).

Breastfeeding initiation. *During the hour or so after physiologic birth, peak oxytocin activity for both mother and baby promotes an ideal "calm and connection" state for breastfeeding initiation. Instinctive newborn behaviors, including "breast crawl" and prebreastfeeding breast massage, can facilitate self-attachment. Early breastfeeding may enhance longer-term success by optimizing the oxytocin and prolactin systems. Even brief separation and/or exposure to analgesia can disrupt newborn sequencing, and breastfeeding initiation.*

Newborn OT elevations, along with elevations in NE (5.1.4), may contribute to the alert newborn state that follows physiologic birth and persists for two hours or so.[313, 315] At this time, an unmedicated and undisturbed newborn, placed naked and skin-to-skin on the mother's body, can enact a series of behaviors that involves: locating and moving to the breast ("breast crawl"[348, 349]); breast massage with the hand; fist or finger sucking, promoting saliva flow; and finally culminating in self-attaching to the mother's breast and suckling.[315] The full sequence can take one hour or longer,[315, 316] and can be significantly disrupted by even brief separation (e.g., for weighing, washing, and dressing) and/or by exposure to labor analgesia.[350, 351] When fully enacted, breast crawl can benefit the onset of lactation and limit early weight loss, possibly through early, effective feeds,[352] leading to strong OT and PRL responses.

In addition, early SSC and breastfeeding initiation (with or without breast crawl) may enhance longer-term breastfeeding success.[336, 353] A recent systematic review found that newborn mortality was halved when breastfeeding was initiated during the first hour, compared with after this time.[353] The mechanisms behind the critical sensitive nature of the first hour or so after birth for breastfeeding are not fully understood but may include the peak in oxytocin sensitivity, as discussed above. In addition, early maternal PRL elevation, which is stimulated by OT release, and PRL itself, may stimulate PRL receptor formation, with benefits to ongoing milk supply (5.1.4).

One study measured women's hormone levels during breastfeeding two days after cesarean or vaginal birth, and found that earlier first suckling increased the number of OT pulses during breastfeeding and the subsequent duration of breastfeeding. Vaginal birth was also associated with more OT pulses compared with CS. Authors comment, ". . . early mother-infant contact together with the passage of the fetus through the vagina during the second stage of labour can enhance the stimulation of OT neurons leading to a more pulsatile pattern of OT release," with ongoing benefits to breastfeeding success.[354(p.116)]

Early newborn contact with the mother's nipple, which maximally stimulates maternal OT release in the first hour,[316] may also be very effective in promoting maternal adaptations[355] and biologic maternal-infant bonding (See "Postpartum sensitive period," below.)

The World Health Organization-sponsored Baby-Friendly Hospital Initiative (BFHI) prioritizes SSC immediately after birth, with support for early and frequent breastfeeding, as effective strategies to increase long-term breastfeeding success.[356-358] Growing knowledge of the major health disadvantages associated with lack of breastfeeding[4, 6, 359] highlights the importance of early SSC and of minimizing maternal-newborn separation to promote lifelong well-being of women and their offspring.

Breastfeeding benefits. *Researchers have found reduced anxiety and increased sociability among new breastfeeding mothers, compared with adult norms, in proportion to oxytocin release during breastfeeding. Brain scans show greater activation of empathy and bonding centers in response to infant cues in breastfeeding versus nonbreastfeeding mothers, which may promote attachment and infant care, and ultimately enhance survival. Repeated hormonal exposure with breastfeeding may give long-term maternal health benefits, related to the duration of breastfeeding. For offspring, oxytocin exposure with breastfeeding may optimally prime oxytocin systems, reducing stress responses longer term, as found in animal studies.*

The release of OT during early breastfeeding and its pulsatile pattern are optimized following physiologic birth, as described above,[354, 360] possibly through the peaks of OT during birth and the early postpartum period. Oxytocin, released during breastfeeding, reduces maternal anxiety, and increases calmness and desire for social contact.[360] In addition, pulsatile OT, released with breastfeeding, promotes PRL release, with possible benefits to early PRL receptor formation and ongoing milk production (see "Prolactin receptor theory" in 6.1.4).

Conversely, dysregulation in the maternal OT system may affect the new mother's mood. Researchers measured women's OT (and other hormone) levels and mood from late pregnancy through to eight weeks postpartum and found that, at eight weeks, women with lower OT levels during lactation had poorer mood scores, including more anxiety and depression.[361] The cause for dysregulation was not clear, and detailed birth variables were not included in this analysis.

Measurements before and after a nursing episode show reductions in women's stress reactivity and stress hormone levels,[354] and an elevation in mood.[362] Repeated exposure to breastfeeding hormones, including OT and PRL, which also has stress-reducing effects (6.1.1), may give long-term physical as well as psycho-emotional benefits. One study found lower risks of diabetes, high blood pressure, and cardiovascular disease in older women in proportion to their lifetime duration of breastfeeding.[363]

Magnetic resonance imaging (MRI) scans comparing the brain responses of breastfeeding and formula-feeding mothers to their infant's cues in the first month found, among breastfeeding mothers, more activation in brain areas concerned with bonding and empathy and, when assessed in interactions with their infants at four months, greater maternal sensitivity.[364] Other studies have shown that a breastfeeding

mother is less likely to abuse or neglect her child, which researchers have also linked to the OT system.[365] According to these authors, "Breastfeeding represents a set of maternal behaviors that enhance the emotional bond between mother and infant via close physical contact and affectionate dyadic interactions . . . breastfeeding may contribute to the development of a range of sensitive maternal behaviors during the early postpartum period."[364(p.1)] Mechanisms likely involve OT and other hormonal systems such as beta-endorphins and PRL. (See "Beta-endorphins and Breastfeeding" in 4.1.4 and "Prolactin and Breastfeeding" in 6.1.4.)

Newborn and infant effects of OT exposure during breastfeeding have not been well studied, but elevated levels, repeated with each nursing episode via suckling-related release, and OT present in breast milk,[174] may contribute to the established lifelong benefits for breastfed offspring,[4, 6, 359, 366, 367] including possible benefits to mental health.[368]

In animal studies, synOT administered daily for two weeks after birth, or stroking (which releases endogenous OT) for five minutes daily over seven days produced lifelong reductions in blood pressure, including in animals genetically programmed for high blood pressure.[369] (In contrast, similar treatments in adulthood had effects that persisted for several days.[159, 370]) These findings suggest that regular OT-rich behaviors in the postpartum period (e.g., SSC, breastfeeding) may also powerfully program human offspring, with long-term benefits, even to the next generation, as shown in animal offspring receiving high levels of nurturing. (See "Maternal-infant attachment: possible impacts of childbearing," below, and "Synthetic oxytocin and epigenetics" in 3.2.3.)

In addition, early contact with the mother's breast also gives long-term benefits for mothers and babies in relation to digestion and nutrition. Klaus summarizes**:**

> . . . when the infant suckles from the breast, there is an outpouring of 19 different gastrointestinal hormones in both the mother and the infant, including insulin, cholesystokinin, and gastrin. Five of these hormones stimulate the growth of intestinal villi in the mother and the infant. As a result, with each feeding, there is an increased intestinal surface area for nutrient absorption. The hormonal release is stimulated by the touch of the mother's nipple by her infant's lips. This increases OT in both the mother's brain and the infant's brain, which stimulates the vagus nerve, then causes the increase in the output of gastrointestinal hormones.[348(p.1246)]

Oxytocin and Maternal Adaptations and Attachment

The perinatal maternal oxytocin peaks that follow prelabor and in-labor physiologic preparations (e.g., increases in receptor numbers) promote maternal adaptations. These include both bodily adaptations (e.g., breast adaptations that promote lactation) and brain-based adaptations, including activation of limbic system circuits that foster maternal well-being and species-specific maternal behaviors.

Among mammals, peaks of OT during and following birth, acting on areas that have been primed by physiologic prelabor and in-labor preparations (e.g., increase in receptor numbers), promote critical maternal adaptations and behaviors. For example, in rats, increased central OT activity after birth (OT, OTRs) fosters licking, grooming, and arched-back nursing behaviors, as well as aggressive defense of offspring.[160] In some species, such as sheep, birth-related vaginocervical stimulation is critical for the rapid onset of maternal adaptations and caregiving, and postpartum VCS can facilitate acceptance of unrelated newborns.[212]

Postpartum sensitive period. *During the initial one to two hours after birth, central maternal peaks of oxytocin and oxytocin receptors promote maternal behaviors that are critical for newborn survival in all mammals. Skin-to-skin and nipple contact may maximally stimulate hormonal systems for mother and newborn at this time, with long-term benefits to maternal adaptations and maternal-infant attachment (via "biologic bonding"), and breastfeeding. The subsequent newborn period may continue to be "sensitive" to some extent for mother-newborn contact and evolving hormone systems.*

Maternal brain elevations of OT may continue for several hours after birth. A study of parturient cows showed high levels of OT in the CSF for at least two hours after birth,[263] with similar results in sheep.[371] This may reflect ongoing central positive feedback, stimulation of release by maternal-newborn interactions, and/or the longer half-life of OT in the brain, around 28 minutes according to animal studies.[166]

This peak activity of OT (and other birth-related hormonal systems; see 4.1.4, 5.1.4, 6.1.4) promotes the maternal behaviors that are critical for newborn survival in all mammals.[372] These include facilitating newborn suckling, and, in women, this may include positioning to facilitate newborn movements and proximity seeking.[373] Like other mammals, human newborns also seek proximity for warmth and safety, and can give a "separation distress cry" when separated.[374]

Following physiologic labor and birth, the new mother has exceptional sensitivity to tactile stimulation, including nipple contact,[316, 333] likely due to high numbers of central OTRs, as found in animals (3.1.2), which sensitize brain areas critical for maternal adaptations and behaviors. Oxytocin released in response to such stimulation therefore likely has greater effects in the postpartum sensitive period than at any other time. In animal studies, the birth-related peaks of OTRs decline within four to twelve hours in the new mother's brain[88] and uterus.[48] A postpartum decline in uterine OTRs and sensitivity may be important in preventing excessive contractions and pain during lactation. Oxytocin responsiveness to nipple stimulation may also decrease rapidly over two hours following birth in women.[316] (See "Maternal Oxytocin After Birth," above.)

Consistent with this mammalian sensitive period and its heightened effects on maternal responsiveness and adaptations, one human study found that new mothers whose newborns licked or touched their nipple in the first 30 minutes after birth left their babies alone in the nursery for shorter periods (enhanced proximity seeking); talked more to their babies while breastfeeding on day four; and had lower serum levels of gastrin (indicative of lower stress) during a breastfeeding episode, compared with control group mothers, whose babies first sucked at a median age of eight hours.[355]

One study randomized new mothers and babies in the first two hours to either early SSC contact, newborn swaddling, or nursery care. At one-year follow up, researchers found positive effects of early SSC on infant self-regulation and mother-infant interactions.[375] Other studies have also found longer-term benefits to maternal-infant relationships from early SSC,[376-380] although methodology has been controversial in some SSC studies. The Cochrane systematic review found positive effects of early SSC on breastfeeding duration and maternal confidence, and possible effects on early maternal-infant relationships.[336] (See also "Skin-to-skin contact," below.)

These findings are consistent with the biologic activation of hormonally-mediated limbic system programs that facilitate maternal-newborn attachment (bonding) among all mammals.[20] This hormonally-mediated biologic bonding may be distinct from "attachment" as commonly understood. According to Bergman, attachment is a uniquely human process that involves the higher-order cortical brain, and can compensate for situations where biologic bonding is missed, (e.g., with adoptive parenting) but may not achieve for example, the prolonged breastfeeding that follows biologic bonding.[20]

While maternal-infant contact in the first hour or so seems to be most consistently associated with, and effective at promoting, the longer-term maternal adaptations of biologic bonding, maternal responsiveness may continue to be elevated for many hours after birth, perhaps reflecting the important plasticity of the maternal brain at this time, as seen in animal studies.[381, 382] Studies have shown benefits to breastfeeding and maternal adaptations from "rooming in" during the days following birth, compared with nursery care for newborns,[383-388] including one older study that found lower levels of abuse and neglect at 17 months among mothers and babies who had roomed in during their two-day hospital stay, compared with controls.[386]

Skin-to-skin contact. *Skin-to-skin contact immediately after birth, the biological norm among all mammals, promotes oxytocin release, which reduces stress and fosters "calm and connection." Postpartum skin-to-skin contact also: stabilizes newborn physiology, promotes maternal-newborn sensory interactions, keeps the newborn warm through maternal oxytocin-related vasodilation, and facilitates newborn self-attachment to the breast, with longer-term benefits to breastfeeding duration and maternal confidence. Through the early weeks, skin-to-skin contact may benefit maternal psychological well-being by release of oxytocin and other hormones. From the perspective of hormonal physiology, maternal-infant separation that disallows skin-to-skin contact is a major intervention that requires a strong indication.*

Skin-to-skin contact immediately after birth promotes OT release,[259, 316] activating the PNS and facilitating calm and connection for mother and baby ("Newborn and later oxytocin" in 3.1.4). Skin-to-skin contact provides the environment that not only facilitates breastfeeding initiation, but also the maternal-infant interactions that regulate and stabilize maternal and newborn biologic processes (mutual regulation). Early postpartum SSC facilitates mutual regulation of newborn temperature, acid-base status, energy use and metabolism, respiration, crying, and breastfeeding behavior. In the mother, SSC benefits maternal attention and behaviors, OT release, initiation and maintenance of breastfeeding, and energy economy, with these benefits continuing through the breastfeeding period.[333]

Skin-to-skin contact also provides the environment that the newborn requires to enact instinctive behaviors, including finding the mother's breast and self-attaching (see "Breastfeeding initiation," above). As described, even brief separation for weighing can disrupt newborn sequencing and reduce the chance of successful suckling.[350, 351, 389]

In addition, early SSC provides a context for other interactions with the newborn that can also release OT, including visualizing[390] and vocalizing.[178] In one study, mothers and fathers in skin-to-skin contact after cesarean had more vocal communications with their babies compared with non-SSC parents, which may reflect the pro-social effects of oxytocin released with SSC.[391]

Olfaction during SSC may also stimulate OT release of newborn and mother,[392] as it does in other mammals[52] (3.1.1), with breast odors found to have calming effects on human newborns.[393, 394] Oxytocin levels in mothers or fathers who are close to, but not in SSC with, their newborn have been found to rise, likely due to non-tactile sensory cues.[395] (See "Newborn and Later Epinephrine-Norepinephrine and Related Stress Hormones" in 5.1.4, for NE and smell.)

During the early sensitive period, vasodilation of the new mother's chest wall due to oxytocin peaks (3.1.1) provides a natural warming mechanism for her newborn.[52] (This is also seen as an OT-mediated flush with female sexual arousal.) One study measuring maternal breast and axillary temperatures after birth in relation to postpartum care practices found that mothers in SSC with their newborns had more variation in breast temperature compared with women whose babies were swaddled or separated. Breast temperature variations were even greater among multiparous mothers and those whose newborns successfully suckled.[396]

Researchers suggest that these SSC mother's breasts are pulsing heat, perhaps related to maternal pulses of OT, which is more efficient for heat transfer than a steady temperature. As reported elsewhere, the SSC newborns in this study had warmer axillary and foot temperatures,[175] even 23 hours later (see 3.2.7). Consistent with this, the Cochrane systematic review of skin-to-skin contact reports warmer temperatures among SSC babies compared with babies wrapped and placed in a bassinet.[336]

Skin-to-skin contact also reduces newborn stress and stress hormone levels (5.1.4), and provides the habitat for breastfeeding initiation. (See "Newborn and Later Oxytocin," above.) The Cochrane systematic review[336] also found the following longer-term benefits of early SSC**:**

- less maternal anxiety and more confidence with their babies at hospital discharge
- higher breastfeeding rates in the early months
- longer total duration of breastfeeding
- no negative effects

Early SSC may also enhance maternal breastfeeding self-efficacy and confidence in the early weeks.[397]

These findings support long-term effects on maternal adaptations from early SSC, likely via hormonally-mediated activation of biologic bonding within the central limbic system. (See also "Postpartum sensitive period," above, and "Pleasure and reward," below.) Keeping healthy mothers and babies together for this time also enhances maternal and newborn physiology and postpartum physiologic adaptations. From the perspective of hormonal physiology, maternal-infant separation is a major intervention that requires a strong indication.[398] (For a full discussion of the possible impacts of separation of healthy mothers and newborns, see 3.2.7.)

Ongoing skin-to-skin contact may provide significant maternal benefits through the early weeks. One study found lower cortisol levels and depression scores over the first month for women experiencing six extra hours of skin-to-skin contact with their newborn in the first week, compared with women in the control group. Two hours of SSC daily through the first month also reduced depression scores and cortisol levels among these new mothers, relative to controls. Researchers highlight SSC as an accessible, cost-effective intervention strategy with no adverse effects, and suggest that OT elevation may be involved.[399] These findings underscore the great benefits of ongoing SSC for infant survival through human evolution, and the development of maternal reward and motivation systems to support this.

Maternal adaptations. *Maternal postpartum adaptations include activation of protective and attachment behaviors that promote well-being and survival in all mammalian offspring. In women, shifts in personality have been found following unmedicated birth, with both reduced anxiety and increased desire for social contact promoting maternal caretaking. Maternal attachment behaviors, and especially proximity-seeking, may foster secure attachment, which has lifelong benefits to offspring psychological and physical health. Maternal attachment and protective behaviors are linked to OT systems in humans and animals. OT levels in pregnant women have been correlated with positive aspects of mothering behaviors*.

A growing body of research from both animal[100, 244, 400-404] and human[5, 240, 244, 374, 404-413] studies is expanding current understandings of the neurobiology of maternal-infant attachment and its long-term implications. However, the precise origins of, and mechanisms to promote, maternal-infant attachment in humans remain uncertain, especially in relation to healthy full-term infants.

Maternal adaptations are obviously more complex in humans than in other animals,[156, 414, 415] perhaps reflecting cortical involvement in human attachment.[20] However, the OT system has been linked to a repertoire of maternal behaviors in women. These include enface (face-to-face) gaze, smiling, high-pitched vocalizations ("motherese"), affectionate touch, and the synchronizing of these behaviors with infant emotional states and responsiveness.[405, 414] In human mothers and babies, these behaviors promote infant brain maturation,[416] cognitive development,[417-419] and attachment security.[420] Oxytocin also promotes proximity seeking, according to animal studies.[406] Proximity seeking keeps newborns in safe, physical contact with the mother, and may also be central for secure attachment in human mothers and babies (see "Maternal-infant attachment and childbearing," below).

Adaptations in personality have been found in women following unmedicated labor and birth, compared with non-pregnant women, suggesting psychological effects from central hormonal peaks. These include reduced anxiety and guilt, and increased desire for social contact, correlated with OT elevations during breastfeeding, as discussed above.[237, 360] Studies have found fewer personality changes among women who may have missed the OT peaks at birth due to epidurals (3.2.5) and cesareans (3.2.6).

In animal studies, OT also promotes "aggressive-defensive" maternal behavior in protection of offspring, which may also involve the related hormone AVP[160] (3.1.1), and possibly PRL (6.1.1). In women, OT may enhance infant survival by increasing vigilance.[421] In one study of women with postpartum depression, intranasal synOT increased maternal protective behaviors, although it had a negative impact on mood.[422] (Intranasal OT gives central effects, possibly via a direct route;[164] see 2.1.1.)

The hormone peaks of labor and birth may also contribute to longer-term adaptations in the brain and OT system of women. Researchers used MRI to record brain activity in new mothers in response to hearing their own infant's cry two to four weeks after birth. They found that women who had given birth vaginally had more activation in arousal, motivation, and reward brain circuits, compared with women who had given birth by PLCS. The authors suggest that exposure to peaks of OT during labor and birth may facilitate these adaptations.[423] (See also 3.2.7.)

Such changes may be faster and/or greater in, multiparous females, who have more central OTRs, with a wider distribution, according to animal studies,[211, 424] likely from previous OT peaks (3.1.3). One study found a more rapid onset of these personality adaptations after birth for multiparous compared with primiparous women.[425]

The influence of the OT system on maternal adaptations may begin in pregnancy. In one human study, OT levels in women in early and late pregnancy were positively correlated with maternal behaviors in the early postpartum weeks such as gaze, vocalizations, positive affect, and affectionate touch.[240] There is also evidence for a trans-generational effect of maternal care in animals[228] and humans,[426, 427] which is thought to act via the OT system. (See "Maternal-infant attachment and childbearing," below.)

Biologic bonding following early SSC may contribute to these adaptations, although early maternal-infant contact was not noted in these studies and models.

Pleasure and reward. *Oxytocin activates the dopamine-associated central reward (meso-cortico-limbic) pathways, which motivate and reward maternal behaviors in all mammals. The peaks of oxytocin (and other hormones) that follow physiologic birth can give a natural euphoria. Animal and human studies suggest changes in central reward centers, also likely due to postpartum hormonal peaks, which increase the reward associated with infant contact and care, benefitting maternal care and infant survival.*

Central OT changes are found in postpartum animals, according to anatomical brain studies,[428] and women, according to MRI studies,[405, 423, 429] discussed in detail below. Effects are likely augmented in new mothers by upregulated brain OTRs in the early sensitive period,[88] acted on by OT elevations with birth and early SSC (see "Postpartum sensitive period," above). Elevated levels of opioids, including BEs, which also activate these reward centers, may also contribute (4.1.4).

These birth and postpartum OT elevations, acting on upregulated central OTRs, may also boost mood and give feelings of euphoria or even ecstasy in postpartum women in relation to birth and baby.[430, 431] This postpartum physiologic OT activation, with elevations in mood, could plausibly protect against post-traumatic stress disorder after birth, as OT dysfunctions have been implicated in this condition (3.1.1).

In addition, these OT elevations may contribute to modifications in central reward circuits that imprint ongoing pleasure and reward in association with newborn contact and care. One MRI study (discussed above in "Maternal adaptations") found greater activation of reward centers in response to infant cues among new mothers who had experienced a vaginal birth, compared with women experiencing PLCS.[423] These different OT experiences may also impact maternal mood, as discussed below.[432] The corelease of OT with BEs, which also activate reward centers (4.1.1), during episodes of lactation and infant contact may be important in decreasing opioid tolerance,[433] which maintains reward-center sensitivity and the "addictive" aspects of maternal-infant contact (see "Beta-Endorphins and Maternal Adaptations and Attachment" in 4.1.4). Activation of reward pathways may contribute to biologic bonding, as discussed in "Postpartum sensitive period," above.

Another study found improved mood in hospital and eight months later among women who experienced earlier, compared with later contact with their babies after birth,[432] suggesting more effective imprinting of reward systems in the early postpartum sensitive period, compared with the subsequent hours after birth (3.1.4). In addition, in one prospective study, women reported an elevation in self-esteem from pregnancy to the postpartum period following spontaneous vaginal birth, a diminution following CS, and no change following instrumental birth,[434] also suggesting hormonally-mediated increases in reward and pleasure. A study of supportive care in labor (see 3.2.1) found significant reductions in postpartum depression (PPD) scores and elevations in self-esteem scores for women randomized to doula care. In this study, 90 percent of supported women had low depression scores at six weeks versus 40 percent of women without doula support.[435]

The stress-reducing and mood-enhancing effects of OT, released with episodes of breastfeeding and maternal caregiving, may make an important contribution to the ongoing emotional well-being of women, as of other mammalian mothers,[45] and may also contribute to the mental health benefits of breastfeeding.[436] In addition, oxytocin released during breastfeeding may enhance maternal sensitivity in caregiving, which has been linked to activation of brain empathy centers, according to one MRI study,[364] and to secure infant attachment.[437, 438]

As discussed in "Breastfeeding benefits" above, OT dysregulation has been implicated in postpartum depression,[361] but studies were not found exploring PPD and OT in relation to childbirth experiences or maternity care interventions. (See also 5.2.1 in relation to posttraumatic stress disorder and childbirth.)

Reward center activation has also been linked to episodes of mother-baby synchrony, where maternal behavior is coordinated with infant signals.[405] Activation of these pathways in association with infant contact augments the "reward value" of offspring,[226] making a critical contribution to offspring survival.

Maternal-infant bonding and attachment. *Maternal-infant bonding has been a biological necessity for survival in mammals. The full spectrum of biologic bonding involves prelabor preparations, in-labor hormonal peaks, and postpartum maternal-infant interactions, which all help optimize maternal adaptations, maternal-infant bonding, and offspring survival. In humans, these processes may also promote secure attachment of mother and babies, with ongoing benefits to offspring psychological well-being.*

Bonding and attachment have been extensively studied among animals in relation to early maternal-newborn interactions. In other mammals, labor and birth peaks of oxytocin and other hormones, acting on brain areas primed by prelabor physiologic preparations,[400] activate central circuits that switch on maternal adaptations,[100, 244] promoting maternal caregiving and infant survival.[156, 401] Postpartum maternal-infant contact may also contribute, as discussed above ("Postpartum sensitive period"), facilitating biologic aspects of mammalian bonding through hormonally-mediated limbic system activation.[20]

The resulting hormonally-mediated maternal adaptations of biologic bonding foster proximity seeking, which facilitates suckling, milk production, and species-appropriate care of the young.[402] Maternal adaptations and behaviors are reinforced through central reward centers,[403] that are likely activated with parturition, ensuring that the new mother is motivated and rewarded to give the dedicated care that every mammalian infant requires until maturity (see "Pleasure and Reward," above).

In mammals, these limbic-based maternal adaptations, along with reinforcing cues and behaviors from offspring in the postpartum period (e.g., vocal, tactile, olfactory, and visual stimuli), lead to the formation of maternal-infant attachment bonds, which program lifelong well-being for offspring, including by optimizing brain-hormone systems.[402, 404] Oxytocin promotes biologic bonding and attachment by promoting proximity-seeking in mothers and newborns,[406] by activating central reward circuits (also likely involving endorphins[410]), and by facilitating lactation and milk transfer. Other hormone systems are also involved.[404] Every episode of lactation reinforces these maternal adaptations and maternal-infant bonding through the release of OT, beta-endorphins (4.1.4), and prolactin (6.1.4).

This animal model of biologic bonding is also relevant to women and babies, for whom the rapid onset of maternal care following birth has also been an evolutionary benefit. Important contributing factors to human maternal-infant biologic bonding and attachment, based on animal models and physiologic understandings, may include**:**

- prelabor physiologic preparations in central maternal circuits, e.g., upregulation in central OTRs ("Maternal Oxytocin in Pregnancy" in 3.1.2)
- peaks of hormones in labor and birth that activate these receptor systems (OT, beta-endorphins, prolactin, norepinephrine) (3.1.3, 4.1.3, 5.1.3, 61.3)
- maternal-infant SSC in the early sensitive period, when peaks in hormones and receptor levels give maximal sensitivity and effects (see "Postpartum sensitive period," above)
- newborn responsiveness, especially in the early sensitive period when maternal systems are primed for interaction and breastfeeding initiation
- increased central autoregulatory OTRs in multiparous women, which may facilitate earlier onset of maternal behaviors (3.1.1)
- the postpartum initiation and maintenance of breastfeeding which reinforces maternal adaptations and reward through hormonal release
- preexisting maternal personality and attachment history, which may influence central oxytocin systems and responsiveness

The maternal adaptations and behaviors that may be promoted through this model, as relevant to human biologic bonding and attachment, may include:

- changes in maternal personality that promote infant care, including reduced anxiety and guilt and increased desire for social contact
- proximity seeking, with physical contact and sensory exchanges (e.g., gaze, odor, and affectionate touch) that reinforce hormonal release
- mother-infant vocalizations (e.g., "motherese")
- mother-infant interactions, including "affect synchrony," which adapts maternal behaviors to moments of infant responsiveness
- ongoing breastfeeding, including related maternal-infant interactions

These behaviors, many of which are also displayed by human fathers, have been linked to the oxytocin system[240] and to the development of "secure attachment" as a personality characteristic. (See "Maternal adaptations," above.) According to Bowlby, who pioneered Attachment Theory as applied to human psychology, secure attachment is formed through mothers and babies maintaining proximity.[411]

Attachment security in infancy has been found to significantly predict attachment security in childhood and adulthood,[439-443] with long-term consequences for health and well-being.[3, 412, 444, 445] One review concludes, "Secure attachment acts as a buffer against HPA activation in response to excessive stress. Infants with insecure attachment lack this buffering effect and may be predisposed to depression and other psychiatric disorders in response to psychosocial stressors."[413(p.219)]

In animal research, females who receive high levels of maternal care in infancy give high levels of care to their own offspring, even among females selectively bred to give low levels of maternal care. These well-mothered mothers have more brain OTRs in infancy, and during pregnancy and birth. Offspring given high levels of maternal care are also less susceptible to excessive stress reactions in adulthood, and have enhanced learning and brain function.[228] Animal researchers explain, "These patterns of maternal care initiate a cascade of epigenetic processes that uniquely shape gene expression, organize the Oxytocinergic system that supports bond formation in mammals, and determine the infant's lifetime capacity to handle stress."[405(p.2604)]

Human research also supports the transmission of maternal care patterns across generations. In an MRI study, first-time mothers with secure adult attachment, as assessed during pregnancy and largely reflecting the quality of maternal care received in early life, had more activation of brain reward centers, and other OT-related brain areas, as they gazed at their infant's face. These secure mothers also had higher OT levels during interactions with their infants at seven months.[427] These researchers comment elsewhere, ". . . a mother's attachment experiences from her own childhood may shape neural circuits which influence how she perceives and responds to her infant's cues one generation later,"[446(p.327)] with these responses contributing to secure attachment in her child.

In other studies, adults reporting better parental care in childhood showed higher peripheral OT, greater activation in OT-rich brain areas, and more sensitive parenting, compared with adults reporting lower-quality parental care. (See Feldman[217] for a summary of research linking OT with parenting behaviors.)

This proposed framework for human maternal biological bonding does not imply that attachment or care is deficient outside of these biological processes, as obviously human parents can form close and enduring bonds with nonbiological children. However, in the context of hormonal physiology, the limbic processes

of biologic bonding may foster the most rapid and effective onset and maintenance of maternal-infant attachment, as has been advantageous through human evolution.

Conversely, disruption to these processes at any level may impair the biologic aspects of bonding. In this situation, maternal-infant attachment may become a more deliberate, cortical process,[20] whereby the mother intellectually "learns" to love her baby, rather than an instinctive, hormonally-mediated, limbic process. As with other perinatal processes, and as seen in animal studies, biologic deficits at this time could plausibly change expected trajectories in maternal and infant brain-hormone systems, with possible ongoing programming effects. (See also 3.2.7, 4.2.7, 5.2.7, and 6.2.7 for possible programming effects in relation to maternal-newborn separation.)

Given the great potential of maternity care practices to facilitate or disrupt the hormonal physiology of childbearing (3.2, 4.2, 5.2, 6.2), including the hormonal systems underlying mammalian biological bonding, as described in this model, and considering the potentially significant impacts of attachment security for offspring well-being, research to further understand and support the processes of biologic bonding and the formation of secure attachment of human mothers and babies in relation to childbearing, including longer-term impacts, is a high priority.

3.2 Common Maternity Care Practices That May Impact Oxytocin Physiology

Common maternity care practices can impact oxytocin physiology. This section examines possible impacts on the oxytocin systems of mothers and babies of: maternity care provider and birth environment; prostaglandins for cervical ripening and labor induction; use of synthetic oxytocin for induction, augmentation, and postpartum care; opioid analgesic drugs; epidural analgesia; cesarean section; and early separation of healthy mothers and newborns.

3.2.1 Maternity Care Provider and Birth Environment: Possible Impacts on Oxytocin

The maternity care provider and birth environment may impact the oxytocin systems of mothers and babies by increasing or decreasing maternal stress and/or stress hormones, with possible effects on oxytocin and labor progress, and/or by increasing or decreasing the chances of interventions that can impact these systems.

In relation to direct measurements of the possible impacts of maternity care providers on maternal OT, one small, randomized study measured maternal OT before and one hour after allocation to emotional support from an untrained labor companion (doula), or control. No between-group difference was seen in OT levels over this time, which may have been too brief to detect significant differences. Other outcomes were not recorded.[447] A similar study of labor support in relation to E-NE also found no hormonal differences at one hour. However, researchers found significant benefits in the group with support to reported in-labor pain and anxiety, and to breastfeeding and maternal emotional well-being at six weeks,[448, 449] including higher self-esteem and reduced anxiety and depression scores, compared with women without such support.[435] These outcomes suggest longer-term enhancement of hormonal physiology, likely including OT, through labor support, although the mechanisms are unclear.

Maternity care providers and birth environments could also alter hormonal physiology of mother and/or baby by increasing or decreasing the likelihood of exposure to maternity care practices and interventions that are known to have hormonal impacts, including practices such as early mother-newborn SSC.

While there is broad practice variation within and across providers, settings, and regions, overall, the chance of induction may be reduced among women choosing midwifery compared with physician care, according to a systematic review,[450, 451] and among women planning a home compared with hospital birth.[452, 453] Planned home birth is also associated with decreased use of labor augmentation and CS.[452, 453]

Studies have also found that the same midwife's practice, including use of interventions, can vary in different environments.[454, 455] Other researchers suggest that ". . . the provision of an environment that midwives experience as calm, non-threatening and supportive may, through the production and release of OT, enhance their capacity to facilitate positive social relationships and provide emotionally sensitive care to childbearing women."[456(p.279)]

Differences in practice styles among care providers and birth environments could also influence the OT systems of mother and baby by increasing or decreasing stress for the laboring woman.

As discussed in "Labor and Birth Stress in Animals" in 5.2.1, animal studies show that excessive stress in labor can disrupt OT release and inhibit contractions, possibly via elevations in E-NE and/or endogenous opioids. Stress can also inhibit pulsatile OT release[460] and the let-down reflex[461] in breastfeeding women, although no studies were found that directly measured the effects of stress on OT levels in laboring women. Stress during reproductive events may inhibit pulsatile OT, inhibiting labor and lactation in unsafe environments, for example, whereas stress outside reproduction increases continuous OT release, which may be differentially regulated[462, 463] (3.1.1).

The possible impacts of maternity care provider and birth environment on the OT systems of mother and baby, potential mechanisms by which stress may inhibit labor, and effective practices to reduce labor stress are important areas for future research.

3.2.2 Prostaglandins for Cervical Ripening and Labor Induction: Possible Impacts on Oxytocin

Prostaglandins for cervical ripening and labor induction may interact with the maternal oxytocin system by triggering positive feedback cycles that progress labor. Prostaglandin induction may be more successful when there is sufficient readiness (including of oxytocin systems) to trigger this cycle, closer to the physiologic onset of labor.

Several studies have investigated interactions between exogenous PGs for induction and endogenous OT release in women. Studies have found variable elevations in OT following PG administration but, in general, PG induction was successful when elevations in OT,[464] or OT and PGs, followed.[256, 465-467]

These findings suggest that induction of labor with PGs may require activation of OT positive feedback cycles, as discussed in 3.1.3. Prostaglandins not only cause changes in the cervix, but also promote contractions and may stimulate the production of OTRs (2.1).[113] Increased OTRs sensitize the uterus to OT, and the ensuing contractions cause more OT release by another central positive feedback cycle (3.1.3).[113] Activation of these cycles, and the establishment of labor, following PG administration is more likely to occur closer to the physiologic onset of labor, when receptors for both prostaglandins and oxytocin increase. The baby is also more likely to be ready for labor and birth at this time (2.1, 2.2).

3.2.3 Synthetic Oxytocin in Labor for Induction, Augmentation, and Postpartum Care: Possible Impacts on Oxytocin

Synthetic oxytocin is used in a variety of clinical situations, including: as a primary induction agent; together with other induction methods; to augment labor; and/or to prevent postpartum hemorrhage. Exposure to synthetic oxytocin in any of these circumstances may have short-term effects on mother and/or baby, as well as longer-term direct and/or indirect impacts on their respective oxytocin systems, including impacts on breastfeeding and maternal adaptations and attachment. Animal studies have found long-term effects on offspring from perinatal exposure to high-dose synthetic oxytocin, with possible implications in human offspring.

Induction of Labor

Induction of labor may foreshorten the complex and interorchestrated prelabor physiologic preparations that precede the physiologic onset of labor in mother and baby, and may hasten the onset of labor before full readiness.

As described in 2.1, there is limited current understanding of the complex, interorchestrated processes that prepare mother and baby for labor and birth, and that also contribute to adaptations that continue through the postpartum and newborn periods and beyond. Induction, whether with synOT or another method, limits the full expression of prelabor physiologic preparations and may hasten the onset of labor and birth before full readiness is established in mother and baby. (See 2.2 for a detailed discussion of possible impacts of scheduled birth, by either induction of labor and PLCS, on the hormonal physiology of mother and baby.)

Efforts to distinguish the complex effects of induction and induction agents on outcomes in mothers and babies have generally not included a hormonal physiology perspective,[130, 131, 135, 151-153, 468-480] which has not been well delineated up to this point.

Augmentation of Labor

The administration of synthetic oxytocin to augment labor carries the risks of drug exposure and effects on mother and baby, with uncertain clinical benefits.

Augmenting (stimulating, speeding) labor with synthetic oxytocin carries the potential risks of this drug to mother and baby, as detailed below. Major clinical benefits remain uncertain.

The most recent Cochrane systematic review found that administering synOT to augment labor in women assessed as making slow progress may reduce labor length by two hours but neither reduces the CS rate,[481] which has been the major aim, nor increases the likelihood of non-instrumental vaginal birth. This study also found increased risks of hyperstimulation, and, while authors found no detrimental outcomes for mothers or babies, they note that numbers were too small to assess perinatal mortality.[481]

Synthetic oxytocin has recently been designated as a "high alert" medication, as discussed below. Clark comments, "We know of no other area in medicine in which a potentially dangerous drug is administered to hasten the completion of a physiologic process that would, if left to its own devices, usually complete itself without incurring the risk of drug administration."[482(p.35e3)] (For more about slow labor and stress, see 5.2.1.)

Synthetic Oxytocin and the Mother

Synthetic oxytocin is recognized as a high-alert drug with potentially dangerous effects. Differences between synthetic and natural, endogenous oxytocin include lack of analgesic and calming effects, increased risks of fetal hypoxia that necessitate monitoring, risk of oxytocin receptor desensitization with prolonged exposure, and possible drug effects in mother and baby.

The administration of synOT in labor can be beneficial for mothers and/or babies in some circumstances. However, the potential hazards of this drug, as discussed below, may not be fully recognized in maternity care settings due to its widespread use and its reputation as a "natural" hormone. Synthetic oxytocin is the drug most commonly associated with preventable adverse events during childbirth,[482] and is one of 12 "high-alert medications" that the Institute for Safe Medication Practices identifies as "bearing a heightened risk of harm" and requiring "special safeguards to reduce the risk of errors."[482, 483] According to Clark, approximately half of all paid obstetric litigation claims allege misuse of synOT.[482]

Physiologic versus synthetic oxytocin in labor and birth. *Synthetic oxytocin, as administered in the perinatal period, is chemically identical to natural (endogenous) oxytocin, but has different effects in the body, mainly because of its route of administration.*

Table 2 summarizes a broad range of known and plausible differences between endogenous OT, as released during physiologic labor, birth, and postpartum processes, and synOT, administered exogenously for labor induction, labor augmentation, and/or postpartum hemorrhage prevention, as discussed below.

Table 2. Established and biologically plausible impacts of physiologic versus synthetic oxytocin in labor and birth

	Physiologic (Endogenous) oxytocin	Synthetic (Exogenous) oxytocin
Source	Released from maternal brain (3.1.1) (intravenous line not required)	Administered into bloodstream via intravenous line
Central maternal impacts	Has brain-based calming, stress-reducing, and analgesic effects (3.1.1) Switches on maternal adaptations and maternal-infant attachment in all mammals (3.1.1), with long-term benefits; may foster "biologic bonding" in the early sensitive period (3.1.4)	Doesn't effectively cross adult blood-brain barrier; minimal central calming, stress-reducing, and analgesic effects (3.1.1) Unclear effects on maternal adaptations and attachment; may interfere with OT release during breastfeeding; may partly restore maternal adaptations when endogenous OT is iatrogenically reduced ("Oxytocin and Maternal adaptations and attachment" in 3.1.4, and "Synthetic oxytocin and central maternal oxytocin," and "Synthetic Oxytocin and Maternal Adaptations," below)

cont'd

	Physiologic (Endogenous) oxytocin	Synthetic (Exogenous) oxytocin
Central fetal impacts and programming	Released from fetal brain at physiologic levels (3.1.3); brain-based calming, stress-reducing, and pain-relieving effects on fetus and newborn (3.1.1) Physiologic release with labor and birth likely to positively epigenetically program evolving offspring OT systems	May cross placenta and into fetal brain at supraphysiologic levels with unknown impacts ("Synthetic Oxytocin and the Baby" and "Synthetic Oxytocin and Offspring, Longer Term," below); indirect impacts via maternal effects of synOT also possible Long-term adverse programming effects possible by direct exposure to high doses (as found in animal studies) and/or by indirect mechanisms ("Synthetic Oxytocin and the Baby" and "Synthetic Oxytocin and Offspring, Longer Term," below)
Release/ administration	Released in pulses at physiologic levels, with rapid metabolism by oxytocinase, giving episodic uterine exposure (3.1.3) OTR sensitivity maintained (3.1.3)	Administered in continuous supraphysiologic doses, giving constant uterine exposure ("Synthetic Oxytocin and the Mother," below) Prolonged use can cause OTR desensitization with reduced OT sensitivity and increased PPH risk; reduced contractions also possible ("Synthetic oxytocin and oxytocin receptor desensitization," below)
OTR numbers	OTRs peak at physiologic onset of labor (3.1.3) Peak uterine OTRs optimize contractions, labor progress (3.1.4, 3.1.5) Peak OTRs in breasts, brain optimize breastfeeding and maternal adaptations, according to animal studies (3.1.3)	OTR numbers likely to be lower with induction, reducing OT sensitivity (3.1.2, 2.2) Supraphysiologic dosage needed to stimulate contractions (2.2); possibility of failed induction, CS (2.2) Low OTRs in breasts, brain may impact breastfeeding, maternal adaptations, and attachment (2.2, "Synthetic oxytocin and central maternal oxytocin," below)
Physiologic versus pharmacologic levels	Physiologic levels are matched to uterine responsiveness, determined by OTRs Unlikely to cause hyperstimulation or fetal hypoxia (3.1.4, 3.1.5)	Pharmacologic levels produce unpredictable results, as uterine sensitivity (determined by OTRs) is uncertain (2.2) Risk of hyperstimulation ("Physiologic versus synthetic oxytocin in labor and birth," below)

cont'd

	Physiologic (Endogenous) oxytocin	Synthetic (Exogenous) oxytocin
Impacts on contractions	Healthy fetus tolerates physiologic contractions well (3.1.3) Continuous monitoring not required	Contractions are longer, stronger, and closer together, with an increased resting tone of the uterus; fetal blood supply reduced to some extent Continuous monitoring required ("Physiologic versus synthetic oxytocin in labor and birth," below)
Fetal protection: catecholamine surge	Full development of fetal CA systems at physiologic labor onset, including E-NE receptors in heart and lungs; protective CA responses to labor hypoxia fully activated. Strongest physiologic contractions occur in late labor, when fetal head is low and CA surge fully activated ("Fetal catecholamine surge" in 5.1.3) CA protection from hypoxia, according to animal studies ("Fetal catecholamine surge" in 5.1.3)	Reduced development of CA systems if induced, including E-NE receptors in heart and lungs (5.1.3, 5.2.3); protective CA responses may be reduced Strong contractions can occur earlier in labor before CA surge fully activated Hypoxia risks increased, monitoring required ("Physiologic versus synthetic oxytocin in labor and birth," below)
Fetal neuroprotection	OT provides fetal neuroprotection around time of physiologic onset of labor, according to animal studies, ("Fetal neuroprotection" in 3.1.3)	Neuroprotective effects reduced outside physiologic onset of labor, and/or with high synOT doses, according to animal studies ("Fetal neuroprotection" in 3.1.3)
Pain and analgesia	Analgesic systems, including central OT receptors, active at physiologic onset of labor (3.1.2, 4.1.2) Contractions and pain build slowly as labor progresses; physiologic rise in OT, BEs to counteract pain (3.1.3, 4.1.3) Analgesic medications less likely to be used	Analgesic systems, including central OT receptors (animal studies), less mature before physiologic onset of labor (3.1.2) Strong contractions in early labor; limited time to build physiologic analgesia ("Synthetic oxytocin and central maternal oxytocin," below) Analgesic medications more likely to be used
Cascade of intervention	Physiologic labor and birth more likely (3.1.3)	Higher likelihood of cascade of intervention, with further drugs and procedures, including risk of failed induction and CS (2.2)

cont'd

	Physiologic (Endogenous) oxytocin	Synthetic (Exogenous) oxytocin
Postpartum hemorrhage (PPH) risk	Peak uterine OTRs with physiologic onset of labor (3.1.2) Physiologic processes maintain uterine OT sensitivity (3.1.3) Postpartum mother-baby skin-to-skin interactions facilitate elevation in maternal OT (3.1.4) Lower PPH risk likely (3.1.4)	Reduced OTRs with scheduled delivery (induction or PLCS) (2.1, 2.2) Possibility of OTR desensitization following prolonged, constant, supraphysiologic exposure Effects of synOT exposure on postpartum physiologic OT release unknown Increased PPH risk ("Synthetic oxytocin and oxytocin receptor desensitization," below)

Note: BE = beta-endorphin, CA = catecholamine, CS = cesarean section, E-NE = epinephrine-norepinephrine, OT = oxytocin, OTR = oxytocin receptor, PLCS = prelabor cesarean section, PPH = postpartum hemorrhage, synOT = synthetic oxytocin.

The administration of synOT for labor induction has unpredictable impacts because an individual woman's uterine response, determined by her OTR numbers, will vary according to how close she is to the physiologic onset of term labor. (See 3.1.2 and 2.1 on proximity to the physiologic onset of labor and cervical status.) If she is very close to the physiologic onset of labor, she will have more uterine OTRs, and lower doses (e.g., four to six mU/minute, which appear to be equivalent to physiologic levels in normal labor[256]) may be effective in inducing labor. If she is further from physiologic onset of labor, she will require higher doses (e.g., 10 to 16mU/minute), which are commonly used in "low-dose" protocols and may give approximately double the levels detected in the physiologic first stage of labor.[256]

Supraphysiologic doses of synOT administered for induction or augmentation may cause more frequent contractions, with an increased resting tone of the uterine muscle (hypertonus), which may compromise fetal replenishment of blood and oxygen between contractions.[484, 485] These effects may occur because, with constant synOT administration, levels do not decline between contractions as much as in physiologic labor, which involves pulsatile OT release, along with increased oxytocinase production[486] (see 3.1.3).

Synthetic oxytocin and central maternal oxytocin. *Synthetic oxytocin-mediated contractions may increase central oxytocin by a physiologic positive feedback cycle. Some studies show a reduction in maternal oxytocin release with early breastfeeding following synthetic oxytocin exposure, but mechanisms are unclear. It is not clear whether synthetic oxytocin might cross into the maternal brain in biologically significant amounts, and what effects it could have, including on maternal endogenous oxytocin release.*

In contrast to many other hormone systems, OT release from the brain is generally not controlled by feedback from OT levels in the body or bloodstream[52, 157, 196] (3.1.1). Thus, according to current understanding, administration of synOT in labor and birth, even at high doses, is unlikely to directly reduce the release of central, endogenous OT from the pituitary. (This is difficult to measure because current testing cannot distinguish physiologic OT and synOT in the bloodstream.)

However, synOT administration can lead to contractions that activate the OT positive feedback cycle whereby the sensations of contractions give feedback to the brain and increase the central release of OT (3.1.3). This increases OT release into the brain and body, accelerating labor. This activation is more likely if uterine OTRs are high, very close to the physiologic onset of labor, giving enhanced uterine responsiveness, stronger sensations, and greater feedback.

It is not clear whether synOT administered to women in labor might have effects within the maternal brain. In non-pregnant adults, central effects require very high synOT dosages given by intravenous injection or, more commonly, administered intranasally,[207] which seems to bypass the blood-brain barrier. (See "Oxytocin Effects" in 3.1.1.) Lower synOT doses administered systemically would be expected to have minimal or no central effects. However, OT sensitivity and effects within the mother's brain may be greatly enhanced due to elevated central OTRs at the physiologic onset of labor, as seen in animal studies (3.1.2). This could heighten central OT sensitivity such that the very small amounts of synOT that likely cross from the body into the brain (from 0.002 percent in animal studies to perhaps 1 percent in humans) following labor synOT administration could have central effects. (See also "Oxytocin Effects" in 3.1.1.)

In support, some studies have shown maternal OT changes following perinatal synOT exposure, including reductions in new mothers' OT release during breastfeeding,[395, 487] and impacts on baseline maternal OT levels at two months[216] (see "Synthetic Oxytocin and the Mother, Longer Term," below). In addition, small positive impacts on maternal adaptations have been found, particularly for women who have missed the OT peaks of labor and birth due to epidural or CS (see Synthetic Oxytocin and Maternal Adaptations and Attachment, below). However, indirect effects (for example, stronger synOT-related contractions giving greater stimulation of central OT release via positive feedback cycles) and/or other non-central mechanisms may also explain these effects.[50, 54]

Reports of greater pain by women administered synOT for augmentation compared with unexposed women[488] suggest that synOT does not have significant central analgesia (3.1.1). (For more detailed discussions, see "Synthetic Oxytocin and Breastfeeding," "Synthetic Oxytocin and Maternal Adaptations," and "Synthetic Oxytocin and the Mother, Longer Term," below.)

Synthetic oxytocin and oxytocin receptor desensitization. *Prolonged exposure to synthetic oxytocin in labor may lead to a compensatory reduction in oxytocin receptors (receptor desensitization). An increased risk of postpartum hemorrhage is recognized following synthetic oxytocin exposure. Oxytocin desensitization could also compromise labor progress and pushing efficacy. Desensitization effects on breast oxytocin receptors, with possible impacts on breastfeeding are biologically plausible but not researched.*

According to biologic principles, exposure to constant, high levels of a hormone may lead to a reduction (down-regulation) in receptor numbers to protect against overstimulation.[489] This is also called receptor desensitization. This does not occur with OT in physiologic labor and birth because of its pulsatile release from the pituitary and rapid metabolism by the enzyme oxytocinase (also called placental leucine aminopeptidase), which is produced by the placenta in increasing amounts in pregnancy[490] (3.1.3) and even greater amounts in labor.[258] Both of these mechanisms contribute to intermittent uterine OT exposure, which maintains OTR sensitivity.

In vitro animal and human studies have found that constant synOT exposure, at clinically relevant concentrations, leads to a time- and dose-related decrease in uterine OTRs, giving a significant loss of response to OT.[489, 491-495] In one study using human myometrium, responsiveness to OT was reduced to 50 percent after four hours of exposure, and to less than 5 percent after six hours.[495] The duration of OTR desensitization effects is not known but, as the biologic processes needed to restore OTR numbers are complex, full restoration could take hours, or even days.[45]

These mechanisms could lead to an eventual slowing of labor with lack of response to both endogenous OT and synOT. Receptor desensitization could also contribute to the prolonged pushing stage and increased risks of operative birth and unplanned CS that have been found in some studies of women administered synOT, compared with unexposed women.[496-500] From the perspective of hormonal physiology, induction may further increase these risks, compared with synOT exposure following the physiologic onset of labor, due to foreshortening of prelabor OTR upregulation. A prolonged pushing stage and associated outcomes such as operative birth and PPH[501-506] may reflect disruption to OTRs due to induction and/or desensitization, as discussed below. (See "Synthetic oxytocin and postpartum hemorrhage" and also 2.2.2 for further discussion of induction impacts on mother and baby.)[501-506]

Mammary OTRs are also elevated at the physiologic onset of labor according to animal studies[86, 87] (3.1.2), and could plausibly also be desensitized from synOT exposure, with potential adverse impacts on breastfeeding. (See "Synthetic Oxytocin and Breastfeeding," below.)

Several studies have compared pulsatile synOT with continuous dosage for induction and/or augmentation, finding equivalent outcomes in mothers and babies at significantly lower doses.[507-513] For example, one study used six-fold lower dosage in the pulsatile group.[512] No difference was found in PPH rates, which were low in both groups (see below).

Synthetic oxytocin and postpartum hemorrhage. *The well-recognized increased risk of postpartum hemorrhage following induction and/or synthetic oxytocin exposure may reflect: fewer oxytocin receptors before the physiologic onset of labor, lack of other physiologic preparations for effective contractions, and/or receptor desensitization from prolonged constant synthetic oxytocin exposure. Increased risk of postpartum hemorrhage following cesarean, and extra risk of retained placenta following synthetic oxytocin exposure, suggest similar mechanisms. Because cervical changes parallel uterine priming, cervical ripeness may be a surrogate for hemorrhage risk after induction and prelabor cesarean.*

Many studies have found an increased risk of PPH following induced or augmented labor.[514-524] The prophylactic administration of synOT after birth has been found to reduce these extra risks in some studies.[514, 525, 526]

Mechanisms for these findings could include:

- reduced OTR numbers due to induction before the physiologic onset of labor
- lack of other prelabor preparations such as PG receptors (2.1)
- OTR desensitization due to synOT exposure (see "Synthetic oxytocin and oxytocin receptor desensitization," above)

Reduced uterine contractility following exposure to synOT with labor induction or augmentation could also increase the risk of retained placenta, as found in bovine research.[527] Studies in women have found higher risks of retained placenta following induction versus physiologic onset of labor,[528] including correlation of risk with duration of exposure to synOT.[529] This is an important area for further research.

Extra PPH risks are also possible following both PLCS and in-labor CS that follows induction and/or exposure to prolonged synOT administration. One study found that, for women exposed to synOT in labor, the dose required to give adequate uterine contractions following surgery was nine times higher than for women with no prior labor (or synOT exposure). Even with this higher dose, average blood loss was doubled to 1.1 liters. The authors suggest that non-synOT uterotonics may be important in this situation to circumvent OTR desensitization effects.[530] Important areas for further research include hormonal and other effects of non-synOT uterotonics and possible negative effects of PGs on prolactin and breastfeeding (see 6.2.2).

Given these understandings from hormonal physiology, it is possible that commonly stated risk factors for PPH may reflect common OT disruptions. For example, associations between prolonged pushing stage, instrumental birth, and PPH[501-506] may reflect low OTRs from induction and/or OTR desensitization effects. Optimizing OT physiology, for example through reducing induction and synOT exposure as far as safely possible, and promoting postpartum SSC (3.1.4), may help prevent PPH. This model also suggests that physiologic labor and birth with early SSC may be an effective strategy for reducing PPH risk without preventative oxytocic drugs. (See "Oxytocin and Postpartum Hemorrhage" in 1.1.4 for a fuller discussion.)

From the perspective of hormonal physiology, a woman's cervical status parallels, to some extent, her prelabor physiologic preparations, including developments in her uterine responsiveness[107] (2.1). Her cervical status might therefore give some guidance in relation to her PPH risk following scheduled birth, including induced labor, PLCS, or in-labor CS following induction (3.2.6). This is an important area for further research.

Synthetic oxytocin when administered postpartum. *Following physiologic birth, skin-to-skin contact and mother-newborn interactions may substantially increase maternal oxytocin, even up to ten-fold, giving physiologic protection from hemorrhage. The routine use of postpartum synthetic oxytocin may not be necessary in these circumstances. In addition, biologically plausible effects of postpartum synthetic oxytocin administration, including transfer to the newborn before cord closure and possible impacts on breastfeeding, raise additional concerns for benefit-harm considerations, including uncertainty about possible longer-term outcomes.*

The prophylactic use of synOT, or drug combinations including synOT, after birth is near-universal in modern maternity care, due to its reported effectiveness in reducing blood loss greater than 500 ml (about 16 ounces) immediately after birth.[531]

As discussed in 1.1.4, increases in the new mother's own OT release, triggered by interactions with her newborn, can increase her OT levels from 50 percent[259, 316] up to ten-fold, as found in some individuals at this time,[316] conferring physiologic protection against PPH. Standard routines frequently involve separating mother and baby soon after birth, giving no opportunity for endogenous OT release to help limit bleeding. For example, less than half of women who participated in the recent national *Listening to Mothers III* survey had their baby mainly in their arms during the first hour after birth.[17] Maternal-newborn separation has other implications for the newborn and breastfeeding initiation and success (3.2.7).

The postpartum administration of synOT, which involves a substantially higher bolus dose than synOT used during labor,[469] could also impact the OT system of the mother, with potential effects on breastfeeding, although studies of postpartum synOT administration have not generally measured breastfeeding as an outcome.[531] (For further discussion, see "Synthetic Oxytocin and Breastfeeding," below.)

Because the umbilical vessels remain patent for several minutes after birth,[532, 533] any drug administered to the mother before cord closure could potentially cross the placenta. Standard protocols for third-stage management recommend synOT administration during, or immediately after birth,[531] giving opportunity for passage to the baby.

In addition, synOT and other drugs used at this time may have unwanted effects in mothers and babies,[469, 534-536] also discussed further below in relation to breastfeeding (see Synthetic Oxytocin and Breastfeeding, below.)

Animal studies, discussed in "Synthetic Oxytocin and Offspring, Long Term," below, raise concerns about possible longer-term effects on offspring exposed to synOT in the newborn period. Given the widespread exposure of mothers and babies to synOT postpartum, and lack of research about hormonally-mediated outcomes including breastfeeding and epigenetic effects, research in this area is urgently needed.

Oxytocin Antagonist Drugs

Because of the major role of oxytocin in labor and birth, oxytocin antagonist drugs have been trialed and used clinically to treat premature labor. Potential adverse effects, according to hormonal physiology understandings, could include interference with the innate fetal neuroprotective mechanisms found in animal studies, and/or with maternal oxytocin processes, including breastfeeding and maternal adaptations. Offspring programming effects are also biologically plausible.

Studies of the effectiveness of OTAs, currently used to halt premature birth, have had mixed results. The most recent Cochrane systematic review found no benefit of the OTA drug atosiban over conventional treatment with beta-agonist drugs or placebo, and noted an excess of fetal-infant deaths in one large trial.[537] No human research was found that looked at other OTA impacts for mothers or babies.

As discussed in "Fetal neuroprotection" in 3.1.3, animal studies suggest that maternal endogenous OT, released during labor, crosses into the fetal brain where it has neuroprotective effects. In these studies, the administration of OTAs, including atosiban, negated these effects[97, 293] (3.1.5). The human fetus has a relatively more mature brain and may produce its own neuroprotective OT, which could also be blocked by OTAs.[293] In women, atosiban crosses the placenta to the fetus,[538] and likely also crosses the permeable fetal blood-brain barrier.[539, 540]

In one animal study, atosiban administered to pregnant rats increased oxidative stress in the plasma and cardiac tissue of offspring. Researchers suggest that atosiban may reverse the anti-oxidant effects of OT, which limit tissue damage due to perinatal inflammation and injury[190] (3.1.1). Atosiban also blocks receptors of the related hormone AVP, which could further compromise fetal adaptations to physiologic labor stress.[540]

Atosiban administered to pregnant animals disrupts OT release with subsequent lactation, reducing offspring growth and survival,[541] and also blocks milk ejection when administered to lactating cows.[542] Human impacts on breastfeeding are also plausible but no research was found in this area. In animal studies, OTAs that are administered centrally, or that enter the maternal brain, can also significantly disrupt maternal behaviors.[543-546] Atosiban is not thought to cross the maternal blood-brain barrier or have direct central effects in women, but no studies were found that assessed this outcome. In animal research, a single OTA administration to the newborn led to disruptions of sexual and parenting behaviors in adult males, suggesting long-term OT and/or AVP disruptions.[539, 547]

Given the current use of OTA drugs to prevent preterm birth, these are critical areas for future research.

Synthetic Oxytocin and the Baby

Exposure to synthetic oxytocin in labor may have impacts on the baby before and/or after birth. Possible mechanisms include: direct effects from synthetic oxytocin transfer through the placenta to the baby; indirect or subtle effects from excessive contractions, including effects from hypoxia and oxidative stress (possibly exacerbated by lack of fetal prelabor physiologic preparation, if following induction); impacts from co-interventions such as epidurals; interference with fetal OT-related neuroprotection, as found in animal studies; and indirect effects via impacts on maternal hormones, oxytocin-related signaling, and related processes, including breastfeeding. Long-term programming effects, as found in animals, are also biologically plausible. Newborn oxytocin disruptions from synthetic oxytocin exposure may impact breastfeeding success, and studies also suggest impacts on the newborn autonomic nervous system. There is conflicting evidence about synthetic oxytocin transfer across the placenta.

Synthetic oxytocin is biochemically identical to endogenous oxytocin, made in and released from the body and brain of the human fetus/newborn. Synthetic oxytocin is regarded as safe to administer to non-pregnant adults (usually intranasally), and is used experimentally and therapeutically to benefit psychological functions and dysfunctions (3.1.1). However, exposure of the fetus/newborn to synthetic oxytocin at supraphysiologic levels via maternal administration raises concerns because of the extreme sensitivity of the fetus at this time.

As discussed in the introduction, evolving evidence highlights this time as a critical period for fetal/newborn programming, when exogenous exposures may have impacts far beyond dose-related, pharmacologic, effects and side-effects.[41] Exposures to hormones and hormone-like substances are especially likely to be have programming and mis-programming effects in the perinatal period, which has been called "hormonal imprinting." This phenomenon has been consistently demonstrated in animal research[41] (see "Synthetic oxytocin and epigenetics," below).

Synthetic oxytocin could impact the baby by direct effects via placental transfer (discussed below) and/or indirectly via maternal effects. For example, synOT could cause excessive uterine contractions, increasing the risks of fetal hypoxia,[478, 548] as reflected in the "high-alert medication" status of synthetic oxytocin (see "Synthetic Oxytocin and the Mother," above).

From a hormonal physiology perspective, fetal hypoxia risks may be even further increased when synOT is used for, or follows, labor induction, because endogenous fetal protective systems involving OT may not be fully developed until just before the physiologic onset of labor, according to animal research (see "Fetal neuroprotection" in 3.1.3). (Additional protective mechanism involving E-NE and the fetal catecholamine surge are also unregulated before labor,[78, 337] as discussed in "Fetal Epinephrine-Norepinephrine and Related Stress Hormones in Pregnancy" in 5.1.2.) In addition, high maternal doses of synOT may counteract these neuroprotective OT effects, according to this research[293] (see "Fetal neuroprotection" in 1.1.3). Suggestions of an additional risk of cerebral palsy in term babies following synOT exposure[549] could reflect the absence of these neuroprotective effects, which have also been implicated in animal models of autism.[295] Given the widespread exposure to induction and/or synOT in labor, these are critical areas for future research.

Also concerning in relation to fetal synOT exposure are studies showing increased oxidative stress[550] and free radical formation[551] in healthy newborns following augmentation with synOT, compared with unexposed babies. These findings suggest that synOT may not have the anti-oxidant effects of endogenous fetal OT, released during labor (3.1.3), and may even promote oxidation, with unknown consequences.

Three studies discussed below ("Synthetic Oxytocin and Breastfeeding") have found detrimental impacts of synOT on newborn breastfeeding behaviors and initiation.[552-554] The mechanisms are not known. As OT is a hormone of satiety (3.1.1), researchers suggest that synOT, acting centrally, could plausibly reduce newborn motivation to suckle.[553]

Another study suggests that synOT exposure in labor may have impacts on the newborn autonomic nervous system (ANS). In an analysis of newborn skin-temperature response to skin-to-skin breastfeeding on the second day after birth, unexposed newborns showed a gradual warming, likely due to OT-mediated vasodilation, with return to baseline over 30 minutes. In contrast, synOT-exposed babies had a steeper temperature rise with a prolonged elevation.[555] In addition, one in-labor study found increased fetal scalp temperature with synOT exposure,[556] also suggesting synOT-induced vasodilation.

The mechanisms for these autonomic effects are not known. Possible explanations include: excessive newborn parasympathetic nervous system (PNS) activity mediated by central effects of synOT; indirect effects from synOT-mediated disruptions to maternal temperature; and/or dysregulation of maternal-newborn temperature synchronizing, by which the mother regulates her baby's temperature when skin-to-skin (see "Skin-to-skin contact" in 3.1.4). The authors comment, "Given the large numbers of women receiving these treatments, even minor effects on newborns might have important future physiological and behavioural consequences for the human population."[555(p.7)] (See also "Synthetic Oxytocin and Breastfeeding" and "Synthetic oxytocin and offspring, human studies," below, for more about possible central fetal/newborn effects from synOT exposure in labor.)

In relation to possible placental transfer of synOT from mother to baby in labor, and potential transfer to the fetal brain, one human in-vitro study found that synOT can easily cross the placenta in both directions.[557] In addition, transfer of substances from the fetal blood into the brain can occur in humans because the fetal blood-brain barrier (BBB) is more permeable, compared with the adult BBB,[558] and may even be permeable to OT in some areas.[54] Permeability is increased in newborns under conditions of inflammation and hypoxia,[559] which may be more likely with synOT exposure. Transfer of maternal endogenous OT to the fetal brain occurs in animals, with beneficial neuroprotective effects at physiologic levels, which are negated by high synOT exposures, suggesting synOT passage to, and impacts in, the fetal brain (3.1.3).

Several studies have measured OT levels in the umbilical artery (UA) and vein (UV) in human newborns who were exposed and unexposed to synOT. In general, unmedicated newborns show greater OT levels in the UA than UV, suggesting endogenous OT production and/or placental degradation ("Fetal Oxytocin in Labor and Birth" in 3.1.3). One study of synOT-exposed newborns found elevations in both UA and UV OT levels,[560] compared with unexposed newborns, while another found a reversal of the usual UA-UV difference, suggesting a net OT transfer from mother to baby.[305] Other researchers have found high correlations between fetal and maternal OT, also suggesting placental transfer.[561] In contrast, other studies have found no significant difference in UA or UV OT levels and/or ratios compared to unexposed babies.[308, 562] Manufacturers of synOT state, "Small amounts of the drug probably reach the fetal circulation."[469] Given the widespread administration of synOT, this is a critical area for future research.

Other possible mechanisms for fetal/newborn synOT effects from maternal exposure in labor include signal-transduction without transplacental transfer. For example, synOT-related changes in maternal physiology could impact the fetus, and/or synOT could disrupt physiologic roles of OT in signaling between mother and fetus.[54] (See "Fetal neuroprotection" in 3.1.4.)

There has been little consideration of the possible effects of maternal postpartum synOT exposure, which involves a single high dose, on the baby. This exposure could have direct newborn effects if administered before cord closure, and/or indirect effects via maternal hormones and processes. (See also "Synthetic oxytocin when administered postpartum," above, and "Synthetic Oxytocin and Breastfeeding," below.)

Synthetic Oxytocin and Breastfeeding

The possible impacts of synthetic oxytocin administration in labor on breastfeeding have been poorly researched, despite synthetic oxytocin being widely used, and oxytocin being a major hormone of breastfeeding. A shorter duration of breastfeeding following exposure has consistently been found. Possible mechanisms include: inadequate preparation (e.g., insufficient mammary oxytocin receptors); receptor desensitization effects; maternal and/or newborn hormonal disruptions; and/or effects of synthetic oxytocin co-interventions such as epidurals. Research suggests changes in the release of oxytocin and other hormones in new mothers following synthetic oxytocin exposure in labor, which could impact breastfeeding success.

Observational and population studies have found detrimental impacts of synOT on breastfeeding, including:

- deficits in newborn suckling behavior,[553] early suckling,[554] and prebreastfeeding cues,[552] compared with unexposed newborns (detailed below)
- more women abandoning their intention to breastfeed following elective induction than following physiologic onset of labor[563]
- lower breastfeeding rates at 48 hours following exposure to IV synOT after birth compared with an unexposed group[564]
- lower breastfeeding or exclusive breastfeeding rates at discharge following induction,[565] elective induction,[566] induction with synOT or prostaglandins,[567] and exposure to synOT in labor,[568] compared with unexposed groups
- shorter duration of breastfeeding following synOT exposure in labor compared with unexposed group[553, 569]

Mechanisms for these reported impacts remain unknown, but could plausibly include:

- lack of prelabor physiologic preparations for lactation (for example, lower numbers of breast OTRs and/or PRL receptors (see 6.2.3)
- desensitization of OTRs in the new mother's breasts due to prolonged exposure to synOT, similar to impacts on uterine OTRs
- consequences of co-interventions such as epidurals and CS in mother and baby
- hormonal and/or other disruptions to the newborn's ability to establish and continue breastfeeding, including satiety from synOT (see "Synthetic Oxytocin and the Baby" above)
- impacts on maternal hormonal systems, including via central synOT exposure (see "Synthetic oxytocin and central maternal oxytocin," above)

SynOT exposure at high, constant levels could plausibly override pulsatile OT release, which could impact prolactin release (see "Prolactin and breastfeeding" in 6.1.4).

In relation to maternal hormonal systems, one study found that women who received synOT in labor had a dose-related reduction in their own endogenous OT release during skin-to-skin breastfeeding two days after birth. In this study, the more synOT a woman had received during labor, the lower her OT release was during breastfeeding. Researchers speculate that exposure to synOT in labor may activate a negative OT feedback cycle that persists for at least two days.[570] New mothers exposed to synOT also had higher baseline cortisol, likely reflecting loss of oxytocin's stress-reducing effects.[487] The mechanisms and duration of these impacts are not known.

One large population study found that women exposed to intravenous (IV) or, to a lesser extent, intramuscular (IM), synOT postpartum had a 32 percent reduced chance of successful breastfeeding at 48 hours compared with unexposed women.[564] (In this survey, the impacts of exposure to synOT only during labor could not be accurately assessed, as virtually all women who received synOT in labor also received it postpartum to prevent PPH.) Authors comment:

> Exogenous oxytocin has the potential to interrupt initiation of lactation by: disruption of endogenous pulsatile secretion and fluctuating concentrations when crucial changes in neuronal architecture are occurring; augmentation of the stress response, which replaces pulsatile secretion with continuous secretion and inhibits lactation; desensitization of myoepithelial receptors and local feedback mechanisms; and, more speculatively, infant or maternal behavior.[564(p.1627)]

Newborn impacts from exposure to synOT may also contribute to breastfeeding difficulties. Studies (mentioned above) have found:

- dose-related disturbances in both early sucking, as assessed up to 48 hours after birth, and breastfeeding duration[553]
- more exposed newborns with low prebreastfeeding cues (21 of 47 compared with 0 of 11 unexposed newborns)[552]
- fewer synOT-exposed babies suckled in the first four hours after birth compared with unexposed newborns [554]

The effect of synOT on breastfeeding is a critical area for future research.

Synthetic Oxytocin and Maternal Adaptations and Attachment

Administration of synthetic oxytocin could potentially impact hormonally-mediated maternal adaptations involving the oxytocin system. Small beneficial effects have been found following epidural and cesarean, where women may miss the oxytocin peaks of labor and birth. In this situation, synthetic oxytocin may partially compensate and beneficially promote oxytocin-related adaptations. The mechanisms by which synthetic oxytocin might have these central effects are not known.

During the perinatal period, peak activity in the maternal OT system (levels, receptors) activates central hormonally-mediated maternal circuits that adapt the new mother to care for her offspring. In women, recognized OT-related adaptations include specific infant-directed behaviors and changes in personality that reduce stress and increase caregiving (3.1.4). Exposure to synOT and other maternity care interventions may impact these adaptations.

One study assessed postnatal changes in personality profile at two days, two months, and six months after birth among 55 breastfeeding mothers with various birth experiences. Following an unmedicated birth, new mothers' anxiety and muscular tension were found to decrease, and social satisfaction and social conforming, which may help mothers to prioritize their baby's needs, increased, with these changes persisting from two days to six months after birth. Women receiving synOT in labor had small but significant dose-related benefits in several personality scales. In contrast, women who received epidural analgesia had minimal early personality changes, which positively shifted over six months, likely due to repeated hormone exposure (OT, beta-endorphins, prolactin) with each breastfeeding episode (3.2.5). However, those women who received synOT in addition to epidural analgesia had some of these adaptive changes from the second day after birth,[571] suggesting that synOT exposure may partly compensate for the negative effects of epidurals on oxytocin release in labor and maternal adaptations (see 3.2.5).

Authors suggest that synOT could have these effects by acting centrally, perhaps bypassing the blood-brain barrier, and/or could activate peripheral reflexes by increasing contraction strength and initiating some of the positive feedback cycles that increase central OT release[571] (3.1.4). Other researchers have suggested that the OT molecule, or biologically active fragments, may access the brain through routes that bypass the blood-brain barrier.[572] Increases in central OT sensitivity, due to peak OTRs at the physiologic onset of labor (3.1.4), may also contribute.

Another study compared nulliparous women post-cesarean who were administered standard doses of synOT (5 international units, IU) with women receiving additional synOT (50 IU) by infusion for clinical reasons. New mothers who received the synOT infusion had more positive personality changes two days after birth, similar to women following unmedicated birth (3.1.4). These mothers also released OT with the first breastfeeding, which did not occur for those who received a single dose of synOT.[395] The author

suggests, "The infusion of oxytocin may have substituted for the release of oxytocin normally occurring during labor."[395(p.67)] (See also 3.2.6.)

These two studies of postpartum personality changes found significant positive effects from synOT following epidurals and CS, where maternal endogenous OT release would be reduced (3.2.5, 3.2.6). However, detrimental effects of synOT have been found in relation to OT release during early breastfeeding[487] (see "Synthetic Oxytocin and Breastfeeding," above), and also dose-related changes in OT levels at two months[216] (see "Synthetic oxytocin and the mother, longer term," below). The diverse findings of these studies highlight the complexity of the OT system in the perinatal period, current limited understandings, and the possibility of longer-term impacts on the OT system. (See also "Oxytocin and Maternal Adaptations and Attachment" in 3.1.4.)

With the widespread use of synOT in labor, birth, and the postpartum period, longer-term outcomes on the OT system, including effects on maternal adaptations and attachment, are critical areas for future research.

Synthetic Oxytocin and the Mother, Longer Term

Given the perinatal plasticity of the maternal brain, longer-term impacts from synthetic oxytocin exposure in labor are possible but poorly researched. Preliminary findings from single studies suggest possible reduced oxytocin sensitivity and lengthening of subsequent labors. There are major gaps in research and understanding in this area.

Postpartum maternal adaptations due to priming of the maternal brain, from prelabor (2.2) through physiologic birth and the early sensitive period (3.1.4), may give longer-term benefits to infant care and survival. Conversely, disruptions to perinatal maternal hormonal physiology could plausibly have longer-term effects. This is not well researched.

In the only identified study that assessed the possible impacts of synOT exposure into future childbearing, multiparous women who had received synOT in a previous labor were found to have a longer active labor, compared with those who were previously unexposed to synOT. Effects were even greater for women with a higher number of previous treated labors.[573]

In another study, women who received synOT in labor had a dose-related increase in basal levels of OT at two months postpartum, compared with unexposed women. Higher OT levels were also found among primiparous compared with multiparous women, and among those who had stopped breastfeeding compared with women who were still lactating.[216] The mechanisms are not clear. It is possible that excessive synOT exposure in labor could lead to a long-term loss of sensitivity (e.g., by reduced OTR numbers), with a compensatory increase in endogenous OT levels. This is supported by the low OT levels found in women unexposed to synOT in labor and/or during lactation, which may reflect greater OTRs and OT sensitivity. (See also "Oxytocin complexities" in 3.1.1.)

The findings of this study are in opposition to the study discussed above ("Synthetic Oxytocin and Breastfeeding"), which found lower OT release in women during early breastfeeding, in inverse proportion to the dose of synOT administered in labor. The reasons for these differences are not clear, but could reflect early, evolving OT systems within the plastic maternal brain;[381] the difference between basal levels and a situational rise with lactation (see "Oxytocin complexities" in 3.1.1); and/or other mechanisms. In relation to maternal effects, OT researchers suggest, "Given the action of natural oxytocin on various endocrine pathways, we anticipate that any effects of intrapartum synthetic oxytocin would be dose dependent and influenced by individual context and maternal history."[45(p.2)]

With the widespread maternal exposure to synOT in labor, birth, and the postpartum period, longer-term outcomes on the OT system, including during the next labor and birth, are critical areas for future research.

Synthetic Oxytocin and Offspring, Longer Term

There has been very little research on possible long-term impacts of synthetic oxytocin exposure in the perinatal period on human offspring. However, effects are biologically plausible, through direct exposure, which gives enduring effects in animal studies, or via indirect effects.

Researchers and clinicians have expressed growing concerns about possible longer-term impacts of synOT on human offspring.[42, 45-54] As discussed in "Synthetic Oxytocin and the Baby," above, several mechanisms are biologically plausible, including:

- direct fetal brain-hormone effects from synOT transfer through placenta
- indirect signaling of maternal OT to fetal brain
- indirect effects from subclinical hypoxia/or oxidative stress (see "Oxytocin Effects" in 3.2.3)
- interference with fetal neuroprotective mechanisms, as found in animal studies (see "Fetal neuroprotection" in 3.1.3)
- fetal/newborn impacts from synOT co-interventions, such as epidural
- long-term programming of offspring OT and other hormonal systems, as found in animal newborns exposed to high-dose synOT, likely via epigenetic effects (see Synthetic oxytocin and offspring, animal studies" below)
- indirect effects via disruptions to maternal OT systems that impact attachment, reward, breastfeeding, and mutual regulation (see 3.1.4; "Synthetic Oxytocin and Breastfeeding," above; and "Synthetic Oxytocin and Maternal Adaptations and Attachment," above)

Synthetic oxytocin and offspring, animal studies. *Animal research clearly shows that synthetic oxytocin, administered systemically at supraphysiologic levels in the newborn period, can have long-term impacts on offspring oxytocin systems and related functions, including reproduction and parenting behaviors. In addition, newborn synOT administration at physiologic levels, or early-life manipulations that raise endogenous oxytocin can have effects into adulthood, with positive effects found in some studies. The implications for perinatal synOT exposure in human offspring are not known.*

Animal studies of perinatal synOT exposure have largely involved prairie voles, a small mammal native to North America that is monogamous and biparental (both parents involved in infant care) and has an extensive central OT system. Among prairie voles, newborn exposure to a single high dose of synOT, administered into the body (via the peritoneal cavity) has dose-dependent impacts on the OT, estrogen, and AVP systems in adulthood, with many impacts differing for males and females (sexually dimorphic).[168] These impacts include:

- more rapid selection of sexual partner among males
- more aggression among females, especially towards other females
- changes in female alloparenting (caring for unrelated young)
- reduction in the number of ovarian germ cells (which later become mature eggs)
- delayed sexual maturity among females, possibly related to fewer germ cells
- increase in cardiac OTRs
- increase in brain estrogen receptors in female offspring
- changes in the way the brain responds during social interactions
- changes in central OTRs

In these and related studies, summarized by Carter[168] and Bales,[574] relatively low synOT doses facilitated mating-related pair bonding in males, who were more sensitive to effects, possibly by effects on the related AVP system (see 3.1.1).

In addition, experimental manipulations expected to increase newborn endogenous OT had sexually dimorphic effects on OTRs, which also varied with the valance of the condition. For example, maternal separation in newborn rats, expected to cause stress-induced OT elevation, led to reduced central OTRs in adulthood, whereas high levels of maternal care, expected to elevate OT levels with a positive valence, led to increased central OTRs in females. Even subtle changes in handling of newborn voles produced changes in adult OTRs,[574] reflecting the sensitivity of OT systems at this time. Other researchers found that a single high-dose injection of synOT in newborn rats caused decreases in adult brain dopamine, serotonin, and norepinephrine levels, with greater effects in males.[575]

Because of these animal findings, researchers have warned against administering synOT for the treatment of labor dystocia in experimental mice, citing "Limited knowledge of the complex physiologic and molecular mechanisms of action of oxytocin"[576(p.10)] and "significant and increasingly recognized behavioral effects."[576(p.12)]

In general, the synOT doses administered directly to offspring in these studies are substantially higher than the equivalent levels that human offspring could be indirectly exposed to via the mother in labor. (Doses administered to pregnant or laboring females are generally limited by uterine OT sensitivity: excessive doses will cause uterine hyperstimulation with deleterious impacts on the fetus/newborn. See "Synthetic oxytocin and central maternal oxytocin," above.)

In relation to synOT exposure with induction, equine researchers found alterations in early pancreatic endocrine development and glucose regulation in foals induced with synOT. Researchers suggest that higher newborn cortisol levels following induced labor may impair glucose metabolism, with possible prolonged metabolic sequelae.[148]

Other studies found impacts through to adulthood from administering synOT at physiologic-type doses to newborn rats, or from manipulations that increased endogenous OT such as stroking with a paintbrush. These include: reduced blood pressure and stress hormone levels; reduced responses to pain; and greater weight. Exposed female offspring subsequently bore larger babies with larger placentas, suggesting possible transgenerational effects.[577] Prairie vole studies involving newborn manipulations that cause high-physiologic OT levels, discussed above, also found long-term impacts on the OT system that varied with the valence of the manipulation.[574] (See "Synthetic oxytocin and offspring, human studies," below, for relevance to human synOT exposure.)

Synthetic oxytocin and epigenetics. *These impacts of synthetic oxytocin exposure on animal offspring into adulthood are consistent with epigenetic effects causing fetal/newborn programming, also called "hormonal imprinting," in relation to exposures during the perinatal period.*

According to veteran researcher Csaba**:**

> Hormonal (chemical) imprinting . . . is a general biological phenomenon which takes place when the developing receptor meets its target hormone for the first time . . . . In mammals, hormonal imprinting takes place perinatally and determines the function of receptor-signal-transduction systems as well as hormone production for life . . . . Excess of the target hormones or presence of foreign molecules which are able to bind to the receptors, provokes faulty imprinting in the critical periods with life-long morphological, biochemical, functional or behavioural consequences.[578(p.1)]

In some hormonal imprinting studies, changes have been inherited through several generations.[41, 578] Dahlen and colleagues call this perinatal phenomenon "epigenetic impact of childbirth" (EPIIC).[42]

The heightened potential for epigenetic changes in the perinatal period, with the possibility of long-term programming effects, is consistent with the "developmental origins of health and disease" (DOHaD) model,[579] and more recently the "developmental origins of health, behavior and disease, DOHBaD[33]), which considers long-term impacts of gestational exposures; and with the "lifecourse health development model" (LCHD).[43] These models acknowledge the extreme plasticity of offspring physiology in the perinatal period, with biologic amplification of experiences at this time. (See further discussion in 1.4.)

Synthetic oxytocin and offspring, human studies. *Short- to longer-term human impacts from exposure to synthetic oxytocin in labor are biologically plausible, but studies are lacking. Preliminary findings suggest possible effects on social and developmental behaviors, with concerns raised about possible links between synthetic oxytocin exposure in labor and autism.*

This area is very poorly researched. One survey found correlations between the duration of exposure to synOT in labor and risk of medically-confirmed attention-deficit hyperactivity disorder (ADHD) among surveyed 3- to 25-year-olds.[580] The authors suggest that subclinical birth hypoxia and/or epigenetic mechanisms may contribute.[295, 580] A recent large population study also found links between induction and ADHD, which researchers relate to shortening of gestation.[581]

In the most detailed study to date, researchers comprehensively evaluated the development of 148 children at age five in relation to synOT exposure in uncomplicated labor. They found that, with uncomplicated labor and birth, exposure to synOT significantly increased the risks of poor developmental scores among children of younger and older mothers, possibly related to prolonged synOT exposure. Exposed children born by instrumental birth or cesarean had lower risks, which researchers ascribe to possible shortening of complicated labors.[582, 583] Duration of breastfeeding was also shorter for exposed children in this cohort,[569] which may contribute to these findings. Researchers conclude, ". . . synthetic oxytocin should be used with caution, reducing fetal exposure as far as possible by administering the lowest effective dose, or even resorting to alternative therapies."[584(p.9)]

One preliminary survey assessed psychosocial function among normal children in relation to synOT exposure, and found subtle shifts among exposed compared with unexposed three-year-olds.[585]

Several researchers have suggested the possibility of links between exposure to synOT in labor and autism,[46, 586, 587] largely because of the deficits in OT-associated social functions found in autistic individuals. In addition, OTR dysfunctions have been implicated in both animal models and humans with autism,[227] and synOT has been found to ameliorate some aspects of autism.[588] Persisting downregulation of fetal OTRs in response to synOT exposure in labor has been suggested as a possible mechanism.[587]

A recent review and meta-analysis found a 20 percent increased risk of autism following induction or augmentation of labor; authors suggest that fetal hypoxia may contribute.[589] An animal model of autism has implicated faulty OT-related neuroprotection[295] (see "Fetal neuroprotection" in 3.1.3). This mechanism is only active around the physiologic onset of labor, and is also compromised by high-dose synOT, according to animal research.[97, 293] This model contributes additional complexity and hypotheses in researching possible links between autism and perinatal exposures.

Kenkel, along with veteran OT researcher Sue Carter and colleagues, comment in relation to developmental risks in human populations: ". . . manipulation of oxytocin levels around the time of birth holds the poten-

tial to induce persistent changes in the fetal brain and behavior, perhaps by affecting not only the oxytocin peptide and its receptor, but also other related peptides such as vasopressin and its receptors."[54(p.2) 168]

Given the widespread exposure of mothers and babies to synOT for induction and augmentation in labor,[18] the possible impacts of this drug in relation to breastfeeding, maternal-infant attachment, and long-term maternal and offspring adaptations and development are critical areas for future research.

3.2.4 Opioid Analgesic Drugs: Possible Impacts on Oxytocin Physiology

Opioid drugs, including those naturally derived from the opium poppy (opiates), are widely used as analgesics in labor and birth, either systemically by intramuscular or intravenous injection, or as components of epidural analgesia. Opioid drugs can have hormonal impacts because they have similar effects to beta-endorphins and other natural (endogenous) opioid hormones.

Opioid drugs used in labor, administered systemically by IM or IV injection, or as a component of epidural analgesia, include:

- morphine, a natural opiate
- meperidine (Demerol, pethidine), derived from morphine
- fentanyl (Sublimaze), sufentanyl (Sufentanyl), and remifentanil (Ultiva), synthetic opioids, also commonly used in epidurals
- tramadol, a synthetic opioid that also impacts serotonin and NE
- meptazinol (Meptid), nalbuphine (Nubain), pentazocine (Fortral), butorphanol (Stadol), and buprenorphine (Temgesic, Buprenax), partial agonists, which partly activate and partly block opioid receptors

These drugs have differing pharmacologic and adverse effects profiles. Systematic reviews have not found one opioid to be superior when administered systemically by intramuscular or intravenous injection for labor analgesia, from current evidence, but quality studies are lacking.[590, 591]

Opioid Drugs and the Mother

Endogenous opioids such as beta-endorphins reduce oxytocin release within the brain, possibly as part of a contraction-inhibiting response to labor stress. Studies suggest that opioid drugs, working on the same receptors, may also reduce maternal oxytocin release and slow labor. Opioids may also act directly in the uterus to reduce contractions. Opioid drugs may reduce beta-endorphins and may also counter the euphoric and amnesic effects of oxytocin in labor and after birth.

One study found incremental reductions in OT levels, measured in blood, following the gradual IV administration of morphine to women in early labor.[592] Opioid-induced OT reductions would be expected to prolong labor, although this has not been well studied. In a literature review of the impacts of pethidine (meperidine) on labor, Thomson and Hillier concluded, "There is a strong suggestion in the literature that the use of this drug is associated with a lengthening of labor and that this association is dose-related."[593(p.448)]

In addition, studies have found that laboring women are more frequently administered synOT following systemic administration of meperidine[594] and fentanyl,[595] compared with no medication, suggesting reduced contraction efficacy. Researchers have found mu opioid receptors (MORs, receptors for beta-endorphin and most opioid drugs) in the human uterus with relaxant effects,[596] suggesting that opioid drugs may slow labor by acting locally, as well as centrally to reduce OT release. One human study did

not find changes in uterine contractions following a single low systemic meperidine dose.[597] The 2011 Cochrane systematic review of systemic opioid analgesia in labor found no increase in instrumental delivery or CS for laboring women using meperidine compared to placebo,[591] but did not assess labor length.[591, 597, 598]

Slowing of labor in response to opioid drugs may mirror the physiologic effects of endogenous opioids such as BEs, which may reduce contractions as an adaptive response to stress in labor (see 4.1.3). The opiate drug morphine has been recommended systemically to facilitate "therapeutic rest" for women with a prolonged latent stage of labor.[598] According to Greulich, 85 percent of women administered meperidine for prolonged latent phase will benefit from 6 to 10 hours of rest and awaken in active labor.[598]

One study found that, for women who had received systemic opioid drugs in labor, the memory of labor pain intensified over time, compared with women who used no medication, whose recall of labor pain diminished with time.[599] Possible mechanisms include a more intense experience of labor pain and/or an opioid-mediated reduction in central OT, with loss of its amnesic and euphoric effects. (See also "Epidural Analgesia and the Mother" in 3.2.5.)

Opioid Drugs and the Fetus/Newborn

Opioid drugs can readily cross the placenta and enter the fetal brain. Many detrimental opioid effects relate to fetal and newborn sedation. In addition, opioid drugs could plausibly reduce central oxytocin in the baby, although cord blood measurements have not shown oxytocin reductions in the blood of newborns exposed to systemic opioids, compared to unexposed babies. Opioid exposure via epidurals may also have fetal/newborn effects.

Fetal opioid sedative effects may include: reduced fetal heart rate accelerations, reductions in beat-to-beat variability[600] and, for the newborn, added risks of respiratory depression[601] and deficits in prebreastfeeding behaviors and abilities.[315, 350, 351, 602-604] Some of these effects may also occur following epidural opioid exposure (3.2.5).

Opioid drugs can easily cross the placenta and enter the fetal brain.[591] According to hormonal physiology understandings, opioids could reduce central fetal OT, potentially reducing neuroprotective and calming effects. While studies did not find reductions in cord blood OT levels in relation to labor exposure to systemic meperidine[309] or morphine,[605] central OT in labor is obviously impossible to measure.

Uninterrupted skin-to-skin contact, which physiologically increases OT (3.1.1), has been found to lessen the impacts of labor opioid exposure on newborn prebreastfeeding behaviors.[351] This suggests that OT-related "calm and connection" effects may be important for newborns exposed to opioid drugs in labor (3.1.2).[309, 351, 605]

Opioid Drugs and Breastfeeding

Opioid drugs may detrimentally impact breastfeeding through maternal and/or newborn sedation and possibly through oxytocin reductions in both. There is a lack of high-quality research in this area.

Few high-quality studies have looked at breastfeeding success in relation to opioid exposure in labor compared to no medication.[591] One large observational study found a significant reduction in breastfeeding success at 48 hours following opioid use in labor, compared with no analgesics.[564] It is unclear whether this is due to maternal factors, such as OT inhibition; newborn factors, as above, including sedation after birth; or both (4.2.4).

One study found that low-therapeutic doses of morphine inhibited the maternal OT surge associated with breastfeeding in new mothers.[606] Morphine administration also caused a dose-related OT reduction in dairy cows, with inhibition of the OT-mediated let-down reflex at high doses.[607] Opioid drugs such as meperidine may also have prolonged pharmacologic effects, especially for the baby, whose metabolizing systems are immature.[608]

These possible opioid impacts on maternal OT and breastfeeding are important considerations, as opioids are commonly used for post-CS analgesia,[609] and are often administered for several days postpartum, when early lactation is being established. While newborn exposure may be minimal, because most opioid drugs are excreted in only small amounts in breast milk,[610, 611] impacts on the maternal OT system and let-down reflex could have significant detrimental effects on breastfeeding success. One study found reduced breastfeeding episodes and lower newborn weight gain over 11 days among women randomized to post-CS epidural with the opioid buprenorphine, compared with epidural with only local anesthetic (bupivacaine).[612] These are critical areas for future research.

Opioid Drugs and Offspring, Longer Term

As with other drugs administered in the perinatal period, it is possible that opioid drugs could have longer-term programming effects, including on offspring OT systems.

Possible programming effects of perinatal opioid exposure on offspring are discussed in 2.2.4.

3.2.5 Epidural Analgesia: Possible Impacts on Oxytocin Physiology

Epidural analgesia is the most commonly used and effective analgesia in labor. However, epidurals can significantly disrupt hormonal systems, including oxytocin, leading to common side effects such as slowing of labor.

Epidural analgesia involves the administration of local anesthetic (LA) drugs into the epidural space around the covering of the spinal cord. This blocks the nerves that traverse this space, similar to the action of a dental anesthetic, including both the sensory nerves, leading to numbness, and the motor nerves that control movement, giving some degree of paralysis in the lower body. Modern epidurals typically also include opioid drugs, which augment LA effects. This allows for effective analgesia using lower concentrations of LA drugs, with potentially less motor block and paralysis.

Epidural analgesia is widely understood to be the most effective form of pain relief in labor and birth.[613] It is the most widely used method of pain relief among US women, with 67 percent of respondents to a recent national survey reporting that they had received an epidural around the time of birth.[17] While epidural analgesia can be beneficial for many women, it can also have significant impacts on the progress of labor and birth, as well as side effects for mother and baby, many of which are attributable to impacts on the OT system. Recent studies have also shown subtle disruptions in maternal and newborn postpartum physiology following epidural exposure in labor, raising concerns about possible prolonged impacts on OT systems, as detailed below.

Epidural Analgesia and the Mother

Epidural analgesia can have significant effects on the mother, many of which may be due to OT impacts.

The most recent Cochrane systematic review[614] documents the following impacts for laboring women using epidural analgesia, most of which are consistent with OT disruptions, as described below**:**

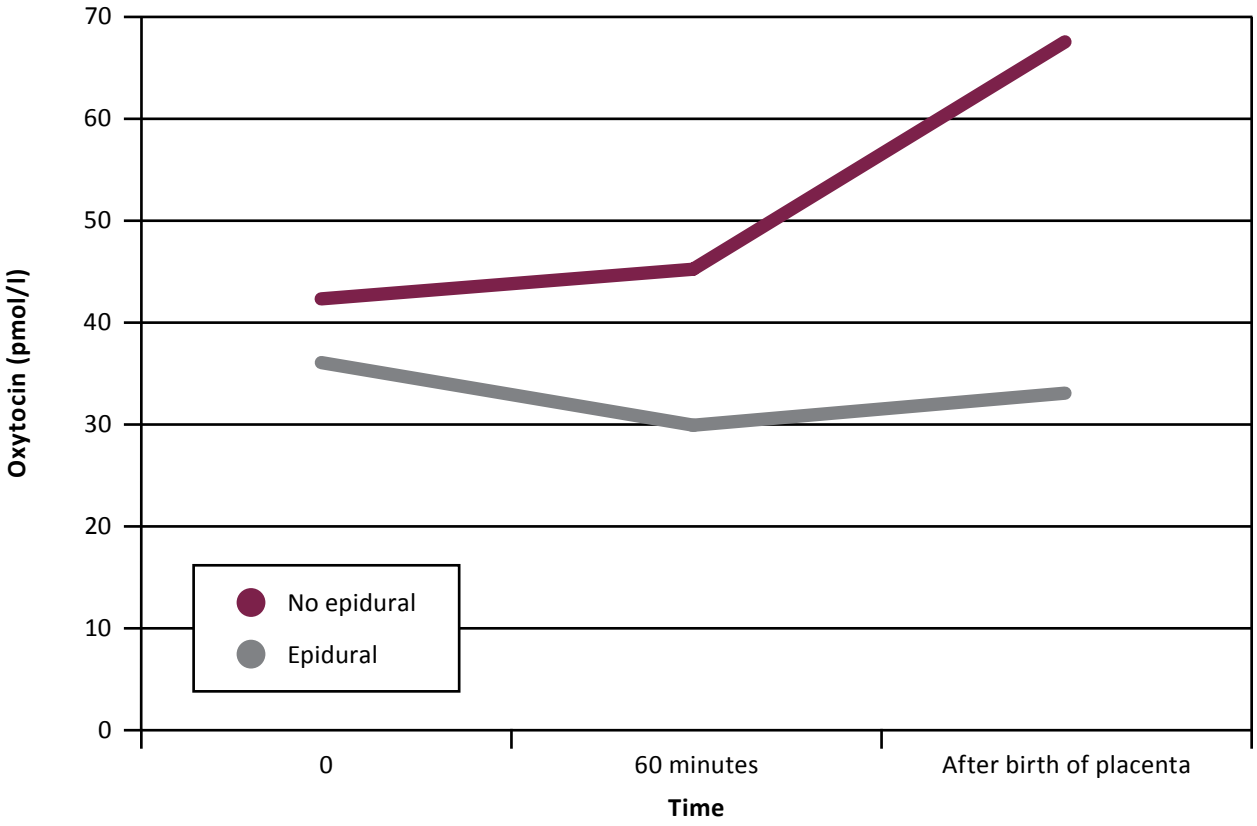
- increased use of synOT augmentation
- prolonged second stage of labor
- increased use of forceps or vacuum assistance at birth
- increased use of CS for “fetal distress”

Epidural analgesia and oxytocin systems in labor. *Epidurals reduce maternal oxytocin, likely because of lack of the sensations and sensory feedback that releases oxytocin from the brain. This can lead to slower labor and increased need for synthetic oxytocin. Late-labor oxytocin reductions may contribute to a longer pushing stage and extra need for forceps or vacuum assistance. The administration of synthetic oxytocin as a common co-intervention may also contribute to epidural impacts.*

Studies show a decline, or a lack of the expected rise, in laboring women's OT levels after epidural administration,[615-618] as shown in Figure 2.[616] A small transient OT rise preceding this decline, as seen in another study,[618] may reflect a sudden drop in epinephrine, which may have been inhibiting OT (3.3.5). The subsequent OT decline occurs following epidurals both with[616] and without[618] opioids and also spinal analgesia,[618] which generally involves an opioid drug injected close to the spinal cord. (See 3.3.5 for more about spinal effects and side effects.)

Figure 2. Maternal oxytocin levels, with and without epidural analgesia

(0 = level just before epidural administration or, for control group, at similar 4.5 cm cervical dilation. Duration from 0 to birth: 128 minutes without epidural, 200 minutes with epidural.)



Source: adapted from Rahm[616]

Low OT levels in the pushing stage, as seen in Figure 2, may be due to loss of the normal positive feedback cycle ("Ferguson reflex," see 3.1.3), which gives peak OT levels that ensure an effective pushing stage.[619] Loss of this OT peak may contribute to the prolonged pushing stage and increased risks of instrumental birth following epidural analgesia.[614, 619]

Maternal postpartum OT levels, as measured in the blood, are around 50 percent of normal at birth following epidural analgesia.[616, 619] Animal studies of sheep[620] and cows,[263] where central OT levels can be measured, have found reductions in brain as well as blood levels of OT following LA-only epidural administration, with significant impacts on maternal behaviors. (See "Epidural Analgesia and Maternal Adaptations," below.)

The exact mechanism by which epidurals reduce OT release is not certain. Epidural-induced numbness interrupts the uterine sensations that activate a central positive feedback cycle, augmenting OT release from the brain (see "Positive feedback cycles" in 3.1.3). According to mammalian physiology principles, "Sensory input from female reproductive structures is paramount for the co-ordination of neuroendocrine changes at parturition."[621(p.1013)] In addition, local anesthetic drugs are derivatives of cocaine, which reduces central OT in animal studies.[622]

Reduced OT release likely accounts for the increased use of augmentation, longer second stage of labor, and increased risk of instrumental birth among women receiving an epidural.[614] The increased use of synOT in women receiving compared with not receiving epidurals[623] may mask impacts on the length of the first stage of labor. In addition, prolonged synOT exposure leading to OTR desensitization (see "Synthetic oxytocin and oxytocin receptor desensitization" in 3.2.3) could further contribute to prolonged pushing and increased instrumental birth. Reduced endogenous OT release in labor and the postpartum period, following epidural exposure, also raises concerns about breastfeeding and maternal adaptations, explored below.

Epidural analgesia and maternal temperature regulation in labor. *Around one in ten women receiving an epidural develop a fever in labor, which may be related to oxytocin changes.*

It is estimated that 10 to 20 percent of women who receive an epidural experience a temperature elevation in labor,[624, 625] whereas epidurals generally decrease temperature outside of labor.[626] The mechanism behind this paradoxical effect is currently thought to involve maternal inflammation and inflammatory processes.[627]

Oxytocin disruptions could contribute to epidural fever through loss of OT anti-inflammatory effects (3.1.1) and/or through changes in brain-based temperature regulation, which may also involve the OT system.[48] Maternal inflammation likely contributes to the increase in inflammatory substances found in cord blood of epidural-exposed newborns compared with unexposed babies,[628] with unknown implications.[625, 628-630]

Fetal/newborn effects of maternal fever are discussed below ("Epidural Analgesia and the Fetus/Newborn").

Epidural Analgesia and the Fetus/Newborn

Drugs administered via epidural will pass to the baby and may impact the fetal/newborn oxytocin system. This has not been well studied. Preliminary studies show elevated newborn oxytocin with epidural exposure, which may reflect increased fetal stress, and also subtle disruption to newborn oxytocin-related autonomic nervous system functions, possibly persisting into infancy. Maternal fever can increase risks to the baby's brain, and also necessitate newborn separation and testing, with loss of early oxytocin-rich mother-newborn interactions and breastfeeding initiation. Epidural co-interventions may also impact the baby.

The opioid drugs commonly used in epidurals pass through the placenta to the baby and can also cross to the fetal brain. In some cases, fetal central opioid exposure with epidurals may be high enough to cause newborn respiratory depression.[631] Such high central levels could also disrupt OT release, although this has not been directly measured. One older study found that fetal OT production was increased with exposure to epidurals, although opioid drugs were likely not administered in epidurals at that time.[309] Stress-induced

OT release could contribute (see 4.2.5 for more about epidurals and fetal/newborn stress). Epidurals may also impact newborn neurobehavior, as suggested by dose-response findings in relation to LA drugs,[632-636] and by findings from more comprehensive testing.[635-637] However, findings are controversial and complicated by differing understandings and measurements of newborn neurobehavior,[638] and by comparisons with newborns exposed to opioid drugs, which can impact newborn neurobehavior via sedation.

A study of newborn skin temperature response to skin-to-skin breastfeeding, mentioned above ("Synthetic Oxytocin and the Baby" in 3.2.3), also found disruptions in relation to epidural exposure. In contrast to the normal physiologic gradual elevation and decline with SSC breastfeeding, epidural-exposed newborns had an initial, elevated skin temperature, which decreased during skin-to-skin breastfeeding.[555] Authors speculate that epidurals may adversely impact newborn OT-related ANS functions, perhaps due to the impacts of the opioid drug sufentanil, used in this study, which easily crosses the placenta to the fetal brain, where it could inhibit OT release.[555] In this study, slightly younger infants had higher initial skin temperatures, suggesting a short-term and/or pharmacologic effect on the baby, or possibly on the mother via epidural-related disruptions in maternal temperature responses.

Maternal fever in labor (see **"Epidural analgesia and maternal temperature regulation in labor,"** above) can have detrimental impacts on the baby, whose body and brain will also be heated. Fetal heating increases vulnerability to neurologic damage and increases the risk of low Apgar scores, severe breathing difficulties, and early-onset neonatal seizures, all with possible longer-term impacts.[625] In addition, newborns of febrile mothers are likely to be separated for a "septic workup," with blood tests and, usually, presumptive treatment with antibiotics.[630] Separation may last several days, interfering with important OT-related interactions, such as SSC and breastfeeding, with possible impacts on the newborn OT system (3.2.7).

Another study found abnormal defense-type autonomic reactions to novel stimuli among eight-month-old infants who had been exposed to epidurals at birth, compared with normal orienting reactions among unexposed infants.[639] This defensive reaction also suggests ANS disruption. Long-term follow-up studies of monkey offspring exposed to epidurals also suggest developmental impacts.[640] (See 4.2.4 and 4.2.5 for animal studies on long-term impact of opioid drugs and epidurals.)

Because epidurals generally slow labor and increase the need for synOT to compensate (above), the fetal/newborn impacts of epidurals may also include the impacts of synOT (see "Synthetic Oxytocin and the Baby" in 3.2.3).

Given current widespread exposures, the full effects of epidurals on the baby in the short and longer term are critical areas for future research.

Epidural Analgesia and Breastfeeding

Epidurals may negatively impact breastfeeding success, with some evidence for shortened duration, but studies are contradictory, and high-quality research is lacking. Exposure to both epidurals and synthetic oxytocin in labor may significantly reduce maternal oxytocin release with breastfeeding. The exact mechanisms and short or long-term implications are not known. Epidural effects on the newborn may also impact breastfeeding.

Many factors contribute to breastfeeding initiation and continuation, including maternal and fetal/newborn hormones and other factors. These are complex to disentangle in epidural studies, including the effects of co-interventions such as synOT.[642]

Randomized studies in this area are problematic, as it has not been possible to include women randomized to no analgesia, for ethical reasons.[643, 644] Observational studies report contradictory findings.[47, 286, 487, 554, 555, 570, 604, 642, 645-657] Reduced duration of breastfeeding has been found in several studies.[286, 642, 649-651]

Studies in settings that strongly support breastfeeding, with routine postpartum SSC and rooming in for mothers and babies have generally better outcomes.[642, 653-656] Early SSC may benefit newborn breastfeeding initiation by activating maternal and infant OT, beta-endorphins, and PRL systems, with calming and rewarding effects for both that may reduce epidural-related hormonal disruptions (3.2.5, 4.2.5, 5.2.5, 6.2.5). Early SSC enhances breastfeeding initiation and success,[336] as promoted by the Baby-Friendly Hospital Initiative (3.1.4, 4.1.4, 5.1.4, 6.1.4).

From a hormonal physiology perspective, epidural-related maternal OT reductions in labor and birth could impact OT functions and release during breastfeeding, including OT-related prolactin secretion (6.1.4). Researchers analyzed the release of hormones during breastfeeding in new mothers according to interventions in labor, and found that women exposed to epidurals alone had no differences in OT or PRL release. However, exposure to synOT in addition to epidurals was associated with the lowest OT levels during breastfeeding, [487] and also the highest levels of the stress hormone cortisol,[570] compared with any other intervention or with unmedicated labor. These findings[570] suggest that the combination of epidurals plus synOT may be especially disruptive to postpartum OT release, and may impact stress responses, although the mechanism is not clear.

Given current widespread exposures, and the increasingly recognized detrimental effects in mother and baby of not breastfeeding, the full effects of epidurals on breastfeeding are critical areas for future research.

Epidural Analgesia and Maternal Adaptations

Epidural-related reductions in oxytocin, especially the oxytocin peak at birth, could potentially affect maternal adaptations in women, as has been demonstrated in animals. Studies in women have found subtle disturbances in maternal adaptations and in maternal-newborn interactions that may compromise evolving attachment.

Researchers have administered epidurals to laboring sheep[620] and cows,[263] and found reduced or absent maternal behaviors such as licking and maternal bleating (ewes), along with reduced central OT levels. In the sheep studies, primiparous ewes, and those administered early epidurals were more affected than their multiparous and later-administration counterparts.[620] Researchers subsequently injected synOT into the brain of affected ewes, replacing the epidural-related central loss, and found a substantial but not total reinstatement of mothering behaviors.[262] This is consistent with the understanding that hormones such BEs, NE, and PRL, which can all be affected by epidurals, may also influence maternal adaptations and behaviors (4.2.5, 5.2.5, 6.2.5).

As discussed in the Introduction (1.2), maternal behaviors are much more varied and complex, and difficult to quantify in women, compared with other mammals. However, several studies have found subtle differences in maternal adaptations and maternal-infant interactions following epidural analgesia, which may reflect disruptions to maternal OT attachment systems.

Findings include:

- reduced proximity seeking in new mothers in hospital, in proportion to epidural dosage of the LA drug bupivacaine[635]
- more unsettled newborn behavior, in proportion to bupivacaine exposure[636]
- more unsettled newborn behaviors and lower scores on Neonatal Behavioral Assessment Scale compared with unexposed mothers[637]
- maternal characterization of babies as less social and rewarding and more bothersome at one month, compared with unexposed mothers[637]

Dose-response findings in some of these studies suggest that, from a hormonal perspective, the numbing effects of LA drugs may disrupt the laboring woman's sensory feedback, which usually increases OT release within her brain as labor progresses (see "Positive feedback cycles" in 3.1.3). Lack of central OT elevations may give subtle disruption to maternal adaptations, including reduced OT-related adaptations and attachment systems. The postpartum OT system usually promotes proximity seeking (see "Maternal-infant bonding and attachment" in 3.1.4) and activates reward centers that promote ongoing contact and care, likely also involving beta-endorphins (4.1.4). With epidural-associated OT reductions, maternal reward center activation in relation to infant contact and care may be reduced, so that the baby is less rewarding, in a biologic sense (see "Oxytocin and Maternal Adaptations and Attachment" in 3.1.4 and also 4.2.5 for epidural-related reductions in BEs). Epidural-associated shifts in newborn neurobehavior and functioning may also contribute.[637]

In another study, researchers found that women exposed to epidurals in labor did not experience the normal early-postpartum shift in personality, whereby anxiety and muscular tension decrease and "socialization" increases[571] (see "Maternal Adaptations" in 3.1.4). Authors comment, ". . . lack of oxytocin during this "sensitive period" may result in a lack of development of long-term maternal adaptations.[571(p.344)]

Due to limited research, these findings are not definitive, and do not imply that women receiving epidural analgesia in labor will have deficits in mothering, or in relationships with their infants. However, from the perspective of hormonal physiology, epidurals may interfere with OT-related processes that give calm, connection, and ongoing pleasure and reward to new mothers in relation to contact and care with their newborn, and may interfere with biologic aspects of bonding (3.1.4). Findings also suggest that epidural-exposed mothers and babies may benefit from assistance with OT-related processes after birth, including breastfeeding and SSC, which may both be important in optimizing maternal OT systems.

Given the current high use of epidurals, and the low level of understanding of the impacts of epidurals on OT–related processes, including breastfeeding and biologic aspects of maternal adaptations and bonding, these are critical areas for future research.

Epidural impacts on memory and reward

Epidural-related oxytocin disruptions, and the related co-interventions, may contribute to dissatisfaction with the experience of birth. Loss of positive oxytocin effects on memory may contribute to a stronger memory of labor pain and distress.

Studies have shown that, while women using an epidural generally experience effective pain relief,[614, 658] they are no more satisfied with the birth overall,[658-662] and may even be more dissatisfied with their birth experience, compared with women who used no analgesia. [663-666] In addition, even though women using epidural analgesia report less pain during labor, they may remember more distress and trauma, even five years later, according to one study.[667]

These findings may relate to preexisting characteristics, to co-interventions, and/or to a more intense experience of pain before epidural administration. However, OT impacts may also contribute. As discussed in "Oxytocin Effects" in 3.1.1, OT not only relieves pain, but also reduces the memory of pain. Epidural-associated decreases in OT, and especially loss of the late-labor OT surge, may leave women with a stronger memory of pain and distress, without the assistance of OT-mediated analgesia and calm, and without post-birth euphoria mediated by OT and other hormones (see "Pleasure and reward" in 3.1.4 and "Maternal Beta-Endorphins After Birth" in 4.1.4).

3.2.6 Cesarean Section: Possible Impacts on Oxytocin Physiology

The impacts of cesarean section on the oxytocin systems of mothers and babies will vary with cesarean timing (pre- or in-labor), with the nature of labor onset (with an in-labor cesarean following induction implying deficits in physiologic prelabor preparations for mother and baby), and, for prelabor cesarean, with the proximity to when physiologic onset of labor would otherwise have occurred. In relation to oxytocin hormonal physiology, an in-labor non-emergency cesarean may be the most beneficial type of cesarean for mother and baby.

With a cesarean section, mothers and babies lack the full processes of labor and birth, including full activation of the OT system, and the physiologic OT peaks of labor and birth. With a prelabor CS (or an in-labor CS following induction), both may also miss important OT preparations, including OTR upregulation in the maternal uterus, and possibly also in the breasts and maternal brain (as found in animal studies; see 3.1.2, 3.1.3). In addition, following a cesarean, mother and baby may also miss postpartum skin-to-skin contact during the early sensitive period (see "Postpartum sensitive period" in 3.1.4). Disruption of OT physiology may contribute to increased risks for healthy mothers and babies undergoing CS, compared with those experiencing vaginal birth.

Table 3 summarizes this information and is ordered according to the increasing impact on the OT systems of mother and baby. The physiologic differences in CS types may explain some variations in research findings about effects of CS.

A CS could also be planned and in-labor following physiologic onset of term labor. Although this approach is not common or well researched, prelabor physiologic preparations for mother and baby in this situation may promote newborn transitions and breastfeeding, and reduce risk of PPH, among other benefits (3.1.4). A planned in-labor CS be may be beneficial to the oxytocin adaptations of the large group of women and babies having planned repeat CS. Non-hormonal aspects of surgery will obviously influence benefit/harm considerations. This is an important area for future research.

In any CS situation, the mother's cervical changes may give an indication of her readiness for labor and birth, likely including her uterine OTR numbers. This may also indicate her risk of postpartum hemorrhage (see "Oxytocin and postpartum hemorrhage" in 3.1.4). Because readiness is coordinated between mother and baby, this may also indicate her baby's readiness for life outside the womb and risk of CS morbidities, especially respiratory morbidity. Possible associations between pre-cesarean maternal cervical status, newborn outcome, and PPH (below) are important areas for future research.

With PLCS, labor has not been initiated or experienced, and so there is likely to be significantly reduced prelabor physiologic preparations in mother or baby (3.1.2, 2.1, 2.2), and no labor processes or peak hormone levels to complete these preparations. With an unplanned in-labor CS, labor may have been physiologically initiated, with full prelabor preparations for mother and baby, or labor may have been induced, with an unknown degree of readiness for birth. Mother and baby will have experienced some labor processes and hormonal activation. In addition, exposure to synOT for labor augmentation may impact OT systems (3.2.3), including via OTR desensitization effects that may increase post-CS PPH risk.

Table 3. **Established and biologically plausible oxytocin processes and impacts, by type of cesarean**

Type of cesarean	Prelabor physiologic preparations in mother and baby	In-labor processes and oxytocin activation in mother and baby	Expected impact on the mother's oxytocin system	Expected impact on the baby's oxytocin system
In-labor, planned (uncommonly performed)	Complete, as labor has been physiologically initiated (3.1.2, 2.1)	Some OT activation,* with likely benefits for mother and baby† (3.1.3)	• Full OTRs; OT positive feedback cycles active* (3.1.2, 3.1.3) • No OT surge at birth (3.1.3) • May miss newborn contact during early sensitive period (3.1.4)	• Full pre-labor preparations (3.1.2, 2.1) • Limited in-labor processes* (3.1.3) • May miss maternal contact during early sensitive period (3.1.4)
In-labor, unplanned following physiologic onset of labor, no augmentation	Complete, as labor has been physiologically initiated (3.1.2, 2.1)	Some OT activation,* with likely benefits for mother and baby† (3.1.3)	• Full OTRs; OT positive feedback cycles active* (3.1.2, 3.1.3) • No OT surge at birth (3.1.3) • May miss newborn contact during early sensitive period (3.1.4)	• Full prelabor preparations (3.1.2, 3.1) • Limited in-labor processes* (2.1.3) • May miss maternal contact during early sensitive period (2.1.4)
In-labor, unplanned following physiologic onset of labor, with augmentation	Complete, as labor has been physiologically initiated (3.1.2, 2.1)	Some OT activation,* with likely benefits for mother and baby† (3.1.3)	• Full OTRs; OT positive feedback cycles active* (3.1.2, 3.1.3) • No OT surge with birth (3.1.3) • Prolonged high-dose synOT synOT may desensitize OTRs and increase PPH risk. • Possible effects on breastfeeding (3.2.3) • May miss newborn contact during early sensitive period (3.1.4)	• Limited in-labor processes* (3.1.3) • High-dose synOT exposure may reduce OT neuroprotection (animal studies) • May miss maternal contact during early sensitive period (3.1.4)

cont'd

Type of cesarean	Prelabor physiologic preparations in mother and baby	In-labor processes and oxytocin activation in mother and baby	Expected impact on the mother's oxytocin system	Expected impact on the baby's oxytocin system
In-labor, unplanned following induction	Depends on proximity to physiologic onset of labor, with more preparation at later gestation (3.1.2, 2.1)	Some OT activation,* with likely benefits for mother and baby† (3.1.2)	• Reduced OTRs before physiologic onset of labor (3.1.2) • OT positive feedback cycles may not be prepared and fully active (3.1.3) • No OT surge with birth (3.1.3) • Prolonged high-dose synOT synOT may desensitize OTRs and increase PPH risk. Possible effects on breastfeeding (3.2.3) • May miss newborn contact during early sensitive period (3.1.4)	• No pre-labor preparations (3.1.2, 2.1) • Limited in-labor processes* (3.1.3) • High-dose synOT exposure may reduce OT neuroprotection, (animal studies) • May miss maternal contact during early sensitive period (3.1.4)
Prelabor cesarean section (also called planned, elective, scheduled)	Depends on proximity to physiologic onset of labor, with more preparation at later gestation (3.1.2, 2.1)	No OT activation for mother or baby (3.1.2, 3.1.3)	• Reduced OTRs before physiologic labor onset (3.1.2) • No OT positive feedback cycles, giving reduced central OT • No OT surge at birth (3.1.3) • May miss newborn contact during early sensitive period (3.1.4) PPH risk may be increased (3.1.4)	• No prelabor preparations (3.1.2, 2.1) • No in-labor processes (3.1.3)† • May miss maternal contact during early sensitive period (3.1.4)

Note: OT = oxytocin, OTR = oxytocin receptor, PPH = postpartum hemorrhage, synOT = synthetic oxytocin

*Degree of hormonal activation depends on labor stage prior to cesarean section.

†Newborn hormonal benefits from labor include the catecholamine surge (5.1.6, 5.2.6).

Cesarean and the Mother

With a cesarean, the mother misses the oxytocin peak at birth and may also miss early contact with her newborn, which can beneficially activate both maternal and newborn oxytocin systems, giving calm and connection, an ideal environment for breastfeeding initiation, and possibly important central oxytocin adaptations and biologic bonding processes for both. Fewer uterine oxytocin receptors due to lack of prelabor physiologic preparations with prelabor cesarean, or to receptor desensitization following prolonged synthetic oxytocin exposure in labor, may increase risk of postpartum hemorrhage. The frequent lack of mother-newborn skin-to-skin contact after cesarean section could also contribute to increased hemorrhage risks.

Following any type of cesarean, the maternal peak of OT during the pushing stage (see "Maternal Oxytocin in Labor and Birth" in 3.1.3) will be absent, giving lower OT levels at birth. Skin-to-skin contact between mother and newborn, and the first opportunity to breastfeed, are typically delayed after CS,[17, 432] so that the new mother may miss opportunities to release her own OT, which would activate central OT systems and may also help to reduce bleeding (see "Oxytocin and postpartum hemorrhage" in 3.1.4). Delayed SSC and/or breastfeeding initiation may also impact longer-term success (see "Cesarean and Breastfeeding," below; 3.2.7; and 3.1.4).

There may be a sensitive period for mothers following CS as for vaginal birth (3.1.4), which may be triggered by contact with her baby[391, 395] (see "Cesarean Section and Maternal Adaptations," below).

Studies show that CS is a risk factor for PPH, including bleeding severe enough to require blood transfusion and even postpartum hysterectomy.[668-671] For women with a PLCS, or who experience an unplanned cesarean following an induced labor, low uterine OTR numbers due to lack of physiologic prelabor preparations may contribute. Women whose cesarean follows the physiologic onset of labor may have the normal prelabor increase in OTRs, and lower PPH risk, although this subset has not been specifically studied. Even if labor onset is physiologic, prolonged exposure to synOT with labor augmentation may desensitize OTRs and increase PPH risk following CS. As discussed above, pre-CS cervical status could be a marker for proximity to physiologic labor onset, uterine OT sensitivity, and PPH risk, excluding in-labor synOT exposure (see "Synthetic oxytocin and postpartum hemorrhage" in 3.2.3).

Skin-to-skin newborn contact may help to release maternal OT and could plausibly reduce PPH risk after CS, as after physiologic birth, when mother-newborn interactions may increase maternal OT by two-fold, and even up to ten-fold (see "Oxytocin and maternal-newborn contact and interactions" in 3.1.4). One CS study showed elevations in maternal OT (maximum around 50 percent) in the first hour, with equivalent levels for mothers with SSC or close non-physical contact. In this study, fathers who were in contact with their babies also had OT elevations.[395]

Cesarean and the Fetus/Newborn

Oxytocin levels are lower in newborns in the early hours following prelabor cesarean, likely from lack of labor eustress. Maternal skin-to-skin contact and breastfeeding may be important to elevate newborn OT and reduce stress hormones. Levels of immature forms of the oxytocin molecule are elevated following cesarean, with unknown implications.

Immediately following PLCS, newborns have OT levels that are one-half to one-third of levels in vaginally-born babies,[174, 306, 307] likely due to lack of the beneficial eustress of labor (3.1.3). Low OT levels may contribute to higher newborn pain sensitivity following CS.[302] After the initial hours, newborn levels may be equivalent for CS and vaginally born babies.[174] Newborn OT elevations with SSC and breastfeeding produce "calm and connection" effects and may be important in reducing high E-NE levels, which can persist following CS[672] (see also "Oxytocin and maternal-newborn contact and interactions" in 3.1.4 and "Cesarean and the fetus/newborn" in 5.2.6).

One study found that, following PLCS, newborns had higher levels of "extended forms" of OT, also called OT-X, compared with vaginally born babies.[673] These are immature forms of the OT molecule that have not had the terminal section enzymatically cleaved. The role of OT-X in labor and for the newborn is uncertain. OT-X levels are elevated in autistic individuals[674] and increased risks of autism following CS compared with vaginal birth have been found in some studies.[675-678] (See also "Cesarean and Offspring, Longer Term," below, and "Cesarean and the Fetus/Newborn" in 5.2.6 for more discussion of possible long-term CS effects.)

Cesarean and Breastfeeding

Breastfeeding initiation rates are lower following prelabor cesarean, but continuation rates following cesarean and vaginal birth may be similar. Following in-labor unplanned cesarean, oxytocin and prolactin release may be reduced, possibly reflecting a prolonged delay to first breastfeed. Early mother-newborn contact and breastfeeding initiation may be important following cesarean to optimize hormonal physiology for both.

A recent systematic review concluded that breastfeeding initiation rates are reduced following PLCS, but not in-labor unplanned CS, compared with vaginal birth. Authors suggest, " . . . the metabolic or endocrine milieu of labor may be paramount to initiating lactation."[679(p.1131)] This implicates the OT system and likely also PRL, where receptor numbers may also be low when full preparations for labor are missed (6.1.2). If breastfeeding is initiated, rates are not reduced at six months following CS compared to vaginal birth, according to this review.[679]

Researchers have found disruption to hormonal release during breastfeeding, two days after an emergency CS. Specifically, new mothers had reduced or absent OT pulses, along with lack of the expected rise in PRL levels (probably due to reduced OT), compared with women following vaginal birth. Breastfeeding initiation occurred on average at 240 minutes after CS compared with 75 minutes following vaginal birth, and the delay in first breastfeeding correlated with fewer OT pulses. In addition, the number of OT pulses predicted the duration of excusive breastfeeding following vaginal birth.[354] Authors suggest, ". . . early mother-infant contact together with the passage of the fetus through the vagina during the second stage of labour can enhance the stimulation of oxytocin neurons . . . ."[354(p.96)] Both vaginal birth and early contact promote OT elevations in mother and baby, which may contribute to these breastfeeding benefits. Oxytocin-stimulated PRL elevation may also contribute (6.1.4).

In a CS study mentioned above, newborns who were randomized to uninterrupted maternal SSC breastfed earlier than infants in the control group, who were separated from their mothers for 25 minutes while in SSC with the father.[395] The calming effects of SSC and maternal odors may contribute via newborn OT release (see "Skin-to-skin contact" in 3.1.4).

These findings suggest that early SSC, with opportunities to initiate breastfeeding, may be especially important for mothers and babies following CS.

Cesarean and Maternal Adaptations and Attachment

Peaks of oxytocin and other hormones released during labor, birth, and the early postpartum period promote maternal adaptations that enhance infant care and survival. The absence of these peaks has major impacts on maternal behaviors in animals, but high-quality human research is lacking.

Cesarean and psychological well-being. *Psychological well-being after cesarean has not been well studied. Research has suggested poorer maternal adaptations, elevated risk of postpartum depression, and the possibility of post-traumatic stress disorder, along with a reduction in self-esteem from pregnancy levels. Lack of the hormonal peaks of physiologic birth may contribute*

Psychosocial studies show that women who have experienced a cesarean, compared with those who birth vaginally, may have: lower satisfaction with the birth,[680] with high numbers of women reporting one or more distressing events;[681, 682] poorer mood in hospital and at 8 months, correlated with the delay in first contact with their newborn;[432] and diminution in mood and self-esteem from levels in pregnancy, compared with women birthing vaginally who experienced an elevation in self-esteem (detailed below).[434]

Some but not all studies have found associations between CS and postpartum depression.[683] A 2007 review of psychosocial outcomes after CS concluded, " . . . women who deliver by cesarean section have more negative perceptions of their birth experience, their selves, and their infants, exhibit poorer parenting behaviors, and may be at higher risk for postpartum mood disturbance compared to women delivering infants vaginally."[680(p.2272)]

Because CS studies are not randomized, these findings may reflect some degree of preexisting psychological differences among mothers with CS.[684] However, a prospective trial of new mothers showed that, following vaginal birth, women experienced an elevation in mood and self-esteem, compared with their levels in pregnancy, while women who experienced CS had diminished mood and self-esteem, with women having instrumental births experiencing, on average, no change compared with pregnancy baseline.[434] Central effects from hormonal peaks may contribute (3.1.4).

Other studies have suggested that post-traumatic stress symptoms, or even full post-traumatic stress disorder (PTSD), may be more likely after planned[685] and/or unplanned CS.[686-688] The relative roles of subjective traumatic experiences and loss of hormones such as OT, which reduce stress and increase calm and connection, have not been investigated. Outside of childbearing, therapeutic synOT has been trialed as a treatment for PTSD,[206] and postpartum OT elevations following birth and/or with newborn contact could plausibly be protective against PTSD for new mothers (see "Pleasure and reward" in 3.1.4).

Researchers have also found a decrease in the expected shifts in maternal personality—decreased anxiety and increased "social desirability" (3.1.4)—among women who experienced an unplanned in-labor CS compared with women who gave birth vaginally. Researchers suggest that peaks of central OT with birth (see "Maternal adaptations" in 3.1.4) may play a role in these adaptations to motherhood.[360]

This is a complex area with many determinants, but absence of the positive central effects of labor-related hormones may be a significant unintended adverse effect of CS for new mothers. Early newborn skin-to-skin contact may be especially important for women following CS to activate OT systems and elevate mood. Given current high rates of cesarean section, and concerns about maternal postpartum psychological well-being, these are critical areas for future research.

Cesarean and attachment. *Maternal-infant attachment following a cesarean may be impacted by reduced prelabor and in-labor physiologic preparations, including the central oxytocin receptor elevations that promote maternal-infant attachment in animal studies. Post-operative delays in maternal-infant contact, and surgery-related reductions in maternal odors and hormonally-mediated warmth may also have adverse effects in mother and baby. Central maternal circuits may be less activated in new mothers following cesarean. A hormonally sensitive period may exist following cesarean.*

Animal studies show adverse impacts on maternal behavior and attachment following CS.[100, 212, 372] In some species, vaginocervical stimulation, mimicking the process of birth and releasing a surge of OT (see "Maternal Oxytocin in Labor and Birth" in 3.1.3), reinstates maternal behaviors.[211]

Attachment between human mothers and babies following CS has not been well studied. One review found that "Caesarean delivery may exert at least short-term adverse impacts on mother-infant attachment."[432(p.73)] A recent study using magnetic resonance imaging (MRI) (also discussed in "Maternal adaptations" in 3.1.4) found a reduction in the brain responses of new mothers on hearing their babies' cry two to four weeks after PLCS, compared with mothers who had given birth vaginally. In particular, sensory processing, empathy, arousal, motivation, reward, and habit-regulation circuits were less activated. Authors suggest that ". . . differential release of oxytocin with the vagino-cervical stimulation of VD [vaginal delivery]" may explain these findings.[423(p.1045)] Loss of early contact, with opportunities for biologic bonding (3.1.4), may also contribute.

One study that randomized post-CS newborns to SSC with the mother or father found that newborns cried more in SSC with the mother than the father. Researchers suggest that surgical cleaning, leading to lack of maternal skin and breast odors, which are soothing to the newborn;[689] and/or cooler body temperature, due to lack of OT-associated postpartum vasodilation, may contribute. (In contrast, fathers "presumably retained their natural capacity to calm the infant, by warmth, pleasant odors, and vocalizations."[395(p.63)]) Cooler maternal body temperatures could also fail to activate, and mutually regulate, newborn OT systems (see "Skin-to-skin contact" in 3.1.4).

In this study, mothers in SSC released moderate levels of oxytocin (levels elevated about 50 percent compared with those at birth), with equivalent levels in women who were close to, but not touching, their babies. These are lesser elevations compared with mothers in SSC following physiologic birth, whose OT increased around two- and even, in one case, ten-fold. These findings suggest significant maternal reductions in OT sensitivity, perhaps due to lack of OT prelabor physiologic preparations and/or birth peaks (3.1.2), with likely additional effects from surgery and stress.

This study (also discussed in "Synthetic Oxytocin and the Mother, Longer Term" in 3.2.3) found that women who received extra synOT by IV infusion post-CS (but not those who received only a standard single dose) had an increase in their own OT levels, with several peaks, during subsequent breastfeeding and also experienced the usual maternal adaptations and personality changes two days after CS (see "Maternal adaptations" in 3.1.4). Researchers suggest that synOT in this situation may have central effects, although the mechanism is unknown, and conclude that a sensitive period may also exist for women following CS, with possible benefits to future mother-infant interactions.[395]

As with epidurals (3.2.5), possible CS effects on maternal adaptations are subtle, according to current understandings, but may be significant in the longer term. Post-CS, mother and newborn may benefit from strong support for early and uninterrupted mother-baby contact, including undisturbed SSC for the first hour or more after cesarean birth. These are important areas for further research.

Cesarean and Offspring, Longer Term

Evolving evidence suggests long-term impacts of cesarean birth, including possible impacts on oxytocin systems. Preliminary findings in relation to childhood social functioning are contradictory. Animal studies suggest changes in brain structure and function. High-quality long-term human studies, especially studies with a control group unexposed to other drugs and procedures, are lacking.

From the perspective of hormonal physiology, cesarean birth is a very different experience for offspring from the stimulation and eustress of labor and birth (3.1.3, 4.1.3, 5.1.3, 6.1.3). Evolving evidence suggests that CS birth may have ongoing, even lifelong impacts on human offspring,[40, 690-693] some of which may be due to deficits in hormonal experiences and exposures, including lack of hormonal stimulation.

Animal studies show enduring effects on brain-hormone systems.[27-31, 138-141] (further described in "Cesarean and the Fetus/Newborn" in 5.2.6.) Associations between CS and childhood obesity[691, 692] could also involve the OT system and its role in satiety and autonomic nervous system balance. Cesarean newborns also experience major alterations in gut colonization, which could also contribute.[147] (See also "Cesarean and the Fetus/Newborn" in 5.2.6 for discussion of possible long-term impacts for CS offspring in relation to stress systems.)

Studies examining psychosocial functioning in CS offspring, compared with children from vaginal births, have found both beneficial[694] and detrimental[695] CS effects. A Chinese study found the highest levels of negative internalizing and externalizing behaviors among children born with forceps and the lowest by maternal-request CS. The drugs and interventions that accompanied vaginal birth were not stated in this study, and exposure to synOT and other drugs may have mediated the poorer outcomes for children following vaginal birth. (Similarly, a study of children exposed or not to synOT, found worse developmental scores among children following vaginal birth compared with CS, which was related to the duration of synOT exposure[582, 584] (see "Synthetic oxytocin and offspring, human studies" in 3.2.3). In contrast, another study found more internalizing, and also anxiety/depression, withdrawal, and sleep problems, among five-year-old children born by CS, compared with vaginal birth.[695]

Given current high CS rates, including CS for non-clinical reasons, elucidating and modeling the links between CS, offspring hormonal functions, and later health are critical areas for future research.

3.2.7 Early Separation of Healthy Mothers and Newborns: Possible Impacts on Oxytocin

Early separation disallows the maternal-infant contact that activates the oxytocin systems of mother and baby, with beneficial longer-term effects for both.

Postpartum transitions for mother and baby are optimized by early and ongoing SSC[696] during the postpartum sensitive period (see "Skin-to-skin contact" and "Postpartum sensitive period" in 3.1.4). The pre- and in-labor physiologic preparations of physiologic birth, as detailed in 2.2, 3.1.2 and 3.1.3, can maximize these benefits, with peak postpartum levels of oxytocin,[259, 316] acting on peak oxytocin receptors in the brain and mammary gland, according to animal studies.[86-88, 98, 99, 244] Early uninterrupted SSC and breastfeeding initiation can benefit maternal breastfeeding hormones,[354] maternal adaptations and attachment,[336, 375, 384] newborn aspects of breastfeeding,[351] and possibly postpartum hemorrhage, as discussed in 3.1.4.[316] Separation of mother and baby after birth disallows these processes, and may adversely affect OT system functions in the short and possibly longer-terms.

Early Separation and the Mother

For the mother, early separation removes the opportunity to release her own oxytocin through interactions with her newborn, which may give physiologic protection against postpartum hemorrhage.

Postpartum SSC between mother and baby is a prerequisite for the maternal-newborn interactions, especially infant hand massage of the mother's breast, that increase maternal OT release during the hour after birth, as measured in the blood in women.[316] Release of oxytocin in response to breast stimulation seems to be maximal in the first hour after birth (see "Oxytocin and maternal-newborn contact and interactions" in 3.1.4). Postpartum oxytocin peaks also occur in the maternal brain, according to animal studies.[263, 371]

Women experiencing early separation may miss these opportunities for OT release, which may act on upregulated uterine OTRs to cause uterine contractions and reduce PPH, although this has not been well

researched (see "Oxytocin and postpartum hemorrhage" in 3.1.4). In addition, central OT peaks, acting on maximally sensitive brain areas with peak OTRs at this time (animal studies), may activate maternal circuits and adaptations, with ongoing benefits to maternal caregiving and maternal-infant attachment[375, 384] via biologic bonding processes (see "Early Separation and Maternal Adaptations and Attachment," below, and 3.1.4).

Early Separation and the Newborn

For the baby, lack of skin-to-skin contact, and the associated oxytocin elevations, may increase, or fail to decrease, stress and stress hormone levels, with possible detrimental effects to newborn stress systems.

For the newborn, OT release through SSC reduces the "stress of being born"[337] and associated stress hormone elevations[175] (5.1.4). One study of newborns who were randomized to separation or SSC for the first two hours postpartum found persisting detrimental impacts on autonomic function (colder feet, reflecting higher levels of E-NE and/or lower levels of OT) for up to 23 hours postpartum among separated newborns.[175] (For a full discussion about newborn stress with separation, see 5.1.4 and 5.2.7.)

Other studies have found less stable temperature, heart rate, and breathing, and less optimal neurobehavioral responses among separated babies compared with SSC newborns. (See Moore[336] for a systematic review.) This homeostatic dysregulation may reflect excessive stress hormones and low OT levels among separated newborns (5.1.7).

Early Separation and Breastfeeding

Early separation has well-established, detrimental effects on breastfeeding initiation, possibly via oxytocin and/or prolactin disruptions.

The detrimental impacts of early separation, with delayed initiation of breastfeeding, on overall breastfeeding success are well established.[336, 353] Loss of early stimulation of the OT system likely contributes (3.1.4), possibly also affecting PRL, which is stimulated by OT release. (See also "Prolactin receptor theory" in 6.1.4.)

Early Separation and Maternal Adaptations and Attachment

Studies have suggested that early maternal-newborn separation and loss of skin-to-skin contact during the hour or so after birth can compromise maternal adaptations and behaviors, with longer-term detrimental impacts on the mother-infant relationship.

Studies comparing SSC and separated mothers and newborns have found impacts on attachment behaviors for up to three years.[697-700] One randomized study that analyzed mother-infant interactions at one year found that mother-newborn contact soon thereafter ("rooming in") did not compensate for loss of early SSC after birth,[375] perhaps highlighting the critical and brief nature of this sensitive period for biologic aspects of bonding (see **"Postpartum sensitive period"** in 1.1.4). Although not well studied, there may also be a maternal sensitive period for attachment following CS birth,[395] so that early SSC may also be important in this situation (3.2.6, 5.2.6).

Early separation and attachment. *The detrimental impacts of early separation of healthy mothers and newborns could have long-term consequences by disrupting the early development of offspring attachment and attachment systems. Trans-generational programming effects are possible via epigenetic mechanisms, according to animal models.*

Optimizing early attachment through supporting SSC for healthy mothers and newborns may be a simple strategy that benefits all mothers and babies in the period after birth, including those at risk of poor

attachment, neglect, and abuse, by initiating hormonally-mediated biologic bonding (3.1.4). Conversely, early separation, with loss of hormonal support for maternal adaptations and attachment, may be especially detrimental in this group. In one study, separation after birth was associated with twice the risk of infant abandonment, compared with mothers and babies who experienced postnatal SSC contact in a Baby-Friendly Hospital.[701] These are important areas for future research.

In animal studies, maternal-newborn separation also negatively impacts the offspring HPA-stress system, giving lifelong increased susceptibility to stress among offspring separated for several hours per day during the newborn period (5.3.7).[35, 702] Lack of OT generated through maternal contact could contribute to these impacts. (See 5.2.7.)

In addition, animal studies show epigenetic changes in the OT systems of female offspring in relation to the quantity of maternal care received during infancy. Females exposed to low levels of maternal care give low levels of care to their own offspring, and have reduced central OTRs.[35] (See "Maternal-infant attachment" in 3.1.4 for full discussion.)

Early separation and maternal well-being. *Maternal well-being may also be impacted by early separation, according to animal studies, with anxiety and depression-like effects among separated mothers. Loss of the positive effects of oxytocin and other hormones may contribute.*

Separating the mother from her newborn, or delaying reunion after birth, may have detrimental impacts on maternal physiology and well-being. Animal studies show anxiety and depression-like behavior in mothers who have been separated from their newborns for several hours per day.[703, 704] This has been suggested as an animal model for postpartum depression.[704] Loss of opportunities to release OT through lactation and infant contact may contribute.

In women, a longer period before first contact after birth has been correlated with poorer mood in hospital and at eight months, compared with those who had earlier contact with their newborns.[432] Lack of OT and other mood-elevating hormones (3.1.4, 4.1.4, 6.1.4) and their longer-term central reorganizing effects that promote biologic bonding and reward center activation in the early sensitive period (3.1.4), likely contribute. The mood-enhancing benefits of maternal-infant SSC may continue after birth. One study found reduced postpartum depression scores during the first month among mothers who had at least two hours of SSC daily with their newborns[399] (see 3.1.4).

Given the major morbidities for mothers and babies affected by postnatal depression,[705] the correlations between SSC/early separation and maternal emotional well-being are critical areas for future research.

3.3 Oxytocin Physiology: Summary

3.3.1 Oxytocin: Normal Physiology

Oxytocin is a powerful reproductive hormone with widespread effects on the brain and body of all mammals, for example, by mediating sperm ejection, labor contractions, and milk ejection. Oxytocin also reduces stress by centrally activating the parasympathetic nervous system, which promotes calm, connection, healing, and growth; and by reducing activity in the sympathetic nervous system, which reduces fear, stress, and stress hormones, and increases sociability. Oxytocin has a short half-life, but its effects can be prolonged because it modulates other brain-hormone systems (neuromodulation).

In the perinatal period, oxytocin optimizes labor, birth, and postpartum transitions of mother and baby through:

- central oxytocin release into the maternal bloodstream, causing rhythmic uterine contractions, including the late-labor oxytocin surge that benefits pushing (Ferguson reflex)
- central calming and analgesic effects in mothers and babies in labor through the postpartum period
- positive feedback of central oxytocin on itself, especially in multiparous mothers, augmenting and accelerating in-labor effects (animal studies)
- postpartum maternal adaptations that reduce stress, increase sociability, and prime reward centers, imprinting pleasure with infant contact and care, therefore promoting longer-term infant survival

Prelabor increases in uterine oxytocin receptors (human studies) and oxytocin receptors in brain and mammary glands (animal studies) maximize these effects.

The hour or so after physiologic birth is a sensitive period, when skin-to-skin maternal-newborn interactions foster peak oxytocin activity. Benefits may include:

- stronger contractions, likely reducing postpartum hemorrhage risk
- natural warming for the newborn through vasodilation of mothers' chest
- activation of hormonally-mediated maternal-infant biologic bonding
- facilitation of breastfeeding initiation, including by reducing maternal and newborn stress

3.3.2 Common Maternity Care Practices That May Impact Oxytocin Physiology

Common maternity care practices may disrupt these and other beneficial oxytocin effects, with short- and longer-term impacts in mothers and babies. High-quality research is lacking.

While the administration of synthetic oxytocin for induction or augmentation is beneficial in selected circumstances, adverse impacts have been found in women and babies. Synthetic oxytocin administered in labor is not thought to cross into the maternal brain in biologically significant amounts, and so may lack calming and analgesic effects. However, when synthetic oxytocin stimulates contractions, positive feedback cycles may lead to central oxytocin release, promoting further contractions, labor progress, and continued central release.

Synthetic oxytocin may impact maternal oxytocin and physiology. Possible effects include:

- uterine hyperstimulation with potential fetal hypoxia, requiring monitoring
- stronger contractions and increased pain without central oxytocin analgesia
- synthetic oxytocin overexposure causing desensitization of oxytocin receptors, contributing to reduced contractility, prolonged pushing, instrumental birth, and/or postpartum hemorrhage
- disruption of newborn breastfeeding behaviors, reduced maternal oxytocin release with breastfeeding, and possible reduced breastfeeding duration

Physiologic principles, animal studies, and evolving human evidence suggest that perinatal synthetic oxytocin exposure may have longer-term impacts on offspring. While high-quality research is lacking, potential mechanisms include:

- direct fetal brain-hormone effects from synthetic oxytocin transfer through placenta
- indirect signaling of maternal oxytocin to fetal brain
- indirect effects from subclinical hypoxia
- interference with fetal neuroprotective mechanisms (animal studies)
- fetal/newborn impacts from synthetic oxytocin co-interventions such as epidural
- long-term programming of offspring hormonal systems, likely via epigenetic effects (animal studies)
- indirect effects via disruptions to maternal oxytocin systems that impact attachment, reward, breastfeeding, and/or mutual regulation

Epidural analgesia reduces maternal oxytocin in labor, likely due to numbing of the sensory feedback that promotes central oxytocin release. Possible impacts include:

- slowed labor with increased need for synthetic oxytocin
- prolonged pushing stage with increased use of assisted vaginal birth
- disruption of maternal adaptations and attachment

These can also adversely affect the newborn. High-quality research is lacking.

With prelabor cesarean section, mothers and babies miss their complete prelabor physiologic oxytocin preparations; and with any cesarean section, the full oxytocin processes, including the maternal late-labor oxytocin surge and postpartum oxytocin peaks, may be reduced or absent. Impacts on breastfeeding, maternal adaptations, and postpartum hemorrhage have been found. Scheduled cesarean carried out after the physiologic onset of labor may have fewer adverse oxytocin impacts than prelabor cesarean section.

Postpartum separation of healthy mothers and newborns may have detrimental short-and longer-term impacts on the oxytocin system, including:

- reduced oxytocin due to lack of skin-to-skin contact, with increased newborn stress and stress hormones, hypoglycemia, and hypothermia
- disruptions to breastfeeding initiation and long-term success
- deficits in maternal hormones and adaptations, with longer-term impacts on maternal-infant attachment

In animal studies, variations in maternal caregiving in the newborn period lead to epigenetic programming of offspring oxytocin systems, with enduring effects on offspring stress reactivity, and on the maternal care given by female offspring.

4
Beta-Endorphins

Beta-endorphins are included in this report because of their roles in reducing stress and pain during childbearing, and, in activating central reward centers that motivate and reward reproductive behaviors, including labor, birth, postpartum infant care, and lactation. In addition, a growing body of research suggests important roles in health and well-being, including mental health. Beta-endorphins are not as well researched as some other hormone systems, especially in relation to possible impacts of maternity care interventions. However, epidural analgesia and opioid analgesic drugs may especially impact the physiologic functioning of beta-endorphins, with uncertain effects into the future.

4.1 Beta-Endorphins: Normal Physiology

Beta-endorphins have important roles in reproduction due to their stress-reducing effects and also involvement with brain-based motivation and reward circuits, which promote mammalian maternal behaviors.

Beta-endorphin and related hormones (referred to here as "beta-endorphins" or BEs) have not been as well researched as oxytocin. However, as with oxytocin, there is a growing awareness of the importance of these and other endogenous opioid substances in many biological processes, including reproduction, immune function, social interactions, and psychological well-being.[706]

Beta-endorphins are included in this report because of their important role in reducing excessive stress and pain in mother and baby during physiologic labor and birth and, along with oxytocin (3.1.4), in activating brain-based motivation and reward circuits that optimize mammalian maternal adaptations.[404] In addition, according to principles of epigenetics and fetal/newborn programming (3.1.2, 3.2.3), the functioning of BEs in the perinatal period may be important in priming offspring BE systems lifelong.

4.1.1 Beta-Endorphins: Introduction

Beta-endorphins are a group of peptides (biologic chemicals made from amino acids) that have major roles in pain management and brain reward center activation, with effects that overlap with opioid drugs such a meperidine and morphine.

Beta-endorphins ("endogenous morphines") have properties in common with opioid (opiate-related) drugs, including pain relief and reward system activation.[706] Commonly used opioid drugs (discussed further in 4.2.4 and 3.2.4) include**:**

- opiates, naturally derived from the opium plant: morphine and codeine
- synthetic opioids: meperidine (Demerol, pethidine), heroin (diamorphine), fentanyl (Sublimaze, Duragesic), tramadol, methadone, meptazinol (Meptid), nalbuphine (Nubain), pentazocine (Talwin, Fortral), buprenorphine (Temgesic, Buprenax) and butorphanol (Stadol)

Opioid antagonists, including the short-acting drug naloxone (Narcan) and the longer-acting naltrexone (Revia), reverse the effects of both endogenous and exogenous opioids by binding with the mu opioid receptor (MOR, discussed below).

Beta-Endorphins Effects

Beta endorphins act primarily in the central nervous system, where they inhibit nerve function, producing analgesia, among other effects.

Beta-endorphins are produced in both peripheral body tissues and in the central nervous system (CNS), including the hypothalamus and pituitary gland, through the chemical cleaving of the pro-hormone pro-opiomelanocortin (POMC). This produces several endorphin-like substances, including: beta-endorphin proper, also called BE (1-31); beta-lipotropin; N-terminal derivatives; and other related peptides, which are released into the bloodstream. Because most analytic techniques have not been able to differentiate among these,[707] they have been collectively called "BE immunoreactive material (BE-IRM)" or "beta-endorphins,"[708] as used in this report.

Beta-endorphins act primarily within the CNS, where they inhibit the functions of other nerves, including those that transmit pain, giving powerful analgesic effects. Nerve cells (neurons) that produce BEs extend down into the spinal cord, where they inhibit sensations arising from the body. In addition, BEs are released from the pituitary into the bloodstream in situations that include pain, exercise, sexual activity, and social interactions. Effects from bloodstream release are not well understood, and, as with OT (3.1.1), blood levels of BEs may not reflect brain-based (central) levels and effects.[709]

Beta-endorphins and the stress response. *Release of beta-endorphins in the central nervous system is part of the medium-term stress response, designed to restore homeostasis. This response involves other hormones such as cortisol and, in some situations, prolactin. Hormone responses to appropriate, healthy "eustress," such as the stress of labor and birth, are generally beneficial. However, excessive stress, with elevated or prolonged stress hormone levels, can have maladaptive or even harmful effects. The balance between healthy and harmful stress and stress hormone levels varies across individuals.*

In humans, as in other mammals, stress, distress, or pain trigger release of the major stress hormone corticotropin releasing hormone (CRH, also known as corticotropin releasing factor, CRF) from the hypothalamus, which stimulates the release of BEs both within the brain and from the nearby pituitary into the bloodstream.

Beta-endorphins are generally co-released into the bloodstream with adrenocorticotropic hormone (ACTH), which promotes the release of cortisol from the adrenal gland as part of the medium-term (hours to days) hypothalamic-pituitary-adrenal (HPA) stress response. Short-term stress responses (usually seconds to minutes), which involve release of the fight-or-flight hormones epinephrine and norepinephrine (E-NE, adrenaline and noradrenaline), also stimulate CRH release and the subsequent release of BEs (see also 5.1.1).

As part of this general stress response (also called "general adaptive syndrome" or GAS[710]), which is designed to restore homeostasis, BEs are also released into the brain, with BE (1-31) acting as a neurotransmitter with central analgesic effects. In addition, BEs promote the release of prolactin (PRL), which can also function as a stress hormone, with multiple adaptive effects on the body[121] (6.1.1). These complex, coordinated processes all enhance adaptations to excessive stress.

In general, brief and/or mild-to-moderate elevations of these stress hormones, or appropriate elevations in relation to physiologic events (also termed "eustress"[711]) are part of the GAS, with beneficial effects. This includes elevations in BEs that aid with stress and pain in labor, and that adapt the woman to new motherhood after birth. However, extreme and/or prolonged elevations of BEs can have detrimental effects by reducing motor and social behaviors.

Too-low levels of adaptive hormones in response to stress and pain may also be detrimental by giving insufficient assistance. It seems that with BEs, as with stress in general,[712] there is an adaptive mid-range level of response, which depends on individual systems and sensitivity and likely reflects receptor numbers. This level is not currently possible to quantify for the individual, which may complicate attempts to correlate levels of BEs in response to stress with beneficial or detrimental effects,[709] as detailed below (4.1.3).

Beta-endorphins, other effects. *Other effects of beta-endorphins include activating brain reward centers that motivate and reward essential behaviors such as eating, mating, birthing, lactating, caring for infants, and adult social behaviors. High levels may signal satiety and reduce motivation. Beta-endorphins are also involved with the immune, respiratory, and gastrointestinal systems, and implicated in conditions that include anxiety, addiction, obesity, depression, and autism.*

Within the brain, BEs not only enhance adaptations to stress, but also activate powerful dopamine-associated reward circuits, giving pleasure and even euphoria.[706] Beta-endorphins are involved with motivating and rewarding important survival behaviors, including the following:

- food ingestion[713]
- sexual activity and mating[714]
- labor and birth (4.1.3)
- lactation (4.1.4)
- maternal caretaking behaviors (4.1.4)

BEs are also released during exercise,[715] especially if strenuous,[716] or repeated.[717] Exercise-related mental health benefits, equivalent to anti-depression treatments according to a recent review,[718] are likely related to elevations in BEs, which can persist for one hour following strenuous exercise.[719] (See 4.1.3 for effects of exercise on labor pain.)

The elevated levels that follow activities such as exercise, sexual activity and food ingestion may also signal satiety, and promote cessation by reducing motivation. In contrast, low or declining levels of BEs may increase motivation. For example, declining BEs in the postpartum period may motivate mothers to seek closeness ("proximity seeking") and to care for newborns (4.1.4). Very high levels of opioids, for example high doses of morphine,[720] disrupt maternal behaviors in animals, which may reflect high satiety and low motivation.

Opioids, including BEs, are also released during mammalian adult social interactions, when they motivate and reward social affiliation and cohesion. This has important survival value, both for animals living in the wild, and for humans alive today. This may even make aspects of mammalian social behavior "addictive phenomena."[404]

The endorphin BE (1-31) is recognized as a powerful analgesic when released within the CNS, but it is ineffective when administered into the body because it does not easily cross the blood-brain barrier.[721] However, central administration gives analgesic effects in animals[722, 723] and humans.[724] In one clinical case, BE (1-31) was shown to give prolonged analgesia over 21 hours when administered directly into the brain of a man with intractable cancer pain.[724]

New understandings of the endogenous opioid system also suggest major and widespread influences on health and well-being. Beta-endorphins are involved in functioning of the immune, respiratory, and gastrointestinal systems (with inhibiting effects similar to those of opioid drugs); and dysfunctions have been implicated in arthritis, epilepsy, binge-eating, and alcoholism.[725, 726] Dysfunctions in BEs have also been implicated in obesity, depression, anxiety, addictions, and possibly other mental health issues.[706, 725, 726] In addition, excessive opioid activity (levels and/or receptors), which could reduce social motivations, has been implicated in autism.[727, 728] (See 4.2 for impacts of maternity care interventions on BE systems and possible implications.)

Beta-Endorphins: Regulation and Receptors

Beta-endorphins are primarily released in response to pain and stress.

Beta-endorphins receptors. *The major endorphin, beta-endorphin (1-31), acts by binding with the mu opioid receptor. Oxytocin and prolactin promote release of beta-endorphins, and in turn beta-endorphins promote prolactin. Beta-endorphins inhibit oxytocin release in the lead-up to labor, possibly restraining labor onset.*

Among the BEs, beta-endorphin (1-31) is thought to be the major effector of stress and pain responses,[707] and acts by binding with the MOR, of which there are several subtypes. Mu and other opioid receptors have also been found in the myometrium of women in late pregnancy, where mu activation has relaxant effects[596] (4.1.3).

Regulators and promoters of BEs relevant to the context of childbearing include**:** oxytocin (OT), which promotes release of BEs (3.1.3), assisting with labor stress and pain; and prolactin, which also promotes BEs.[125] In addition, BE promotes PRL release in the context of stress[121] (4.1.3). In the lead-up to labor, central BEs inhibit OT release, which may help to prevent premature contractions prior to the physiologic onset of labor, according to animal studies.[95]

Beta-endorphins complexities. *There are significant complexities in understanding the healthy functioning of beta-endorphins and interpreting studies of endogenous BEs at an individual level. These include methodological problems with measurements and a wide variation in individual baseline levels that may reflect differing sensitivity and receptor systems. Mid-level beta-endorphin responses to stress may be most adaptive.*

As discussed above, the technical ability to differentiate the BEs in blood samples, and their relative contribution to physiologic effects such as analgesia, has been problematic. In addition, the major role of BEs is within the CNS, where levels are not measurable in human studies. Because levels measured in the blood have generally correlated with physiologic effects, it has been presumed that this reflects central effects, but, as with oxytocin, this is not certain. In some studies, levels in cerebral spinal fluid (CSF), which more accurately reflect central release, have not correlated with blood levels.[709]

In addition, measurement of baseline BEs in individuals has not always correlated with the expected characteristics and effects. As with levels of BEs in response to stress, individual differences likely reflect differing receptor numbers and sensitivities, which may be related to early hormonal experiences. For example, high baseline BEs has been associated with greater pain sensitivity, likely reflecting lower MORs.[709] In stress responses involving BEs, as with other stress hormones such as cortisol, low levels may reflect an inadequate response, while high levels signal excessive stress. Because of apparent individual differences in sensitivity, the mid-range, adaptive level of BEs is likely to be unique to the individual, as discussed above.

4.1.2 Beta-Endorphins in Pregnancy

Levels of BEs rise in pregnancy. Animal studies show peak central BEs and receptors around the physiologic onset of labor. The fetus, membranes, and placenta also release BEs. Regular exercise in pregnancy may promote the release of BEs in labor, promoting endogenous analgesia.

During pregnancy, levels of BEs rise, as measured in maternal blood.[729-731] Plasma levels in pregnancy follow a diurnal pattern, being lowest around 8 a.m. and 8 p.m. and peaking around midday and midnight.[239] The immunosuppressive effects of BEs may also be important in making the mother tolerant to her immunologically-foreign fetus.[732, 733]

Maternal pain tolerance increases in late pregnancy, giving a “pregnancy induced analgesia” that peaks on the day when labor starts, as demonstrated in women[734, 735] and animals.[736, 737] This is likely due to increases in central mu opioid receptor numbers[92-94] and central levels of BEs,[92, 96] which both peak around the physiologic onset of labor, according to these animal studies. In addition, the pregnancy hormones estrogen and progesterone trigger the activation of non-BE opioid systems (kappa and delta opioid receptors) in the spinal cord, according to animal studies, giving additional analgesia that continues through to the postpartum period.[77]

Beta-endorphins are also produced by fetal tissues within the placenta and are also present in high levels in the amniotic fluid from early pregnancy.[738] It has been suggested that placental BEs (PBEs), which increase with gestation as measured in the maternal blood, may reward the mother for gestating her baby.[732] The placenta and amniotic fluid also contain placental opioid-enhancing factor (POEF), which potentiates the effects of non-BE opioids, and may also promote maternal behaviors.[739] Most non-human mammals eat the placenta after birth,[740] giving extra sources of rewarding and pain-relieving hormones at this time.[740]

In women, several studies have correlated levels of BEs in pregnancy with later outcomes, although results are not easy to interpret. Low levels[730] or dysregulation in relation to ACTH[741] have been associated with greater analgesia requirements in labor. In other research, non-depressed women with higher BEs in mid-pregnancy were more likely to experience postpartum depression than non-depressed women with lower mid-pregnancy BEs. Researchers suggest that postpartum depression may be related to the larger drop in BEs postpartum in these women, who may have an underlying dysregulation of the HPA axis that is masked during pregnancy[731] (4.1.4).

One study randomized pregnant women to flexibility and endurance exercises or a control group and found higher levels of BEs in labor, with less reported pain, among women who exercised in pregnancy.[742] Another study found that the release of BEs in response to exercise was enhanced in pregnancy.[743] Together, these suggest that regular exercise in pregnancy may enhance BEs in pregnancy and labor, with reduced need for analgesia.

The complex central interactions involving BEs and other hormones may be modified in pregnancy and labor. As discussed above, high central BEs in late pregnancy inhibit OT release in the brain, which may restrain the onset of labor,[251] according to animal studies. Conversely, oxytocin within the brain increases the release of BEs,[744] which may contribute to labor peaks of both hormones (3.1.3, 4.1.3).

4.1.3 Beta-Endorphins in Labor and Birth

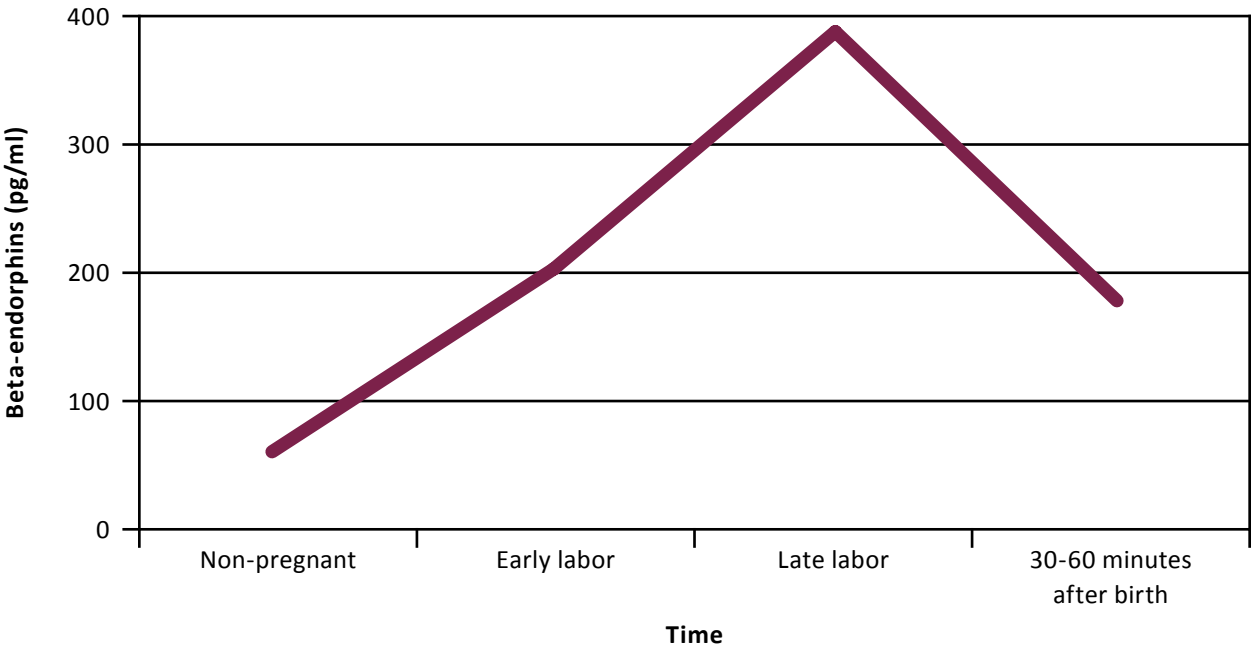
Maternal Beta-Endorphins In Labor and Birth

In physiologic labor and birth, eustress raises beta-endorphins (as measured in blood), assisting with stress and pain. However, excessive stress and pain may elevate central beta-endorphins above physiologic levels, inhibiting oxytocin release and slowing labor, as seen in animal studies. Some non-pharmacologic methods of labor pain relief may act via beta-endorphins. Peaks of BEs at birth may induce euphoria by activating pleasure and reward centers.

As shown in Figure 3,[745] levels of BEs, as measured in maternal blood, rise from early labor, peak in late labor, and decline in the early postpartum period. Levels are positively correlated with contraction strength, labor progress, self-reported pain, and rupture of membranes.[746-748] Peak levels during the pushing phase are four to eight times higher than levels prior to labor,[745, 747, 749, 750] and equivalent to those of athletes during endurance performance.[751] Analgesic effects are likely to be maximal during labor because of increased central MORs at this time (4.1.2).

Researchers using rapid sampling in laboring heifers found that BEs were released in pulses with each contraction,[752] possibly triggered by pulses of oxytocin, which stimulates its release (see “Beta-Endorphins: Regulation and Receptors“ in 4.1.1). Peripheral levels may reflect not only pituitary-derived, stress-related BEs, but possibly also BEs released from the placenta and amnion, which may have a local, but as yet undefined, role in labor progress[753] (4.1.2).

Figure 3. Women's beta-endorphins levels non-pregnant, in labor, and after birth



Source: adapted from Hoffman[745]

These elevations in BE activity (levels of BEs and receptors) may help the laboring woman deal with the stress and pain of labor. This keeps the labor experience within eustress levels without disruption to labor processes. Physiologic analgesic systems in labor—including BEs, non-BE opioid mechanisms (4.1.2), and oxytocin (4.1.3)—do not usually abolish pain entirely, although some women report no pain in labor.[754]

Some studies have found that women with higher levels of BEs in labor report less stress and/or pain,[742, 753, 755-757] whereas others have found elevated BEs to be associated with higher levels of stress and pain.[758-760] In one study, multiparous women had higher levels of BEs than primiparous women,[748] suggesting that prior experience fostered a more responsive BE system. This finding could also reflect stronger contractions and/or more stimulation for release of BEs. In another study of unmedicated multiparous women, "A considerable increase in beta-endorphin was found without severe stress or pain."[747(p.785)]

In relation to studies of BEs and non-pharmacologic measures to reduce pain, exercise training in pregnancy, as above,[742] and exercising during labor for 20 minutes on a bicycle,[756] both increased BEs with less pain reported, compared with controls, as did water immersion, in one study.[753] According to another study, electro-acupuncture increased levels of BEs and reduced labor pain.[761]

Outside of labor, high-frequency transcutaneous electrical nerve stimulation (TENS) has been shown to work though opioid mechanisms, likely involving BEs.[762] Diffuse noxious inhibitory control (DNIC), which involves producing a second pain elsewhere on the body, has also been shown to stimulate opioid mechanisms.[763] This may be the mechanism for the analgesic effects of procedures such as sterile water injections and acupressure in labor.[764]

In studies involving rats[251] and pigs,[765] excessive stress from disturbance in labor produced very high levels of BEs, which reduced central oxytocin release and inhibited labor. In women, stress-related elevations in BEs may act centrally and also locally on uterine MORs, which have been recently discovered in human myometrium, with inhibiting effects.[461] In addition, opioid drugs, which have BE-like effects, may slow labor, as discussed in 4.2.4. All of these observations suggest that the BE system may constitute another stress pathway in women, acting, in addition to E-NE, to slow labor in situations of stress and potential danger.[766] (See 5.2.1.)

These findings support a model of physiologic labor and birth in which physiologic elevations of BEs assist with the expected pain and eustress of labor, but excessive stress, pain, and elevation of BEs can inhibit oxytocin release and labor progress. This model, also supported by understandings of the E-NE system (Chapter 5), implies that attention to reducing maternal stress as far as possible, including through attending to maternal emotional well-being in labor, may be an important priority for supporting the physiologic processes of labor and birth of mother and baby. The higher rates of physiologic birth, reduced need for interventions, and good maternal-newborn outcomes that are associated with environments and maternity care providers that support maternal emotional well-being (4.2.1, 5.2.1) also support this model.

High levels of BEs also inhibit the transmission of visual and acoustic information[767] and may contribute to the altered state of consciousness that is reported with physiologic labor and birth.[768, 769] Although not specifically researched, this altered state might benefit the laboring mother by protecting her from external disturbances and directing her attention to sensations in her body, giving physical feedback in relation to her baby's position, so that she is more likely to move to facilitate optimal positioning. (See 5.1.4 for comments about E-NE aspects of this altered state of consciousness.)

High levels of endogenous opioids are associated with euphoric states via activation of central reward and pleasure centers.[404, 706] Central BE effects, including reward center activation with labor, birth, and newborn contact, are likely optimized by peak MORs at the physiologic onset of labor, as found in animal studies (4.1.2). Peak BEs in unmedicated labor, birth, and the postpartum period, may therefore promote "pleasure and transcendence" for the new mother.[768]

In addition, maternal elevation of BEs in labor may assist with subsequent lactation by promoting prolactin release[125] (6.1.1).

Fetal Beta-Endorphins in Labor and Birth

Beta-endorphins, released with labor hypoxia, may give fetal neuroprotection, as found in animal studies.

Both the fetal brain and the placenta can produce BEs during labor and birth. In humans, under normal conditions, BEs may be predominantly produced in the placenta.[729, 770] However, with hypoxic stress, the fetus releases additional BEs from the pituitary, giving central effects. Levels have been found to be several times higher in newborns who experienced excessive labor hypoxia.[729, 771] In animal studies, elevated fetal BEs give neuroprotective effects by maintaining blood flow to the brain under hypoxic conditions,[128, 129] which may also occur for the human fetus.

4.1.4 Beta-Endorphins after Birth

Maternal Beta-Endorphins after Birth

Levels of beta-endorphins, as measured in maternal blood, decline in the hour after birth but central levels may be elevated for many hours, with ongoing reward and reward system activation. Postpartum maternal-newborn interactions may contribute.

Levels of BEs, as measured in maternal blood, peak around the time of birth and decline over 30 to 60 minutes.[745] In one study, another peak occurred as the mother birthed her baby's placenta.[772]

Levels slowly decline to those of late pregnancy over one to three days postpartum.[750, 773] In relation to BE (1-31), the plasma half-life is estimated to be 37 minutes, but central effects may continue for 21 hours or longer, according to one human study[724] (4.1.1). After birth, ongoing contact between mother and newborn, including skin-to-skin contact (SSC) and breastfeeding, may continue to release BEs for mothers and babies, as found in animal studies.[404]

This not only gives reward and pleasure at the time, but may also prime reward and pleasure responses in association with infant contact, so that the new mother will continue to find her offspring rewarding into the future. Postpartum OT peaks may also contribute, and OT may assist reward center activation by reducing tolerance to BEs and the behaviors that promote release. (See "Beta-Endorphins and Maternal Adaptations and Attachment," below.)

Newborn and Later Beta-Endorphins

Newborn beta-endorphins also decline after birth, which may reinforce contact-seeking with the mother. Beta-endorphins in colostrum may reduce the stress of newborn transitions.

In human newborns, BEs continue to be elevated for several hours after birth, with a gradual decline to about 24 hours, possibly due to stress reduction with SSC.[774] Declining levels of BEs may trigger newborns to seek maternal contact and milk, which again elevates BEs.[404] As with the mother (4.1.1), there is likely to be an optimal individual level that assists with newborn motivation and reward in relation to maternal contact. Animal studies suggest that opioids also help the newborn to learn maternal odors,[404] and both animal and human evidence supports a role for opioids in mediating the positive effects of touch (including SSC) on infant calming, analgesia, and self-regulation.[774]

Beta-endorphins are present in colostrum at levels two-fold higher than in maternal plasma.[775, 776] These BEs are available to the newborn and ". . . may be of importance in overcoming stressful perinatal situations along with vaginal birth and in the postnatal development of several related biologic functions of breastfed infants, like analgesia, steroidogenesis, cardiovascular and endocrine functions, neuroimmunomodulation, sleep-wake patterns and behavior."[776(p.161)] These researchers found around 40 percent higher levels of BEs in colostrum among mothers experiencing vaginal birth compared with prelabor cesarean section (PLCS).[776] The possible impacts on babies who miss this assistance due to cesarean or formula feeding (4.2.6) are not known.

As with oxytocin, biologic principles suggest optimal epigenetic programming (also called "hormonal imprinting"[41]) for offspring exposed to physiologic levels of BEs and activity that promotes BEs, in the perinatal period. This could program offspring hormonal systems to function lifelong in a positive, adaptive way, plausibly including, for BEs, beneficial impacts for analgesic, motivation, reward, and immune functions, among others. (See also 3.2.3 and 4.2.4 for discussion of possible epigenetic effects due to perinatal hormonal disruptions of BEs.)

Beta-Endorphins and Breastfeeding

Maternal beta-endorphins released during breastfeeding promote prolactin release, and the baby also ingests beta-endorphins with milk. This exposure during breastfeeding may motivate and reward mother and baby in relation to breastfeeding.

Maternal BEs are also released during lactation,[777, 778] with levels in women peaking in the blood around 20 minutes after initiation,[778] giving further motivation and reward for this critical mammalian behavior. In addition, BEs promote prolactin release,[121, 724] assisting with ongoing breast-milk production.

In animals, central MORs decline from early lactation, which may be important for maternal adaptations. Excessive opioid activity can reduce maternal motivation and behavior,[94] possibly by signaling satiety[403] (4.1.1). Multiparous mothers have even higher MORs in some brain areas during lactation, according to animal studies, and are also less sensitive to disrupting effects from high doses of exogenous opioids.[213] The mechanisms are not clear.

Beta-Endorphins and Maternal Adaptations and Attachment

Beta-endorphins facilitate maternal adaptations and may promote mother-infant contact and attachment by priming maternal reward centers at birth. The co-release of oxytocin with beta-endorphins with breastfeeding and maternal-infant contact may maintain maternal "addiction," with benefits to infant survival.

As discussed (4.1.1), BEs are important facilitators of maternal adaptations and behaviors in mammals,[404] motivating and rewarding infant contact and care. As with other aspects of BEs, low levels tend to facilitate maternal behaviors, and high levels may signal satiety and inhibit.

Central MORs in the maternal brain are elevated through the immediate postpartum period,[94] enhancing and likely priming maternal attachment by activating dopamine-associated reward circuits, according to animal studies.[403] In rats, new mothers will choose contact with newborns over exposure to cocaine,[779] indicating the extreme reward value of newborn contact at this time. Priming of these maternal reward circuits may ensure that the new mother will continue to be motivated to give the devoted care necessary for offspring survival among all mammals.[404]

Oxytocin additionally stimulates reward circuits (3.1.4) and, when co-released with endogenous opioids, may inhibit the development of opioid tolerance.[433] Episodic OT release with contact and nursing may therefore maintain the rewarding and "addictive" nature of infant contact.[403] Up-regulation in central oxytocin receptors (OTRs), including autoregulating OTRs, in multiparous females (3.1.2) may also promote BEs and rewarding effects.

A magnetic resonance imaging (MRI) study (also discussed in 3.1.4) supports this model in women. Among new mothers two to four weeks after birth, researchers found that those who had given birth vaginally had greater activation of brain reward centers in response to hearing their baby cry, compared with mothers who had experienced prelabor cesarean section.[423] (See also 3.1.4 and 3.2.6.)

4.2 Common Maternity Care Practices That May Impact Beta-Endorphins Physiology

The impacts of maternity care practices on beta-endorphins are less researched, compared with oxytocin. However, several practices may have significant effects on this important system. In particular, the use of pain relieving drugs—systemic opioids and regional analgesia—may disrupt endogenous BE systems, with potential impacts in mothers and babies. Epigenetic principles suggest that disruption of BEs during the perinatal period may program offspring (and possibly maternal) BE systems in the longer term.

4.2.1 Maternity Care Provider and Birth Environment: Possible Impacts on Beta-Endorphins

The maternity care provider and birth environment may impact beta-endorphins of mothers and babies by increasing or decreasing the chances of interventions that are consequential for beta-endorphins systems, or by increasing or decreasing stress, with excessive stress possibly slowing labor by elevating maternal beta-endorphins, as seen in animals.

No studies were found that directly assessed the impacts of maternity care provider and birth environment on the BE systems of mother or baby. However, Cochrane systematic reviews have found that women who receive midwifery care[451] or continuous support in labor[780] have a reduced use of analgesic drugs and epidurals. The use of labor epidurals, which likely include an opioid drug, is also reduced among women planning home birth.[453] Other maternity care providers may facilitate similar benefits.[781] Reduced exposure to opioid drugs in labor will reduce any potential exposure-related impacts on BEs of mother and baby, as discussed in 4.2.4.

In addition, as discussed in 5.2.1, the maternity care provider and birth environment may also impact BEs by increasing or decreasing stress for the laboring woman. For example, attendance by an unfamiliar care provider may be stressful. Excessive stress may elevate BEs, reducing central OT, as occurs in other animals, and possibly directly inhibiting uterine contractions in women (4.1.3). Oxytocin (3.1.3), E-NE (5.1.3), and prolactin (6.1.3) may also mediate responses to labor stress.

4.2.2 Prostaglandins for Cervical Ripening and Labor Induction: Possible Impacts on Beta-Endorphins

Studies suggest that prostaglandins may elevate beta-endorphins, but this is not well researched. Inducing women by any method may preempt the increases in central opioid receptors with the physiologic onset of labor, and diminish endogenous analgesia in labor.

No studies were found that directly assessed the impacts of prostaglandins (PGs) for cervical ripening and induction on BEs of mother or baby. However, researchers found immediate but transient increases in BEs following administration of prostaglandins to pigs in late pregnancy,[782] and cows in labor.[752] Researchers also found elevation of BEs, including in amniotic fluid, following PG administration to women in mid-pregnancy.[783] The mechanisms or consequences are not known.

Any method of induction will preempt the complete preparation of endogenous analgesic systems. This may result in fewer MORs, which peak close to the onset of labor;[94] reduced non-BE spinal opioid systems; and deficits in the oxytocin system, which is also analgesic in labor (3.1.3). This may increase the laboring woman's sensitivity to pain and her need for analgesic drugs. Reduced central MORs with induction could potentially reduce postpartum activation of pleasure and reward circuits in relation to birth and to newborn contact and care (4.1.4).

4.2.3 Synthetic Oxytocin for Induction, Augmentation, and Postpartum Care: Possible Impacts on Beta-Endorphins

Impacts of synthetic oxytocin on beta-endorphins are unclear. As with prostaglandins, induction may preempt the complete readiness of endogenous opioid systems and compromise endogenous labor analgesia.

As discussed in 4.1.2, the stress and pain of labor, along with central surges of oxytocin, trigger the release of BEs from and within the brain, according to current understandings. Effects of synthetic oxytocin (synOT) on this system are not clear.

One study found that women administered synOT to augment labor had no rise in BEs, whereas untreated women's BEs more than doubled from early to late labor.[784] However, another study found higher BEs in women induced with synOT and even higher levels following artificial rupture of membranes, both likely causing increased pain.[785] Another study found equivalent elevations in BEs following physiologic onset of labor, induction with synOT, and induction with PGs.[786]

As discussed above (4.2.2), induction with synOT or any other method may pre-empt the full development of analgesic systems, including central MORs (4.1.2). Given the widespread use of induction with synOT and other methods, these are important areas for future research.

4.2.4 Opioid Analgesic Drugs: Possible Impacts on Beta-Endorphins

Opioid Drugs and the Mother

Opioid drugs administered systemically have a modest analgesic effect and well-known side effects. Studies of their impacts on beta-endorphins are contradictory, which may reflect differences in women's subjective experience of analgesia efficacy.

Opioid drugs are commonly administered systemically by intramuscular (IM) or intravenous (IV) injection as labor analgesia, and are also typical components of epidural analgesia. (See 3.2.4 for more background.)

A handful of older studies have looked at levels of BEs following systemic opioid drug administration, with conflicting results. Three studies found no reduction in BEs for laboring women following meperidine administration,[279, 787] one study found a higher peak,[788] while one study found lower levels at each stage of labor.[785]

Outside of labor and birth, systemic opioid drug administration reduces pain and consequently the need for, and release of, BEs.[767] It is likely that, as one study found,[773] in labor, opioid drugs (and other analgesic methods) reduce an individual woman's BEs in proportion to their effectiveness at reducing her stress and pain. As discussed in 4.1.2, there may be wide individual variation in BE systems, including MOR numbers, which influence opioid sensitivity and the effective dose of systemic opioid drugs. There are also individual differences in opioid responses that affect dosage and side effects.[789]

In general, laboring women report a modest reduction in self-reported pain scores following systemic opioid administration.[591] This reduction may be sufficient to shift the experience from distress to eustress. However, these drugs can have other significant in-labor side effects in mothers and babies, generally related to central opioid effects such as dysphoria, sedation, and gastrointestinal effects.[591] In addition, because opioids reduce central oxytocin release (3.1.1), opioid drugs may cause slowing of labor, as found in animal and human research. (See 3.2.4 for a full discussion of possible opioid impacts on OT and labor progress.)

Opioid Drugs and the Fetus/Newborn

Opioid drugs cross the placenta to the fetus and can cause sedation and other side effects. One study did not find impacts of maternal opioid drug administration on fetal beta-endorphins. Longer-term impacts, including impacts on breastfeeding and possible epigenetic programming effects, have been suggested but not studied in high-quality research.

As discussed in detail in 3.2.4, recognized opioid fetal/newborn effects from maternal administration in labor mainly derive from sedation. This can reduce fetal movements and cause fetal heat rate (FHR) changes, including reductions in FHR accelerations and variability.[600, 790, 791] Sedation can also impact newborn breastfeeding behaviors and success.[315, 350, 351, 602-604] Opioid effects on breastfeeding have not been subjected to high-quality research.[590, 591] Opioid exposure via epidural analgesia, while generally lower for mother and baby than systemic administration by IM or IV injection, can also cause significant effects, including newborn sedation (see 4.2.5 below).

In one study, opioid exposure did not change newborn BEs,[792] probably reflecting lack of analgesic effects on the baby. However, therapeutic doses of opioid drugs, administered directly to the fetus during intrauterine procedures, were found to reduce fetal BEs,[793] suggesting that an effective analgesic dose can have fetal effects.

Longer-term effects of perinatal exposure to opioid drugs on the BE system of offspring have not been well studied, although epigenetic programming principles suggest concerns in this area, as with oxytocin (3.2.3). Primate studies using a single exposure to meperidine or the opioid alfentanil in labor found subtle developmental impacts on exposed offspring such as reduced locomotor behaviors through to 12 months, roughly equivalent to four to five years in humans. [794]

Authors comment, "Disruption of the normal ontogeny of the endogenous opiate system by perinatal meperidine is a mechanism for which some precedent has been established."[794(p.625)] In rats, researchers found that a single, high-dose perinatal exposure to BE (1-31), producing supra-physiologic levels, altered brain serotonin, uterine estrogen receptor numbers, and sexual behaviors in adulthood.[795]

Long-term impacts on human offspring from perinatal exposure to opioid drugs are not well researched. Two cohort studies found that exposure to opioid drugs in labor, especially in multiple doses, was associated with increased risk of opioid addiction in adulthood.[796, 797] Researchers speculate that imprinting of the opioid system may be involved. In contrast, another study did not find such effects from meperidine exposure.[798]

Hartwig comments, "When clinicians administer opioids, they are not simply dealing with pain relievers, but with a family of drugs and hormones that interact at a fundamental level with the body's homeostatic metabolic functions. The implications of this must not be overlooked."[767(p.77)]

Given the widespread perinatal exposure of babies to opioid drugs, including opioids in epidurals, impacts on breastfeeding and possible programming effects are critical areas for future research.

4.2.5 Epidural Analgesia: Possible Impacts on Beta-Endorphins

Because of their effectiveness at reducing pain, epidurals may reduce maternal beta-endorphins substantially, with potential impacts on mother and baby.

Epidural analgesia acts by blocking the nerves that transmit pain signals (3.2.5) and is highly effective in reducing labor pain.[614] Because of this efficacy, maternal BEs and other hormonal responses to stress and pain decline significantly following epidural administration, as discussed below (Epidural Analgesia and the Mother"; see also 5.2.5.) These effects can also impact the baby.

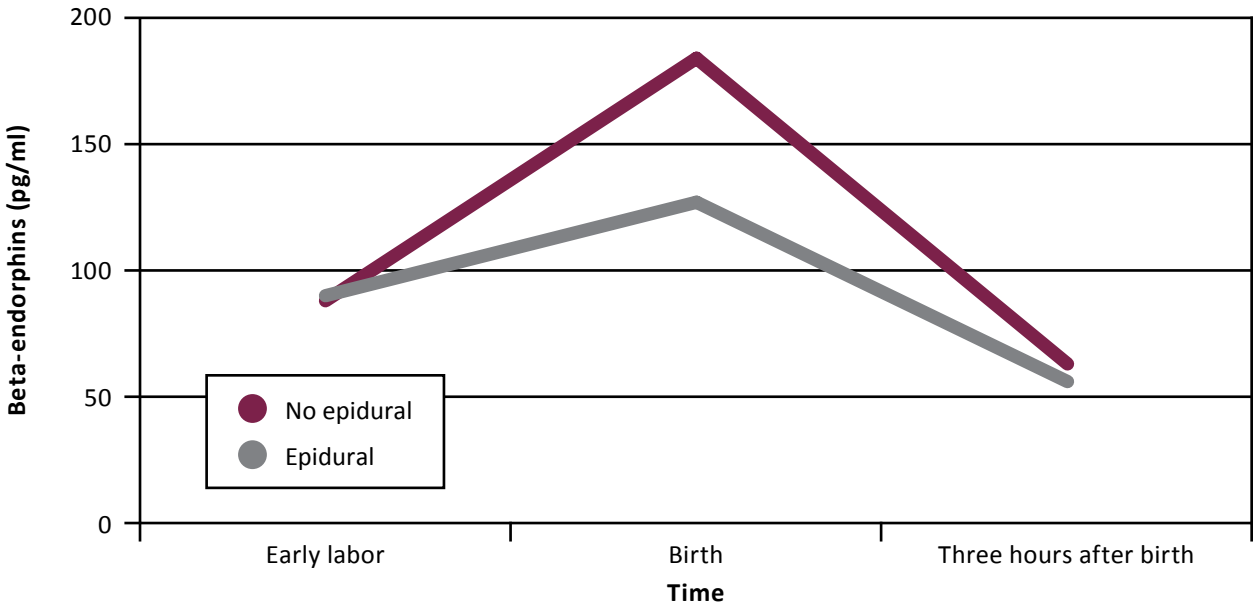
Epidural Analgesia and the Mother

Maternal levels of beta-endorphins decline after epidural administration due to reductions in stress and pain. Postpartum levels may be significantly reduced in comparison with women not using epidural, which could reduce activation of central maternal pleasure and reward circuits, with possible longer-term effects.

Studies show that maternal BEs drop substantially (around 50 percent) in the hour after epidural administration,[617, 745, 747, 785, 799] with lower levels at birth compared with women not using epidural analgesia[788] (Figure 4). In one study, levels at birth were 20 percent of those in women not using epidural analgesia.[792] One study found no significant differences.[800]

The use of spinal analgesia in labor, usually involving an opioid drug, has similar effects on maternal levels of BEs.[802] The excessive pain that women can feel when their epidural is allowed to wear off, frequently intended to facilitate pushing,[803] may reflect insufficient time to restore endogenous analgesia and BEs.

Figure 4. Maternal beta-endorphins levels, with and without epidural analgesia



Source: adapted from Riss[788]

While the reduction in stress and pain following epidural, with associated reduction in BEs, can be beneficial (5.2.5), it may also diminish the BE–related alteration in consciousness reported with physiologic labor (4.1.3). Women laboring with an epidural may therefore behave in a more "normal" and socially expected way.[804]

After birth, epidural-related reductions in both BEs and oxytocin (3.2.5) may adversely impact maternal adaptations, including personality shifts (3.2.5) and the activation of reward centers that promote postpartum pleasure and euphoria (see also "Pleasure and reward" in 3.1.4). Deficits in the perinatal peaks of OT (3.1.4) and BEs (4.1.4) that may prime longer-term activation of reward centers in relation to infant contact[423] may compromise such an effect. (See also 3.2.5 for a full discussion of epidurals and oxytocin.)

Epidural Analgesia and the Fetus/Newborn

Epidurals do not reduce fetal/newborn stress or pain and may even increase fetal stress and stress hormones. Animal studies suggest possible longer-term developmental impacts, which have not been researched in humans.

While epidurals generally give very effective analgesia for laboring women, their babies do not experience analgesia because the local anesthetic drugs are not administered adjacent to the baby's nerves (5.2.5). However, babies will be exposed to epidural drugs, including local anesthetic and opioids, which readily cross the placenta. In some studies, newborn drug levels may be up to 80 to 100 percent of maternal levels.[805, 806] In addition, because the baby's excretory capacity is immature, epidural drugs may persist for prolonged periods in the newborn. For example, one study found bupivacaine metabolites in newborn urine up to 36 hours after spinal anesthetic for cesarean section.[807]

In relation to fetal/newborn BEs, one study of nulliparous women found high levels of BEs and other stress hormones (ACTH, CRH, E-NE) in the cord blood of epidural-exposed babies (specific epidural drugs not stated), with BEs around double those of babies born by unmedicated vaginal birth.[800] Other studies have found equivalent levels of BEs (other stress hormones not measured) in epidural-exposed and unexposed newborns.[628, 792, 808] Local anesthetic drugs, as used in epidurals, may stimulate CRH release, with potential effects on newborn stress hormone levels.[809] (See 5.2.5 for full account.)

Possible longer-term offspring effects of epidural exposure are very poorly researched in humans. Primate researchers administered epidurals (bupivacaine only) to rhesus monkeys in late pregnancy and found developmental impacts, including delayed onset of object manipulations in infancy and greater motor disturbance behaviors in later infancy. Authors comment, "Not enough is known about the mechanism of bupivacaine action on brain to identify systems whose development could be 'reprogrammed'."[794(p.625)] Researchers suggest that opioid systems could be involved.

4.2.6 Cesarean Section: Possible Impacts on Beta-Endorphins

Cesarean and the Mother

The effects of cesarean section on maternal beta-endorphins may vary with anesthesia and type of cesarean. Following prelabor cesarean (or cesarean following induction), new mothers may have lower central opioid receptors, which may reduce postpartum analgesia and reward center activation with newborn contact. Early skin-to-skin contact may be important to increase beta-endorphins for mothers and newborns following cesarean.

While cesarean section is less activating of maternal stress systems than physiologic birth, the associated surgical and psychological stresses have been found to cause some degree of elevation in BEs and other maternal stress hormones.[745] The use of epidural anesthesia generally blocks this surgery-related increase in BEs, because it is so effective in blocking pain (4.2.5), whereas surgery with general anesthetic is associated with elevations in BEs.[810]

Mothers experiencing a cesarean birth with epidural anesthesia have lower levels of BEs compared with unmedicated mothers giving birth vaginally.[800] In addition, women experiencing PLCS may also miss the prelabor upregulation in central receptors, as found in animal studies, with compromise to postpartum analgesic and reward systems. After cesarean, new mothers are also more likely to experience a delay in first contact with their newborns, which may reduce the possibility of rewarding initial interactions with their babies, which may further impact postnatal BEs of mother and baby.

It may be especially important to expedite early skin-to-skin contact and breastfeeding after cesarean in order to activate maternal physiologic BEs, which have not been maximally activated by labor processes (4.1.4). More research is needed on optimizing maternal and newborn postpartum adaptations, including in the BE system, following cesarean.

Cesarean and the Fetus/Newborn

Cesarean newborns have generally lower levels of beta-endorphins and other stress hormones at birth, but levels may be subsequently elevated in the early newborn hours, possibly because of maternal separation. Newborns and infants may display altered responses to stress following cesarean, suggesting programming effects due to loss of the beneficial eustress of labor and birth. Long-term implications are not known.

Researchers have measured BE levels in vaginally- and cesarean-born babies, usually as a single measurement in cord blood, with varying results. Some older studies found equivalent levels of BEs in babies born vaginally without analgesia, and by cesarean.[792, 811, 812] However, more recent studies found lower levels of BEs in cesarean newborns, along with lower levels of stress hormones such as cortisol, compared with babies born vaginally.[26, 137, 800, 813, 814] Researchers have concluded that cesarean is "less stressful" for the baby. (See "Fetal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth" in 5.1.6.)

Another study measured newborn levels of BEs for up to two hours following vaginal birth or cesarean (with epidural), finding that cord blood BEs at birth were higher among vaginally born babies (mean 111ng/ml) compared with cesarean babies (64 ng/ml). However, at two hours, vaginally born babies' BE levels had halved, while cesarean babies' levels had doubled.[672] They conclude,". . . irrespective of the route, the delivery is stressful to the newborn infant. In newborns delivered by caesarean section the stress response comes after birth."[815] These findings may also reflect the common delays in maternal-infant contact following cesarean, with reduced opportunities to lower excessive newborn stress and increase oxytocin through skin-to-skin contact (3.2.7, 4.2.7).

As noted, BEs are also produced in other fetal tissues, including the membranes and placenta, and may reach the fetus from these sources. One study found lower levels of BEs in the fetal chorion and amnion following cesarean compared with vaginal birth,[816] likely reflecting lack of labor eustress, with unknown implications. Researchers have also found lower levels of BEs in new mothers' early breast milk (colostrum) following cesarean compared with vaginal birth,[775] such that the cesarean babies missed this benefit to newborn adaptation (see 4.1.4).

A recent study found that cesarean newborns reacted less to brief separation from the mother than vaginally-born babies, which correlated with lower cortisol levels at birth. Researchers suggest that this altered attachment behavior and response to stress may relate to lack of stress and stress hormones at birth. In animal studies, newborn separation distress involves opioid systems.[404] Studies also show altered stress responses in infancy following CS.[814] (See 5.2.6 for further discussion of stress responses following cesarean birth.)

4.2.7 Early Separation of Healthy Mothers and Newborns: Possible Impacts on Beta-Endorphins

Early separation can cause stress for mothers and especially for separated babies. Animal studies show significant disruptions to offspring BE systems through to adulthood from brief daily separations in the newborn period. This has not been studied in humans.

No studies were found that directly assessed the impacts of separation of healthy mothers and newborns on BEs of mother or baby.

As described, BEs are elevated in mothers and newborns following physiologic birth, declining significantly over the first hour in the bloodstream,[745] but may be elevated for a longer time in the brain of both, due to the longer central half-life (4.1.4). Interactions such as mutual touch and breastfeeding may continue to episodically elevate this hormone at physiologic levels in the hours and days that follow for human newborns, as demonstrated in animal studies.[404] As with oxytocin, BEs activate reward circuits that motivate maternal-infant contact and may "mutually addict" mother and newborn[199, 404] (4.1.4). Exogenous opioids can reduce newborn separation stress in many species.[404] This suggests that maternal contact may reduce newborn stress by an opioid mechanism.

Separation of healthy mothers and their newborns may cause excessive stress with likely excessive BEs for both. One human study found high levels of stress, on brain monitoring, in solitary sleeping versus cosleeping newborns. (See 5.2.7 for more about early separation, stress, and stress hormones.) According to fetal/newborn programming principles (3.2.3), early separation stress could plausibly contribute to longer-term mis-setting of brain-hormone stress systems, including BEs.

Consistent with this, animal studies have found that maternal separation (e.g., 15 minutes daily in the first week) disrupts offspring opioid systems, with alterations in pain sensitivity and opioid receptor function in adulthood.[817] Maternal separation also increases susceptibility to addiction[818, 819] and is used in rats as an animal model for addiction research.[820 821, 822] (See also 3.1.4 and 5.2.7.)

4.3 Beta-Endorphins: Summary

4.3.1 Beta-Endorphins: Normal Physiology

Beta-endorphins are endogenous opioids that give analgesic and adaptive responses to stress and pain. Beta-endorphins also activate brain reward and pleasure centers, motivating and rewarding reproductive and social behaviors, and support immune function, physical activity, and psychological well-being.

From labor through the postpartum period, beta-endorphins promote:

- endogenous analgesia though prelabor increase in central receptors (animal studies) and increases in beta-endorphins as labor progresses
- an altered state of consciousness that may help with labor stress and pain
- fetal neuroprotection from hypoxia (animal studies)
- postpartum peaks of beta-endorphins (along with oxytocin) that may facilitate maternal euphoria and prime reward centers, imprinting pleasure with infant contact and care
- reward and reinforcement of breastfeeding in both mother and baby
- newborn support with the stress of postpartum transition, including via beta-endorphins in colostrum

Excessive maternal stress in labor may lead to excessive (supraphysiologic) beta-endorphins, which may inhibit oxytocin and slow labor (animal studies). Alternatively, too-low levels of beta-endorphins (infraphysiologic) may not give adequate stress and pain reduction, or activate postpartum pleasure and reward. Optimal levels of beta-endorphins to reduce stress and pain and promote labor progress likely vary among women.

4.3.2 Common Maternity Care Practices That May Impact Beta-Endorphins Physiology

Laboring women may experience excessive stress in relation to their maternity care providers and birth environments (e.g., if not familiar, calm, and private), which may increase BEs to supraphysiologic levels and slow labor. (Stress mechanisms in women are not clear but may also involve oxytocin and/or epinephrine-norepinephrine.)

Labor analgesia that effectively reduces pain will reduce maternal beta-endorphins to some degree. This may be beneficial if excessive stress is inhibiting labor. However, reduced beta-endorphins, as found with epidurals, may also reduce postpartum reward center activation and priming, potentially impacting hormonally-mediated maternal adaptations and attachment, also involving oxytocin.

Women experiencing a cesarean section may miss prelabor opioid receptor increases (animal studies), in-labor peaks of beta-endorphins, and/or postpartum reward center activation. Cesarean newborns have lower levels of beta-endorphins at birth than vaginally born babies, but levels may rise after birth with separation stress.

Separation of mother and newborn in the early sensitive period following physiologic birth, when levels of beta-endorphins are elevated, may interfere with reward center activation of both. In animal studies, repeated brief separations in the newborn period leads to detrimental impacts on offspring opioid systems, likely via epigenetic programing, with enduring effects on pain sensitivity and addiction.

5
Epinephrine-Norepinephrine and Related Stress Hormones

Epinephrine and norepinephrine are major hormones of the fight-or-flight stress response system. Although not classically considered to be reproductive hormones, they may have important roles for the laboring woman by switching off labor under conditions of excessive stress. Epinephrine and norepinephrine are critical in protecting the baby during the powerful late-labor contractions and also in preparing for life outside the womb. The stress hormone cortisol, also considered in this chapter, facilitates important adaptations of mother and baby.

5.1 Epinephrine-Norepinephrine and Related Stress Hormones: Normal Physiology

In situations of perceived stress or danger, epinephrine and norepinephrine activate the flight-or-flight reflex, which involves the sympathetic nervous system. Expected and healthy stress (eustress), with physiologic elevations in stress-hormone levels, is beneficial, but excessive stress and stress hormones can be harmful, and can inhibit labor processes and other reproductive functions.

Epinephrine and norepinephrine (E-NE, also known as adrenaline and noradrenaline) are chemically related hormones that have critical homeostatic functions throughout the body, nervous system, and brain, where NE also functions as a neurotransmitter. Although not recognized as classical reproductive hormones, their functioning, and especially their role in activating the fight-or-flight response, facilitated by the sympathetic nervous system (SNS), has profound implications for reproduction, including childbearing.

In addition, stress-related E-NE release can lead to activation of longer-term stress responses involving the related stress hormone cortisol, also considered in this chapter. Both short- and longer-term stress system activations are known to be detrimental in reproduction, including during childbearing. This section (5.1) considers the role of physiologic stress (eustress) in labor and birth, and section 5.2.1 (below) includes a discussion of excessive stress in prenatal and childbirth care.

The distinction between healthy, physiologic stress (eustress), and excessive, pathologic stress during childbearing is important in relation to E-NE and stress systems, as it is in relation to beta-endorphins (BEs) (4.1.1). In general, a certain amount of stress is normal and beneficial to healthy functioning, including the physiologic eustress of labor, birth, and the postpartum period for mother and baby. For example, as discussed in this chapter, the eustress of labor activates the fetal "catecholamine surge" (CA), a large outpouring of E and NE that prepares the baby for life outside the womb (5.1.3). Labor eustress may also raise maternal E-NE levels, which keep the laboring woman alert, and cause cortisol elevations that enhance early maternal adaptations (5.1.4). In contrast, excessive stress, as discussed in 5.2.1, can cause supra-physiologic elevations in E-NE that can disrupt labor and postpartum processes.

A useful model in understanding the stress system is suggested by Bergman, who describes reproduction, nutrition, and defense as mutually exclusive biological systems. This means that defense-related activation of the SNS, with E-NE elevations, may shut down reproductive functions.[20] This is consistent with research reviewed in this chapter.

5.1.1 Epinephrine-Norepinephrine and Related Stress Hormones: Introduction

Epinephrine and the related hormone norepinephrine are the major hormones of the fight-or-flight stress response, and are chemically referred to as catecholamines.

Epinephrine-Norepinephrine and Related Stress Hormones Effects

Stress, cold, hunger, and exertion can trigger epinephrine and norepinephrine release, leading to redistribution of blood to enact flight-or-flight. The hypothalamic-pituitary-adrenal system can be co-activated, giving medium-term stress responses and releasing cortisol. Effective stress responses are critical for all animals, and also function to benefit laboring females.

In response to danger, or a perceived threat of danger, the SNS is activated and stimulates the adrenal glands, situated on top of each kidney, to release high levels of epinephrine into the body, where it facilitates fight or flight, as follows:

- increasing blood pressure, which increases blood supply to the heart, brain, and major muscle groups
- shifting blood away from the peripheries, skin, and non-essential organs
- dilating the pupils for better vision
- dilating airways to enhance respiration
- mobilizing fuels such as glucose within the bloodstream
- reducing the functioning of digestive and other organs that are not essential to fight-or-flight

During the fight-or-flight response, the adrenals co-release NE with E, which has overlapping effects on the body. Norepinephrine is also released within the brain, where it enhances alertness and memory formation to help avoid dangerous circumstances in the future.[823] Other circumstances that can trigger the fight-or-flight response, with E-NE elevations, include: anxiety, cold, low blood sugar, emotional distress, excitement, physical exertion, and hemorrhage.[824] These hormones are also released during sexual activity, with peaks at female[825] and male[171] orgasm. Epinephrine and norepinephrine have half-lives (time taken to reduce levels to 50 percent) of two to three minutes,[826] giving very transient direct effects. However, activation of the SNS also initiates longer-term stress responses by stimulating the hypothalamic-pituitary adrenal system (HPA system), as described below.

Activation of the HPA system, including by the SNS, begins with release of corticotropin releasing hormone (CRH, also known as corticotropin releasing factor, CRF) from the hypothalamus, which triggers release of adrenocorticotropic hormone (ACTH) and usually beta-endorphins (BEs, see 4.1.1) from the adjacent pituitary into the bloodstream. ACTH travels to the adrenal glands, where it triggers the release of the medium-term stress hormone cortisol, which gives effects over hours to days. (See "Maternal Epinephrine-Norepinephrine and Related Stress Hormones in Pregnancy" in 5.1.2 and 2.1 for more about CRH in pregnancy.)

Although stress and stress hormones are often considered harmful, effective SNS and HPA responses are critical for successful adaptation in every animal, including modern humans.[827] These systems are also designed to maximize adaptation and safety for mammalian mothers giving birth in the wild. However, the stress response can be inadvertently triggered for women in modern childbirth settings, with potentially adverse consequences in mothers and babies (5.2.1).

As well as these elevations with perceived danger and stresses, E, NE, and cortisol are also present under normal (baseline) conditions and can be measured in the blood, urine and saliva. Baseline levels vary widely according to the individual, even by factors of 10 to 20,[828] and to the time of day (diurnal rhythm), with E-NE levels lowest during the night, as measured in women.[829] This nocturnal decrease, along with diurnal changes in the sleep hormone melatonin (2.1), may facilitate the more common nighttime onset of labor in day-living species, including humans,[830, 831] and conversely the daytime labor onset in nocturnal species.[832]

The SNS, including E and NE, is part of the autonomic nervous system (ANS), which is also involved with the functioning of internal organs and body systems. In general, the functions of the SNS and related hormones (E-NE) oppose those of the parasympathetic nervous system (PNS) and related hormone oxytocin (OT), which tend to reduce SNS activity and levels of E-NE and cortisol (3.1.1). Similarly, E and NE may reduce OT release and functions (5.2.1).

Epinephrine-Norepinephrine and Related Stress Hormones: Regulation and Receptors

Epinephrine and norepinephrine have differential effects by generally activating different receptors. In pregnancy, norepinephrine causes constriction of uterine blood vessels and stronger contractions, whereas epinephrine generally causes vasodilation and uterine relaxation. At extreme levels, co-release can paradoxically stimulate contractions, with evolutionary benefits for late-laboring females under threat in the wild.

Epinephrine and norepinephrine act on two major receptors—alpha- and beta-adrenoceptors—of which there are several subtypes. Receptor differences are important because some maternity care interventions, including beta-adrenergic drugs used to treat premature labor (below) and epidural analgesia (5.2.5) may differentially affect alpha- and beta-adrenoceptors.

Norepinephrine mainly activates alpha-adrenoceptors, causing smooth muscle contraction, including constriction of blood vessels (vasoconstriction). This increases blood pressure and also redirects blood away from organs that are not essential for fight-or-flight, including the uterus. Alpha-adrenoceptor activation also promotes uterine contractions.[833]

Epinephrine mainly activates beta-adrenoceptors, causing dilation of blood vessels (vasodilation) and airways (bronchodilation), and relaxing smooth muscle, including in the uterus. Because of this effect, beta-adrenergic drugs are used to inhibit premature labor. In one early study, intravenous epinephrine administered to ten laboring women reduced uterine activity by 55 percent within two minutes, and its discontinuation caused hyperstimulation within a few minutes in four of the ten women,[834] likely by a "rebound" phenomenon.

Rebound occurs when a sudden drop in hormone levels provokes exaggerated and opposite effects. In the uterus, a sudden reduction in E (which relaxes the uterus and reduces contractions) can cause a sharp increase in tone and contractions (hyperstimulation), which can potentially compromise fetal blood supply.[834] This may occur with epidural and spinal analgesia, which can cause rebound hyperstimulation by rapidly reducing E levels (5.2.5).

Epinephrine and norepinephrine are co-released in situations of fear or danger. Together, these hormones lead to a rise in blood pressure and a reduction in blood flow to non-essential organs, including the uterus, due to alpha-mediated blood redistribution.[835-839] During labor, fear or stress can reduce fetal blood supply to some extent by this mechanism. At moderate to high levels, combined E-NE reduces or stops contractions (beta-mediated), whereas, at extreme levels, E can activate alpha-adrenoceptors and, like NE, strengthen contractions. This makes extreme levels of stress, and of combined E-NE, paradoxically uterotonic, as demonstrated in animal studies.[840] This may give important safety advantages by promoting a quick birth in the presence of danger in late labor (5.1.3). (See also "Maternal Epinephrine-Norepinephrine and Related Stress Hormones in Pregnancy" in 5.1.2 and "Maternal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth" in 5.1.3)

Outside of reproduction, E and NE are involved in many biologic functions, including: food intake and metabolism, pancreatic function, and insulin activity;[841] blood pressure and heart function;[842] pain mechanisms;[843] regulation of tumor growth;[844, 845] and wound healing.[846] Norepinephrine also has neuroprotective,[847, 848] antidepressant,[849] and anti-anxiety[850] effects within the brain, and suppresses inflammation.[851] NE also regulates alertness and sleep-wake cycles.[852] Dysregulations of E and NE have been implicated in anxiety,[853] depression,[849] attention-deficit hyperactivity disorder (ADHD),[854] and post-traumatic stress disorder.[855] Some antidepressant drugs act by increasing central NE levels and effects.[849]

Many factors and substances influence the release and effects of E and NE, both centrally and in the body. For example, in animal studies, repeated central administration of synthetic OT (synOT) reduces stress responsiveness by reducing NE activity in many parts of the brain.[167] (3.1.1)

Cortisol, also discussed in this chapter, is a glucocorticoid (GC) hormone with an essential role in maintaining homeostasis in response to external and internal stresses and changes. Cortisol release from the adrenal gland is the final result of activation of the HPA stress system (see "Epinephrine-Norepinephrine and Related Stress Hormones, Effects" above) and exerts its effects by binding with GC receptors, which are present in almost every cell, highlighting the extensive effects of this hormone. Cortisol can also bind to the related mineralocorticoid receptor, and is inactivated by specific enzymes (hydroxysteroid dehydrogenases), which also influence its concentrations and effects.[856]

5.1.2 Epinephrine-Norepinephrine and Related Stress Hormones in Pregnancy

Maternal Epinephrine-Norepinephrine and Related Stress Hormones in Pregnancy

Maternal stress responses decrease as pregnancy advances, which may be important in protecting the growing baby from long-term adverse developmental effects from transplacental cortisol. Maternal epinephrine-norepinephrine elevations could also adversely impact the fetus directly and/or indirectly by reducing blood supply. Late-pregnancy changes in receptors (adrenoceptors) may promote increased responsiveness to these hormones in labor. The related stress hormone corticotropin releasing hormone is made by the placenta and promotes fetal maturity, maternal readiness, and uterine sensitivity to oxytocin and prostaglandins, in the lead up to labor.

Pregnancy involves a reorganization of maternal stress systems, giving an overall reduced response to stress. This is very important, as exposure to chronic stress, severe acute stress, and/or stressful life events in pregnancy has been shown to have significant detrimental effects on pregnancy and birth outcomes in both animals and humans.[857] According to human studies, increased risks of stress in pregnancy include: premature birth, intrauterine growth retardation (IUGR), and reduced newborn head size, reflecting suboptimal brain growth.[858, 859] The effects of prenatal stress on offspring, as assessed in childhood, may include deficits in emotional regulation, cognitive performance, and structural brain development.[860] Prenatal stress may impact the baby by several possible mechanisms, including triggering maternal and fetal E-NE and/or HPA stress systems involving cortisol, as detailed below. (See also 5.2.1)

There is conflicting evidence about whether maternal E-NE can pass through the placenta to the fetus.[861-863] Placental enzymes may substantially metabolize these hormones, reducing potential fetal effects.[862, 864] However, indirect fetal effects are also possible. For example, stress-related maternal NE elevations may activate alpha-adrenoceptors, inducing uterine artery vasoconstriction, and potentially compromising fetal blood supply. An acute reduction in fetal blood supply would likely trigger fetal E-NE release, in order to preserve blood flow to essential organs (5.1.3), with frequent or ongoing episodes possibly impairing fetal growth. Maternal E-NE elevation also stimulates the HPA system and leads to medium-term cortisol release, making it difficult to disentangle the effects of short- versus longer-term stress and of these stress hormones.

It is difficult to directly measure NE effects on the uterine arteries in pregnant women. However, in vitro studies have found vasoconstriction in response to NE exposure in arteries from pregnant women[865] and animals.[835, 837-839] In pregnant animals, high levels of cortisol increase alpha-adrenoceptors, which magnifies the vasoconstricting effects of NE.[838] This may also occur in women late in pregnancy, as below. These findings suggest an increased capacity in pregnancy, perhaps even greater in labor, to redistribute blood supply away from the uterus and baby, in conditions of stress.

In the uterus, alpha-adrenoceptors (which promote contractions) are present at term,[866-870] possibly contributing to activating effects with the onset of physiologic labor (2.1.3). Whereas some subtypes of beta-adrenoceptors (which relax the uterus) decrease in late pregnancy, which overall promotes contractions, beta-three subtypes (also relaxant) have been found to increase with labor onset.[871] These findings also suggest increased uterine responsiveness to E-NE in labor and birth (see 5.1.3).

In relation to clinical effects on the uterus and baby, one study directly administered NE to laboring women and found increases in uterine resting tone, and the intensity and frequency of contractions, although the pattern was uncoordinated.[826] A similar study administering E to laboring women found generally reduced contractions, although two of ten women had increases in contractions,[834] possibly reflecting alpha-adrenoceptor stimulation at what might be excessive levels for these individual women. Studies in pregnant sheep have found reductions in uterine blood supply in response to both NE[872, 873] and E,[874, 875] although fetal adaptations preserved blood and oxygen supply in these studies.[872, 874] (See also "Maternal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth" in 5.1.3, below.)

In relation to cortisol in pregnancy, maternal levels have been found to rise as pregnancy advances, with salivary levels at term around two-fold higher than levels in non-pregnant women.[876-878] This likely reflects elevations due to CRH, derived from placental production (5.1.1), and also to reorganization of the HPA system.

Maternal cortisol can cross the placenta in small but biologically significant amounts,[861] so that excessive maternal cortisol levels from excessive stress can lead to elevated fetal levels, potentially affecting development of fetal neurologic, metabolic, and other systems. Stress-induced elevations of maternal cortisol, as measured in the saliva or urine, have been associated with early miscarriage, premature labor, and low birth weight,[879] and are implicated in the well-established long-term detrimental effects of pregnancy stress on offspring, as discussed above.[857]

During pregnancy, the placenta also makes CRH, with hormonal reorganization at this time to reduce maternal HPA responses to these elevated levels. This hormone has been called the "biological clock," as mid-pregnancy levels of CRH, produced by the placenta, have been correlated with length of gestation.[76] Levels of CRH rise exponentially in late pregnancy,[880] reaching 1,000- to 10,000-fold above non-pregnant levels, and receptor numbers and bioavailability also increase as the physiologic onset of labor approaches. The effects of CRH include: promoting fetal growth; amplifying fetal readiness for labor by increasing fetal cortisol, which promotes maturity; promoting estrogen production;[76] enhancing uterine contractions at the onset of physiologic labor by increasing uterine sensitivity to prostaglandins (PGs) and OT;[89, 90, 881] and stimulating inflammatory changes,[91] which also promote labor onset. (See also "Maternal related stress hormones in labor and birth" in 3.1.3 and 2.1.)

Fetal Epinephrine-Norepinephrine and Related Stress Hormones in Pregnancy

Maternal anxiety and/or epinephrine-norepinephrine elevations may affect the fetus in pregnancy, likely via reduction in blood flow to the uterus and baby. Physiologic late-pregnancy increases in fetal cortisol promote prelabor preparations, including clearing lung fluid and increasing epinephrine-norepinephrine receptors and responsiveness to the in-labor "catecholamine surge."

The direct biologic effects of maternal stress and stress hormone elevations on the fetus in pregnancy are not well researched. One study subjected women to brief, mild stress at several times during pregnancy and found reduced fetal movements and increased fetal heart rate (FHR) variability, both consistent with responses to reduced blood supply. While maternal physiologic responses to stress decreased from 24 to 36 weeks, in accord with reduced stress responses with advancing pregnancy, fetal responses increased, which may reflect increased E-NE sensitivity due to maturing of the fetal ANS.[882] Increased fetal E-NE responses at term may benefit adaptations to labor stresses via the catecholamine surge (5.1.3).

Other studies have linked maternal psychological well-being, including specific measures of anxiety, with differences in uterine artery resistance (indicating blood flow).[883-887] These findings also suggest that maternal stress may cause NE-mediated vasoconstriction and, conversely, maternal relaxation may improve blood flow.[887]

In relation to fetal E-NE, levels begin to rise a few days before the physiologic onset of labor, triggered by rises in cortisol produced by the maturing adrenal[78] (2.1). Elevated cortisol levels in the last weeks of pregnancy prepare the fetus for birth and for life outside the womb by maturing the lungs, gut, and thyroid, among other effects. Fetal adrenal maturation promotes maternal estrogen production (2.1), ensuring that maternal and fetal readiness for labor and birth is aligned and coordinated. Cortisol prepares the fetal E-NE system by increasing beta-adrenoceptors in the fetal heart and lungs,[78] which promote protective responses in labor via the "catecholamine surge" (5.1.3). Cortisol also activates physiologic mechanisms that will clear the lungs of fluid during labor,[78, 476] and cortisol-related mechanisms initiate a 25 percent reduction in lung fluid, even before labor begins, according to animal studies.[888] Late-pregnancy prolactin increases may potentiate cortisol's maturing effects on the fetal lungs.[889] (See also 2.1 and "Fetal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth," below.)

Researchers suggest that, in response to hypoxia and other stresses, medium-term fetal cortisol release may promote placental production of CRH and ACTH, with beneficial vasodilating effects that improve fetal blood and oxygen supply. In this model, unresolved hypoxia, causing even greater CRH elevations, could stimulate the onset of labor (2.1), possibly explaining some cases of preterm birth.[890]

5.1.3 Epinephrine-Norepinephrine and Related Stress Hormones in Labor And Birth

Evolutionary Model

Among all mammals, and through human evolution, laboring females have been vulnerable to predators and other dangers in the wild, and so have sought a safe, undisturbed environment for labor and birth. A perception of danger in labor may promote epinephrine-norepinephrine release, with slowing of labor and redistribution of blood away from uterus and baby to facilitate flight or flight. The flight-or-flight reflex may also be activated in modern women, slowing or stopping labor in unfamiliar environments and/or with unfamiliar attendants.

Through millions of years of mammalian evolution, biologic processes have evolved to safeguard the birthing female.[832, 891] All mammals seek a safe place to give birth, usually choosing a familiar environment and sometimes creating a nest to receive their offspring.[832] Many animals give birth in private or hidden locations. For some species—including elephants, mice, dolphins, and humans—one or more familiar female companions are usually present during labor and birth.[832, 891] This may reflect the extreme vulnerability of the laboring female, who will be compromised in her ability to defend herself and her newborn offspring against danger through to the postpartum period. In addition, predators are likely to be attracted by her unusual behavior in labor and birth, by the smell of blood and amniotic fluid, and by the small vulnerable newborn.

Dutch comparative biologist Cornelius Naaktgeboren comments: In all mammalian species, the course of delivery can be influenced by environmental disturbances . . . . Anxiety and fright inevitably lead to prolongation of the duration of labour . . . . Suppression of uterine activity is a life-saving adaptation, because in cases of danger the animal is able to either fight or to flee. Afterwards the animal can give birth to the young in peace and safety . . . . This adaptive mechanism clearly shows the importance of a perception of safety and avoidance of disturbance during parturition.[832(p.801)]

A perception of safety and lack of disturbance are also evolutionary requirements for human birth. When the laboring woman has a subjective sense of disturbance or danger, her fight-or-flight response is likely to be activated. This operates at an instinctive, subcortical level and draws on sensory information such as smell, sound, and sight. This may lead to E elevations that can inhibit or even stop labor, with NE rises leading to redistribution of blood to her major muscle groups, and away from her uterus and baby. Slowing of labor and some degree of fetal hypoxia, which may be detectable as a non-reassuring fetal heart rate (FHR), are therefore possible consequences when the laboring woman does not feel private, safe, and undisturbed. (See 5.2.1.)

In modern maternity care, slowing of labor often occurs when women move from home to hospital, especially before the processes of labor, including the OT-associated positive feedback loops, are fully established (3.1.5). This phenomenon has been called "pasmo," and may even include the possibility of regression of cervical dilation.[892]

Midwifery and obstetric texts from the 19th century, as researched by Gaskin,[892] document many incidents where labor slowed or even stopped in response to the arrival of attendants, especially unfamiliar and/or male attendants, into the female domain of the birth room. For example, Dorland opines in his 1901 obstetrics textbook, in relation to contractions**:** Mental emotion of any kind will temporarily diminish their intensity or even absolutely suppress them; the entrance of the physician into the lying-in room may have the same effect.[893(p.122)]

These observations highlight the historical knowledge that women, like animals, can be highly sensitive to their surroundings in labor. E and NE elevations likely mediate these processes. (See 5.2.1 for more about stress in labor and birth.)

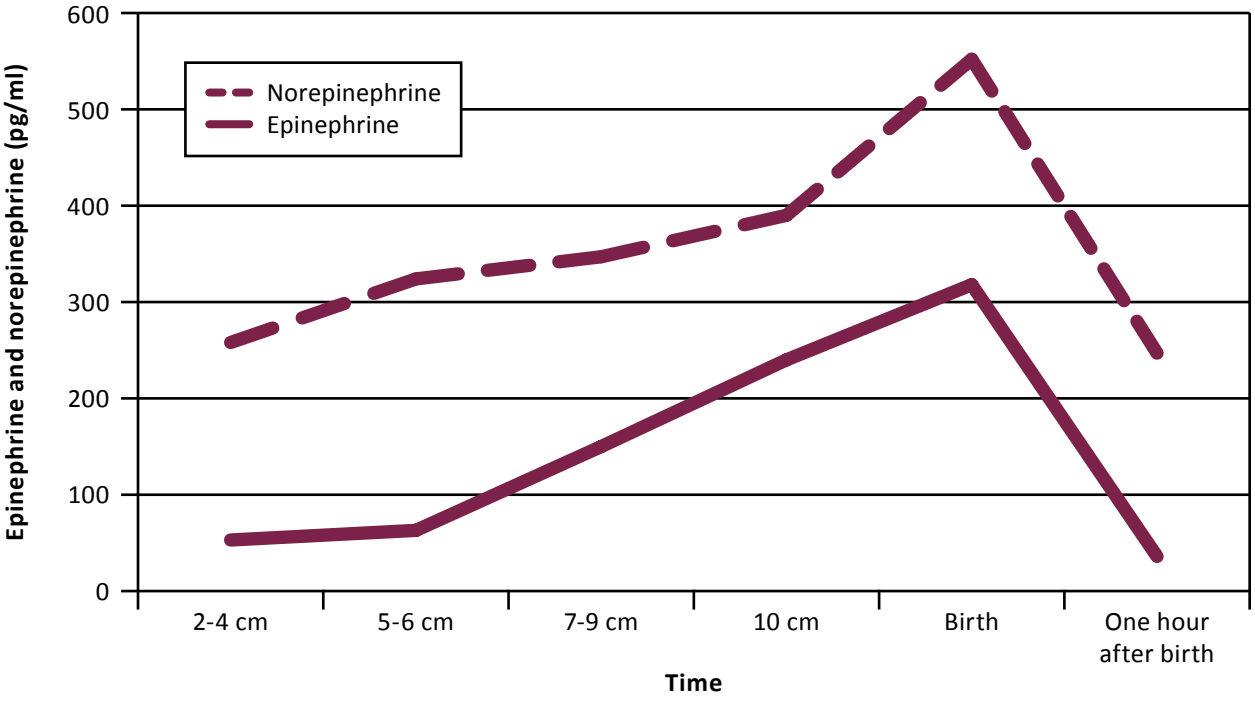
Maternal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth

Maternal Epinephrine-Norepinephrine in Labor and Birth. *Epinephrine levels in laboring women may increase up to eight-fold, compared with baseline, likely reflecting stress and pain. Norepinephrine levels are more moderately increased. These elevations may promote alertness and vigilance and increase metabolic fuels in labor.*

According to the evolutionary model, sudden and/or large increases in maternal E and NE in early labor due to fear and danger may evoke a fight-or-flight E-NE response, with potentially negative effects on labor progress and fetal blood supply (5.2.1). However, studies in laboring women also show a gradual rise in these hormones as labor progresses, with E levels reaching up to eight-fold higher than individual baseline levels.[110, 829, 894] This is likely due to the pain and eustress of labor, with one study finding a close correlation between E levels in labor and self-reported pain.[895] Norepinephrine elevations are mostly confined to late labor, and may reflect the muscular work of this stage.[110]

Figure 5[894] shows mean in-labor maternal E-NE levels, with significant peaks of both hormones at birth and declines after birth, especially for epinephrine. A similar study that uniquely controlled for individual and diurnal hormone variations by comparing laboring women's urinary E-NE levels, collected hourly, with their own levels at the same time of day in late pregnancy found that E levels for women in the pushing phase were more than eight times their own baseline levels, with NE levels one and one-half times higher.[110] These labor elevations are consistent with other studies.[896-902]

Figure 5. Maternal epinephrine and norepinephrine levels in labor, at birth, and after birth



Source: adapted from Neumark[894]

Elevations in E-NE would be expected to enhance alertness and attentiveness to sensory input, as occurs outside labor,[827] and may help to ensure that the laboring female remains vigilant to danger, even in the midst of active labor. Women experiencing an unmedicated labor may seem in a dream-like altered state of consciousness, due to elevations in BEs (4.1.3), but alert senses may be important to attune them to any possible danger to themselves or their babies. In modern maternity care settings, E-NE elevations may make laboring women extremely sensitive and alert to the concerns or comments of their attendants.

In contrast, studies in other mammals have found comparatively lower levels of E-NE in early to midlabor, with more moderate but steep elevations at birth.[903, 904] A hormonal and physiologic study in laboring horses found that, in the absence of disturbance, equine labor is dominated by the PNS, with low levels of E-NE and SNS activity.[904] While SNS activation in labor may be more detrimental in prey animals such as horses, whose main response to danger is an immediate flight reaction that could be counterproductive in labor, the differences in these studies may be important. Findings could imply that E-NE elevations in labor, as found in human studies, may actually be an artifact of labor disturbances, which

are common in maternity care (5.2.1). (For example, in this human study, women were catheterized to collect urine for E-NE analysis and experienced vaginal examinations every two hours.) It is plausible that parasympathetic dominance in early labor (supported by a private and undisturbed environment, with low stress and E-NE) may optimize parturition by maximizing the late-labor shift to sympathetic dominance (e.g., fetus ejection reflex and effective pushing stage, discussed below). The ideal ANS balance in labor to promote physiologic childbearing in women, and the ideal circumstances to support this, are critical areas for future research.

Late-labor elevations in E-NE levels (seen in women and other mammals) cause the release of metabolic fuels, including glucose and free fatty acids, which are also used in the synthesis of prostaglandins.[905] Rising maternal E-NE levels near the end of labor, and even higher levels with the fetus ejection reflex (see "Fetus ejection reflex," below) could therefore increase PG production, further augmenting uterine contractions.[906, 907]

The fetus ejection reflex. *The "fetus ejection reflex" model is based on physiologic understandings of the stimulating effects of extreme epinephrine levels, and clinical observations of a rapid and involuntary pushing stage following an essentially undisturbed labor and birth. This reflex may be important for safety during mammalian birth in the wild, and may also be triggered in women by fear and/or epinephrine elevations in late labor.*

Extreme levels of E-NE in late labor may paradoxically stimulate, rather than inhibit, contractions, augmenting the OT positive-feedback cycle ("Ferguson reflex," discussed in "Maternal Oxytocin in Labor and Birth" in 3.1.3) and creating several powerful and involuntary contractions that birth the baby quickly and easily.

This model, based on physiologic understandings and clinical observations of births with low levels of disturbance, has been called the "fetus ejection reflex" (FER),[908] and is characterized by signs of E-NE elevation such as increased muscular strength, dry mouth, upright posture, and verbal or non-verbal expressions of what Odent calls "physiologic fear," such as, "I'm dying."[908] The FER is consistent with the understanding that extreme levels of E can activate alpha- more than beta-adrenoceptors, with uterine stimulating (uterotonic) effects (5.1.1). In vitro animal research suggests that extreme levels of mixed E and NE are also uterotonic.[840]

The FER may have evolved to protect female mammals birthing in the wild where, in the presence of danger in late labor, an acceleration of contractions leading to a quick birth would be more adaptive than physiologic attempts to slow labor when the positive feedback cycles (3.1.3) are well established and the birth may have already commenced.

According to Odent,[908] a genuine FER may be triggered by a sense of danger and E-NE surge in late labor, or may occur spontaneously when labor has been essentially undisturbed, which may reflect PNS dominance, discussed above. This is consistent with studies of E-NE in laboring animals,[903] discussed above ("Maternal Epinephrine-Norepinephrine in Labor and Birth"). According to this model, the FER represents an important adaptation, being the quickest and therefore safest birth for all mammals in the wild, but may be rare in modern maternity settings because labor is so commonly disturbed, subtly or overtly (5.2.1), such that the SNS system is dominant. Women birthing out of hospital, or those whose babies are born unexpectedly quickly before, or just after arrival in hospital are most likely to experience the involuntary pushing of an FER, which Odent suggests could be used as a marker of physiologic birth.[908]

Maternal related stress hormones in labor and birth. *Cortisol levels rise as much as 10-fold in labor compared with baseline, and may contribute to labor efficiency and preparations for breastfeeding. Elevations in corticotropin releasing hormone promote uterine sensitivity to oxytocin and prostaglandins, and effective contractions.*

Levels of cortisol also rise in labor, with salivary cortisol levels in late labor more than ten times the woman's own late-pregnancy baseline levels, according to one study.[110] In this study, cortisol levels, adjusted for diurnal variation, correlated with self-reported fear and pain during labor. Other studies have linked higher cortisol levels in labor with higher self-reported pain, but also with a more positive labor experience, as reported 24 hours after birth,[909] perhaps reflecting cortisol's euphoric effects.

Animal studies show the following beneficial effects of cortisol in labor**:**

- upregulation of OT receptor production, which increases the positive feedback of OT on local PG production (3.1.3) up to 100-fold, and increases labor efficiency[98]
- increase in alpha-adrenoceptor formation,[838] augmenting pro-contraction effects in labor (5.1.1)
- promotion of prolactin receptor formation[910] (see also 3.1.4)

Note that cortisol's physiologic role is to restore homeostasis in conditions of stress, including stress and pain in labor. Other hormones that help the laboring mother deal with stress and pain include**:**

- oxytocin, which has analgesic and calming effects (3.1.1)
- beta-endorphins, which have analgesic and stress-reducing effects (4.1.1)
- prolactin, which has calming effects (5.1.1)
- natural benzodiazepines, which also have calming effects in labor[911]

The stress hormone CRH may also play an important activating role in labor and birth by increasing uterine responsiveness to PGs and OT,[89, 90, 881] and possibly by promoting inflammation.[91] (See also "Maternal Epinephrine-Norepinephrine and Related Stress Hormones in Pregnancy," above, and 2.1.)

Fetal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth

For the fetus, E and NE provide critical safety mechanisms during labor and birth.

Late-gestation elevation in cortisol, produced by the maturing fetal adrenal,[78] promotes the formation of adrenoceptors in the heart, lungs, and brain[78] (2.1). For the fetus, NE is the main catecholamine and levels are up to five times greater in early labor than before labor (as measured in newborns following prelabor cesarean section, PLCS) and another 10- to 15-fold higher in late labor, as measured in fetal scalp blood samples.[337] This "fetal catecholamine surge" helps to protect against low oxygen levels during the long, strong, closely-spaced contractions of late labor, and also prepares the fetus for life outside the womb.[78, 337]

Fetal catecholamine surge. *The late-labor fetal surge in epinephrine and norepinephrine promotes adaptations to labor stress and hypoxia, protects the heart and brain, and prepares the baby for postpartum transitions including respiratory, metabolic, and thermoregulatory. This surge, along with cortisol, also activates fetal physiologic systems in preparation for life outside the womb.*

Late-labor pressure on the fetal head and the inevitable hypoxia due to frequent strong contractions stimulate the fetal adrenal to release large amounts of NE, and to a lesser extent E. These facilitate:

- increased blood pressure to maximize blood supply
- preserved blood flow to the essential fetal organs: heart, brain, and adrenals
- slowed fetal heart rate (bradycardia), which conserves oxygen and fuels

A more mature fetus may respond to hypoxia with more E than NE release, reflecting more advanced adrenal development. High E levels are more likely to promote tachycardia and/or decreased heart-rate variability, rather than NE-associated bradycardia.[337] In addition, a baby who misses the final weeks of gestation through prematurity or scheduled birth may need to release even more E-NE in an attempt to trigger these important adaptations, which may still be less successful, because of foreshortening of the late-pregnancy cortisol elevations that increase beta-adrenoceptors (see "Fetal cortisol," below).

The fetal CA surge ensures that blood flow to essential organs is maintained in the face of hypoxia. More severe hypoxia can cause fetal E-NE levels that are hundreds of times higher than baseline adult levels, and sufficient to cause a stroke in an adult,[337] but providing a critical adaptive response for the fetus. Newborns with low acidity (pH) in the cord blood, indicating hypoxia in labor, but high E-NE levels (even 10 to 20 times higher than normal) maintain their condition and Apgar score, whereas those with low pH and a lesser E-NE response have lower Apgar scores.[337]

In addition, the CA surge promotes important physiologic changes that optimize fetal-to-newborn adaptation.[78, 337] These include:

- clearing lung fluid in preparation for breathing
- increasing lung surfactant, which acts as a lubricant
- increasing lung compliance (elasticity), still measurable two hours after birth[313]
- dilating the airways
- mobilizing metabolic fuels (glucose and free fatty acids), which protect against newborn low blood sugar
- increasing liver glycogen to facilitate ongoing glucose supply after birth
- maintaining blood flow to vital organs (brain, heart)
- increasing alertness
- dilating pupils, which facilitates maternal interactions and bonding
- metabolizing brown fat for heat production (thermogenesis)

Because of the vulnerability of the baby to labor hypoxia, protective feedback systems between baby and mother in labor are likely but not as yet delineated. Researchers have suggested that fetal urinary E-NE metabolites, excreted into the amniotic fluid, could act on the adjacent decidua and myometrium and promote contractions. This mechanism could beneficially hasten labor in response to fetal hypoxia, but direct evidence is lacking.

Many other fetal systems are activated during labor and birth, possibly triggered by the surge in CA and cortisol. These adaptations are, in general, fully present for a vaginally-born baby, and significantly reduced for babies born by cesarean section (CS) and especially following PLCS.[337] The vulnerability of PLCS babies to breathing difficulties, low blood glucose, hypothermia, poor tone, and reduced alertness can be attributed to lack of the labor-induced CA surge (see 5.2.6).

Fetal cortisol. *The baby's cortisol levels rise in the lead up to labor, with critical roles in maturing the fetal organs and in preparing for labor.*

Cortisol up-regulates fetal adrenoceptors to ensure an effective CA surge, with all the benefits as listed above. The large increase in fetal cortisol with the eustress of labor promotes rapid newborn adaptations in multiple systems, supporting the transition to life outside the womb,[78, 337, 912] and activating the HPA system with possible longer-term programming effects[148] (5.2.6). In addition to fetal production, maternal cortisol may cross readily to the baby in labor.[913]

Cortisol levels in cord blood have been correlated with acidity (pH, related to hypoxia),[814] reflecting the stress response to labor hypoxia. Other researchers have found greater increases, with labor stress, in the related adrenal hormone corticosterone than cortisol, suggesting that this may be the dominant fetal adrenal hormone in labor.[913]

5.1.4 Epinephrine-Norepinephrine and Related Stress Hormones after Birth

Maternal Epinephrine-Norepinephrine and Related Stress Hormones After Birth

Maternal epinephrine levels drop rapidly after birth, which may be important to optimize uterine contractions and prevent hemorrhage. Warmth and undisturbed skin-to-skin contact between mother and newborn may facilitate this. Postpartum physiologic elevations in cortisol may promote euphoria and attachment, possibly by potentiating oxytocin effects.

Maternal E levels, as measured in the blood, peak at birth and drop steeply after birth[894] (Figure 5). In one study, mixed maternal CAs (combined E-NE) had dropped at 30 minutes postpartum to almost 50 percent of levels measured immediately after birth.[914] This rapid drop in E may be important in preventing postpartum hemorrhage. At the very high levels of late labor and/or the FER, E may paradoxically stimulate contractions (via alpha-adrenoceptors) but, as levels decline postpartum, this effect may revert to inhibitory, via beta-adrenoceptors.

In support of this model, researchers have found correlations between high levels of E-NE and postpartum hemorrhage (PPH).[915] Older research found that drugs that inhibit E release are effective in preventing postpartum hemorrhage.[916] These findings suggest that circumstances that decrease E-NE postpartum may reduce PPH risk. Facilitators of low E-NE levels in the new mother likely include: a warm environment (cold can trigger E-NE release, 5.1.1), low stress, and undisturbed SSC with her baby, which promotes OT release (3.1.4), decreasing E-NE and SNS activity (3.1.1).

Cortisol levels are elevated in the new mother for several days following vaginal birth. Cortisol is not only a stress hormone; it is also associated with romantic attachment.[917] There is some evidence that elevated levels of cortisol-like hormones may potentiate the behavioral effects of OT, possibly by increasing the binding of OT to its receptors.[187] In relation to attachment, Esch comments, ". . . some degree of strong, yet manageable, stress may be necessary for very strong bonds to form."[917(p.177)] In addition, cortisol may be necessary, along with prolactin, in promoting early milk production (lactogenesis)[918] (6.1.4).

Studies have found that new mothers with elevated cortisol levels have more positive recollections of labor[909] and interact with their newborns more affectionately.[919] In one study, first-time mothers with elevated cortisol were more attracted to their newborn's scent,[919] which may reflect cortisol's potentiating effects on the OT system (above).

Cortisol declines to normal adult levels over the first week,[920] reflecting a gradual return to normal following the major pregnancy adjustments of the HPA system. The initiation of breastfeeding may contribute to this decline,[920] which has also been implicated in postpartum depression.

Newborn and Later Epinephrine-Norepinephrine and Related Stress Hormones

Newborn epinephrine levels drop rapidly, which is crucial to preserve energy stores. Skin-to-skin contact with the mother reduces stress and stress hormones. Early norepinephrine elevations promote learning of maternal odors. Newborn cortisol peaks after birth aid in newborn physiologic transitions, and promote alertness, likely benefitting breastfeeding initiation.

Newborn E-NE levels, as measured in cord blood following labor, are extremely high, and even higher if there has been hypoxia (5.1.3). Levels drop rapidly from these peaks, with E dropping by more than 80 percent within 15 minutes after birth.[922] This rapid postnatal decrease is important, as the fetal CA surge increases metabolic turnover, depleting newborn energy stores that will not be replaced until breastfeeding is well established.[337]

Skin-to-skin contact with the mother reduces the "stress of being born"[175, 337] by increasing OT levels, which switch off the fight-or-flight response and reduce E-NE levels.[175] Lack of SSC after birth can keep newborn E-NE levels elevated, which can have ongoing detrimental effects on the autonomic nervous system and newborn metabolism (5.2.7).

Newborn NE levels drop more slowly than E levels. Physiologic NE elevations in the early newborn hours are associated with olfactory learning among human newborns, helping the baby learn the mother's smell.[923]

Postpartum maternal and newborn E-NE levels may be correlated and reflect previous stresses in labor. In one study, women whose babies had nuchal cords, including one baby with a true knot in the cord, had higher than average levels of E and NE at birth,[901] although other studies have not found correlations between maternal and fetal levels.[898] (See also discussion of maternal-fetal E-NE transfer in 5.1.3.)

Newborn cortisol levels continue to rise after birth, peaking a few hours later at levels about six times higher then those in late gestation. This provides important assistance with newborn transitions, including liberating the metabolic fuels that are needed until breastfeeding is established.[78] For the newborn, as for adults, cortisol may give feelings of well-being and euphoria, and help to form strong bonds. In one study, newborn cortisol levels were higher after a longer labor and correlated with alertness,[912] which is likely to benefit breastfeeding initiation.

Epinephrine-Norepinephrine and Related Stress Hormones, and Breastfeeding and Maternal Adaptations and Attachment

Maternal cortisol elevations promote prolactin receptor formation, benefitting breast-milk production, and enhance newborn transitions via transfer into breast milk. Norepinephrine promotes maternal behaviors.

During early breastfeeding, physiologically elevated maternal cortisol levels may promote prolactin receptor formation, as found in animal studies,[910] with benefits to ongoing milk production (6.1.4). In addition, elevated levels of cortisol, which is transferred into milk,[921] may assist with newborn transition to life outside the womb. Cortisol levels in maternal blood correlate with levels in breast milk.[775]

Animal research suggests that NE released during labor may be important for subsequent maternal behavior. Mice bred to be deficient in NE do not care for their infants unless NE is injected back into the brain before birth.[924] Within the brain, NE centers make critical connections with OT centers, facilitating

the processes of labor, birth, and postpartum maternal adaptations, according to animal studies.[252] In animals,[404] and in human newborns,[923] NE is important for olfactory learning. In primates, including humans, NE may also facilitate social learning and affiliation, beginning from birth.[404]

As described above ("Maternal Epinephrine-Norepinephrine and Related Stress Hormones After Birth"), postpartum cortisol elevations may elevate maternal mood and promote attachment.

5.2 Common Maternity Care Practices That May Impact Epinephrine-Norepinephrine and Related Stress Hormones

Many common practices can disturb epinephrine-norepinephrine and related stress hormones in mothers and babies. This chapter considers the effects of stress in childbearing (including pregnancy, labor, and birth), on these hormones, including cortisol, in women and babies in relation to maternity care provider and birth environment. Other maternity care practices that may disrupt these systems in mothers and babies, as described in this section, include the administration of epidural analgesia, cesarean section, and the postpartum separation of healthy mothers and newborns.

5.2.1 Maternity Care Provider and Birth Environment, Including Prenatal and Childbirth Care: Possible Impacts on Epinephrine-Norepinephrine and Related Stress Hormones

This area has not been well researched in relation to direct effects. One randomized study found no reduction in maternal epinephrine and norepinephrine levels following birth attendant (doula) support. However, this study found benefits of doula support to mood, labor pain recall, and breastfeeding, suggesting overall benefits to hormonal systems.

One randomized study measured E, NE, and cortisol among laboring women before and one hour after allocation to additional care from a supportive birth companion (doula) or control. Researchers found no measurable differences in these hormones or in overall labor progress, compared to women without doula support.[448, 449]

However, this research did find that women who received doula care had lower analgesia requirements and reduced blood pressure in labor, and subsequently reported: less postpartum anxiety and better mood scores, less recollection of labor pain and difficulty, and higher breastfeeding continuation than women not receiving labor support. In addition, a follow-up study found lower levels of postpartum depression among women randomized to labor support.[435] These findings are consistent with enhancement of hormonal physiology.

Several factors might account for the lack of measured hormonal changes in this study. First, the physiologic rise in these hormones in labor, as found in human studies (5.1.4), could mask decreases due to reductions in stress and anxiety. In addition, the second sample, taken just one hour after allocation, may not have allowed sufficient time for the laboring women to form a new relationship and benefit from the doula's support. A systematic review of doula support found less analgesia requirements, lower CS risk, and lower rates of dissatisfaction,[780] also suggesting hormonally-mediated benefits (see "Childbirth and Stress," below).

Prenatal Care and Stress

Maternal stress and stress hormones may be impacted by aspects of prenatal care, including nocebo (negative placebo) effects, prenatal testing, fears about fetal well-being, and concerns about pain in labor. Prenatal care that benefits maternal relaxation and/or reduces anxiety and fear could benefit maternal and fetal outcomes by enhancing hormonal physiology.

Maternity care providers could potentially influence E-NE and related stress hormone levels in pregnant women through elevating or reducing maternal anxiety and perceived stress in relation to pregnancy care, including prenatal testing.[925-927] Given the solid evidence showing adverse impacts of pregnancy stress, including impacts on prematurity, birth weight, and infant and child development (5.1.2), reducing pregnancy stress could have significant benefits for mothers and babies.

Aspects of our current maternity care system may increase, or fail to decrease, anxiety and stress for pregnant women. Studies have linked increased maternal anxiety with routine prenatal tests including**:**

- ultrasound,[928-930] with false-positive scan results negatively affecting maternal-infant attachment, even after birth[931]
- prenatal testing for Down syndrome[926, 932, 933 934]
- electronic fetal monitoring in pregnancy[935]

The World Health Organization estimates that, in many countries, an average woman receives in excess of 150 tests during pregnancy.[936] False positive findings, which become more likely as the number of tests increases, can create anxiety. For example, in a survey from Germany, two-thirds of women reported an abnormal test result during pregnancy, the majority relating to an ultrasound scan and eventually found to be normal. More than half of these women reported being acutely worried and, five weeks later, one-quarter were still concerned.[937]

Sakala identifies the nocebo effect, an unintended negative effect (reverse placebo), as of concern in relation to conventional maternity care, which can create a "climate of doubt" rather than a "climate of confidence" for pregnant women and their ability to gestate, birth, and breastfeed their babies.[938] Odent comments, "The nocebo effect is inherent in conventional prenatal care, which is constantly focusing on potential problems. Every visit is an opportunity to be reminded of all the risks associated with pregnancy and delivery."[939] Odent recommends that maternity care providers "create such interactions that a pregnant woman feels even happier after a prenatal visit than before . . . or at least less anxious."[925(p.311)]

Common maternity care language and terms can imply deficits in the pregnant woman's body and its functions. Examples include: "incompetent cervix," "growth retardation," "trial of labor," "failed induction," "failure to progress," "inadequate pelvis," and "elderly primagravida." These may also have a nocebo effect on childbearing women.

Maternal fear about the baby's well-being, which may be exacerbated through prenatal testing, has been linked to attention-regulation deficits in infancy, as has fear of pain in labor,[940] another area where conventional prenatal care does not generally provide an empowering context for pregnant women. The national *Listening to Mothers II* survey of women who gave birth in 2005 found that 53 percent of all women felt fearful as they approached labor, including almost two-thirds of first-time mothers.[941]

In relation to pregnancy care, increases or decreases in stress hormones could mediate some of the documented differences in outcomes between different care providers. For example, a Cochrane systematic review found that women randomized to midwifery-led continuity of care were less likely to experience

preterm birth and to lose their baby before 24 weeks, compared with women using other models of care.[451] Similarly, a meta-analysis of women who chose to give birth at home, the majority under midwifery care, found lower rates of prematurity, with fewer low birthweight babies, compared with similarly low-risk women giving birth in hospital.[453] A recent (non-randomized) study of doula support beginning in pregnancy, found a four-fold reduced risk of premature birth among socially-disadvantaged women compared with women without doula support.[942]

Some of these findings could relate to a lower risk status among women choosing midwifery or doula care and home birth, although the Cochrane review was limited to randomized controlled trials and US studies have shown that midwifery clients include women with a variety of risk profiles.[452, 943] Enhanced emotional support and reduced anxiety, which may be more likely among women accessing midwifery care, could also contribute, reflecting a paradigm of the fundamental normalcy of childbearing, possibly acting via low maternal E-NE levels optimizing uterine blood supply. Other maternity care providers and models of care that encompass emotional support and minimize nocebo effects in pregnancy may similarly benefit maternal and fetal outcomes, according to this model.

A recent systematic review of effects of relaxation techniques in pregnancy found beneficial effects in relation to: women's emotional state, maternal and fetal physiologic stress markers and/or hormones, hospital admission, premature birth and low birth weight, cesarean section rate, and newborn neurobehavior, among other pregnancy and postpartum benefits. Effective techniques included guided imagery (such as a guided relaxation audio program), progressive muscle relaxation, yoga, and massage. Researchers suggest that identifying pregnant women at risk and treating from early pregnancy could improve obstetric and developmental outcomes for the mother and her fetus.[944] This evolving evidence suggests that some forms of relaxation and relaxation training may improve not only physiologic and hormone stress markers but also meaningful outcomes in mothers and babies. Reduction of stress and anxiety in pregnancy may have significant and long-term benefits to offspring, and therefore substantial public health benefits.

Given the links between maternal and fetal stress responses, and the long-term effects of maternal stress, as detailed here, reducing anxiety and fear during pregnancy is likely to be clinically relevant and is an important area for high-quality research.

Childbirth and Stress

Providing an environment that laboring women perceive as private, safe, and undisturbed may be important for labor progress, as it is in other animals, and may reduce requirements for interventions. Conversely, perceived stress may elevate epinephrine and norepinephrine, slowing labor and potentially reducing fetal blood supply. Laboring women may perceive many common maternity care practices as stressful.

In many traditional cultures, a major role of the care provider in labor is to ensure a safe and undisturbed environment for the laboring woman, with emotional support when needed, so that perceived stress is reduced.[945] Techniques used by traditional care providers include massage, physical support, reassurance, and rituals, among other practices.[945, 946] An emphasis on maternal emotional well-being, with simple, nonpharmacologic tools for support, is also applicable in contemporary settings[947-952] and is likely to maintain physiologic E-NE levels in labor, with benefits to laboring women. This approach may contribute to the low requirement for intervention among women giving birth at home[452, 453] and in birth centers in the United States,[953, 954] and internationally.[955, 956]

For women giving birth in hospital, continuous labor support provided by a doula may also reduce stress (and possibly excessive E-NE levels, if measured for an adequate time) and has been shown to have the following benefits, in comparison with standard care, according to the Cochrane systematic review:[780]

- reduced need for pain relief and operative birth, including CS
- reduced duration of labor
- improved newborn Apgar score
- increased chance of maternal satisfaction with the birth experience

Given the costs and risks of high levels of interventions, and the consistent and significant reductions in interventions associated with low-technology models such as midwifery care and doula support, understanding the mechanism of these benefits, and how to apply them generally in institutional birth settings, are important areas for future research.

Farmers, animal breeders, and zoo staff, among others, recognize that stress in labor and birth is hazardous in other animals[832] (see "Evolutionary Model" in 5.1.3 and "Stress in Animals and Birth," below). This has not been well researched in women. Early studies by Lederman and colleagues measured self-reported anxiety and blood levels of E, NE, and cortisol in laboring women in relation to birth outcomes. They found associations between anxiety in early labor, elevated early E levels, and both prolonged labor and abnormal FHR patterns suggestive of hypoxia.[899, 900, 957] A more recent study using urinary E-NE measurements found that women with high E levels in early labor had significantly longer labors.[110]

These studies support a hormonal model of labor progress whereby excessive fear and anxiety may potentially elevate maternal E and NE levels, activating both alpha- and beta-adrenoceptors. Effects therefore may include beta-mediated slowing of labor, and alpha-mediated reduction in fetal blood supply (5.1.4), both found in these human studies. Animal research suggests that a healthy fetus can adapt to moderate hypoxia (e.g., from an epinephrine injection) by increasing oxygen uptake from placental blood. However, a compromised fetus may already be extracting maximal amounts, and be unable to further compensate.[874] In contemporary maternity care, slow labor and suspected fetal hypoxia are common indications for labor interventions. This may reflect high levels of stress and anxiety, and high E-NE levels, among laboring women.

Some aspects of contemporary maternity care may contribute to stress. Simkin retrospectively surveyed women about the stressfulness of labor events, and more than one-third of women rated each of the following as maximally stressful:[958]

- labor induction or augmentation
- restriction of movement in bed
- administration of anesthesia
- vacuum or forceps delivery
- limited time with newborn

Other common potential labor stressors in the maternity care environment may include: presence of unfamiliar or undesired personnel, including trainees; hurried or brisk personnel; separation from loved ones; bright lights; loud noises; time pressure (e.g., for dilation or pushing); lack of privacy; practices that restrict or encroach upon the laboring woman's body (e.g., a bladder catheter or external and internal electronic fetal monitoring); and an emphasis on facility routines rather than individualized response to women's needs and preferences.

The effects of stress and fear in labor may continue beyond birth. Respondents to the national *Listening to Mothers II* survey reported high levels of post-traumatic stress symptoms, with 9 percent of women's responses to a validated instrument consistent with posttraumatic stress disorder and another 18 percent with elevated levels of posttraumatic stress symptoms.[685, 941] As discussed in "Pleasure and reward" in 3.1.4, elevated levels of OT during physiologic labor, birth, and postpartum period may give feelings of euphoria that could plausibly protect against this condition. (See also "Stress in Animals in Birth," below, and "Other hormonal influences on oxytocin in labor and birth" in 3.1.3 for involvement of the OT system in labor and birth stress.)

Inter-individual transmission of emotional states via mirror neurons[959] and "emotional contagion"[960] suggests that fear and stress in care providers could plausibly impact the laboring woman, with possible relevance to labor and birth outcomes. In one randomized study, women who had a companion sitting calmly, silently, and inconspicuously in the room for the duration of labor experienced reductions in the use of maternity care interventions compared with women receiving standard care.[961] Odent suggests knitting as a silent rhythmic activity to keep E-NE levels low among labor attendants.[962]

The specific impacts of the environment on the experiences, stress levels, and outcomes for mothers and babies, including greater understanding of the impact of caregivers and their emotional states, are important areas for future research.

Labor and Birth Stress in Animals

Animal research shows significant hazards from labor stress, including slow labor and fetal hypoxia. For women, as with other mammals, birth environments that support private conditions may be ideal for fostering labor progress. Stress may slow labor via epinephrine-norepinephrine directly inhibiting contractions and/or indirectly reducing oxytocin. Stress may also directly inhibit pulsatile oxytocin and/or may reduce central oxytocin by increasing beta-endorphins

Research with other mammals has increased our understanding of the effects of stress in labor. In a series of early experiments with laboring mice, Newton found that mild intermittent stress (being held in cupped hands between the births of offspring) prolonged labor, even among those animals accustomed to handling.[963] More severe stress—laboring in a clear bowl with the smell of cat urine—not only slowed labor by about eight and a half hours, but also increased offspring mortality by 50 percent compared with the control group.[964]

In relation to E-NE levels, researchers exposed sheep in advanced pregnancy to mild electric shocks and found a rapid 25 percent elevation in NE levels, which peaked at 30 seconds and subsided over 10 minutes. At the same time, uterine blood flow was reduced by 32 to 52 percent, although there were no measured adverse effects on the fetus.[965]

In other studies, primate researchers subjected rhesus monkeys to significant stress in late pregnancy, beginning with the surgical placement of catheters and measuring devices in mother and baby. Subsequent stresses, including bright lights, shouting, and the presence of an observer, caused hypoxia and decreased fetal blood pressure within 50 seconds of onset, evidenced by bradycardia and late decelerations on FHR monitoring, with recovery a few minutes after cessation of stress. There was no change in uterine tone or activity, suggesting that effects were mediated by alpha-adrenoceptor vasoconstriction. Monkey mothers who were more approachable and responded more calmly to human contact had fetuses with less severe reactions.[966] In other primate research, fetuses that were already hypoxic (with lower pH) had more severe and prolonged reactions to maternal stresses.[967]

As well as illuminating the mammalian response to labor stress, these findings suggest that the mother's perception of stress or danger, rather than objective events, determines her E-NE activation, and that this may impact her uterine blood supply and fetus. Effects will also depend on the physiologic state of the fetus: in these studies, fetuses that were already hypoxic became severely compromised in response to maternal stress.[836, 967]

Animal studies have found that stress in labor also reduces maternal OT release, illustrating another mechanism by which stress can affect mother and baby. In mice, studies suggest that elevations in E-NE lead to OT reductions,[457] whereas in rats and pigs, endogenous opioids including beta endorphins may mediate stress-related reductions in OT and slowing of labor (4.1.3).[458, 459] Beta-endorphins could also slow labor by acting locally on uterine opioid receptors, which have been found in women.[461] Stress in labor may reduce pulsatile rather than constant OT release, with inhibiting effects on labor[462, 463] (see 3.2.1). It is not clear which of these pathways are predominantly involved with stress responses in laboring women. (See also 3.2.1.)

As discussed in 5.1.3, laboring animals are also significantly disturbed by direct observation and/or by contact with strangers,[832] which can slow or halt labor. This may also be true for laboring women, who will often seek the smallest and least visible place for labor and birth (e.g., bathroom, shower),[968] when mobile and able to choose. Birth environments that support private conditions, which can still be compatible with the necessary monitoring and care of mother and baby, may be ideal for fostering labor progress.

5.2.2 Prostaglandins for Cervical Ripening and Labor Induction: Possible Impacts on Epinephrine-Norepinephrine and Related Stress Hormones

Maternally-administered prostaglandins may promote fetal lung maturation directly and/or indirectly via induction of labor and the catecholamine surge.

No studies were found that directly assessed possible impacts of PGs for cervical ripening and induction on E-NE and related stress hormones of mother or baby.

However, researchers have trialed maternal administration of PG one hour before CS to promote a fetal CA surge and improve newborn respiratory transition. While numbers may have been too small to detect a difference in lung function, NE levels were higher in newborns of treated mothers.[969] More studies may be justified,[970] including assessment of possible adverse outcomes such as hyperstimulation. Animal studies suggest that PGs may directly promote fetal lung maturation and lung surfactant production,[971, 972] although high levels of PGs can also impair other elements of respiratory transitions.[973]

5.2.3 Synthetic Oxytocin For Induction, Augmentation, and Postpartum Care: Possible Impacts on Epinephrine-Norepinephrine and Related Stress Hormones

The administration of synthetic oxytocin may increase maternal pain, and epinephrine-norepinephrine levels, and may be perceived by laboring women as stressful. Stronger contractions may increase hypoxic stress in the fetus, possibly promoting the beneficial catecholamine surge. If labor is induced long before the physiologic onset of labor, lack of prelabor adrenoceptor upregulation could limit fetal adaptations to hypoxia.

One study was found that assessed possible impacts of the use of synOT for augmentation on maternal E-NE systems. Researchers found almost three-fold elevations in late-labor E levels among women administered synOT,[901] likely related to increases in stress and pain.

In Simkin's survey (5.2.1), 76 percent of women rated induction of labor (likely with synOT) as moderately or most stressful.[958] Another study found almost three-fold elevation of ACTH, another stress hormone, in women administered synOT for induction compared with women whose labor was physiologic in onset.[880]

In the fetus, induction or augmentation of labor may increase hypoxic stress due to the longer, stronger, and more closely spaced contractions.[974, 975] Hypoxic stress can increase fetal and newborn E-NE up to twenty-fold,[976] enhancing fetal adaptations.

Induction in animals with synOT was found to promote fetal lung fluid clearance and surfactant production via the CA surge,[977] especially when the fetus had been exposed to cortisol,[978] which upregulates adrenoceptors in the lungs. In addition, animal studies suggest that newborn neurologic transitions and longer-term brain function may benefit from the CA surge[979] (5.2.6).

One equine study found cortisol levels elevated two-to threefold at birth and for up to ten days thereafter among induced compared with spontaneously born foals, which researchers linked to abnormalities in glucose metabolism[148] (see 3.2.3).

These findings support the advantages of labor, including induced labor, over PLCS for lung fluid clearance and newborn neurologic transitions via E-NE elevations. However, babies induced at an early gestation may have reduced adaptations to labor hypoxia due to lower beta-adrenoceptors[337] (5.1.2). Long-term impacts of induction on offspring metabolic and stress systems remain unknown.

5.2.4 Opioid Analgesic Drugs: Possible Impacts on Epinephrine-Norepinephrine and Related Stress Hormones

Studies support physiologic understandings that maternal cortisol decreases with analgesia to the extent that labor stress and pain decrease.

Opioid analgesics drugs administered systemically by intramuscular (IM) or intravenous (IV) injection may reduce intrapartum maternal cortisol levels, compared with no analgesic medication, likely in proportion to their efficacy in reducing labor stress and pain, as with BEs (4.2.4). Studies have found lower cortisol levels following systemic meperidine administration in women with induced labor, compared with induced women with no analgesia,[980] and higher cortisol levels in women administered systemic opioid drugs versus epidural analgesia[894] (see 5.2.5 below). (See also 3.2.4 for more background on opioid analgesic drugs.)

5.2.5 Epidural Analgesia: Possible Impacts on Epinephrine-Norepinephrine and Related Stress Hormones

Epidural analgesia has well-documented impacts on the maternal E-NE system, some of which contribute to common epidural side effects, with potential indirect impacts on the baby. Direct effects on fetal and newborn E-NE systems are suggested in some studies but less well researched.

Epidural Analgesia and the Mother

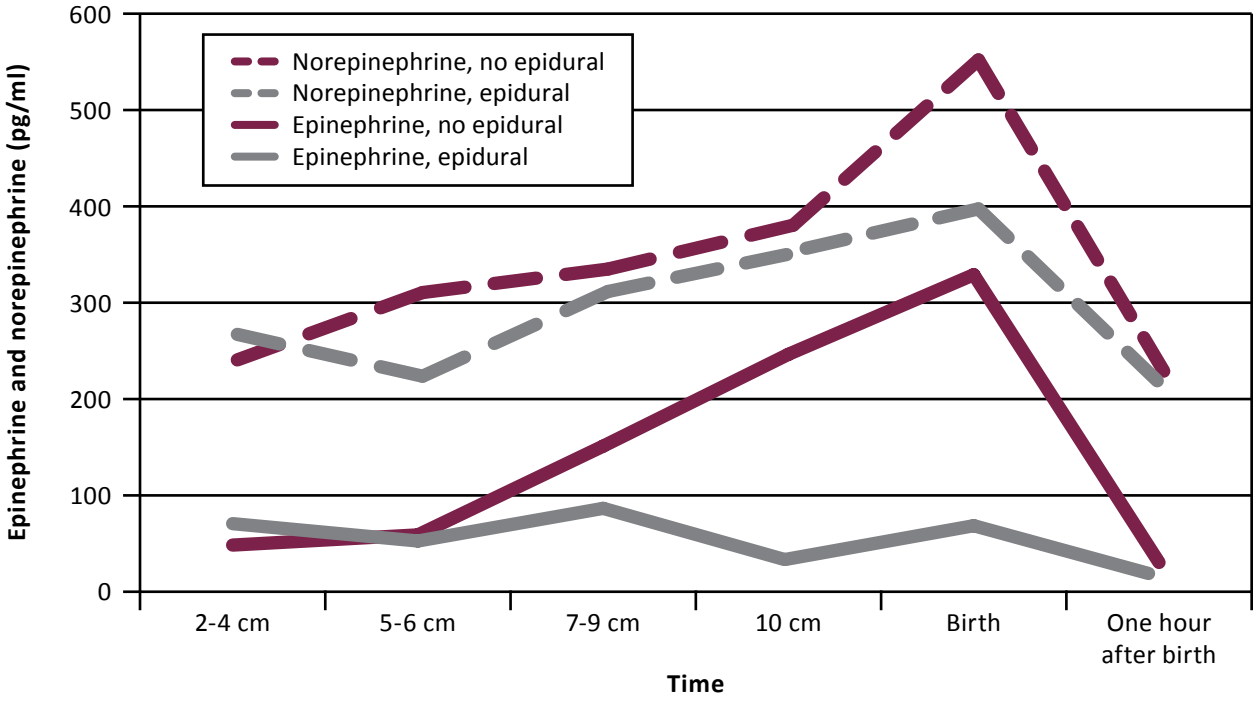
Following epidural administration, maternal epinephrine levels rapidly decline and remain low through labor. This may benefit women for whom stress, pain, and epinephrine elevations are slowing labor. Epidural impacts on epinephrine and norepinephrine can contribute to side effects, including hypotension, hyperstimulation, and prolonged and difficult pushing. Reduction in cortisol may impact maternal postpartum mood and adaptations. Epidural exposure may alter hormonal release with subsequent breastfeeding.

Laboring women administered epidural analgesia exhibit a rapid decline in E levels within 30 to 60 minutes of administration.[617, 894, 981] Levels of E remain significantly lower than those of women not administered epidurals, with maternal levels at birth that are 25 to 70 percent of E levels among women using meperidine or no pain relief.[110, 800, 894, 898] In these studies, NE levels were not significantly decreased.

Figure 6[894] illustrates mean E and NE levels during labor, birth, and the early postpartum period among 18 women administered epidural analgesia and eight women administered meperidine. This figure shows loss of the late-labor E surge, with levels at birth around one-quarter of those in women using meperidine. Other data in this study (not shown) record a significant drop in each woman's E levels one hour after epidural placement.[894]

These lower E and NE levels also reflect reductions in stress and pain following epidural administration, which may benefit labor physiology for women in some situations. For example, if stress and pain are excessive, with very high E-NE levels inhibiting contractions and even fetal blood supply, epidural-related reductions may allow labor to progress, or alternatively, may provide the laboring woman a welcome opportunity to rest. (See 3.2.6 for epidural-related reductions in OT.)

Figure 6. Maternal epinephrine and norepinephrine levels, with and without epidural analgesia



Source: adapted from Neumark[894]

However the rapid epidural-related reduction in E (which inhibits uterine contractions) with less reduction in NE (which stimulates contractions) can also cause rebound uterine hyperstimulation (5.1.1) with potentially deleterious effects on the baby, as detected by FHR changes. This is especially likely following spinal analgesia (including as part of combined spinal-epidural, CSE), likely because of the swift onset of

analgesia, which drops E levels very rapidly.[982-984] Hyperstimulation can compromise fetal blood supply and necessitate emergency measures including CS. Epidurals increase the risk of CS for "fetal distress"[614] (non-reassuring FHR patterns).

The sudden decrease in E levels can also cause a drop in maternal blood pressure,[614, 985] which may further compromise fetal blood and oxygen supply, although severe hypotension is usually prevented by IV fluid administration before epidural placement. These rapid blood pressure shifts and stimulating (or hyperstimulating) effects are generally temporary, with contraction strength subsequently declining due to the epidural-related decrease in OT. Many women receive synOT administration to compensate. (See 3.2.5 for a full discussion of epidural impact on OT.)

Reductions in E-NE in late labor may cause other significant problems. As noted in 5.1.3, physiologic elevations in E-NE at the end of labor can stimulate contractions, giving women assistance with the pushing stage and birth. Loss of these peaks with epidural analgesia, along with reductions in OT and the Ferguson reflex (3.2.5), likely contribute to the epidural-associated lengthening of the pushing phase, the increased need for forceps and vacuum assistance, and the associated increased risk of perineal tears.[614, 985]

Studies have also found lower levels of maternal cortisol in new mothers exposed to labor epidurals compared with unexposed mothers, as measured in the blood or saliva.[110, 800, 912, 914]

Studies have found no rise in salivary cortisol levels from labor to birth among women using epidurals, compared with doubling or tripling of levels for women without epidural analgesia.[110, 894] Elevated cortisol in labor may benefit mothers and babies by enhancing OT effects and contraction efficiency, as in animal studies (3.1.3), along with postpartum benefits to maternal mood and postpartum adaptations, as found in human studies (5.1.4).

In addition, one study found an exaggeration of the usual cortisol decline (lower cortisol levels) with skin-to-skin breastfeeding two days after birth among women exposed to epidural analgesia in labor, and a reduced cortisol decline (higher levels) among women exposed to epidural plus synOT, compared with women unexposed to these interventions. These findings may reflect alterations in OT release, which generally reduces cortisol (3.1.1). In this study, epidural exposure was associated with increased oxytocin release with skin-to-skin breastfeeding, and epidural with synOT was associated with reduced OT release. The mechanisms are not clear.[570]

Disruptions to cortisol in the postpartum period could adversely impact breastfeeding, as cortisol promotes the development of prolactin receptors, with benefits to ongoing milk production, according to animal studies. (See also "Prolactin receptor theory" in 6.1.4, and 3.2.5 for discussion of epidurals and breastfeeding.)

Epidural Analgesia and the Fetus/Newborn

Epidural analgesia has no direct stress or pain reducing effects for the fetus, who may be indirectly impacted by maternal hormonal impacts such as hypotension and hyperstimulation. Local anesthetic drugs may directly impact fetal stress systems, and changes in newborn inflammatory markers have also been found. Newborn respiratory distress may be increased.

Epidural does not provide analgesia or direct stress-reducing effects to the fetus or newborn (4.2.5). However other impacts on fetal/newborn E-NE and stress hormones are possible through direct and indirect mechanisms.

Clinicians have suggested that epidural-related reductions in maternal stress and stress hormones (above) may benefit the baby by increasing uterine blood flow.[987, 988] While reductions in excessive maternal stress may be beneficial, benefits to FHR, suggesting improved fetal blood supply, are generally not demonstrated following epidural administration; and in fact studies show increased rates of non-reassuring FHR changes following epidural administration,[790, 984, 989] with 20 percent or more of exposed babies affected in some studies.[984, 989]

Such impacts may reflect maternal hormonally-related side effects (see "Epidural Analgesia and the Mother," above) including hyperstimulation and low blood pressure. Local anesthetic drugs used in epidurals may also directly cause constriction of the uterine arteries and reduction of blood flow to the baby.[990] The co-administration of synOT, may additionally predispose to hyperstimulation and fetal hypoxia, as detected on FHR.[790, 991]

Epidurals may also have direct effects on fetal stress systems. Researchers have found that local anesthetic drugs, as used in epidurals, can cause CRH release,[992, 993] which generally triggers the release of other stress hormones, including E-NE, beta-endorphins, and cortisol.[809, 992-994] In the fetus, CRH also triggers a positive feedback cycle that may further augment stress hormone release.[76] Several studies have found elevations in newborn E, NE, and/or other stress hormones following epidural exposure in labor,[800, 898, 913, 914] including very high CRH levels,[800] possibly reflecting these processes.

Studies have generally not shown differences in cord blood cortisol levels between newborns exposed and unexposed to labor epidurals.[800, 912] This unexpected finding in the context of other stress hormone elevations, may reflect the influence of maternal cortisol, which is reduced following epidural, and is correlated with fetal levels, likely due to transplacental passage.[912] However, elevations in fetal corticosterone, which may be more specific to fetal stress responses, have been found with epidural exposure.[913] (See also "Fetal Epinephrine-Norepinephrine and Related Stress Hormones in Labor and Birth" in 5.1.3.) Skin-to-skin contact after birth may be especially important for babies exposed to epidurals in labor to reduce possible stress and stress hormone elevations, and may also benefit breastfeeding (see "Epidural Analgesia and Breastfeeding" in 3.2.5).

Recent research has found increased risks of newborn respiratory distress on the day of birth following epidural exposure. In this study, opioid exposure via intravenous or oral administration did not increase risk.[995] These findings may relate to the depressant effects of opioid drugs on respiration, but epidural-related hormonal disruptions may also contribute.[996] Ward Platt comments, in relation to this study, "The effects of epidurals and other maternal analgesia and anaesthesia have largely been reported in relation to benefits and harms for mothers, with little regard for babies."[996(p.F98)]

Given the widespread use of epidural analgesia in labor, research into possible impacts on the fetus and newborn, including stress activation and respiratory outcomes, are high priorities.

5.2.6 Cesarean Section: Possible Impacts on Epinephrine-Norepinephrine and Related Stress Hormones

Cesarean section may have significant impacts on physiologic epinephrine-norepinephrine systems for mothers and babies, who will both miss, to some extent, their respective physiologic late-labor epinephrine-norepinephrine elevations.

Cesarean and the Mother

Following prelabor cesarean, women have lower levels of epinephrine, norepinephrine, cortisol, and other stress hormones due to lack of labor eustress, with possible deficits in postpartum mood elevation.

Researchers have generally found reduced levels of maternal E, NE, and cortisol following PLCS compared with vaginal birth.[800, 896, 897, 997-1000] In one study, maternal E and NE levels following PLCS were around 50 percent of levels following vaginal birth, as sampled 60 to 120 seconds after birth. Other maternal stress hormones such as BEs, ACTH, and CRH, were also reduced in this study, with cortisol levels around one-third of those in women following vaginal birth.[800, 896, 998, 999] These lower hormone levels may reduce the euphoria and early adaptations associated with maternal hormonal elevations, according to animal and human studies (3.1.4, 4.1.4, 5.1.4). Delayed contact with her newborn may contribute[432] (see 5.2.7). Reduced cortisol may adversely impact breastfeeding success following PLCS.[1001]

Cesarean and the Fetus/Newborn

Babies born by cesarean miss, to some extent, the eustress of labor and birth, which promotes fetal-to-newborn transitions via the catecholamine surge. Respiratory morbidity is increased, including mild, moderate, and severe conditions, along with hypoglycemia, hypothermia, and neurobehavioral effects. Breastfeeding initiation may also be compromised. Studies suggest that longer-term stress responsiveness may also be altered, and epigenetic impacts for in cesarean newborns, found in human studies, may contribute to long-term cesarean effects. Animal studies suggest that lack of perinatal stress hormones may have long-term effects on brain function and behavior.

Loss of the fetal CA surge may significantly contribute to increased morbidities among CS-born newborns, especially following PLCS, when newborn NE levels are 20 to 50 percent of those of vaginally born babies.[800, 896, 976, 1002, 1003] Consequences for PLCS newborns may include:

- compromised respiratory transition, with increased risks of transient tachypnea (correlated with reduced NE;[1004] respiratory distress,[1005] even at 40 weeks' gestation;[1006] and the life-threatening condition persistent pulmonary hypertension[1007]
- increased risk of hypoglycemia in PLCS-born newborns,[1003, 1008] with low levels of metabolic fuels and blood glucose[1003]
- lower body temperature among PLCS compared with in-labor CS newborns,[1009] due to deficits in CA-promoted thermogenesis
- lower blood flow into limbs, which may benefit cardiovascular adaptations[1002]
- neurobehavioral impacts, including increased stress scores[1010], and lower neurological score correlated with NE and persisting for up to five days following PLCS compared with vaginal birth[1011, 1012]

These detrimental effects likely contribute to higher rates of respiratory morbidity[1007, 1013] and neonatal intensive care unit (NICU) admission following CS than vaginal birth.[1014, 1015] Even healthy cesarean newborns have been found to have poorer lung function,[1016] delayed lung fluid clearance,[1017] and lower lung compliance, correlated with lower NE levels,[313] compared with vaginally-born babies. Studies have found reduced morbidity,[1018, 1019] including respiratory morbidity, among babies born following in-labor CS compared with PLCS, likely due to CA effects.

Fetal and newborn E-NE systems, and the CA surge, will be most impacted by PLCS. An in-labor CS following the physiologic onset of labor will allow E-NE prelabor physiologic preparations and some degree of labor-related elevations for the baby. Babies born following in-labor CS have a lower risk of NICU admission and of death before hospital discharge than newborns following PLCS, according to one large study that compared these two groups.[11] (See also 3.2.7.)

Breastfeeding initiation is less likely following PLCS,[679] (3.2.6), with anesthesia and surgery likely reducing alertness for mothers and newborns, who are also less likely to achieve important early breastfeeding behaviors.[1020-1022] (See also "Cesarean and Breastfeeding" in relation to OT in 3.2.6.) Early maternal-infant hormonal and adaptation systems may also be compromised following CS (3.2.6, 4.2.6, 6.2.6).

Studies have also found reduced levels of cortisol in the cord blood of CS- compared with vaginally-born newborns,[137, 813, 814, 913] along with reduced newborn responses to pain[137] and maternal separation.[136]

In longer-term studies, infants born by CS, [26] and those with low cortisol at birth[814] (also related to exposure to combined spinal-epidural in this study) had reduced cortisol responses to immunization pain at 2 months of age. These studies suggest that infraphysiologic levels of stress at birth could mis-program the HPA system, with unknown duration.

In animal studies, newborn rats born by CS had signs of low-grade brain hypoxia for the first 24 hours compared with vaginally-born offspring.[30] In adulthood, cesarean offspring were found to have alterations in social behaviors and stress responses,[27, 141] and in brain function in areas related to NE[31] and the related brain chemical dopamine.[28] These impacts were modified by either an episode of hypoxia, which provoked E-NE release,[30] or administration of an injection of E straight after CS,[27] suggesting that lack of E-NE exposure in the perinatal period may produce these longer-term detrimental brain effects. In these studies, males and females were differently affected.[31] Elevations in cortisol-like hormones were found in infant piglets born by CS,[29] also suggesting longer-term disruptions to stress systems (5.1.1).

Researchers have analyzed human newborn tissues, including blood cells, for DNA methylation. This is a marker of epigenetic changes, and a mechanism for switching off ("silencing") genes, with potentially widespread and even inheritable impacts on body functions. Studies have found greater methylation in specific (single) gene areas in CS offspring,[23-25] including in areas associated with type 1 diabetes.[23] This study also found a beneficial dose-response modification with labor exposure, suggesting that the eustress of labor may have an epigenetic benefit for the baby.[23]

Many other body systems are activated through physiologic labor and birth, perhaps secondary to the fetal surges of CAs and cortisol, with considerable implications for long-term outcomes following CS and especially PLCS.[40, 148] Changes in immune function following CS may also reflect lack of the beneficial gut colonization with vaginal birth.[148]

These widespread CS-related alterations in newborn hormonal and physiologic transitions, including loss of the eustress of labor and birth with PLCS, may contribute to increased longer-term risks that include: asthma and allergies, type 1 diabetes, overweight and obesity, and celiac disease.[40, 148]

Given the large numbers of mothers and babies experiencing cesarean birth, and the accumulating evidence about possible short and longer-term impacts, these are critical areas for future research.

5.2.7 Early Separation of Healthy Mothers and Newborns: Possible Impacts on Epinephrine-Norepinephrine and Related Stress Hormones

Separation of mother and newborn disallows the skin-to-skin contact that reduces stress and stress hormones for both, with benefits to newborn physiology and metabolism and possibly maternal hemorrhage risk. Postpartum separation could have longer-term detrimental effects on offspring stress systems, as found in animal studies. Separated human newborns display high levels of anxious arousal.

No studies were found that directly assessed possible impacts of early separation of healthy mothers and newborns on E-NE and related stress systems in mother or baby.

As discussed in 5.1.5 and 5.1.6, there is a rapid decrease in both maternal and newborn E-NE levels in the early minutes following unmedicated labor and birth, which may be enhanced by SSC. Skin-to-skin contact also benefits mother and newborn by releasing OT, which reduces E-NE and "the stress of being born,"[175, 337] and switches on "calm and connection" via the PNS.[175]

Early separation of healthy mothers and newborns may further increase, or fail to decrease, these physiologically elevated E-NE levels, with potentially detrimental effects. In the new mother, persisting high E-NE levels could antagonize effective uterine contractions and increase the risk of postpartum hemorrhage (3.1.4, 5.1.4). In the newborn, ongoing E-NE elevation may cause depletion of glucose and free fatty acids—metabolic fuels that will not be replenished until breastfeeding is established (5.1.4).

Consistent with these understandings of the metabolic effects of newborn separation and E-NE elevations, one randomized study found that blood glucose in newborns who were placed in a cot was 20 percent lower compared with SSC newborns.[1023] In this study, separated babies were also cooler; cried more; and had a slower reduction in base excess, indicating a later return to energy-conserving metabolism, likely due to persisting E-NE elevations and/or lack of beneficial OT (3.1.4). Other studies have found more stress and crying, and less organized behavior, among separated newborns compared with SSC babies.[1024] Separation, with loss of SSC, can also destabilize newborn heart and breathing rhythms, because of excessive E-NE with no opportunity for stress reduction and physiologic regulation via contact with the mother's body.[333, 1025]

One study found reductions in newborn foot temperature that persisted up to 23 hours for separated newborns versus those who received SSC after birth.[175] These findings suggest greater separation-related activity in the stress-related SNS system, with vasoconstriction, and less activity in the PNS "calm and connection" system, which promotes vasodilation and warming. These findings suggest a programming effect of unknown duration.[20] (See also 3.1.4.)

Newborns following CS may particularly benefit from SSC, which beneficially reduces stress and stress hormones following this sudden transition. In addition, SSC elevates newborn OT and provides an environment in which the newborn can become calm and enact instinctive breastfeeding behaviors (3.1.4).

Longer-term studies of the impact of early maternal separation on E-NE systems in human newborns are lacking. Primate studies involving relatively brief separations—for example, 30 to 120 minutes daily in the first month of life—found increases in E, NE, and cortisol for separated offspring not only at the time, but also one year later. Changes in behavior and brain structure were found through to adolescence in this study.[1026]

This finding is consistent with a large body of animal research linking newborn separation with stress hormone elevations and permanent changes in brain and behaviors, suggesting an epigenetic programming effect [1027] (3.2.7, 4.2.7, 6.2.7). Permanent changes in the HPA stress-response system, as well as in the serotonin system, have also been found in separated animal newborns, who also have depression-like behaviors in adulthood.[1028] Maternal separation is used as an animal model for adult depression,[1028] a condition where NE disruption is also implicated.[1029] In addition, animal mothers who are separated from their newborns also have long-term physiologic maladaptations, with depression-like behavior, even following brief separations from their offspring—for example, 15 minutes daily in the first two weeks in rats.[703]

Human research is lacking in this area. One study found that solitary-sleeping newborns, even when rooming-in with the mother, had high levels of nervous system "anxious arousal," indicating SNS activation, along with large decreases in quiet sleep. Both of these effects may have potentially harmful long-term neurodevelopmental impacts. Researchers comment, "Maternal separation may be a stressor the human neonate is not well-developed to cope with and may not be benign."[1030(p.817)]

Contact with her baby may also benefit the new mother's mental health, with research suggesting that SSC in the early weeks may reduce early postpartum depression[399] (3.1.4). In contrast, typical postpartum care currently involves some amount of separation in the early sensitive period (3.1.4) and further long periods of maternal-newborn separation during hospital stay.

Given the above concerns, research into the short-and longer-term physiologic impacts of separation for mothers and babies, and into workable solutions that preserve mother-baby contact within current maternity care systems, is a high priority.

5.3 Epinephrine-Norepinephrine and Related Stress Hormones: Summary

5.3.1 Epinephrine-Norepinephrine and Related Stress Hormones: Normal Physiology

Epinephrine (adrenaline) and norepinephrine (noradrenaline) mediate "fight or flight" stress responses. Epinephrine-norepinephrine release with perceived danger has promoted safety for laboring females in the wild through human evolution by:

- slowing or stopping labor, giving time for fight or flight
- redistributing blood to heart, lungs, and major muscle groups, and away from uterus and baby, to maximize fight-or-flight actions

This epinephrine-norepinephrine response, which acts at an instinctive, subcortical level in all laboring mammals, may inhibit labor when women do not feel private, calm, safe, and undisturbed in labor.

However, if the laboring female perceives stress or danger in late labor, epinephrine-norepinephrine elevations may paradoxically stimulate contractions via differential receptor effects. This "fetus ejection reflex" may also occur physiologically when labor has been largely undisturbed, creating powerful, effective, and involuntary pushing. High-quality research in relation to this reflex and its implications for birth is lacking.

In addition to maternal epinephrine-norepinephrine elevations with perceived stress or danger, a physiologic rise in epinephrine with advancing labor has been found in women. This may benefit laboring women by promoting alertness and may promote labor progress by increasing prostaglandin production. The healthy stress (eustress) of labor also elevates the medium-term stress hormone cortisol as much as ten-fold. Cortisol may promote contractions, increase central oxytocin effects on maternal adaptations and attachment, and enhance postpartum mood.

For the baby, late-labor epinephrine-norepinephrine elevations (catecholamine surge) provide critical adaptations to labor hypoxia and facilitate newborn transitions, e.g., by:

- preserving blood flow to heart and brain
- promoting respiratory transitions, including clearing of lung fluid
- mobilizing metabolic fuels for the newborn period
- promoting newborn thermoregulation by burning brown fat
- promoting newborn alertness and energy for breastfeeding initiation

After birth, epinephrine-norepinephrine levels drop steeply in mother and baby. These decreases promote uterine contractions, which may limit maternal bleeding, and, for the newborn, reduce energy consumption. Warmth and undisturbed skin-to-skin contact may be important in facilitating maternal and newborn epinephrine-norepinephrine reductions.

5.3.2 Common Maternity Care Practices that May Impact Epineprine-Norepinephrine and Related Stress Hormones Physiology

Aspects of contemporary pregnancy care may have unintended negative (nocebo) effects by increasing maternal stress and anxiety. Stress and anxiety in pregnancy can elevate maternal stress hormones, including epinephrine-norepinephrine and cortisol, with detrimental long-term effects on offspring, including impacts on brain development and stress responsiveness, as established in human and animal studies. Studies suggest that maternal relaxation techniques may reduce pregnancy stress and its detrimental effects, but high-quality research is lacking in this important area.

In labor, anxiety or situations in which the woman does not feel private, safe, and undisturbed may provoke epinephrine-norepinephrine elevations, which may slow or stall labor and reduce fetal blood supply via epinephrine-norepinephrine effects. Stress may also slow labor by reducing pulsatile oxytocin and/or by increasing beta-endorphins.

Attention to emotional well-being may promote labor progress. The reduced need for labor interventions associated with doula and midwifery care may reflect this beneficial focus. Conversely, many common maternity care practices may be stressful for laboring women. High-quality research is lacking in relation to physiologic aspects of labor stress, and methods for ameliorating this.

Epidural analgesia can beneficially reduce maternal pain and epinephrine levels, which may have been inhibiting labor. However, the rapid drop in epinephrine may contribute to hypotension and uterine hyperstimulation. More commonly, contractions reduce over time because oxytocin also decreases. Reductions in both epinephrine-norepinephrine and oxytocin with epidural analgesia may contribute to a prolonged pushing stage and assisted vaginal birth. Epidurals do not assist with, and may increase, fetal hypoxia, stress, and stress hormones in labor, and the risk of cesarean for fetal distress.

With cesarean section, both mothers and babies may miss late-labor epinephrine-norepinephrine elevations, and be less alert after birth for breastfeeding initiation. Lack of the fetal catecholamine surge may significantly contribute to newborn morbidities following cesarean section, including breathing difficulties, hypoglycemia, hypothermia, and drowsiness that may impact interactions and breastfeeding. Cesarean birth may impair newborn and infant stress responses.

Separation of healthy mothers and newborns is more likely following cesarean section, leading to newborn stress and stress hormone elevations. Early separation may also be stressful to the mother, depriving her of the opportunity to reduce epinephrine-norepinephrine for herself and her baby through oxytocin elevations with skin-to-skin contact and mutual interactions. In animal studies, repeated brief separations in the newborn period can lead to detrimental impacts on offspring stress hormone systems, likely via epigenetic programming, with enduring effects including depression-like behaviors in adult offspring and also in separated new mothers.

6
Prolactin

Prolactin is included in this report because of its critical role in lactation and in maternal adaptations, including brain-based (central) adaptations to maternity in all mammals, including women. There is less research in relation to the impacts of maternity care practices on prolactin compared with other hormone systems. However, its importance for breastfeeding, and the contribution of breastfeeding to long-term health and well-being of mothers and babies, gives this information great importance in maternity care.

6.1 Prolactin: Normal Physiology

Prolactin has an extensive influence on reproductive physiology, including well-recognized roles in fertility, pregnancy maintenance, and postpartum adaptations. Among the hormone systems in this report, prolactin is the least well researched in relation to labor and birth, although its functions at this time may be critically important for subsequent lactation

6.1.1 Prolactin: Introduction

An essential hormone for milk synthesis, prolactin is primarily made in the pituitary gland and has effects on both the body and the brain of all mammals.

Prolactin (PRL) is best known as the major hormone of breast-milk synthesis, for which it is essential in all mammals. It is structurally related to growth hormone and the placental lactogen hormones, which are produced by the placenta in all mammals and cross-react with PRL and PRL receptors (PRLRs)[125, 1031] (6.1.2).

Prolactin is predominantly made in the anterior pituitary gland, from where it is released into the body. Prolactin can reenter the brain from the body, and may also be released into local brain areas, with both routes giving important psycho-emotional and behavioral effects in reproduction.[125] Its release is principally controlled by dopamine, which inhibits PRL release. In addition, high PRL levels inhibit further PRL release. These negative feedback effects are significantly lessened from pregnancy through lactation to maintain the necessary high PRL levels (hyperprolactinemia)[1032] (6.1.2).

Prolactin Effects

Prolactin has more than 300 recognized effects on the brain and body that are primarily concerned with reproduction and homeostasis. Prolactin promotes maternal and paternal behaviors in humans, mammals, and other species.

Prolactin has a large number of physical and behavioral effects—more than 300 in total, according to animal studies[1033]—that primarily organize and coordinate processes necessary for successful reproduction. These include:

- supporting conception and early pregnancy[172, 1034]
- adjusting appetite, fluid balance, and immune function from pregnancy through lactation[1032]
- optimizing postpartum maternal adaptations, including maternal behaviors, maternal-infant attachment, and milk production (lactogenesis)[1032]
- enhancing infant growth and brain development[1032]

Because of these effects, PRL is also known as the "mothering hormone."[125] In women, postpartum PRL elevations during breastfeeding have been correlated with personality changes that are adaptive to motherhood[237, 360] (6.1.4).

Prolactin has also been named the "hormone of paternity" because of its association with paternal behaviors in species from birds and fish to humans.[1035] Human studies show elevations in PRL in association with fatherhood[1036-1039] (6.1.4). Animal studies also show PRL elevation in individuals who are in contact with, and/or caring for, unrelated infants (alloparenting).[1040, 1041]

In addition to its reproductive functions, PRL has critical homeostatic functions related to appetite, body weight regulation, fluid balance, and immune regulation. Prolactin is also released in response to some forms of stress, with release varying by gender, hormonal state, and specific type of stress.[125, 1032]

In humans, PRL is released during sexual activity, signaling satiety and possibly also promoting implantation of the fertilized egg.[1042] High or dysregulated PRL has been related to infertility (male and female), decreased bone density, and elevated risk of breast and prostate cancers.[1031, 1043] Prolactin malfunctions have also been implicated in autoimmune diseases.[1044]

Prolactin Regulation and Receptors

Prolactin release is triggered by factors including estrogen, beta-endorphins, and some forms of stress. Pulsatile oxytocin, as occurs with labor and lactation, also promotes prolactin release. Prolactin promotes the release of beta-endorphins and oxytocin. Prolactin receptor formation is increased by estrogen, by prolactin itself (with cortisol) and by contact with infants, according to animal studies. Previous reproductive experience may be associated with increased prolactin receptors and prolactin sensitivity in women, as found in animals.

Prolactin secretion is promoted by estrogen and thyroid releasing hormone,[346, 1045] and also by norepinephrine (NE) and some forms of stress[125] (see below in this section). Oxytocin (OT) also promotes PRL release within the brain, but this may occur only when OT is released in pulses, as with labor and lactation[123] (3.1.1). Prolactin also promotes OT release.[124] Beta-endorphins (BEs) and other opioids also promote PRL release by inhibiting dopamine, and PRL promotes the release of BEs.[125, 1046] Prolactin has a circadian rhythm, with higher levels at night in human studies; and nighttime suckling elevates PRL and stimulates breast-milk production more than daytime suckling.[125]

Prolactin acts via PRL receptors in the brain and body, with several PRLR subtypes.[1031] Prolactin receptors, indicating physiologic roles for PRL, have been found in the breasts, ovaries, pituitary glands, heart, lung, thymus, spleen, liver, pancreas, kidney, adrenal gland, uterus, skeletal muscle, skin, and areas of the central nervous system.[125]

As with other hormones, higher PRLR numbers increase sensitivity to PRL and enhance PRL functions. Prolactin receptor numbers are increased (upregulated) by:

- exposure to estrogen (including during pregnancy)[1045]
- elevation of serum PRL levels[1047, 1048] (6.1.3)
- contact with infants, according to animal studies[125, 1041, 1049] (6.1.4)

According to animal studies, cortisol-like hormones, released during labor and birth, may also be needed for postpartum upregulation of PRLRs.[910, 1050] In women, cortisol, which is elevated following vaginal birth, is also thought to be necessary, along with PRL, to promote postpartum PRLR formation and effective breast-milk production[918] (5.1.4, 6.1.4). (See 6.2.6 for possible adverse implications for breastfeeding following prelabor cesarean.)

Previous reproductive experience increases PRL receptors, according to animal studies,[1051, 1052] which beneficially increases PRL responsiveness, promoting lactation and maternal adaptations. In rats, a minimum lactation of 21 days (approximately equal to the length of gestation) is needed for this effect. In women, low PRL levels, suggesting increased PRL sensitivity and PRLR numbers, have been found following the first pregnancy[1053-1055] and lactation.[1056-1058] (See "Prolactin and Breastfeeding" in 6.1.4.)

6.1.2 Prolactin in Pregnancy

Maternal Prolactin in Pregnancy

Prolactin levels rise through pregnancy, promoting maternal physiologic adaptations. Levels peak at the physiologic onset of labor, and may promote prelabor receptor formation and "nesting" behavior, as found in animals. Prelabor increases in central connections between prolactin and oxytocin promote effective release and interorchestration in labor and postpartum. Prolactin is also produced within the uterine lining, and may be involved in labor and birth.

Prolactin supports success in conception and early pregnancy,[172, 1034] when it may be critical in protecting the growing baby by reducing stress and stress responses.[1059] Other pregnancy effects, as found in other mammals, include: promoting appetite, energy intake, food storage, and insulin production;[172, 381, 1032] limiting maternal fever response to protect the developing fetal brain;[1060] and stimulating growth in the mother's brain (adult neurogenesis) to adapt to maternity.[1061]

Through pregnancy, the expectant woman's anterior pituitary increases by 30 percent in weight, with almost 200-fold increases in PRL-producing cells, compared with nonpregnant women.[1062] Maternal PRL levels rise steadily as pregnancy progresses due to increases in estrogen and possibly progesterone.[1063, 1064] Late pregnancy PRL levels in women are up to 20-fold higher than early pregnancy levels,[1065] with steep increases at term, according to one study (6.1.3). Researchers found that PRL levels more than doubled between 35 and 38 weeks, and correlated with fetal weight.[102]

Prolonged elevations in PRL, usually over several days, promote PRLR formation[1066] (6.1.1), so that the late-pregnancy PRL peaks in women may be important in upregulating PRLRs and beginning critical preparations for lactation and maternal adaptations, as occurs in other mammals in the mammary glands[103-105] and brain.[126, 1047, 1067] In some species, steep PRL and PRLR elevations occur just before the physiologic onset of labor, reflecting the prelabor decline in progesterone that has been inhibiting PRL activity.[105] Progesterone levels do not drop before labor in women, for whom prelabor PRL elevations, and likely mammary PRLR formation, are more gradual.

In other mammals, maternal prelabor PRL elevations are associated with "nesting" behavior,[124] and may be essential for development of the "nipple pheromone," which newborns use to find and latch.[1067] A late-pregnancy nesting phenomenon has also been documented in women.[1068]

Animal studies show increased central connections between the PRL and OT systems from late pregnancy, making OT release in labor a powerful PRL-releasing factor.[122] Prolactin also stimulates OT synthesis and release,[124] contributing to PRL and OT peaks at birth (6.1.3, 3.1.3). The increased central oxytocin receptors (OTRs) that precede the physiologic onset of labor, according to animal studies,[88, 1069] (3.1.2), could augment these effects. Beta-endorphins also stimulate central PRL release (4.1.1), augmenting PRL during labor in preparation for breastfeeding.[1045] Scheduled birth may negate or foreshorten these PRL preparations, as with OT (3.2.3), with possible adverse impacts on breastfeeding and maternal adaptations (6.2.3).

Progesterone, produced by the placenta, inhibits PRL effects on breast-milk production until after postpartum placental expulsion. The placenta also produces hormones with PRL-like effects, known as placental lactogens, which bind to PRLRs and have prolactin-like effects during pregnancy, including promoting fetal growth. Human placental lactogen (hPL) also enhances maternal free fatty acids and also acts as an "anti-insulin," inhibiting glucose uptake from the blood and ensuring a steady supply of fuels for the growing baby. Levels of hPL peak in the last month of human pregnancy.[1063]

Throughout human pregnancy, the uterine lining (decidua) and fetal membranes also synthesize and secrete PRL. Prolactin is released into the amniotic fluid, which fills the fetal lungs and is swallowed by the fetus (see "Fetal Prolactin in Pregnancy," below). At term, PRL levels in the amniotic fluid are up to 20 times higher than in the maternal circulation.[1045] Decidual PRL includes different forms of PRL (isoforms) that may act differently than pituitary-derived PRL. For example, decidual PRL may, in the presence of low vitamin C levels, promote prelabor rupture of membranes and preterm labor.[1070] During labor, PRL[1071] and PRLRs[1072] increase in the decidua and membranes, suggesting a role for local PRL in labor (see "Maternal Prolactin in Labor and Birth," below).

Fetal Prolactin in Pregnancy

Prolactin levels also rise in the fetus, with possibly important roles in fetal development and in prelabor physiologic preparations, especially for newborn breathing and heat production.

The human fetus also produces increasing amounts of PRL from the pituitary, with steep increases near term to reach levels equivalent to maternal PRL.[1073] Prolactin may have a crucial role in fetal growth, maturation, and brain development.[124, 1073] Decidual PRL, transmitted via amniotic fluid (see "Maternal Prolactin in Pregnancy," above) additionally exposes the fetal lungs to PRL, which may benefit lung maturation. (See 6.1.4 for newborn implications.)

In animals, fetal PRL potentiates the late-pregnancy effects of cortisol, enhancing maturity of the adrenal, lungs, liver, and other fetal organ systems,[889] and also stimulates the production of surfactant, the lung lubricant that protects against respiratory distress syndrome (RDS).[1074] In animals, late gestation peaks of PRL and cortisol also upregulate PRLRs, increasing PRL activity as labor approaches.[1075] In the human fetus, higher PRL levels at later gestational ages may also contribute to enhanced respiratory maturity[106] (6.1.4).

6.1.3 Prolactin in Labor and Birth

Maternal Prolactin in Labor and Birth

Prolactin secretion is multiphasic in labor, with an in-labor decline and late-labor surge that persists for several hours postpartum. Positive effects on receptors are likely but not researched. Local prolactin may promote cervical changes and labor contractions.

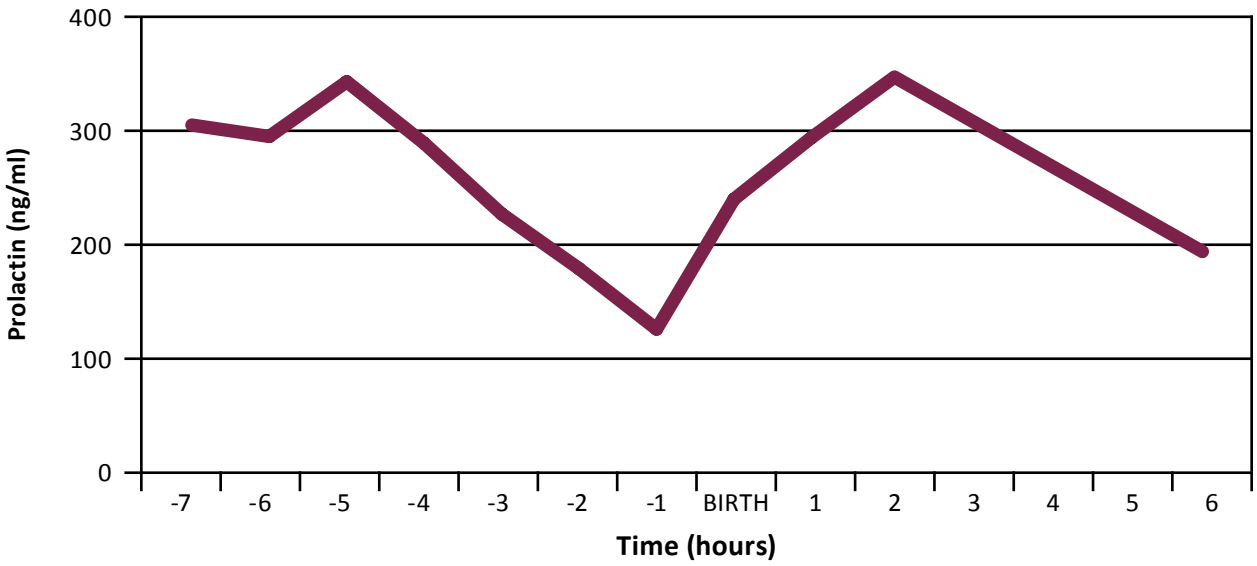
Studies in other mammals show a maternal surge in PRL that begins soon before the physiologic onset of labor,[1067, 1076] with a rapid increase in mammary PRLRs around this time.[103, 105] Prelabor shifts in the progesterone:estrogen balance may contribute.[1077]

In women, steep PRL increases as the physiologic onset of labor approaches may also prime the PRL system, and promote PRLR formation, in the maternal brain and breasts (see "Maternal Prolactin in Pregnancy" in 6.1.2). Interactions between PRL and prostaglandins may promote cervical ripening and dilation before and during labor,[102, 1078] and local PRL, which increases with labor,[1071] may act directly on uterine muscle to stimulate contractions.[1078] In animals, drugs that block PRL significantly disrupt labor and birth,[1079] suggesting an important role for PRL (perhaps local PRL) in the processes of parturition, but this is not well researched in human birth.[1071]

Studies in women show a multi-phasic pattern of PRL release during labor and birth[102, 1080-1083] (Figure 7).[1082] After an initial PRL elevation in early labor, levels decrease as labor progresses, with a nadir close to full dilation. Women with a longer labor may have an even greater decrease in PRL levels.[1084] These findings suggest a prelabor reorganization in the PRL system, such that the stresses of labor cause a paradoxical decrease in PRL levels, instead of the usual stress-associated rise.[1085]

At the end of labor, PRL levels sharply increase, likely due to stimulation of the laboring woman's cervix and the associated OT peak,[102] which promotes PRL release (6.1.1). Prolactin levels vary by up to nine-fold among individual laboring women, which may reflect differences in PRLR numbers and PRL sensitivity, possibly from previous pregnancies and lactation (6.1.4).

Figure 7. Maternal prolactin levels in labor, at birth, and after birth



Source: adapted from Stefos[1082]

Researchers have suggested that this multi-phasic pattern may help to pace labor, with lower first-stage PRL levels restraining contractions to some extent, and higher levels in second stage facilitating effective, expulsive contractions.[102] Prolactin peaks at birth and early postpartum, or even the gradient of rise, could plausibly upregulate breast PRLRs, with benefits to breastfeeding (6.1.4). Postpartum OT elevations, especially pulsatile OT release with early breastfeeding, likely also contributes to PRL release (4.1.2, 4.1.4).

Fetal Prolactin in Labor and Birth

Studies suggest fetal prolactin elevations in labor, both centrally and via amniotic fluid.

Maximal PRL levels in newborns following in-labor planned cesarean section (CS), compared with prelabor cesarean section (PLCS)[106] (6.2.6) suggest that labor stress may elevate fetal/newborn PRL. The fetus is also exposed to local prolactin, via the amniotic fluid, which fills the lungs and is also swallowed, with possible benefits (see "Newborn and Later Prolactin," below).

6.1.4 Prolactin after Birth

Prolactin is a central hormone in breastfeeding and maternal adaptations, optimizing outcomes for mothers and babies in the short- and longer-term.

Maternal Prolactin after Birth

The function of physiologic prolactin elevations in the hours after birth is not known, but may be important in promoting prolactin receptor formation, breast-milk production, and maternal adaptations.

In postpartum women, PRL levels remain elevated for several hours, peaking at one to three hours and then declining slowly over the next six to eight hours.[1082, 1083] One study found a second nadir at nine hours that was maintained for up to 24 hours after birth.[1063] As with labor, the function of this biphasic postpartum pattern is unknown, although it may be involved in promoting breast-milk production (possibly via PRLR upregulation) and maternal adaptations, including caregiving circuits, which are the major postpartum roles of PRL. Maternal-newborn skin-to-skin contact (SSC) after birth may contribute to maternal PRL elevations (6.1.1).

In animals, early maternal postpartum elevations of the stress hormone corticosterone (equivalent to human cortisol, 6.1.4) enhance the production and binding of mammary PRLRs,[910] suggesting that the eustress of labor and birth (but not excessive stress) may benefit milk production. (See also "Prolactin and Breastfeeding," below.)

Newborn and Later Prolactin

Newborn prolactin elevations may assist with breathing and thermal transitions, and deficits have been associated with respiratory morbidity. In animal studies, PRL is important for offspring development, including the development of prolactin and other hormonal systems.

Prolactin levels are elevated in the newborn,[106] peaking from 30 to 60 minutes after birth, then declining.[1083, 1086] This PRL surge, which is thought to be triggered by thyroid releasing hormone,[106] may assist with newborn transitions. Animal researchers have found PRLRs in newborn brown fat, and suggest that PRL may also be important for postpartum heat production among mammalian newborns.[106] Lower levels of PRL have been found in newborns with RDS,[1087-1090] and newborn PRL is also correlated with length of gestation.

Bioactive forms of PRL, present in breast milk[1091-1093] and ingested during breastfeeding, may be critical for infant brain and body development.[1032] In animal studies, offspring deprived of PRL in milk in the neonatal period were found to have higher mortality, poorer growth, and poorer endocrine system development, compared with controls, along with hyperprolactinemia in adulthood, which suggests lower PRLRs and PRL sensitivity. Female offspring deprived of PRL were at higher risk of precocious puberty, irregular reproductive cycles, and polycystic ovaries.[1092-1094] In human studies, preterm infants with lower PRL levels, associated with formula feeding, have poorer growth and clinical outcomes.[1091]

Prolactin and Breastfeeding

Postpartum progesterone reduction, and elevations of prolactin and cortisol are all necessary for early milk production (lactogenesis II).

Following birth, breast-milk production increases slowly in women, with milk usually "coming in" (reflecting lactogenesis II) at 30 to 40 hours postpartum. This timing is related to the postpartum decline in progesterone, which inhibits PRL's lactogenic effects.[1095] Maternal PRL levels are maximal in women two to four days after birth, according to one study.[1096]

Cortisol is also necessary for these processes in animals[1097, 1098] and humans[918] (5.1.4). In women, physiologic postpartum cortisol elevation following the eustress of labor and birth may also be important for lactogenesis II.[1001] (See 6.2.6 for relevance to PLCS.) However, while labor eustress may benefit milk production, excessive, pathologic stress in labor and birth may inhibit lactation,[1021, 1099] possibly via excessive, supra-physiologic cortisol.[1099] (See also "Prolactin release with lactation," below, for discussion of labor stress and lactation.)

Prolactin release with lactation. *Maternal prolactin release with lactation, and prolactin content in breast milk, is maximal in early lactation. Central prolactin release with lactation may benefit maternal adaptations. Stress may disrupt lactation by reducing prolactin release, possibly via epinephrine-norepinephrine elevation and/or suppression of pulsatile oxytocin.*

During each nursing episode, PRL is released from the maternal pituitary gland in response to suckling (nipple stimulation), milk removal, and parallel pulses of OT. Prolactin levels peak in maternal blood between 20 and 45 minutes after the start of breastfeeding,[1095, 1100] with higher levels during nocturnal suckling due to PRL circadian rhythms (6.1.1). Prolactin is also active in the mother's brain during lactation and plays an important role in her behavioral and psycho-emotional adaptations to motherhood[124] (see "Prolactin and Maternal Adaptations," below). Prolactin is also present in breast milk (6.1.4), with milk PRL levels highest in the early postpartum period.[1101]

After the early weeks, basal PRL levels decrease in breastfeeding women, although every nursing episode still stimulates a PRL peak.[1102] Prolactin has a long half-life, so that frequent feeding, even later in lactation, may maintain high PRL levels.[1102 1095] Night-time breastfeeding gives higher PRL peaks and greater benefits to milk production[1103] (6.1.1). Throughout lactation, PRL elevations may contribute to reduced fertility, although the exact mechanisms are not clear.[1104] At later stages of lactation, PRL release may be permissive rather than essential for milk production, which shifts to control by local factors such as milk removal rather than hormonal factors.[1095]

Studies have suggested that stress in labor, including due to in-labor unplanned CS, can delay the onset of lactation, particularly in first-time mothers.[1099] Stress-induced PRL disruption may contribute. In relation to postpartum stress and lactation, in a study of mothers of preterm infants, high salivary markers of epinephrine-norepinephrine (E-NE) were correlated with low PRL, suggesting stress-related E-NE elevations as a contributory mechanism by which postpartum stress can impair PRL release and lactation.[1105] In lactating women, even mild stressors such as noise and mental calculation have been shown to inhibit[460] the let-down reflex[1106] and oxytocin pulses,[460] which would be expected to also reduce PRL. (Outside pregnancy and lactation, stress usually increases PRL.) (See also 5.1.4 for discussion of cortisol, stress, and lactation).

Prolactin receptor theory. *Early postpartum prolactin elevation from early and frequent suckling, may be critical for establishing prolactin receptors and an abundant ongoing milk supply ("prolactin receptor theory").*

Animal studies show that PRLRs increase sharply in early lactation,[105] and that receptor formation is upregulated through suckling.[1048, 1107] According to the "prolactin receptor theory,"[1108] PRLR numbers increase in early lactation then remain constant, with frequent early feeding stimulating maternal PRL release and upregulating PRLR numbers to promote ongoing milk production. Conversely, if feeding is infrequent, PRL levels may be insufficient to upregulate PRLRs (6.1.1), with detrimental effects on ongoing milk production. In addition, according to this theory, breast engorgement may cause PRLRs to become distorted and dysfunctional. Both effects could have long-term detrimental effects on milk supply.[1102]

In accord with this, studies show that early and frequent breastfeeding, beginning immediately after birth, is associated with longer-term breastfeeding success, as evidenced by the Baby Friendly Hospital Initiative.[1109] Early and frequent feeding to upregulate PRLRs may be especially important for first-time mothers, who have higher PRL levels,[1058] suggesting lower PRLR numbers and sensitivity, compared with multiparous women.

Exposure to repeated PRL peaks with episodes of lactation is likely to upregulate PRLRs longer term in women, increasing PRL sensitivity and effectiveness. Studies in lactating multiparous women have found lower basal PRL levels but higher milk production,[1058] and also earlier postpartum onset of lactogenesis II,[1095] compared with first-time mothers. Both of these differences are consistent with upregulated mammary PRLRs (6.1.1). For women who have previously lactated, compared with women who have not lactated, increased PRLRs and reduced PRL levels may contribute to significant protection against breast cancer, which has been correlated with duration of the first lactation.[1057]

Prolactin and Maternal Adaptations

Prolactin promotes postpartum maternal adaptations in all mammals. In women, prolactin fosters adaptations that increase vigilance and help the mother prioritize her baby's needs. Prolactin is also involved with non-maternal infant caregiving in many species, including in human fathers.

In animal studies, PRL administration to females that have been hormonally primed to mimic pregnancy leads to the rapid and reliable onset of maternal behaviors.[1032] Similarly, negating PRL effects through receptor-blocking drugs or genetic modifications disrupts maternal behaviors.[1110] These findings suggest that the PRL system makes a major contribution to the mammalian maternal adaptations and behaviors that develop immediately after birth and promote maternal-infant attachment, even in the absence of prior maternal experience.[1052]

Studies suggest that PRL-related adaptations may also apply to women. Researchers have found correlations between basal and breastfeeding-related PRL levels and personality changes soon after birth. Higher postpartum PRL levels have been correlated with:[237, 360, 1111]

- increased "social desirability," which helps the new mother put her baby's needs first
- decreased "monotony avoidance," which may help with repetitive aspects of infant care
- decreased tension and muscular tension
- some increases in anxiety and aggression, which may promote maternal vigilance

Animal studies show that, following the first pregnancy and lactation, maternal brain PRLRs are upregulated in brain areas critical for maternity.[1051, 1112] This may contribute to the reduced response to stress, lowered anxiety, and better memory, found both inside and outside maternity in reproductively experienced females.[1052] In women, changes in central PRLRs may explain the reduction in stress-responsiveness that continues after lactation.[1113, 1114] These findings suggest long-term mental health benefits from breastfeeding for women.

In other mammals, contact with, or carrying of, infants increases PRL levels[1040, 1041] (6.1.1). In women, contact-related PRL elevation could contribute to beneficial effects of SSC on milk production[1115] and maternal depressive symptoms.[399] Infant contact and carrying may also release OT (3.1.1), which may also contribute to these effects (see "Oxytocin and Maternal Adaptations" in 3.1.4).

In relation to paternal behaviors, PRL has been shown to rise in men during their partner's pregnancy, especially in men who experience sympathetic symptoms and display more concern about their baby's cries after birth.[1038] Prolactin levels are higher among: experienced than inexperienced fathers;[1116] fathers with infants under one year, compared with fathers of older children;[1036] and fathers who are more responsive to infant cues, compared with less responsive fathers.[1038, 1039, 1041]

6.2 Common Maternity Care Practices That May Impact Prolactin Physiology

The impact of maternity care interventions on prolactin has not been well researched. However, many common maternity care interventions can potentially impact this important system, with significant long-term detriments in mothers and babies if breastfeeding is unsuccessful or foreshortened.

6.2.1 Maternity Care Provider and Birth Environment: Possible Impacts on Prolactin

The maternity care provider and birth environment may impact the prolactin systems of mothers and babies by increasing or decreasing the chances of interventions that can impact these systems, and/or by increasing or decreasing stress during or after birth. The success of breastfeeding may have long-term impacts on the prolactin systems of both mother and baby.

No studies were found that directly assessed the impacts of maternity care provider and birth environment on the PRL systems of mother or baby.

However, care provider and birth environment could plausibly impact PRL systems by:

- increasing or decreasing the chance of induction, with possible impacts on the PRL systems of mother and baby (6.1.2, 6.2.3)
- increasing or decreasing the risk of prelabor or in-labor unplanned CS, with possible impacts on the PRL systems of mother and baby (6.1.2, 6.2.6)
- increasing or decreasing stress in labor, birth, and the early postpartum period, with possible impacts on PRL and early lactation, including via cortisol (6.1.4)
- increasing or decreasing the timing and duration of early maternal-newborn contact and breastfeeding, with possible impacts on maternal PRL and PRLR formation, and breastfeeding success (6.1.4, 6.2.7)

In addition, maternity care practices that promote, support, and protect breastfeeding could have long-term benefits to the PRL systems of mothers and babies (6.1.4).

6.2.2 Prostaglandins for Cervical Ripening and Labor Induction: Potential Impacts on Prolactin

Administration of prostaglandins may impact maternal prolactin in labor with possible effects on milk composition and immunity, according to animal studies. Breastfeeding success may be impaired.

Studies assessing the effects of induction with prostaglandins (PGs) on PRL levels in labor in women have had conflicting results. One study using PGE2 gel found no difference in PRL levels or patterns of release during labor, compared to induction with synthetic oxytocin (synOT) or with other studies of physiologic PRL release in labor.[1078] However, another study using oral PGE2, which gives higher blood levels,[1117] found reductions in PRL through to birth, compared with women induced with synOT.[1118]

Researchers suggest possible gastrointestinal effects of PGs on estrogen. However, prostaglandins are known to reduce PRL release, possibly by increasing central dopamine (6.1.1), and have been used as an effective postpartum treatment to inhibit lactation.[1119] In addition, vaginally-administered PGs can enter the fetal circulation,[1117] with unknown effects on fetal/newborn hormone systems.

Animal studies have found in-labor PRL elevations following PG induction in pigs[1120] and goats.[1121] These studies found associated changes in subsequent milk composition, including lower immunoglobulin levels. Prostaglandin-exposed newborn piglets had lower white cell numbers,[1120] suggesting further effects on offspring immunity.

In relation to breastfeeding in women, a study found an 11 percent reduced chance of successfully breastfeeding at 48 hours among new mothers induced with PGs compared with no labor medications, rising to 15 percent for primiparous women.[564] If confirmed in other studies, this may reflect direct PRL impacts and/or possible induction-related loss of PRL preparations (see 6.1.2, 6.2.3), although this study found no significant breastfeeding impacts following induction with no drugs, with synOT, or with a combination of drugs.

Given the widespread use of PGs for labor induction, research into effects on PRL and breastfeeding is a high priority.

6.2.3 Synthetic Oxytocin For Induction, Augmentation, and Postpartum Care: Possible Impacts on Prolactin

Induction may impact prolactin systems by reducing prelabor physiologic preparations in the prolactin and oxytocin systems. Ergot drugs, used alone or with synthetic oxytocin to prevent hemorrhage after birth, are known to inhibit prolactin release and some studies suggest impacts on breastfeeding success.

Several studies have looked at the impact of synOT on laboring women's PRL levels, as measured at birth. One study found higher in-labor PRL levels following synOT induction without analgesia, perhaps due to increased pain and stress, compared with women induced and administered meperidine, or unmedicated women following the physiologic onset of labor.[980] Stimulation of PRL release by synOT, or by the stronger contractions and OT feedback cycles (3.1.3), may also contribute. Other studies have found: PRL elevations in women following synOT exposure,[1122] and no differences in the pattern or levels of PRL release in women induced by amniotomy and low-dose synOT,[1078] compared to those with physiologic onset of labor.

With induction by any method, both mother and baby are likely to miss the full prelabor physiologic preparations. For the mother, this may include prelabor elevations in PRL (and possibly PRLRs) and in the related OT system (3.1.2) that prepare her for breastfeeding and motherhood, according to animal studies (6.1.2, 3.1.2). The baby is likely to miss the late-gestation PRL elevation that fosters organ maturation and promotes respiratory transitions (6.1.2). (See 2.2 for effects of scheduled birth on the baby.)

Researchers measured PRL release with breastfeeding in relation to synOT exposure in labor and found that, among synOT-exposed mothers, the PRL peak with breastfeeding occurred earlier and lasted longer, compared with that in unexposed women.[487] In addition, OT release was reduced in a dose-dependent manner, compared with women unexposed to synOT. This finding is unexpected, as reduced OT would be expected to also reduce PRL. The mechanisms are unclear.

Other studies have suggested possible impacts of induction with synOT on breastfeeding success (see "Prolactin and Breastfeeding" in 6.1.4 and "Synthetic Oxytocin and Breastfeeding" in 3.2.3.). Impaired or foreshortened breastfeeding may have significant and possibly long-term effects on prolactin systems in mothers and babies (see 6.1.4).

Synthetic oxytocin is also used, alone or in combination, to prevent bleeding after birth. Ergot-derived drugs such as ergonovine (Ergometrine) and methylergonovine (Methergine), which may be used in combination with synOT (e.g., syntometrine) or as alternatives to synOT, are chemically related to bromocriptine and inhibit PRL release.[1123] Older studies showed inhibition of PRL following postpartum ergot administration,[1124-1126] including with a single dose of methylergonovine.[1126]

One study measured PRL levels two to three days after birth in new mothers administered a single postpartum dose of Ergometrine to prevent PPH, and found no difference compared to levels in women following "physiologic management." However, in this study, more treated mothers had stopped breastfeeding by four weeks, mostly due to perceived insufficient milk.[1127] Another study found a 23 percent reduced chance of breastfeeding success at 48 hours among women administered combined Ergometrine and synOT (Syntometrine), and 36 percent reduced success with Ergometrine, including almost 50 percent reduction for primiparous women administered Ergometrine.[564] (See also "Synthetic Oxytocin and Breastfeeding" in 3.2.3.)

Given the widespread postpartum use of ergot drugs, alone or in combination with synOT, research into effects on prolactin and breastfeeding is a high priority.

6.2.4 Opioid Analgesic Drugs: Possible Impacts on Prolactin

Opioid drugs can reduce breastfeeding success. Impacts on the prolactin system are possible but not well studied.

Opioid drugs (and endogenous opioids such as BEs) may impact physiologic PRL systems in labor and after birth by increasing central PRL release.[1046] This could give elevated levels in labor, instead of the usual decline (6.1.1, 6.2.6), but no studies of this were found in humans.

One study (mentioned above) found higher PRL levels in women induced with synOT and given systemic opioid drugs during labor, compared with those induced but not administered opioids, but effects on breastfeeding were not recorded.[980] Other studies have found reduced breastfeeding success from exposure to opioids in labor, which may reflect disruption of PRL and/or OT, as well as sedating effects on mothers and newborns. (See 3.2.4 for more background and also a fuller discussion of opioids effects on the OT system.)

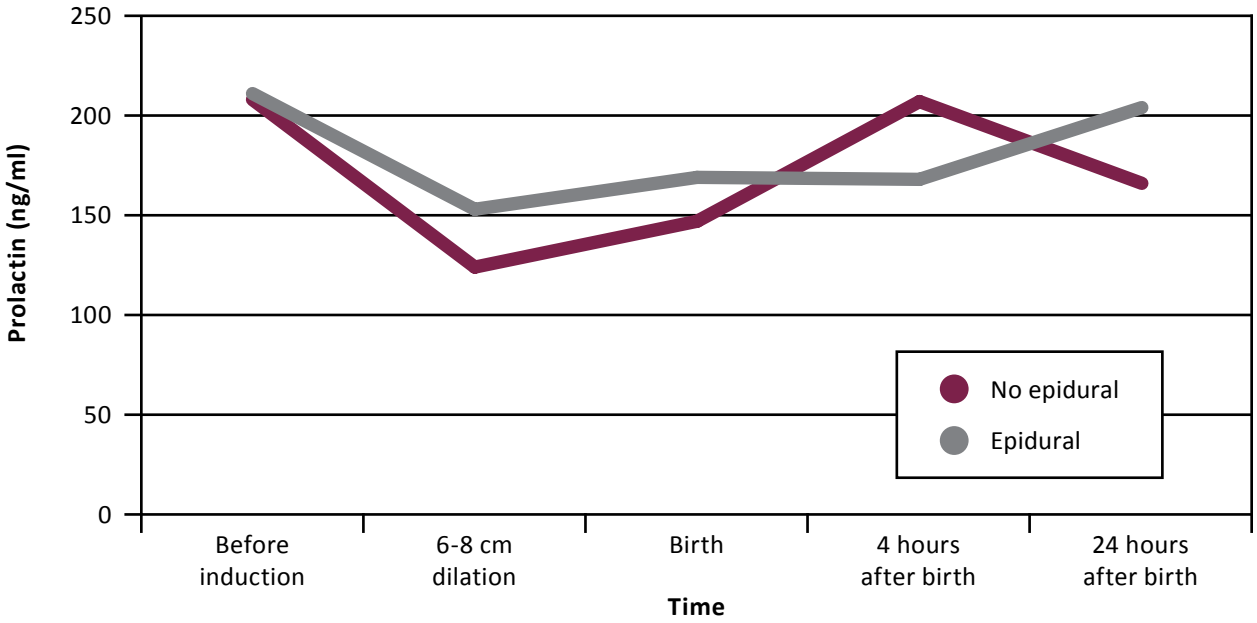
6.2.5 Epidural Analgesia: Possible Impacts on Prolactin

Several studies have found impacts of epidurals on prolactin release in labor, with unclear implications. Lower postpartum prolactin levels, as suggested in two studies, could impact developing prolactin systems and breastfeeding, but this has not been specifically studied. Epidurals may have effects on breastfeeding success, discussed elsewhere, with significant longer-term impacts on maternal and offspring prolactin systems.

Several studies have looked at the impact of labor epidural analgesia on maternal and/or newborn PRL. One study, shown in Figure 8,[1128] found relatively higher levels (i.e., a reduced physiologic decline) in PRL from early labor through to birth among women with epidurals. This was followed by lower levels after birth and in particular, absence of the early postpartum PRL peak[1128] (6.1.4) and then elevation in PRL at one day. In this study, all women were induced with synOT, which could promote stress-related PRL elevations (6.2.3). Other studies have found reduced basal PRL levels for up to 24 hours after epidural exposure (local anesthetic only);[652] and higher PRL at 48 hours among exposed women, along with earlier and greater milk production, compared with women in the control group (labor medications in control group not stated, article in Chinese).[1129]

Other researchers measured PRL in a single sample of maternal and newborn cord blood after birth. They found no significant differences in PRL levels for mothers exposed and unexposed to labor epidurals.[800] However, this single postpartum sample could reflect the juncture between supra-physiologic levels in labor and infra-physiologic levels after birth, as seen in Figure 8.

Figure 8. Maternal prolactin levels, with and without epidural analgesia



Source: adapted from Jouppila[1128]

One study looked at PRL release during breastfeeding on day two and found that epidural-exposed women had some reduction in PRL release throughout the breastfeeding episode, though differences were not statistically significant in this small study.[570] (See also "Epidurals and Breastfeeding" in 3.2.5 for OT impacts in this study.) Other studies have suggested possible detrimental impacts of epidurals on breastfeeding success. Unsuccessful breastfeeding may have significant and possibly long-term detrimental effects on prolactin systems in mothers and babies. (See 3.2.5 for a full discussion of epidural impacts on OT and breastfeeding.)

6.2.6 Cesarean Section: Possible Impacts on Prolactin

As with induction, lack of prelabor physiologic preparations could impact prolactin systems and possibly breastfeeding success, as could surgical stress and delays in mother-newborn contact. Researchers have found reduced breastfeeding-related prolactin release following in-labor unplanned cesarean compared with vaginal birth. Lower fetal/newborn prolactin along with deficits in prelabor preparations, could impact newborn breathing and temperature transitions. All these factors may contribute to reduced breastfeeding success following prelabor cesarean.

Women experiencing a prelabor cesarean section (PLCS) will likely miss the physiologic PRL elevation near term, the in-labor decline, and the subsequent surge at birth, with possible impacts on breastfeeding success (see below), which is reduced following PLCS (see 3.2.6).

Surgical and post-operative stresses may also contribute to maternal PRL disruptions. Outside childbearing, surgery-related stress and tissue damage generally increase PRL levels, which are also higher when surgery is performed under general anesthetic (GA) compared with epidural or spinal anesthetic.[1130, 1131] One study found transiently elevated PRL levels following CS with GA, likely reflecting surgical tissue damage, with subsequent postpartum declines.[1083] Other studies (anesthesia not stated) found: almost doubled maternal PRL levels immediately following CS, compared with vaginal birth;[800] and equivalent levels.[998]

The presence or absence of maternal-newborn contact (not stated in these studies) may also influence maternal PRL levels postpartum. Early and ongoing maternal-newborn contact, ideally with unlimited opportunities for SSC and breastfeeding, enhances breastfeeding initiation and continuation.[336, 1109] Following CS, SSC may benefit breastfeeding initiation and time to initiation, newborn temperature and stress, and maternal bonding and satisfaction; and may reduce formula feeding in hospital, according to a recent review.[1132]

Optimization of postpartum PRL systems may contribute to these benefits of SSC for breastfeeding. The PRL receptor theory (6.1.4) suggests that early and frequent contact and breastfeeding will increase the numbers of PRLRs, with benefits to ongoing milk production and breastfeeding success. The OT system may also contribute to the benefits of early maternal-newborn contact for long-term breastfeeding success (3.1.4).

Several studies have found differences in breastfeeding and breast-milk composition in relation to CS compared with vaginal birth. One study found lower rates of breast-milk transfer from days two to six following CS compared with low-intervention vaginal birth.[1133] Transfer was higher following in-labor CS than PLCS, suggesting benefits from experience of prelabor and/or in-labor processes, possibly involving PRL. Another study found 20 percent lower levels of protein in new mothers' colostrum (day two) following PLCS, compared with vaginal birth. Authors comment, ". . . breast milk proteins have a critical role in the defense against infections and facilitate optimal development of important physiologic functions in newborns,"[1134(p.4)] and suggest that hormonal alterations are a likely explanation.

One study measured new mothers' hormonal release during breastfeeding on day two in relation to mode of birth. Researchers found that women who experienced an in-labor unplanned CS had no PRL peak (4.1.4) and fewer OT pulses during suckling on day two, compared with women experiencing vaginal birth. Among women giving birth vaginally, those with more OT pulses had a longer duration of exclusive breastfeeding. Authors suggest that a reduction in labor-related OT release may disrupt PRL release.[354]

Another study found lower breastfeeding rates in the delivery room, at seven days, and at three and six months, following PLCS compared with vaginal birth, which correlated with lower PRL levels measured during breastfeeding on day three.[1001] This study also found lower maternal cortisol levels following PLCS, which was also associated with lower early breastfeeding rates. Animal studies show that cortisol enhances PRLR production (6.1.2, 61.3), with reductions in both likely following PLCS.

Some studies have shown higher newborn PRL levels following labor compared with CS,[106, 1135] while others have found equivalent levels.[800, 998, 1090, 1136] The higher PRL levels among babies born following in-labor CS compared with PLCS[106] suggest that fetal PRL release may reflect labor or birth stress.

Babies born by PLCS may miss the enhanced decidual production of PRL during labor (6.1.3), which may reach the fetal lungs and benefit newborn respiratory adaptation. Prolactin effects may be even more significant than the late-labor catecholamine (CA) surge for breathing and thermoregulation, according to one researcher.[106]

Given the prevalence of CS, including PLCS, and the importance of breastfeeding for lifelong well-being of mother and baby, high-quality research into CS impacts on PRL and breast-milk production is a high priority. Studies that measure breastfeeding and other hormonally-mediated outcomes following PLCS versus in-labor CS, and following induced versus physiologic-onset labor, are also high priorities.

6.2.7 Early Separation of Healthy Mothers and Newborns: Possible Impacts on Prolactin

Early postpartum separation could have significant effects on the prolactin systems of mothers and babies by delaying first contact and breastfeeding, with possible effects on prolactin receptor formation and breastfeeding success.

The well-documented benefits of early SSC[336] and suckling, and of early and frequent breastfeeding, on long-term breastfeeding success, as promoted in the World Health Organization's Baby-Friendly Hospital Initiative,[1109] suggest that early SSC and suckling optimize maternal and newborn hormonal physiology, including PRL.

Early separation may have detrimental impacts on mother, baby, and/or their interactions, including limiting SSC and breastfeeding, which normally promote the development of PRLRs (see "Prolactin receptor theory" in 6.1.4). One study found that women whose first breastfeed was late (at least six hours) after CS had later colostrum production and milk letdown compared with women whose first breastfeed was early (around one hour) after CS. The authors suggest that disruption to postpartum PRL systems is an underlying factor.[1137] (See 3.2.7 for effects of separation on the interrelated OT system.)

6.3 Prolactin: Summary

6.3.1 Prolactin: Normal Physiology

Prolactin is a major hormone of reproduction as well as breast-milk synthesis. Prolactin adapts maternal physiology for pregnancy and breastfeeding, promotes maternal adaptations, and is a caregiving hormone in mammalian mothers and fathers. Outside of reproduction, it is a stress and growth hormone.

Maternal prolactin elevations from early pregnancy have stress-reducing effects that also benefit the fetus. Late-pregnancy prolactin elevations promote the formation of prolactin receptors in the brain and mammary gland (animal studies). Near term, prolactin production also increases in the uterine lining (decidua), and may be involved in labor processes. Prolactin in amniotic fluid, which fills the fetal lungs, may assist with respiratory preparations. Fetal prolactic production increases close to the physiologic onset of labor, and may promote newborn transitions.

Maternal prolactin paradoxically declines as labor advances (outside of labor, stress triggers prolactin release). Prolactin increases steeply as birth nears, likely due to peaks of beta-endorphins and oxytocin, both of which stimulate prolactin release. In addition, prolactin stimulates oxytocin release, contributing to oxytocin peaks in late labor and birth.

Postpartum prolactin elevations, persisting for several hours after birth, may promote breast-milk production and maternal adaptations. Peaks in prolactin and cortisol, together with early and frequent breastfeeding, may promote prolactin receptor formation, with benefits to ongoing milk production ("prolactin receptor theory"). Prolactin levels released during early breastfeeding have been correlated with maternal adaptations, including: reduced anxiety, aggression, and muscular tension; and increased social desirability (conformity), which may help mothers to prioritize infant care.

6.3.2 Common Maternity Care Practices That May Impact Prolactin Physiology

High-quality research is lacking in relation to possible impacts of maternity care practices on prolactin physiology. Stress in labor may paradoxically reduce prolactin secretion, giving infraphysiologic levels in labor and birth, possibly contributing to the negative impacts of labor stress on breastfeeding. Epidurals may cause in-labor prolactin elevations and postpartum prolactin reductions, with unknown impacts. Induction with synthetic oxytocin may also impact physiologic prolactin release. Prostaglandins may inhibit prolactin with possible impacts on breastfeeding success.

With cesarean section, the expectant mother may miss her pre-labor prolactin elevation, late-labor peak and/or postpartum elevations, which may all impact milk production and maternal adaptations. Following cesarean section, prolactin release with early breastfeeding may be reduced or absent. These and other factors may contribute to reduced breastfeeding success following prelabor cesarean section. Following cesarean section, newborns may have lower prolactin levels, possibly contributing to breathing difficulties and low temperature. Lack of the catecholamine surge may also contribute.

Separation of mothers and their healthy newborns, which typically follows cesarean section, may also impact postpartum maternal prolactin levels. If separation interferes with early breastfeeding initiation and frequency, disruption to prolactin receptor formation may impact ongoing milk production and breastfeeding success.

7
Conclusions and Recommendations

This chapter presents a summary of the overall conclusions and implications of this material, along with a table that summarizes the impacts of interventions on the four hormone systems covered in this report. The recommendations that follow give guidance for educators, clinicians, researchers, policy makers, advocates, and childbearing families for safely optimizing the hormonal physiology of childbearing.

7.1 Conclusions

According to the evidence summarized in this report, the innate hormonal physiology of mothers and babies—when promoted, supported, and protected—has significant benefits for both during the critical transitions of labor, birth, and the early postpartum and newborn periods, likely extending into the future by optimizing breastfeeding and attachment. While beneficial in selected circumstances, maternity care interventions may disrupt these beneficial processes. Because of the possibility of enduring effects, including via epigenetics, the Precautionary Principle suggests caution in deviating from these healthy physiologic processes in childbearing.

This report documents in detail the hormonal physiology of childbearing, including:

- current understandings of the physiologic onset of labor at term and the possible impacts of scheduled birth on mother and baby
- a detailed discussion of the physiologic functioning of four major hormone systems from pregnancy through the postpartum and newborn periods
- the impact of common maternity care practices on these hormonal systems, according to current and evolving evidence and understandings

Overall, consistent and coherent evidence from physiologic understandings, and human and animal studies, as summarized in this report, finds that the innate hormonal physiology of mothers and babies—when promoted, supported, and protected—has significant benefits for both during the critical transitions of labor, birth, and the early postpartum and newborn periods.

This evidence also suggests that the benefits of physiologic childbearing for mothers and babies may extend into the future through successful breastfeeding and optimizing of mother-baby attachment, with substantial benefits for modern mothers and babies, as they have had for our evolutionary ancestors.

Maternity care interventions are beneficial and even lifesaving in selected circumstances. This report provides considerable evidence that they can also cause significant disruptions to hormonal processes in mother and baby with unintended consequences, as summarized in Table 4.

The hormonal physiology perspective provides additional information, germane to the well-being of women and offspring, for clinicians, women, and others to consider when weighing benefits and harms of maternity care practices and interventions, both for care of individual mothers and babies and at a policy level.

Biologic principles and solid findings from animal studies suggest that hormonal system functioning in the perinatal period, whether optimal or disrupted, may have enduring impacts on offspring hormonal and other biologic systems. This may occur via epigenetic programing, with possible longer-term effects on development, behavior, and/or hormone system functioning, as seen in animal studies.

The known unintended shorter-term hormonal and other impacts of perinatal interventions, and evolving evidence about their possible longer-term effects invoke a strong case for the Precautionary Principle.[1138, 1139] According to the 1998 Wingspread statement, "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."[1140]

Table 4. **Established and biologically plausible impacts of common maternity care interventions on four hormone systems**

Intervention	Oxytocin	Beta-Endorphins	Epinephrine-Norepinephrine	Prolactin
Care provider and birth environment	• ↑ Physiologic birth rates associated with midwife, doula (CE: 3.2.1) may be due to ↑ labor efficiency, including ↓ IOL, ↑ physiologic labor onset→ ↑ OTRs (P: 3.1.4) • ↓ anxiety, stress may ↓ E-NE, ↓ BEs, ↑ OT→ ↑ labor progress (P: 3.1.3)	• ↑ Labor stress with care provider or environment may ↑ BEs→ ↓ labor progress directly (P, LE: 4.1.3) and/or via ↓ OT (P, AS: 4.2.1)	• Excessive stress in pregnancy → ↓ birth weight, ↑ preterm birth, adverse brain, developmental effects (CE: 5.2.1) likely via ↑ maternal cort (P, LE: 5.2.1) • Excessive stress in pregnancy may also ↑ E-NE→ ↓ uterine blood supply, may contribute to ↑ preterm birth, ↓ birth weight (P: 5.2.1) • Excessive stress in labor may → ↑ E-NE → ↓ labor progress, ↓ fetal blood supply via direct effects and/or via ↓ pulsatile OT (P, LE: 5.1.4, 5.2.1) • ↑ Physiologic birth rates associated with midwife, doula (CE: 5.2.1) may be due to ↓ anxiety, stress→ ↓ E-NE→ ↑ labor progress, ↑ fetal blood supply (P: 5.1.4, 5.2.1)	• ↑ Labor stress with care provider or environment may ↑ PRL (limit physiologic decline) in labor, with unknown impacts on BF (P: 6.2.1)
Prostaglandins for cervical ripening and induction of labor	• Successful PG IOL when ↑ OT (LE: 3.2.2) • Successful PG IOL may be more likely if close to spontaneous labor onset with ↑ OTRs, PGRs to activate OT-PG feed-forward cycles (P: 3.1.3, 3.2.2)	• Foreshortening with IOL may ↓ prelabor BEs receptors→ ↓ analgesia, reward (P: 4.2.2)	• Pre CS, PG administration may ↑ contractions→ ↑ fetal E-NE→ benefit fetal transitions, respiration via CA surge (LE: 5.2.2)	• Foreshortening with IOL may reduce prelabor ↑ PRL and possible ↑ PRLR, possible impact on BF (LE, AS: 6.1.2, 6.2.2) • PGs→ ↓ PRL (CE: 6.2.2), may ↓ PRLRs→ ↓ BF success (P, LE: 6.2.2)

cont'd

Intervention	Oxytocin	Beta-Endorphins	Epinephrine-Norepinephrine	Prolactin
Synthetic oxytocin for induction, augmentation, and postpartum care	• IOL associated with ↓ labor efficiency, ↑ risk instrumental birth, ↑ risk PPH (CE: 3.2.5) likely due to foreshortening→ ↓ OTRs and other stimulating factors (P: 2.1.3, 3.2.3) • Successful IOL more likely if close to physiologic labor onset, with ↑ OTRs to activate feed-forward cycles (3.1.3); cervical ripeness may indicate OTRs and uterine responsiveness (P, LE: 3.1.3) • Foreshortening with IOL→ ↓ uterine OTRs; may ↑ PPH risk (P, CE: 3.1.3, 3.2.3) • Foreshortening with IOL→ ↓ brain OTRs may ↓ reward, attachment (P: 3.1.3, 3.2.3) • Foreshortening with IOL→ ↓ breast OTRs may ↓ BF success (P: 3.1.3, 3.2.3) • Prolonged exposure to synOT→ ↓ OTRs→ ↑ PPH risk (CE: 3.2.3) • Lack of readiness may ↑ new-born morbidity (CE: 3.2.3) • Lack of readiness and/or high-dose synOT may ↓ OT-mediated fetal neuroprotection (AS: 3.1.3) • Possible epigenetic effects on offspring (AS, LE: 3.2.3)	• Inconsistent findings in relation to synOT effects on BEs • Foreshortening with IOL may ↓ pre-labor BE receptors→ ↓ analgesia, reward (P: 4.2.3)	• Stress, pain with synOT for IOL or augmentation→ ↑ E-NE, may ↓ labor progress, ↓ fetal blood supply (P: 5.1.3, 5.2.3) • Foreshortening with IOL→ ↓ fetal prelabor preparations, ↓ E-NE receptors→ ↓ fetal adaptations, may hypoxia (P: 5.1.3, 5.2.3) • Stronger contractions→ ↓ fetal blood supply→ large ↑ fetal E-NE (LE: 5.2.3), unknown impacts on fetal/newborn stress, stress hormone systems	• Foreshortening with IOL may reduce prelabor ↑ PRL and possible ↑ PRLR, may impact BF (P: 6.1.2, 6.2.3) • IOL associated with ↓ PRL in labor (LE: 6.2.3), with unknown impacts on maternal PRL and BF • SynOT→ ↓ BF success (LE: 3.2.3); may be due to PRL, PRLR disruption
Opioid drugs	• May ↓ OT→ ↓ labor progress (LE: 3.2.4) • May ↓ OT release for baby→ ↓ newborn calming, analgesia (P: 3.1.4, 3.2.4)	• Effective analgesia may ↓ maternal BEs→ ↓ postpartum reward, pleasure (LE: 4.2.4) • Possible epigenetic effects on offspring BEs and addiction (LE: 4.2.4)	No direct studies found	• May ↑ PRL (limit physiologic decline) in labor (P: 6.2.4); impacts unknown • ↓ BF success (CE: 3.2.4) may be partly due to PRL effects (P: 6.2.4)

cont'd

Intervention	Oxytocin	Beta-Endorphins	Epinephrine-Norepinephrine	Prolactin
Epidural analgesia	• ↓ OT→ ↓ labor progress, ↑ synOT use (CE: 3.2.5) • ↓ OT surge at birth (CE: 3.2.5)→ ↓ pushing efficacy, ↑ instrumental birth (CE: 3.2.5) • ↓ OT release in labor, postpartum (CE: 3.2.5) may ↓ BF success, ↓ attachment (LE: 3.2.5)	• ↓ BEs in labor, postpartum (CE: 4.2.5), may ↓ postpartum reward, pleasure (LE: 4.2.5) • ↑ Newborn stress hormones (LE: 4.2.5); impacts unknown	• Rapid ↓ E→ ↓ blood pressure, ↑ contractions; both can→ ↑ fetal hypoxia (CE: 5.2.5) • ↓ E in labor→ ↓ fetus ejection reflex (P: 5.2.5)→ ↓ pushing efficacy, ↑ operative birth (CE: 3.2.5; 5.2.5) • ↑ Newborn stress hormones (LE: 5.2.5) unknown impacts	• May ↑ PRL (limit physiologic decline) in labor, ↓ PRL postpartum (LE: 4.2.5), impacts unknown • ↓ PRL postpartum may ↓ BF success (LE: 3.2.5, 6.2.5)
Cesarean section	**Prelabor CS:** • ↓ OTRs, especially if far from POL (P: 3.1.3, 3.2.6) • ↓ Uterine OTRs may ↑ PPH risk (LE: 3.1.4, 3.2.6) • ↓ Brain OTRs may ↓ reward, attachment (P: 3.1.4, 3.2.6) • ↓ Breast OTRs may ↓ BF success (P: 3.2.6) • ↓ OT release with early BF after CS (LE: 3.2.6) impacts on BF success unknown • Possible ↓ fetal neuroprotection (AS: 3.1.3) **In-labor CS:** • ↓ OTRs with IOL, may impact PPH, BF, attachment (P: 3.1.3, 3.2.6,) • May ↓ OTRs from prolonged exposure to synOT with above risks to PPH, BF, attachment (P: 3.1.3, 3.2.6) **All CS** • Loss of OT peaks in labor, birth, early postpartum may ↓ reward, pleasure, attachment, BF success (P: 3.1.4, 3.2.6)	• epidural anesthesia→ ↓ BEs (CE: 4.2.6) • GA may ↑ BEs (LE: 4.2.6) • Foreshortening with PLCS may ↓ prelabor BE receptors,→ ↓ postpartum analgesia, reward, pleasure (P: 4.1.4, 4.2.5) • CS may ↓ newborn BEs at birth with later ↑, may be due to maternal separation (LE: 4.2.6) • May mis-prime newborn stress responses (LE: 4.2.6)	• CS, especially PLCS→ loss of fetal CA surge→ ↑ respiratory, thermal, metabolic morbidity (CE: 5.2.6) • PLCS→ ↓ Newborn NE (CE: 5.2.6)→ ↓ postpartum cerebral blood flow→ adult brain dysfunctions (AS: 5.2.6)	• epidural anesthesia→ ↓ PRL into postpartum period (LE: 6.2.6) • Maternal-newborn separation post CS→ ↓ maternal PRL, PRLRs (P: 6.2.6) • ↓ PRL release with early BF after CS (LE: 6.2.6) impacts on BF success unknown • May ↓ newborn PRL→ ↑ respiratory morbidity (LE: 6.2.6)

cont'd

Intervention	Oxytocin	Beta-Endorphins	Epinephrine-Norepinephrine	Prolactin
Early separation of healthy mothers and newborns	• ↓ Maternal-newborn contact→ ↓ maternal OT (P, LE: 3.1.4, 3.2.7), may ↓ contractions, ↑ PPH risk (LE: 3.1.4, 3.2.7) • ↓ Maternal attachment (CE: 3.2.7) due to ↓ activation of OT attachment and reward systems in postpartum sensitive period (LE: 3.2.7) • ↓ BF success (CE: 3.2.7) may be due to ↓ OT in postpartum sensitive period (P: 3.1.4, 3.2.7) • ↓ Maternal-newborn contact→ ↓ newborn OT, calming effects (LE: 3.1.7)→ ↑ newborn stress (CE: 5.1.4, 5,2,7) • May mis-set newborn OT systems, with effects into adulthood (P, AS: 3.2.7)	• ↓ Maternal-newborn contact→ ↓ maternal BEs (P: 4.1.4), may ↓ priming of attachment and reward systems (LE: 4.2.7) • ↓ Maternal-newborn contact→ ↑ newborn stress→ ↑ BEs, may mis-set newborn BE reward/addiction systems with effects into adulthood (P, AS: 4.2.7)	• ↓ Maternal-newborn contact→ ↑ newborn "anxious arousal" with unknown impacts • ↓ Maternal-newborn contact→ ↑ newborn E-NE, ↓ OT→ ↑ newborn stress, hypoglycemia (CE: 5.1.4, 5.2.7) • May mis-set newborn stress systems, with effects into adulthood (P, AS: 5.2.7)	• ↓ Maternal-newborn contact→ ↓ BF in postpartum sensitive period→ ↓ maternal PRL→ ↓ PRLR receptor development (P, LE: 6.1.4) → ↓ long-term milk supply (CE: 6.2.7)

Note: Table refers to maternal processes, unless otherwise noted.

Note about physiology and interventions: BE = beta-endorphin, BF = breastfeeding, CA = catecholamine, CS = cesarean section, E-NE = epinephrine-norepinephrine, IOL = induction of labor, OT = oxytocin (endogenous), OTR = oxytocin receptor, PG = prostaglandin, PGR = prostaglandin receptor, PLCS = prelabor cesarean section, POL = physiologic onset of labor, PPH = postpartum hemorrhage, PRL = prolactin, PRLR = prolactin receptor, synOT = synthetic oxytocin

Note about available support: AS = evidence found is limited to animal studies; CE = consistent evidence from at least several studies, including human studies, and consistent with physiologic principles and understandings; LE = limited and/or emerging evidence, including partial or indirect evidence and evidence from animal studies consistent with physiologic principles and understandings; P = consistent with physiologic principles and understandings

In maternity care, the Precautionary Principle would be operationalized by setting a high standard for deviating from care that promotes, supports, and protects the healthy physiologic childbearing processes of mother and baby, including:

- rigorously verifying the benefits of proposed interventions in individual circumstances before undertaking them
- limiting routine practices to those of proven benefit to healthy mothers and babies
- avoiding the use of interventions for the convenience of women or maternity care providers and systems
- initially using less invasive measures to address challenges, and stepping up to more consequential interventions only as needed

A hormonal physiology perspective also suggests critical new agendas for research. Recurrent questions arise in two broad areas. First, for all of the hormone systems examined in this report, greater elucidation is needed of the underlying innate hormonal physiology as it relates to the processes of childbearing, with a priority for research in humans whenever possible.

Second, better understanding is needed of possible impacts of widely used maternity care interventions. A particularly urgent research priority is longer-term follow up to assess whether interventions—including elective induction; administration of synthetic oxytocin, before, during and/or after labor and birth; epidural analgesia; and prelabor cesarean—impact crucial hormonally-mediated outcomes in women and babies, such as breastfeeding, maternal adaptations, maternal-infant attachment, maternal mood states, and offspring hormonal functioning. Such impacts are plausible given the principles and processes described in this report, but poorly researched. Urgent as well are questions about whether perinatal interventions have enduring developmental, and possibly epigenetic, effects in humans, as found in animals.

All who are involved in maternity care are committed the best possible care, with the least harm, to mothers and babies. The research results synthesized here, along with underlying hormonal physiology principles and understandings, clarify that promoting, supporting and protecting physiologic birth is a simple, low-technology approach to health and wellness that is applicable in the vast majority of maternity care settings.

The perspective of hormonal physiology provides a new framework with which to view childbearing, and can contribute to a salutogenic foundation for the care of mothers and babies. This perspective can provide direction for promoting, supporting, and protecting:

- the physiologic onset of labor at term, with full prelabor physiologic preparations for mother and baby
- safe and effective labor and birth for mother and baby
- optimal maternal and newborn transitions
- breastfeeding,
- maternal-infant attachment

The findings of this report are well summarized by the distinguished Dutch obstetrician-gynecologist, Professor Gerrit-Jan Kloosterman:

> Spontaneous labor in a normal woman is an event marked by a number of processes so complicated and so perfectly attuned to each other that any interference will only detract from the optimum character. The only thing required of the bystanders under these conditions is that they show respect for this awe-inspiring process by complying with the first rule of medicine, that of *nil nocere* [do no harm].[1141 (p.40)]

7.2 Recommendations to Promote, Support, and Protect Physiologic Childbearing

Physiologic childbearing confers valuable benefits to women and babies in the short, medium, and likely longer terms. Benefits of hormonal physiology accrue, so that any safe enhancement of hormonal physiology will likely benefit women and babies to some degree. Greater conformity with physiologic processes is likely to be more beneficial than less conformity. Additional benefits are also likely from averting potential harms associated with unneeded interventions. The synthesis presented in this report supports a series of recommendations for safely optimizing hormonal physiology within maternity care.

Currently available research, as presented in this report, consistently finds that physiologic childbearing confers valuable benefits to women and their babies in the short, medium, and likely longer terms. The benefits that accrue from optimizing hormonal physiology for mother and baby extend along a continuum, according to this framework, with greater benefits likely for any mother and baby with greater experience of physiologic processes. Additional benefits from averting unneeded maternity care practices that have potential to harm women and babies, both known harms and any that are currently unknown, also likely extend along a continuum.

Maternity care systems could be readily adapted to safely optimize hormonal physiology for mothers and babies. As detailed in this chapter, adaptations of the system could include:

- promoting factors such as professional education, competencies of personnel, protocols, performance measures, quality improvement initiatives, innovative payment and delivery systems, and research
- supportive practices directly available to women from pregnancy through the postpartum period, such as reducing pregnancy stress as far as possible, primarily using comfort measures for labor pain and progress, and keeping mothers and newborns together after birth
- protecting women and babies, whenever possible and safe, from practices that disturb healthy physiologic processes

The following high-level recommendations are provided to encourage those who plan, provide, or receive maternity care to help women and newborns experience healthy physiologic processes. The recommendations apply broadly. They do not exclude the timely, appropriate, and safe use of maternity care procedures, medications, and other interventions when needed for the well-being of women and babies, in which case the recommendations can help maximize hormonal physiology as far as possible, and safely move women and babies along the salutogenic continuum.

The Appendix identifies selected resources that support implementation of these recommendations for professionals, and for women and childbearing families.

7.2.1 Education, Policy, and Consumer Engagement Recommendations

Education

Educate all maternity care providers in the hormonal physiology of childbearing.

RATIONALE: Shared knowledge and skills for optimizing hormonal physiology as far as possible for each mother and baby are foundational for all maternity care providers. This will foster provision of high-quality care, effective care teams, and more judicious use of maternity care interventions.

GUIDANCE**:** It is optimal for all members of teams caring for women and newborns to have a shared basis of understanding of the hormonal physiology of childbearing, including hormonal processes and their benefits, policies and environments that promote them, essential skills and knowledge to support and protect them from disruption whenever possible, and any unintended effects of common maternity care practices on them. This will enable a more complete and accurate assessment of possible benefits and harms. It is important for health professionals to be able to provide physiologic care to the extent safely possible for women and babies with special conditions, needs, and care requirements.

This knowledge and associated skills, along with a meaningful practical experience of physiologic childbearing, should be a foundational component of all levels of professional education within all of the disciplines that care for childbearing women and newborns. These subjects should be introduced in entry-level education, well represented during more advanced professional training, and prioritized within continuing education, including maintenance of certification programs.

Policy

Use effective quality improvement strategies to foster reliable access to physiologic childbearing.

RATIONALE**:** Given the considerable potential gains for maternal-newborn health and well-being from more reliable experience of physiologic childbearing, as suggested in this report, a priority for quality improvement initiatives is to foster spread of conditions that make such experiences widely available.

GUIDANCE**:** Implementation science helps identify effective quality improvement strategies. These include: addressing physiologic childbearing within quality collaboratives, developing relevant performance measures and using them for quality improvement, developing and implementing protocols that promote physiologic childbearing, using innovative payment and delivery systems to foster appropriate care practices, and implementing evidence-based clinical practice guidelines including those to safely reduce use of cesarean section and other consequential interventions.

Strengthen and increase access to care models that foster physiologic childbearing and safely limit use of maternity care interventions.

RATIONALE**:** Current evidence shows that physiologic birth is more likely under models of care that include birth centers, midwifery care, and doula support. These and other models and maternity care providers that prioritize and support physiologic processes should be encouraged. Facilities, maternity care providers and/or models of care with good safety outcomes and low rates of maternity care interventions likely are skilled in promoting, supporting, and protecting physiologic birth.

GUIDANCE**:** Within the context of collaborative practice, models of care that value, prioritize, and enhance physiologic processes should receive resource and policy support for broad access and reliable insurance coverage.

Professional development can help maternity care facilities and practitioners with limited ability to facilitate physiologic childbearing obtain the needed knowledge and skills to provide optimal care for healthy childbearing women and newborns.

Maternity care providers with skills and expertise in the care of women and babies with higher-risk and/or specific conditions provide critical maternity care services. The principles of physiologic birth are benefi-

cially applied to such care to optimize hormonal physiology of mothers and babies. For example, women with challenging conditions would likely benefit from one-on-one care in labor and skin-to-skin contact after birth. Similarly, breastfeeding in the early sensitive postpartum period following cesarean section is a priority. Models of care and protocols that safely apply these principles to women at higher-risk should be developed.

Engaging and supporting childbearing women

Use effective consumer engagement strategies to inform women about physiologic childbearing and involve them in related aspects of their care.

RATIONALE**:** From the perspective of the core principles of health care ethics—autonomy, beneficence, nonmaleficence, and justice—it is imperative to inform women of the beneficial innate hormonally-driven childbearing capacities of women and their fetuses/newborns and to support them in gaining access to such physiologic processes, as safe and appropriate.

GUIDANCE**:** A consumer booklet has been prepared as a companion to this report (see Appendix). This booklet, and related resources that can help women understand the hormonal physiology of childbearing, should be widely distributed and recommended to pregnant women and women planning pregnancy. Childbearing women should also have access to publicly reported results of performance measures that provide relevant information for choosing a care provider or group and a birth setting. Relevant content should be incorporated into childbirth education. Priority decision aids for childbearing decisions of great consequence should include relevant information and be routinely incorporated into maternity care practice. Providers and women are encouraged to engage in shared decision-making, which includes knowledge of options, best evidence of the potential risks and benefits inclusive of hormonal impacts, and consideration of the individual woman's values and preferences.

All women should have access to care that safely supports physiologic childbearing and to care environments that promote such care and protect women from the harm of unneeded disturbance of physiologic processes, as described in this report. Where childbearing deviates from optimal hormonal physiology, or extra assistance or interventions are required, women should be fully supported to maximize hormonal physiology.

Journalists have a role to play in informing childbearing women and the general public about these matters.

7.2.2 Care Practice Recommendations Whenever Safely Possible

Prenatal care

Provide prenatal care that reduces stress and anxiety in pregnant women.

RATIONALE**:** Significant levels of stress and anxiety in pregnancy are detrimental to maternal and fetal physiology; they may adversely impact maternal well-being, gestational length, and fetal and child development. Some aspects of prenatal care, including fetal testing, may contribute to, or fail to reduce, maternal stress and anxiety.

Reduction of stress and anxiety in pregnancy may have significant and long-term benefits to offspring, and therefore substantial public health benefits. Evolving evidence suggests that some forms of relaxation and relaxation training may improve not only physiologic and hormone stress markers but also meaningful outcomes in mothers and babies. (See 5.2.1.)

GUIDANCE**:** Maternity care providers are encouraged to be aware of, and screen for, stress and anxiety in pregnancy, including in the context of pregnancy testing that could arouse anxiety. Current evidence suggests that effective relaxation techniques that reduce stress may favorably influence maternal emotional states, stress hormones, and responses; and fetal growth and behavior, premature birth rate, mode of birth, and newborn neurobehavior, among other impacts.

Foster the physiologic onset of labor at term.

RATIONALE**:** As described in this report, maternal and fetal readiness for labor and birth at term, for postpartum transitions, and for ongoing well-being, including breastfeeding and maternal-infant attachment, are complex and incompletely understood processes that begin to develop in the weeks before the physiologic onset of term labor. Some of these processes may be ready only in the preceding days or hours. Scheduled birth, whether by induction or prelabor cesarean, will foreshorten these processes in mothers and babies, with potentially significant consequences for their physiologic transitions. With a prelabor cesarean, mothers and babies also miss beneficial processes of labor that activate maternal and fetal hormonal systems to optimize postpartum transitions of both. (See chapter 2.)

GUIDANCE**:** Maternity care providers are encouraged to support the physiologic onset of term labor and avoid induction and scheduled prelabor cesarean, except where indications for individual women are supported by high-quality evidence and informed decision making. From the perspective of hormonal physiology, when a scheduled cesarean is needed, waiting when possible for labor to start on its own may offer benefits to mothers and babies. This has not been well researched. Due to many currently unanswered questions about possible hormonally-mediated effects of scheduled birth, policies that support the physiologic onset of labor at term and discourage unneeded induction of labor or prelabor cesarean in healthy mothers and babies are prudent.

Encourage hospital admission in active labor.

RATIONALE**:** As discussed in this report, the laboring female in all mammals is very sensitive to the environment. Disturbance in labor—including being in an environment that is not perceived as familiar, private, or safe—may slow or stop labor by increasing stress and stress hormone levels. Impacts on fetal blood supply are also possible. In women who plan hospital birth, moving from the familiar environment of home to the unfamiliar environment of hospital may slow labor, especially before the positive feedback cycles that progress labor are fully established, making labor less vulnerable to disturbance. These cycles may be slower to establish in primiparous than in multiparous women. Waiting for active labor before moving from home to hospital may reduce the risk of physiologic disruptions and is associated with increased likelihood of vaginal birth. (See “Childbirth and Stress” in 5.2.1; 4.2.1; and “Positive feedback cycles” in 3.1.3.)

GUIDANCE**:** Maternity care providers are encouraged to support women to remain at home until active labor is well established. Providing telephone support and/or a caregiver who is available to attend and assess the laboring woman at home, if needed, could be a cost-effective way to enhance physiologic processes, especially in first-time mothers.

Support privacy and reduce anxiety and stress in labor.

RATIONALE**:** As discussed above, disturbance in labor—including being in an environment that is not perceived as familiar, private, or safe—may slow or stop labor by increasing stress hormone levels, with potential impacts on fetal blood supply. (See “Childbirth and Stress” in 5.2.1, and 4.2.1.)

GUIDANCE**:** Maternity caregivers are encouraged to ensure that the physical and social environment for labor and birth and the early postpartum period helps the laboring women feel private, safe, and undisturbed. In addition, caregivers can provide support to reduce anxiety in labor. Ideally, this support is tailored to the laboring woman's individual requirements and begins in pregnancy with a discussion of her needs and possible comfort measures for labor. Establishing a trusting relationship with caregivers is also likely to be beneficial. Continuous labor support (doula care), as described below, may facilitate this.

Make non-pharmacologic comfort measures for pain relief routinely available, and use analgesic medications sparingly.

RATIONALE**:** As described in detail in this report, the administration of opioid and epidural drugs in labor can have significant unintended effects on the hormonal physiology of mother and baby, in addition to other potential side effects. Disruption of the hormonal physiology in labor, birth, and the postpartum period by pharmacologic interventions and their co-interventions may also have detrimental effects on breastfeeding and maternal-infant attachment. When mother and baby are in good condition and coping well, it may be safer and preferable to offer non-pharmacologic comfort measures. This may reduce the need for pharmacologic interventions, with benefits for mother and baby. (See 3.2.4, 3.2.5, 4.2.4, 4.2.5, 5.2.4, 5.2.5, 6.2.4, and 6.2.5.)

GUIDANCE**:** Maternity care personnel who care for laboring women are encouraged to become skilled in, and to offer to women, non-pharmacologic comfort measures and other alternatives to pharmacologic pain relief in labor.

Make non-pharmacologic methods of fostering labor progress routinely available, and use pharmacologic methods sparingly.

RATIONALE**:** As described in detail in this report, the use of synthetic oxytocin to foster labor progress may have significant undesirable effects on the hormonal physiology of mother and baby, in addition to other potential side effects. Disruption of the hormonal physiology in labor, birth, and the postpartum period by pharmacologic interventions may also have detrimental effects on breastfeeding and maternal-infant attachment. Routinely making non-pharmacologic measures to foster labor progress available may reduce the need for these interventions, with benefits for mother and baby. (See 3.2.3 and 5.2.1.)

GUIDANCE**:** Maternity caregivers are encouraged to become skilled in and offer to the women in their care, alternatives to pharmacologic methods to foster labor progress. When mother and baby are in good condition, it may be safe and preferable to allow labor to progress at a slower rate, with attention to any source of stress that may inhibit contractions. Simple measures that may foster progress by optimizing hormonal physiology include increasing the laboring woman's sense of privacy and safety and minimizing her anxiety.

Promote continuous support during labor.

RATIONALE**:** Continuous support during labor from a supportive companion (doula) has been shown to reduce the need for maternity care interventions, likely by reducing stress and stress hormones.

In addition, doulas are generally skilled in providing non-pharmacologic measures to deal with stress and pain and to foster labor progress, thus addressing preceding recommendations and reducing the need for stronger interventions and potential hormonal disruption. (See 5.2.1, 3.2.1, 4.2.1, and 6.2.1.)

GUIDANCE**:** Maternity care providers are encouraged to support the provision of doula care. This may be a cost-effective strategy for reducing stress and stress hormones, reducing interventions, and improving outcomes for mothers and babies.

Foster spontaneous vaginal birth and avoid unneeded cesareans.

RATIONALE**:** From the perspective of hormonal physiology, and from other perspectives beyond the scope of this report, cesarean procedures that lack clear benefit for a woman and/or her baby may have consequential downsides. This report identifies many ways that cesareans may impede optimal postpartum transitions in women and newborns.

GUIDANCE**:** Maternity care professionals and professional societies increasingly recognize that current high cesarean section rates may be causing more harm than good to women and babies. Important resources to safely address cesarean overuse include evidence-based guidance documents and a national endorsed standardized cesarean section performance measure.

This report identifies care pathways that can help women avoid unneeded cesareans. Care models that foster physiologic childbearing, noted above, are associated with reduced likelihood of cesarean section. Many quality improvement strategies, as discussed above, can contribute.

Postpartum care

Support early and unrestricted skin-to-skin contact after birth between mother and newborn.

RATIONALE**:** As described in detail in this report, skin-to-skin contact (SSC) between mothers and babies after birth has significant favorable effects on the postpartum transitions and hormonal physiology of both. Skin-to-skin contact reduces stress and stress hormones, promotes oxytocin release (which may also reduce maternal bleeding), and may also benefit the new mother's prolactin system, with long-term optimizing of breastfeeding. Conversely, evidence reviewed in this report suggests that separation of mothers and newborns may provoke newborn stress and be detrimental to breastfeeding initiation and maternal mood. (See "Skin-to-skin contact" in 3.1.4, 3.2.7, 4.2.7, 5.2.7, and 6.2.7.)

GUIDANCE**:** Maternity care providers are encouraged to support immediate and unrestricted skin-to-skin contact, as the norm in the early postpartum period for mothers and newborns, who should only be separated in exceptional circumstances. This includes encouraging rooming in and may require new procedures and policies. Institutions can support this by securing the "baby friendly" designation of the Baby-Friendly Hospital Initiative (BFHI).

Support early, frequent, and ongoing breastfeeding after birth.

RATIONALE**:** Early and frequent breastfeeding, with unlimited newborn access to the mother and her breasts, has been shown to optimize breast-milk production and breastfeeding continuation, likely by optimizing hormonal physiology. The early days after birth may be a sensitive period for upregulation of the prolactin system in particular, with long-term impacts on breast-milk production. (See "Prolactin and Breastfeeding" in 6.1.4, 3.1.4, and 4.1.4.)

GUIDANCE**:** Maternity care providers are encouraged to support ongoing and unlimited postpartum contact between mother and newborn, with extra support if needed during early breastfeeding.

7.2.3 Research Recommendation

Identify and carry out priority research into hormonal physiology of childbearing, and routinely incorporate this perspective in childbearing research.

RATIONALE**:** This report identifies many critical gaps in current knowledge in relation to both the hormonal physiology and the possible impacts of maternity care interventions on mothers and babies in the short, medium, and longer terms. Gaps include the frequent omission of priority medium-term outcomes including breastfeeding, maternal-infant attachment, and maternal emotional well-being, which are hormonally mediated and potentially susceptible to disruption of hormone systems through prior interventions and/or maternal stress. A related concern is the lack of long-term follow-up for possible impacts on offspring health and development. Biologically plausible effects on hormonally-related functions inside and outside reproduction, as described in each hormone chapter, also require high-quality research and long-term follow-up.

GUIDANCE**:** Researchers and the institutions that fund research in maternity care are encouraged to foster and carry out research to expand our understanding of the hormonal physiology of childbearing in mothers and babies, including**:**

- hormonally-mediated processes of physiologic childbearing
- shorter- and medium-term impacts of maternity care interventions that are discussed in this report
- parallel impacts of other widely used but less researched interventions
- possible longer-term offspring outcomes of maternity care experiences, including developmental outcomes, impacts on long-term hormonal functioning, and epigenetic effects

Appropriate research designs and measurements include randomized controlled trials, whenever applicable and possible.

High-quality studies are particularly needed that investigate consequential and biologically plausible, but as-yet poorly examined, impacts of maternity care practices and interventions on the medium- and long-term health and well-being of mothers and babies. These include outcomes of labor induction, augmentation, opioid and epidural analgesia, and cesarean section, and of stress in childbearing. Effective strategies to reduce stress and incorporate stress reduction support into prenatal care are also needed.

7.3 Conclusions and Recommendations: Summary

Overall, consistent and coherent evidence from physiologic understandings and human and animal studies finds that that the innate, hormonal physiology of mothers and babies—when promoted, supported, and protected—has significant benefits for both in childbearing, and likely into the future, by optimizing labor and birth, newborn transitions, breastfeeding, maternal adaptations, and maternal-infant attachment. There are likely additional benefits from avoiding potential harms of unnecessary interventions, including possible adverse epigenetic programming effects.

From the perspective of hormonal physiology, these are not all-or-nothing benefits, but rather accrue along a continuum. Every mother and baby is likely to benefit from additional support for physiologic childbearing, as far as safely possible, including when interventions are used. The hormonal physiology perspective provides additional considerations for weighing possible benefits and harms of maternity care interventions, and suggests new agendas for research. Research priorities include better understanding

of many aspects of hormonal physiology and of impacts of maternity interventions on breastfeeding, maternal adaptations, maternal mood, and other short-, medium-, and longer-term hormonally-mediated and developmental outcomes.

Given the uncertainty and potential for significant harms to women and babies in relation to maternity care interventions, application of the Precautionary Principle would be wise in maternity care. Such a standard would involve**:**

- rigorously verifying the benefits of proposed interventions in individual circumstances before undertaking them
- limiting routine practices to those of proven benefit to healthy mothers and babies
- avoiding the use of interventions for the convenience of women or maternity care providers and systems
- initially using less invasive measures to address challenges, and stepping up to more consequential interventions only as needed

A table in the report summarizes the established and potential effects of the maternity care practices addressed in the report on the four hormone systems.

The following recommendations for education, policy, practice, and research arise from the synthesis presented here. Care practice recommendations below are intended to apply whenever safely possible. To optimize hormonal physiology in childbearing**:**

- Educate all maternity care providers in the hormonal physiology of childbearing.
- Use effective policies and quality improvement strategies to foster consistent access to physiologic childbearing.
- Strengthen and increase access to care models that foster physiologic childbearing and safely limit use of maternity care interventions.
- Use effective consumer engagement strategies to inform women about physiologic childbearing and involve them in related aspects of their care.
- Provide prenatal care that reduces stress and anxiety in pregnant women.
- Foster the physiologic onset of labor at term.
- With hospital birth, encourage admission in active labor.
- Foster privacy and reduce anxiety and stress in labor.
- Make nonpharmacologic comfort measures for pain relief routinely available, and use analgesic medications sparingly.
- Make nonpharmacologic methods of fostering labor progress routinely available, and use pharmacologic methods sparingly.
- Promote continuous support during labor.
- Foster spontaneous vaginal birth and avoid unneeded cesareans.
- Support early and unrestricted skin-to-skin contact after birth between mother and newborn.
- Support early, frequent, and ongoing breastfeeding after birth.
- Identify and carry out priority research into hormonal physiology of childbearing, and routinely incorporate this perspective in maternity care research.

The Appendix identifies resources for learning more and improving maternity care, including a booklet that presents essential findings from this report to childbearing women.

Appendix: Resources for Learning More and Improving Maternity Care

Resources for Health Professionals

Clinical Practice Guidelines and Recommendations

All Wales clinical pathway for normal labour (2004).

American Academy of Nursing. (2014). Choosing Wisely: Electronic fetal heart rate monitoring. Washington, D.C.: The Academy. Available at: https://aan.memberclicks.net/assets/images/Choosing-Wisely/evidence-intermittent%20auscultation%20avery%20revised%2010-3-14.pdf

American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine. (2014). Safe prevention of the primary cesarean delivery. *Obstet Gynecol, 123*(3), 693-711.

Association of Women's Health, Obstetric and Neonatal Nurses. (2014). Position statement: Non-medically indicated induction and augmentation of labor. *J Obstet Gynecol Neonat Nurs, 43*(5), 678-681.

Childbirth Connection Programs, National Partnership for Women & Families. (2015). Pathway to a healthy birth: How clinicians can support beneficial hormonal action in childbirth. Washington, D.C.: Childbirth Connection Programs. Available at: www.ChildbirthConnection.org/HormonalPhysiology [infographic and printable poster]

National Institute for Health and Care Excellence. (2014). *Intrapartum care: Care of healthy women and their babies during childbirth*. London: NICE. Available at: https://www.nice.org.uk/guidance/cg190

Queensland Government. (2012). *Queensland maternity and neonatal clinical guideline: Normal birth*. Herston: Queensland Maternity and Neonatal Clinical Guidelines Program.

Royal College of Midwives. (2012). *Evidence-based guidelines for midwifery-led care in labour.* London: RCM.

Spanish National Healthcare System, Spanish Ministry for Health and Social PolicyMinistry for Science and Innovation. (2010). *Clinical practice guideline on care in normal childbirth.* Health Technology Assessment Agency of the Basque Country (OSTEBA).

Toolkits

American College of Nurse-Midwives. (2014). BirthTOOLS.ORG: Tools for Optimizing the Outcomes of Labor Safely. Available at: http://BirthTOOLS.org [fostering physiologic childbearing and limiting unneeded intervention]

American College of Nurse-Midwives (2014). BirthTOOLS.ORG: Tools for Optimizing the Outcomes of Labor Safely. Available at: http://midwife.org/ACNM/files/ccLibraryFiles/Filename/000000004449/BirthTOOLS-Synopsis-100214.pdf [guide to toolkit]

Promoting Normal Birth. (2010). Available at: www.dhsspsni.gov.uk/mr-high-impact-promoting-normal-birth-2010.pdf

United States Breastfeeding Committee. (2014). *Best practices guide for implementation of newborn Exclusive Breast Milk Feeding in electronic health records.* Available at: www.usbreastfeeding.org/HealthCare/HospitalMaternityCenterPractices/GuideEBMFinEHR/tabid/386/Default.aspx

United States Breastfeeding Committee. (2013). *Toolkit: Implementing TJC Perinatal Care core measure on Exclusive Breast Milk Feeding.* Available at: www.usbreastfeeding.org/HealthCareSystem/HospitalMaternityCenterPractices///tabid/184/Default.aspx

Books, Articles, and Technical Report

American College of Nurse-Midwives. (2014). *Birth matters: Understanding how physiologic, healthy birth benefits hospitals and organizations.* Silver Spring, MD: ACNM.

Avery MD, ed. (2013). *Supporting a physiologic approach to pregnancy and birth: A practical guide.* Ames, IA: Wiley-Blackwell.

Downe, S., ed. (2008). *Normal childbirth: Evidence and debate*, second ed. Edinburgh: Elsevier.

Goer, H., & Romano, A. (2012). *Optimal care in childbirth: The case for a physiologic approach.* Seattle: Classic Day Publishing.

Main, E.K., Morton, C.H., Hopkins, D., Giuliani, D., Melsop, K., & Gould, J.B. (2011). *Cesarean deliveries, outcomes, and opportunities for change in California: Toward a public agenda for maternity care safety and quality.* Palo Alto, CA: CMQCC.

Simkin P. (2002). Supportive care during labor: A guide for busy nurses. *J Obstet Gynecol Neonatal Nurs, 31*(6):721-32.

Simkin, P., & Ancheta, R. (2011). *The labor progress handbook: Early interventions to prevent and treat dystocia*, third edition. Chichester: Wiley-Blackwell.

Simkin, P., & Bolding, A. (2004). Update on nonpharmacologic approaches to relieve pain and prevent suffering. *J Midwifery Womens Health, 49*(6):489-504.

Smith, L.J. (2010). *Impact of birthing practices on breastfeeding* (2nd ed.). Sudbury, MA: Jones and Bartlett Publishers.

Walsh D. (2012). *Evidence and skills for normal labour and birth: A guide for midwives*, second edition. London: Routledge.

Performance Measures

Association of Women's Health, Obstetric and Neonatal Nurses. (2014). *Women's health and perinatal nursing care quality refined draft measures specifications; for testing of feasibility, validity and reliability.* Washington, D.C.: AWHONN.

The Joint Commission. (2014). PC-01, PC-02 and PC-05. In: *Specifications manual for Joint Commission national quality core measures: Version 2015A.*

NCT. (2010). *Normal birth as a measure of the quality of care: Evidence on safety, effectiveness and women's experiences.* London: NCT. Available at: www.nct.org.uk/sites/default/files/related_documents/Normalbirthasameasureofthequalityofcare V3.pdf

Consensus Statements

American College of Nurse-Midwives, Midwives Alliance of North America, & National Association of Certified Professional Midwives. (2012). *Supporting Healthy and Normal Physiologic Childbirth: A Consensus Statement by ACNM, MANA, and NACPM.* Available at: www.midwife.org/acnm/files/cclibraryfiles/filename/000000002179/physioloigical%20birth%20consensus%20statement-%20final%20may%2018%202012%20final.pdf

Royal College of Midwives, NCT, & Royal College of Obstetricians and Gynaecologists. (2007). *Making normal birth a reality: Consensus statement from the Maternity Care Working Party – Our shared views about the need to recognize, facilitate and audit normal birth.* Available at: https://www.rcm.org.uk/sites/default/files/NormalBirthConsensusStatement.pdf

Initiatives

American College of Nurse-Midwives. (2014). The American College of Nurse-Midwives Healthy Birth Initiative. Available at: www.midwife.org/ACNM-Healthy-Birth-Initiative [fostering physiologic childbearing and limiting unneeded intervention]

Institute for Healthcare Improvement. (2014). Improving perinatal care: "Keeping Normal Normal." Available at: www.ihi.org/communities/blogs/_layouts/ihi/community/blog/itemview.aspx?List=0f316db6-7f8a-430f-a63a-ed7602d1366a&ID=31

Khan, K. (2014). The CROWN Initiative. *Obstet Gynecol, 124*(3), 487-488. [choosing the best outcomes of interest]

Northern New England Perinatal Quality Improvement Network. Trial of labor after cesarean delivery (VBAC). Available at: www.nnepqin.org/Guidelines.asp#tabs-6

Resources for Childbearing Families

Essential Guidance from Present Report for Women and Families

Childbirth Connection Programs, National Partnership for Women & Families. (2015). *Pathway to a healthy birth: Helping your hormones do their most wonderful work*. Washington, D.C.: Childbirth Connection Programs. Available at: www.ChildbirthConnection.org/HormonalPhysiology [infographic and printable poster]

Childbirth Connection Programs, National Partnership for Women & Families. (2015). *Pathway to a healthy birth: How to help your hormones do their wonderful work.* Washington, D.C.: Childbirth Connection Programs. Available at: www.ChildbirthConnection.org/BirthPathway [booklet]

Other

American College of Nurse-Midwives, Midwives Alliance of North America, & National Association of Certified Professional Midwives. (2014). *Normal, healthy childbirth for women and families: What you need to know.* Available at: www.midwife.org/ACNM/files/ccLibraryFiles/FILENAME/000000003184/NormalBirthAndYou-092514.pdf

American College of Nurse-Midwives, Midwives Alliance of North America, & National Association of Certified Professional Midwives. (2014). *Un parto normal y saludable para la mujer y su familia.* Available at: www.midwife.org/acnm/files/ccLibraryFiles/Filename/000000004465/NormalBirthAndYou_Spanish-0930414.pdf

Association of Women's Health, Obstetric, and Neonatal Nurses. Go the full 40 campaign. Available at: www.gothefull40.com

Childbirth Connection Programs, National Partnership for Women & Families. (2014). New cesarean prevention recommendations from obstetric leaders: What pregnant women need to know. Washington, D.C.: Childbirth Connection Programs. Available at: www.childbirthconnection.org/article.asp?ck=10685

Childbirth Connection Programs, National Partnership for Women & Families. (2012). Understanding & navigating the maternity care system. Washington, D.C.: Childbirth Connection Programs. Available at: www.childbirthconnection.org/article.asp?ClickedLink=1084&ck=10662&area=27

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Abbreviations

ACTH adrenocorticotropic hormone
ADH antidiuretic hormone
ADHD attention-deficit hyperactivity disorder
ANS autonomic nervous system
AVP arginine vasopressin
BBB blood-brain barrier
BE beta-endorphin
BE-IRM beta-endorphin immunoreactive material
BFHI Baby-Friendly Hospital Initiative
CA catecholamine
CNS central nervous system
CRF corticotropin releasing factor
CRH corticotropin releasing hormone
CS cesarean section
CSE combined spinal-epidural
CSF cerebrospinal fluid
CTG cardiotocogram
DES diethylstilbestrol
DHEAS dehydroepiandrosterone-sulfate
DNIC diffuse noxious inhibitory control
DOHaD developmental origins of health and disease
E epinephrine
EDD estimated date of delivery
E-NE epinephrine-norepinephrine
EPIIC epigenetic impact of childbirth
FER fetus ejection reflex
FHR fetal heart rate
FOAD fetal origins of adult disease
GA general anesthetic
GABA gamma-aminobutyric acid
GAS general adaptive syndrome
GC glucocorticoid
HPA hypothalamic-pituitary adrenal
hPL human placental lactogen
Ig immunoglobulin
IM intramuscular
IOL induction of labor
IUGR intrauterine growth retardation
IV intravenous
LA local anesthetic
LCHD lifecourse health development
MOR mu opioid receptor
MRI magnetic resonance imaging
NE norepinephrine
NICU neonatal intensive care unit
NO nitric oxide
OT oxytocin
OTA oxytocin antagonist
OTKO oxytocin knock-out
OTR oxytocin receptor
OT-X extended forms of oxytocin
PBE placental beta-endorphin
PG prostaglandin
PLCS prelabor cesarean section
PNS parasympathetic nervous system
POEF placental opioid-enhancing factor
POMC pro-opiomelanocortin
PPH postpartum hemorrhage
PRL prolactin
PRLR prolactin receptor
PTSD post-traumatic stress disorder
PVN paraventricular nuclei
RDS respiratory distress syndrome
SNS sympathetic nervous system
SON supraoptic nuclei
SP-A surfactant-related protein A
SSC skin-to-skin contact
synOT synthetic oxytocin
UA umbilical artery
UV umbilical vein
VCS vaginocervical stimulation

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