PHYSIOLOGIC FUNCTION OF OXYTOCIN AFTER BIRTH: INFLUENCE ON POSTPARTUM BLOOD LOSS AND LACTATION

By

Elise N. Erickson

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Abstract

The purpose of this program of research is to examine the physiologic role of the neuropeptide and hormone, oxytocin, and the use of pharmaceutical oxytocin administration during childbirth, on outcomes relevant to childbearing women. These outcomes include postpartum hemorrhage and breastfeeding/ lactation, both of which involve oxytocin function. Through a series of studies and manuscripts, the aims of this work are to 1) investigate the premise for clinical oxytocin use in postpartum hemorrhage prevention, specifically in lower-risk populations, and 2) assess downstream effects of oxytocin use during labor and birth on lactation hormones and breastfeeding outcomes. Four chapters, including one literature review paper and three data-based analyses are included in this body of work. The aims were addressed using variety of methodological and statistical techniques with original prospective, longitudinal as well as cross-sectional data. This work is informed by the conceptual care model of Normal Physiologic Childbirth as well as life-history (evolutionary) theory. Collectively, this dissertation demonstrates that interventions performed with the goal of risk reduction may be in the best interest of some, but not all birthing women. The findings challenge the routine practice of oxytocin administration after birth and active management of third stage labor for women undergoing low-risk physiologically stimulated birth as it may be ineffective or potentially harmful. Additionally, this work highlights the possible role of oxytocin administration during the birthing process to influence the physiology of lactation (e.g. prolactin response). Implications of this work are discussed in terms of advancing personalized risk reduction strategies in maternity care, a need for knowledge development in the physiology of non-pathologic childbirth, in addition to the use of statistical techniques in research to provide clinically meaningful findings.

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Chapter 1: Introduction

Significance

Postpartum Hemorrhage and Oxytocin. National and international health organizations promote universal oxytocin administration during the third stage of labor for postpartum hemorrhage (PPH) prevention (Main et al., 2015). Oxytocin is recommended in response to evidence showing PPH is among the leading causes of maternal morbidity and mortality worldwide (World Health Organization, 2014). In the United States, several interwoven factors contribute to high morbidity from PPH including increasing frequency of maternal comorbid conditions (e.g. obesity, hypertension), high rates of induction/intrapartum oxytocin use, and a rising Cesarean delivery rate (Callaghan, Kuklina, & Berg, 2010; Helman et al., 2015; M. S. Kramer et al., 2013). However, as a means to address the problem for PPH prophylactically, universal administration of oxytocin is advocated, even for women without these risk factors(Main et al., 2015; 2017). Furthermore, research on outcomes related to the practice of prophylactic oxytocin administration rarely considers potential implications of routine oxytocin use on endogenous, physiologic oxytocin functions.

Endogenously-released oxytocin stimulates uterine muscle contraction (S. H. Kim, Bennett, & Terzidou, 2017a), by which labor progresses naturally and bleeding after birth is abated. Oxytocin is also the most important galactokinetic hormone (Crowley, 2015). Oxytocin triggers myoepithelial cell contraction within the mammary gland alveoli, leading to milk-ejection, which is necessary for successful lactation and breastfeeding. In addition, it is well-established that oxytocin also functions as a neurotransmitter (Neumann, 2007), contributing to prosocial behavior (Carter, 2014), relationship building (Campbell, 2010), and stress-modulation (Scantamburlo, Ansseau, Geenen, & Legros, 2009) based on both human and animal models.

Despite its importance, obstetric research on oxytocin use in the clinical setting has not routinely included outcome variables beyond those linked to the direct result of uterine response (e.g. length of labor) or the immediate neonatal transition (e.g. Apgar score, NICU admission, mortality) (Bell, Erickson, & Carter, 2014). This disconnect in current research focused on the management of birth but not including longer term outcomes into the postpartum period means that one cannot accurately assess downstream effects of the drug oxytocin (Pitocin) on endogenous oxytocin function, for example, on maternal milk production.

Breastfeeding Outcomes. Another priority of maternal-child care providers is supporting and improving breastfeeding outcomes, including the initiation and duration of exclusive breastfeeding (Gartner et al., 2005). Promoting exclusive breastfeeding is supported by the growing understanding that it may reduce health risks and mortality rates for both infants and their mothers (Bartick et al., 2016). Initiation of breastfeeding has improved significantly with ongoing public health messaging, health policy, and prenatal education. In 2015, 81.1% of all babies were reportedly initially breastfed according to the CDC Breastfeeding Report Card (Centers for Disease Control and Prevention, 2016). However, the rate of breastfeeding rapidly decreased and was 44.4% at three months and 22.3% by six months (exclusive breastfeeding). Early problems with breastfeeding predict reductions in exclusive or any breastfeeding over first few months (Chantry, Dewey, Peerson, Wagner, & Nommsen-Rivers, 2014; Semenic, Loiselle, & Gottlieb, 2008). The reasons for sharp declines in exclusive breastfeeding are multifactorial including physical difficulties, availability of professional postpartum lactation support, maternity leave policies, maternal self-efficacy and cultural practices (Bomer-Norton, 2013; Dennis, 2006; Jonas & Woodside, 2016; Stuebe et al., 2014).

Women who decide to supplement or stop breastfeeding often report a perception of insufficient milk production (Kent, Gardner, & Geddes, 2016; Murase, Wagner, J Chantry, Dewey, & Nommsen-Rivers, 2016). A recent analysis found that one in eight women who began breastfeeding had undesired early weaning related to pain, latch difficulties and/or issues with low milk supply (Stuebe et al., 2014). The physiologic basis for insufficient milk supply is a growing area of research, with studies examining maternal metabolic characteristics as well as interventions during birth on measures of successful lactation (Dozier et al., 2012; Nommsen-Rivers, Chantry, Peerson, Cohen, & Dewey, 2010). Recently, oxytocin use during labor and/or postpartum has been associated with suboptimal infant feeding behaviors or reduced duration of breastfeeding (Brimdyr et al., 2015; Gu et al., 2016; Jordan et al., 2009). However, these studies are limited by the indications for oxytocin administration and other methodological issues.

Given the shared physiologic pathway of oxytocin for both uterine and breast tissue function, the question of effects of oxytocin administration on later breastfeeding outcomes merits further study. This program of research will examine the function of oxytocin from a pharmacologic and physiologic perspective as it relates to 1) management of bleeding during the third stage of labor and 2) biobehavioral postpartum breastfeeding and lactation outcomes.

Literature Review

Third Stage Labor. Human labor and birth occurs in three stages. In the first stage, a woman's body undergoes immense transformation to effectively dilate the cervix. This occurs, in part, via the mechanisms of uterine contraction which, when complete, lead to the voluntary and spontaneous expulsive forces of stage two (birth) (Posner, Black, Jones, & Dy, 2013). The third stage, however, stands in contrast, as it encompasses elements of both physical labor and motherhood. During this stage, the new baby may be in a woman's arms, possibly even at the

breast, but the birth is not yet over. It is a time of inherent vulnerability for both women and babies. The newborn must transition to extrauterine respiration and gas exchange to survive (Blackburn, 2014). To support transition, the umbilical cord will continue to provide oxygen-rich blood into circulation until it is cut. Meanwhile the mother's uterus must continue to contract efficiently to separate and expel the placenta, an action which also constricts the blood vessels at the placental site on the uterine wall to slow bleeding (Yuko & Kataoka, 2017). When the placenta releases and the immediate bleeding slows, the birth is over, and the woman is in recovery. Third stage labor is termed prolonged if it lasts more than 30 minutes, the placenta deemed retained (Cummings, Doherty, Magann, Wendel, & Morrison, 2016). A woman's risk for postpartum hemorrhage, morbidity, and mortality increases with prolonged third stage labor and retained placenta (Cummings et al., 2016).

Complications of third stage labor. Postpartum hemorrhage is defined as the loss of more than 1000 mL of blood in the immediate postpartum period or blood loss accompanied by signs of hypovolemia (American College of Obstetrics and Gynecology, 2014). The term, postpartum hemorrhage, was recently updated and revised from a two-level definition: 500 mL or more for vaginal birth or 1000 mL or more after Cesarean birth. The prior definition guided research for decades and the change represents a significant shift. The reason for this revision reflects that physiologically, women can typically tolerate up to this level of blood loss due to the adaptations pregnancy confers in preparation for birth. Blood volume, for instance, increases on average by 1250 mL during a normal pregnancy (Hytten, 1985).

Postpartum hemorrhage is associated with increased maternal morbidity, need for blood transfusion, and is a major source of maternal mortality especially in low-resource settings (e.g. developing countries, facilities without access to intravenous fluids or blood products) or in

women who cannot tolerate excess bleeding due to comorbidities (e.g. anemia, chronic infection, malnutrition). In the United States, morbidity and mortality from PPH has increased (Merriam et al., 2017). Influencing factors on PPH include, higher rates of intrapartum oxytocin use (induction and augmentation of labor), placental abnormalities (e.g. placenta previa or accreta) and increased maternal co-morbidity prior to and during pregnancy (Callaghan et al., 2010; Driessen et al., 2011; Helman et al., 2015; M. S. Kramer et al., 2013) .

Physiological Overview of Oxytocin. Oxytocin, a neuropeptide made of nine amino acids, is the dominant hormone of the third stage of labor and has several physiological and behavioral functions. Oxytocin is synthesized in the central nervous system (CNS) by hypothalamic neurons in the paraventricular and supraoptic nuclei, bound to the carrier protein neurophysin. Active forms of oxytocin require cleaving of the preprohormone by an enzyme pathway (A. Romano, Tempesta, Micioni Di Bonaventura, & Gaetani, 2016). Dense core vesicles containing oxytocin-neurophysin complex travel to oxytocin axon terminals to secrete into circulation through the hypophyseal vein. However, oxytocin neurons also have projections into other brainstem nuclei and mesocorticolimbic neural pathways acting as a neurotransmitter within the central and peripheral nervous systems (H.-J. Lee, Macbeth, Pagani, & Young, 2009). Degradation (and inactivation) of oxytocin occurs through P-LAP (placental leucine aminopeptidase) in uterine, placental, plasma, and hypothalamic tissue (Tobin et al., 2014). To exert intracellular action, oxytocin binds to oxytocin receptors (a G-protein coupled receptor), triggering many second messenger responses within peripheral cells or action potential in neurons (Devost, Wrzal, & Zingg, 2008).

In the CNS, oxytocin triggers prolactin release (Crowley, 2015; Mori et al., 1990) and attenuates corticotrophin releasing hormone responses which later result in diminished cortisol

release (E. Q. Cox et al., 2015). Oxytocin release has the physiological impact of decreasing the stress response and can be seen through decreased heart rate and blood pressure and increased parasympathetic activity (heart rate variability), as well as increased anti-inflammatory markers (Gutkowska, Jankowski, & Antunes-Rodrigues, 2014). Oxytocin leads to reduced anxiety-like behavior and reports of anxiety in animal and human models respectively (Neumann & Slattery, 2016).

Oxytocin also binds to receptors along dopaminergic neurons which would link oxytocin-related stimuli, physiology, and behavior to the reward and memory circuitry of the brain (Galbally, Lewis, van IJzendoorn, & Permezel, 2011). The multiple oxytocin pathways would be important for reinforcing (rewarding) the development of the social relationship which, for humans, is implicated in building of trust (Campbell, 2010; Gordon, Martin, Feldman, & Leckman, 2011; Shamay-Tsoory & Abu-Akel, 2016) and also empathic interaction (Rodrigues, Saslow, Garcia, John, & Keltner, 2009; Sue Carter, Harris, & Porges, 2008).

Behaviorally, CNS oxytocin promotes social relationships via anxiety and stress reduction, pain-lowering hormones and an intrinsic sense of reward (Campbell, 2010). The prosocial role of oxytocin is especially important in the context of the psychological stress associated with the novelty of a new partner or the demands of a newborn child (S. Kim & Strathearn, 2016). Finally, a growing body of literature links traumatic or early life experiences with later oxytocin dysfunction in both human and animal models, possibly through genotypic or epigenetic mechanisms (Champagne & Curley, 2009; Jonas et al., 2013; Myers et al., 2014; Neumann & Slattery, 2016; Puglia, Lillard, Morris, & Connelly, 2015). Altogether, the rapid expansion of knowledge in the neurophysiology of oxytocin has key importance for clinical

science given the mental health and behavioral implications, as well as potentially informing obstetric outcomes.

Oxytocin is a primary endogenous hormone propelling labor toward birth (Vannuccini, Bocchi, Severi, Challis, & Petraglia, 2016). Oxytocin may be released from the placenta and decidua during early labor phases of labor (S. H. Kim, Bennett, & Terzidou, 2017b), while maternal pituitary release of oxytocin is seen in the active and expulsive phases of labor (Blanks & Thornton, 2003). Oxytocin also should continue to be released during the third stage of labor, thereby aiding in the completion of the third stage and minimizing bleeding (Vannuccini et al., 2016). Oxytocin is also discharged in response to other stimuli potentially present during the third stage of labor: social interaction, nipple stimulation, holding a baby, and affectionate touch (hugging/kissing) (Campbell, 2010).

Typically, studies of oxytocin release demonstrate decreased blood pressure and heart rates (Gutkowska et al., 2014; Yang, Wang, Han, & Wang, 2013). However, oxytocin shares a close relationship with arginine vasopressin (which broadly serves to increase blood pressure), and rat models demonstrate that oxytocin releases along with arginine vasopressin in response to hypovolemia and arterial hypotension (Yang et al., 2013). Arginine vasopressin, or Anti-Diuretic Hormone, is a related hormone and neurotransmitter, differing from oxytocin by only two amino acids. It is produced in adjacent nuclei within the hypothalamus and plays a role in some social behaviors in addition to general physiologic adaptation (Carter, 2014; Hammock, 2015; Nair & Young, 2006). When arginine vasopressin and oxytocin are expressed at high levels, each peptide may bind with each other's receptors (Yang et al., 2013), which may exert different action than expected (Carter, 2014; Heinrichs, Dawans, & Domes, 2009), this may be one way oxytocin modulates blood pressure in different contexts or settings (e.g. acute hemorrhage versus

social interaction). It has been noted that synthetic oxytocin, when used clinically can result in water intoxication, probably via vasopressin receptor activity (Pharmaceuticals, 2007).

While much experimental discovery about oxytocin has been conducted in animal models, human data suggest aberrant oxytocin function in many pathological conditions including mental health states (Feldman, Monakhov, Pratt, & Ebstein, 2016). Experimentally, oxytocin via nasal spray has been used to study behavioral change in people with autism, schizophrenia and eating disorders, in addition to general psychological studies regarding trust, empathy and parenting behaviors (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2008; Feldman et al., 2016; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010; Hollander et al., 2007; A. Romano et al., 2016). Oxytocin receptor differences (e.g. gene methylation or polymorphisms) have been linked to variation in health and socially-relevant behavior (Bell et al., 2015; Cecil et al., 2014; Jonas et al., 2013; Kimmel et al., 2016; Moons, Way, & Taylor, 2014; S. M. Thompson, Hammen, Starr, & Najman, 2014). Finally, it has been hypothesized that failed lactation and postpartum depression may share underlying mechanisms that involve, among other things, oxytocin function (Stuebe et al., 2014; Stuebe, Grewen, Pedersen, Propper, & Meltzer-Brody, 2012). However, if problems with labor progress or postpartum bleeding share a dysfunctional mechanism that could also influence lactation problems and depression is unknown.

While literature around basic function of oxytocin is robust and growing in the fields of behavioral neuroscience and psychology, exploration of long-term effects of oxytocin on maternal-infant outcomes following childbirth are limited. The low number of obstetric studies on oxytocin from a broader physiologic perspective may be a result of lack of interdisciplinary research, a lack of awareness of the bench science literature, or a belief that because

pharmaceutical oxytocin has no lasting effects due to its short half-life. Additionally, the drug insert information does note that studies on carcinogenesis, mutagenesis and fertility are lacking and that "based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated" (Pharmaceuticals, 2007).

Pharmaceutical Use of Oxytocin. ***Labor and birth process.*** Use of exogenous oxytocin during childbirth is both widely used and cautioned against in the medical literature and considered a "high alert" medication, as it has potential to cause significant harm when used in error (K. R. Simpson & Knox, 2009). Known potential consequences of its use or misuse include fetal acidemia and non-reassuring fetal heart tones (Jonsson, Nordén-Lindeberg, Ostlund, & Hanson, 2008). It is also closely associated with the need for neuroaxial analgesia (Anim-Somuah, Smyth, & Jones, 2011; Osterman & Martin, 2011), and an increased risk for postpartum hemorrhage (Khireddine et al., 2013; M. S. Kramer et al., 2013). Oxytocin misuse is frequently cited in litigation in obstetric malpractice cases (Clark, Simpson, Knox, & Garite, 2009). In addition, a few population based studies have linked oxytocin use during labor to other longer-term outcomes, including maternal postpartum depression (Kroll-Desrosiers et al., 2017) and conflicting results on risk of Attention Deficit Hyperactivity Disorder and autism in children exposed during labor (Gregory, Anthopolos, Osgood, Grotegut, & Miranda, 2013; Henriksen, Wu, Secher, Obel, & Juhl, 2015; Oberg et al., 2016; Smallwood et al., 2016; Weisman et al., 2015).

Clinical use of synthetic oxytocin is ubiquitous in the United States. Oxytocin is used during the first two stages of labor in at least 50% of laboring women in the United States. While exact rates of augmentation are not readily available, the Listening to Mothers III Survey

published in 2014, found that 31% of women self-reported oxytocin use for augmentation (Declercq, Sakala, Corry, Applebaum, & Herrlich, 2014). Reports of induction of labor are 23.8% nationally based on 2015 data (J. Martin, Hamilton, Osterman, Driscoll, & Matthews, 2017). Reasons for these rates may be related to increased morbidity or abnormalities in the birth process. Many professional clinical guidelines endorse induction of labor by 39 or 40 weeks of gestation to limit perinatal morbidity related to advanced maternal age (35 years or older), diabetes, or hypertension (Committee on Obstetric Practice, 2013). Other guidelines encourage induction of labor for pregnancies that extend at least one week post estimated due date, or have spontaneous (pre-labor) rupture of membranes, although the American College of Nurse Midwives (ACNM) supports informed choice in the latter (American College of Nurse-Midwives, 2012). Augmentation of labor (typically with oxytocin) is also routinely recommended if labor slows or is prolonged. Recently, parameters of duration and rate of progress in normal labor has been reevaluated and lengthened, and by extension, length of time of oxytocin treatment recommended during labor (Neal et al., 2017; J. Zhang et al., 2010).

While there are many medical and obstetric indications for oxytocin administration, the approach to providing care for women in labor may also influence a proportion of women for whom oxytocin is recommended. For example, admitting a woman in active labor (more advanced cervical dilatation) significantly reduces the risk of using oxytocin for labor augmentation compared to women who are admitted in latent, or early labor (Neal, 2014). Rates of augmentation may also differ by type of care provider attending the birth, with midwife-led care being slightly less associated with oxytocin augmentation in a recent Cochrane review (RR 0.88, 95% CI 0.78, 0.99) (Sandall, Soltani, Gates, Shennan, & Devane, 2016) and also in a study of obese nulliparous women (Carlson, Corwin, & Lowe, 2017a). Finally, there is some evidence

that women are recommended to have oxytocin when thresholds for labor dystocia (prolonged) have not yet been met by definition, with relatively more risk for poorer outcomes like instrument assisted birth and episiotomy (Bernitz, Øian, Rolland, Sandvik, & Blix, 2014). Put together, high variability in obstetric care providers' strategies prompt the use of exogenous oxytocin, beyond defined indications for its use. Therefore, for a proportion of laboring women, not all oxytocin use is necessary and it may be avoidable. The exact percentage of women needing oxytocin induction and augmentation to reduce harm from obstetric complications remains unclear.

Management of third stage labor. In addition to indications during labor, prophylactic oxytocin is administered to women after birth to guard against uterine atony and PPH, typically given during birth of infant's body or a few minutes after the birth, but prior to the expulsion of the placenta (World Health Organization, 2014). To address and reduce the burden of postpartum hemorrhage globally, particularly in low-resource settings, the World Health Organization has increased promotion of third stage uterotonic administration. This technique is typically included in a patient safety bundle called Active Management of Third Stage Labor (AMTSL) (Begley, Gyte, Devane, McGuire, & Weeks, 2015). AMTSL also includes umbilical cord traction and massage of the uterine fundus to aid in placental expulsion. Immediate cord clamping was previously included in AMTSL, but has come out of favor as it was associated with reduced infant birth weight due to diminished blood transfer via the intact pulsatile umbilical cord (Begley et al., 2015). Numerous variations of AMTSL complicate research on this strategy (Begley et al., 2015). However, it has been recently noted that administration of a uterotonic like oxytocin is an essential, if not, the most essential element of AMTSL (World Health Organization, 2014).

In contrast to AMTSL or prophylactic administration of oxytocin, another approach to third stage labor is termed "physiologic" management of third stage (Dixon et al., 2013; Fahy et al., 2010). Physiologic management relies intrinsically on the maternal release of oxytocin following birth to occur and often is assisted by maternal positioning and/or by putting the baby to breast to stimulate oxytocin release via nipple stimulation. Cohort studies comparing AMTSL or prophylactic oxytocin and physiologic management note higher rates of PPH in the AMTSL group (Davis et al., 2012; Dixon et al., 2013; Fahy et al., 2010). Studies examining skin-to-skin contact with the newborn and breastfeeding as an intervention to minimize PPH are few but have shown reductions in blood loss (Saxton, Fahy, & Hastie, 2014; Saxton, Fahy, Rolfe, Skinner, & Hastie, 2015). Importantly, samples of women in these cohort studies represent relatively low-risk and healthy populations.

One study from 1988 challenged the premise that the laboring woman's posterior pituitary will reliability secrete oxytocin following birth for the physiologic prevention of hemorrhage to occur (Thornton, Davison, & Baylis, 1988). This study compared serial blood samples (obtained every 30 seconds) of 25 women undergoing normal labor from the time of crowning of the fetal head until 15 minutes after birth. All women were managed by immediate clamping of the cord and controlled cord-traction during the third stage (not physiologic management). Ten women received an intramuscular injection of synthetic oxytocin and ergotamine (another uterotonic) immediately after birth and 15 women did not have the injection. The report notes that 6 women who did not have oxytocin injection had a surge in their oxytocin levels that was "similar" to those who had injections, while the other 9 did not demonstrate increases. However, only two women in the non-exposed group had abnormal third stage labors with one having a PPH of 1200 mL and one needing a manual removal of placenta. In all, the

authors concluded that oxytocin should be administered to all women as some appeared to not have a surge during the third stage. Notably, rates of epidural use or skin-to-skin contact with baby following birth were not reported in the study.

Since the Thornton study (1988) was conducted, many larger scale randomized controlled trials have compared third stage management including prophylactic oxytocin or AMTSL with expectant management or placebo injections. These studies do not necessarily use a "physiologic" approach as the control group either. Recent Cochrane meta-analysis reviews have noted significantly decreased risk for PPH for women receiving AMTSL or prophylactic oxytocin as well as decreased risk of blood transfusion or a low postpartum hemoglobin (less than 9.0 mg/dL) (Begley et al., 2015; Westhoff, Cotter, & Tolosa, 2013). However, these reviews are limited by the quality of the trials included and heterogeneity in methods, including the exclusion criteria.

Most studies included in these reviews include women with intrapartum exposure to oxytocin in the samples. Intrapartum use of oxytocin is an important consideration given that women with pharmacologic stimulation of labor may differ from women in labor via endogenous hormonal pathways. Women for whom labor has been stimulated with oxytocin may express different lower levels of oxytocin in the postpartum days (Jonas et al., 2009) and have diminished subsequent receptor function (Balki, Erik-Soussi, Kingdom, & Carvalho, 2013; Magalhaes et al., 2009; Phaneuf, Rodriguez Linares, TambyRaja, MacKenzie, & Lopez Bernal, 2000; Robinson, Schumann, Zhang, & Young, 2003).

Lactation and Breastfeeding. Physiologically, a woman's ability to produce breast milk occurs over three stages, termed: secretory differentiation and secretory activation (formerly known as lactogenesis I, lactogenesis II) (Pang & Hartmann, 2007) and galactopoiesis (ongoing

milk production). Secretory differentiation occurs during pregnancy and promotes mammary gland development (Hurst, 2007; Pang & Hartmann, 2007). During pregnancy and in the first days postpartum, milk secretion is seen, termed colostrum. Secretory activation is the production of more mature milk, which includes all milk components including fat molecules like ß-casein and is associated with lower levels of sodium in milk samples (Crowley, 2015; Trott et al., 2012). This occurs as tight junctions around the epithelium of milk ducts close, resulting in a shift in the potassium and sodium ratio that is found in the extracellular fluid between the epithelial cells (Murase et al., 2016) prior to 72 hours postpartum. Greater than 72 hours labeled as "delayed onset of lactogenesis" (Chapman & Perez-Escamilla, 1999).

Prolactin in lactation. The primary lactagogue, prolactin, is secreted by the anterior pituitary, levels increase during pregnancy, and have been reported to fall during active labor and rise again in following birth of the placenta and subsequent infant suckling (Onur, Ercal, & Karslioglu, 1989). Suckling from the infant will be detected by afferent nerves in breast tissue leading to removal of the tonic inhibition of prolactin by dopamine pathways (Crowley, 2015). These physiologic and behavioral changes, together with thyrotropin releasing hormone and oxytocin, will lead to increased prolactin secretion into circulation. Prolactin binds to prolactin receptors in mammary tissue and it plays a role in mammary development, though the specific mechanisms in humans are not well described (Jonas & Woodside, 2016). From animal model literature, prolactin may help promote milk duct development, proliferation of epithelial cells within glands (Trott et al., 2012).

Oxytocin in lactation. Successful initiation of lactation also depends on oxytocin (Crowley, 2015; Jonas & Woodside, 2016) and is critical to ongoing galactopoiesis. In response to an infant's feeding cues or tactile stimulation, oxytocin, released from the maternal posterior

pituitary, binds to receptors on myoepithelial cells which surround the alveoli of the milk duct lumen. Binding of oxytocin leads to myoepithelial contraction, causing milk to flow down the ducts to the nipple ("let-down" reflex) (Crowley, 2015). Without milk-ejection, the transfer of milk fails to adequately empty the breast. Eventually, negative feedback will lead to diminished production of milk and mammary tissue will return to less responsive pre-pregnant state (E. Jones & Spencer, 2007).

Oxytocin levels in women who are breastfeeding have been found to be higher than non-breastfeeding women (E. Q. Cox et al., 2015). Levels of oxytocin increase over the course of months during breastfeeding in comparison to women providing supplemental milk while breastfeeding (Johnston & Amico, 1986). It is hypothesized that oxytocin, in addition to prolactin, during lactation confer protection to the mother by reducing reactivity to stressors, potentially providing anxiolytic properties (E. Q. Cox et al., 2015; Slattery & Neumann, 2008; Tu, Lupien, & Walker, 2005). Whether preexisting or genetic factors predispose women to have certain oxytocin levels, mental health states, lactation outcomes or if birth experiences or exposures alter the lactation-dependent inhibition of stress reactivity prompts further study (Bell et al., 2014).

Lactation hormones following birth-related interventions. Women undergoing elective Cesarean may not produce the same patterns of prolactin release, possibly due to a lack of labor-related endogenous oxytocin and/or labor pain (Rigg & Yen, 1977). What is less clear is how hypothalamic production of prolactin will respond to increased levels of synthetic oxytocin in peripheral blood circulation when it is administered for induction or augmentation of labor. Some studies note that synthetic oxytocin during labor results in different patterns of prolactin release during and after labor than other groups, (Bremme & Eneroth, 1980; Haning et al., 1978;

Onur et al., 1989) while others did not find a difference (Haddad & Morris, 1983; Lao & Panesar, 1989)[9]. It is proposed in the literature that peripheral oxytocin administration could "feedback" onto the CNS processes and subsequent endogenous release (Jonas et al., 2009). The significance of feedback, direction (positive or negative) and clinical outcomes are not well studied. More recently, non-human primate models have demonstrated that oxytocin administered intravenously passes through the blood brain barrier into the cerebral spinal fluid (M. R. Lee et al., 2017), whether the drug results CNS changes that may affect laboring women was not the focus of this particular study. Furthermore, separating the birth experiences from the obstetric indications (or medical conditions) that have led to them pose a challenge in studying the role of birth-related intervention.

Theoretical Framework

Two frameworks are used to guide and explore the research questions presented in the dissertation: "physiologic childbirth" and "life-history theory" of natural selection. Primarily, the dissertation is guided by the physiologic childbirth model of care (American College of Nurse-Midwives, Midwives Alliance of North America, National Association of Certified Professional Midwives, 2012). A physiologic approach to care of childbearing women proposes to "facilitate normal biological processes of childbirth" (Goer & Romano, 2012) (p.3) particularly for women experiencing uncomplicated pregnancy. Physiologic childbirth is grounded in clinical evidence-based research outcomes important for well-being of mothers and infants, but it is not explicitly theoretically driven. Therefore, an evolutionary theory perspective is also included in the dissertation to prompt consideration of the mechanisms of oxytocin in the broader context of human survival as an extension of the implications for physiologic childbirth.

Physiologic Childbirth. In 2012, a consensus statement and series of papers was generated by the ACNM along with other midwifery organizations to define and describe healthy and normal physiologic childbirth, as an underlying principle guiding midwifery care (American College of Nurse-Midwives et al., 2012; Kennedy et al., 2015). A normal physiologic birth was defined as "one that is powered by the innate human capacity of the woman and fetus" it went on to say that it "would more likely be safe and healthy because there is no unnecessary intervention that disrupts the normal physiologic process." The physiologic childbirth model, based in evidence-based literature, contends it promotes more optimal outcomes for the mother and baby as intervention in the absence of pathology increases risk of disturbing a normal process and causing harm. (American College of Nurse-Midwives et al., 2012; A. M. Romano & Lothian, 2008). The model lists 16 elements of physiologic birth, among which are the tenants that a) labor that starts on its own and b) has physiologic blood loss (See Box 1). While not explicitly

Box 1: Proposed Components of Physiologic Childbirth[24]

Normal physiologic childbirth: is one that is powered by the innate human capacity of the woman and fetus.

1. is characterized by spontaneous onset and progression of labor;
2. includes biologic and psychologic conditions that promote effective labor;
3. results in the vaginal birth of the infant and placenta;
4. results in physiologic blood loss
5. facilitates optimal newborn transition through skin-to-skin contact and keeping the mother and infant together during the postpartum period; and
6. supports early initiation of breastfeeding.

The following factors disrupt normal physiologic childbirth:

7. induction or augmentation of labor
8. an unsupportive environment (ie, bright lights, cold room, lack of privacy, multiple providers, lack of supportive companions)
9. time constraints, including those driven by institutional policy and/or staffing
10. nutritional deprivation (eg, food and drink)
11. opiates, regional analgesia, or general anesthesia
12. episiotomy
13. operative vaginal (vacuum, forceps) or abdominal (cesarean) birth
14. immediate cord clamping
15. separation of mother and infant and/or
16. any situation in which the mother feels threatened or unsupported

stated by the statement, the "innate" characteristics of physiologic birth have been shaped by evolutionary forces. As such, physiologic birth may be viewed in the context of human species' survival, making theories regarding evolution relevant to the study of the physiology of oxytocin in both birth and lactation.

Evolutionary Theory: Life History. One evolutionary theory, called life history theory (Stearns, 2000), might also help explain how oxytocin plays a specific role in bridging the birth and postpartum period—as a mechanism for linking survival from birth (uterine involution, limiting postpartum bleeding) and survival of offspring (milk production). Principals of life history theory include 1) the study of groups of traits that make up the species phenotype and 2) the concept that an organism's place in its life span cannot be viewed without considering what came before and what comes after it (Flatt & Heyland, 2011). Breyland, Heyland and Thomas (2011) write, "A given life history trait can thus be thought of as a functionally complex phenotype resulting from the integration of a suite of morphological, physiological, or behavioral phenotypes" (p.6). From a lifespan perspective, pregnancy and birth are forces that may shape lactation. Indeed, it has been proposed that pregnancy and lactation are co-evolved and integrated, as survival depends on both elements for reproductive fitness (Muehlenbein, 2010)(Chapter 20).

Putting the two frameworks together, if physiologic birth is grounded in innate characteristics of human physiology, they may be phenotypic traits in a very broad view of birth itself. If the woman's body is functioning normally, intervention in one element could have the potential to disrupt other aspects of the reproductive process also dependent on the normal, innate physiology. From a research perspective, we can then consider long-term effects of our routine interventions and reexamine the physiologic mechanisms of what makes up humans'

evolutionarily primed process. Study of the impact routine care during childbirth may have on women's postpartum physiology, however, may be a considerable paradigm shift from the modern obstetric view of what is occurring during birth-related intervention.

Specific Aims and Chapters

This program of research will explore the physiologic role of oxytocin and birth practices that include exogenous oxytocin on outcomes important to the postpartum period including blood loss and breastfeeding through two specific aims (see Table 1). Figure 1 illustrates the relationship between the variables described throughout chapter one and the proposed aims for the manuscripts.

Table 1: Specific Aims and Chapters

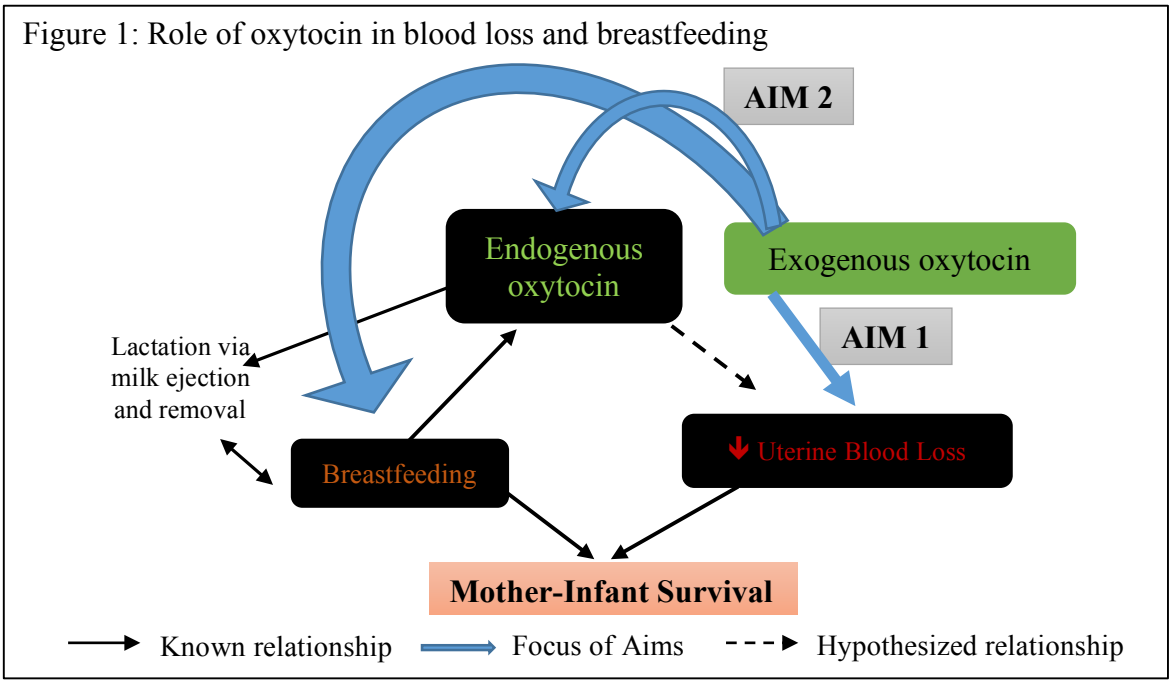
Aim	Chapter/ Title
1: Investigate the premise for clinical oxytocin use in postpartum hemorrhage prevention, specifically in lower-risk populations	- **Chapter 2:** Role of Prophylactic Oxytocin in Third Stage Labor: Physiologic Versus Pharmacologically Influenced Labor and Birth - **Chapter 3:** Physiologic Childbirth and Active Management of the Third Stage of Labor: A Latent Class Model of Risk for Postpartum Hemorrhage
2: Assess downstream effects of oxytocin use during labor and birth on lactation hormones and breastfeeding outcomes.	- **Chapter 4:** Breastfeeding outcomes after oxytocin use during childbirth: an integrative review - **Chapter 5**: Prolactin Response in Breast Feeding Women: Use of Synthetic Oxytocin During Childbirth and Newborn Weight Loss.

Aim 1: Investigate the premise for clinical oxytocin use in postpartum hemorrhage prevention, specifically in lower-risk populations. Chapter 2 of this proposal examines risks for PPH and further morbidity (blood transfusion) among women without intrapartum oxytocin administration and the efficacy of prophylactic oxytocin administered during third stage for

women in spontaneous labor. It also examines the utility of the practice given the shifting definition of a PPH (or the widened definition of normal blood loss) to 1000 mL or symptoms of hypovolemia. Chapter 3 examines a database of perinatal outcomes of the Faculty Nurse Midwifery Practice at Oregon Health and Science University from 2012-2016. By practice guidelines, these women were undergoing relatively low-risk births and approximately 25% opted out of prophylactic oxytocin following birth. Their bleeding outcomes related to intrapartum and postpartum oxytocin exposure (third stage management) will be analyzed.

Aim 2: Assess downstream effects of oxytocin use during labor and birth on lactation hormones and breastfeeding outcomes. In Chapter 4, an integrative review presents the English-language literature published through 2016 reporting a breastfeeding outcome (maternal or infant) in relationship to intrapartum or postpartum oxytocin administration. This review describes and synthesizes findings from 26 studies reporting on measures of initiation and/or duration of breastfeeding, physiology of lactation, or infant feeding behaviors. The

Figure 1: Role of oxytocin in blood loss and breastfeeding



chapter, in part, serves as a foundation for the study that will be reported in the final dissertation chapters.

Finally, Chapter 5 will describe the findings of a prospective, longitudinal study conducted at Oregon Health and Science University, examining the role of oxytocin used for augmentation of labor and/or postpartum prophylaxis on biobehavioral maternal-infant breastfeeding outcomes compared to women who had no oxytocin administration. The first manuscript will relate the postpartum (day 4 to 5) expression of oxytocin and prolactin in maternal plasma to birth experiences and breastfeeding outcomes including exclusivity and frequency of breastfeeding, infant weight changes, onset of secretory activation (lactogenesis II), and maternal psychometric evaluations (breastfeeding self-efficacy, generalized anxiety, postnatal depression).

Implications for Nursing Science

This body of work contributes to the gaps in knowledge about the function of oxytocin on two important outcomes for childbearing women: postpartum blood loss and breastfeeding. As recommendations for universal administration of oxytocin to women giving birth are promoted by major nursing, midwifery, and obstetric organizations, this is a pivotal time to continue to examine the evidence for prophylactic oxytocin and potential impact. Simultaneously, breastfeeding promotion and prevention of attrition remains a top priority for care providers in maternal-child health. Broadening and deepening knowledge of the physiology of oxytocin during childbirth, particularly the biobehavioral aspects can allow for further discovery and inform intervention.

Summary

The purpose of this program of research is to examine the function of oxytocin from a pharmacologic and physiologic perspective as it relates to bleeding during the third stage of labor and biobehavioral postpartum breastfeeding and lactation outcomes. Through these chapters, several multi-dimensional and complex phenomena are weighed including physiologic, behavioral and clinical considerations. This body of work is informed by principles of evolutionary theory and a model of childbirth care that acknowledges and promotes the innate processes guiding normal birth. It is intended that this line of inquiry may challenge current medical-obstetric paradigms regarding oxytocin use and function. It may also stimulate further research on the physiology of childbearing with the consideration of lactation as a connected and integral component of the reproductive process.

Chapter 2: Role of Prophylactic Oxytocin in Third Stage Labor: Physiologic Versus Pharmacologically Influenced Labor and Birth

Authorship	Elise N Erickson Christopher S. Lee Cathy L. Emeis
Journal	Journal of Midwifery and Women's Health
Journal Description	***The Journal of Midwifery & Women's Health*** (JMWH) is the official journal of the American College of Nurse-Midwives. This peer-reviewed journal presents new research and current knowledge across a broad range of clinical and interdisciplinary topics including maternity care, gynecology, primary care for women and newborns, public health, health care policy, and global health. With a focus on evidence-based practice, JMWH is dedicated to improving the health care of women throughout their lifespan and promoting excellence in midwifery. Impact Factor: 1.432
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- This manuscript represents a significant contribution to the Dissertation work.

Precis

Prophylactic oxytocin for prevention of postpartum hemorrhage may not confer the same benefits to women undergoing spontaneous labor compared to women with oxytocin stimulated labor.

Abstract

Introduction: Obstetric care providers administer oxytocin prophylactically to prevent postpartum hemorrhage (PPH). Prophylactic oxytocin is generally considered effective and safe and is promoted by national organizations for standardized use. In this article, the evidence supporting prophylactic oxytocin administration for women undergoing spontaneous labor and birth compared with women whose labors included administration of exogenous oxytocin for induction or augmentation is explored. **Methods:** Using data from randomized controlled trials included in 2 recent Cochrane meta-analyses papers, only studies with women in spontaneous labor were selected for inclusion (n=4 studies). Outcomes of immediate postpartum bleeding volumes (greater than or equal to 500 mL or 1000 mL), risk for blood transfusion, and risk for administration of more uterotonic medication were pooled from these 4 studies. Focused random effects meta-analytics were used. **Results:** Compared to women without prophylactic oxytocin, women who received prophylactic oxytocin had a lower risk of having a 500 mL or higher blood loss. However, prophylactic oxytocin did not lower risk of PPH (1000 mL or more), blood transfusion, or need for additional uterotonic treatment. **Discussion:** Prophylactic oxytocin may not confer the same benefits to women undergoing spontaneous labor and birth compared to women laboring with oxytocin infusion. Reasons for this difference are explored from a pharmacologic perspective. In addition, the value of prophylactic oxytocin given recent changes in the definition of a postpartum hemorrhage from greater than or equal to 500 mL to 1000 mL

or more after birth is discussed. Finally, gaps in research on adverse effects of prophylactic oxytocin are presented. More research is needed on reducing risk of PPH for women in spontaneous labor.

Keywords

Active Management Third Stage Labor, Postpartum Hemorrhage, Oxytocin, Adverse Drug Effects, Third Stage of Labor

Quick points

- Intrapartum oxytocin use increases a laboring woman's risk for postpartum hemorrhage due to uterine atony.
- According to this analysis, the risk for postpartum hemorrhage, the need for blood transfusion or further uterotonic treatment is not improved by prophylactic oxytocin in women without intrapartum oxytocin exposure.
- Using the updated definition of postpartum hemorrhage from the reVITALize initiative, further research should be done in women experiencing spontaneous labor and birth regarding routine prophylactic oxytocin for prevention of postpartum hemorrhage.

Case

A 30-year-old G1P0 underwent induction of labor at 41 2/7 weeks gestation secondary to late term gestation and borderline oligohydramnios (amniotic fluid index of 6.2). Her medical and obstetric history were otherwise uncomplicated and she had a BMI of 27.5 at term. Following cervical ripening for 24 hours with vaginal dinoprostone (Cervidil), oxytocin (Pitocin) was titrated over the next 18 hours to a maximum of 16 mU per minute. She requested an epidural at 6 centimeters dilatation, progressed to complete dilatation and pushed for 3 hours. She had an uncomplicated spontaneous vaginal birth. Immediately after giving birth she was

given 10 units of oxytocin intramuscularly (IM) to help prevent postpartum hemorrhage (PPH). The umbilical cord was cut after 90 seconds of delayed cord clamping and the placental section was drained into the graduated collection bag that collected birth fluids, potentially increasing the estimated blood loss. Eight minutes after birth, she had brisk bleeding during placental separation. The midwife performed uterine massage and administered methylergonovine maleate (Methergine) intramuscularly. A few minutes later, her uterus was firm and bleeding slowed. She sustained deep sulcus and 2nd degree perineal lacerations. Her total blood loss weighed in the collection bag was 800 grams which equates to about 800 mL. On her first full postpartum day, her hemoglobin and hematocrit were 9.6 gm/dL and 29.2% respectively, which was a change from her admission values of 11.0 gm/dL and 32.4%. Aside from the drop in hemoglobin and hematocrit, her postpartum course was unremarkable and she was discharged home without symptoms of hypovolemia or anemia. She breastfed with difficulty related to painful nipple breakdown in the first days and lactogenesis II onset occurred on day 4 postpartum.

Introduction

Postpartum hemorrhage (PPH) contributes to morbidity and mortality for birthing women worldwide and remains an important area of attention for clinicians, educators and researchers as well as for quality improvement measures (World Health Organization, 2014). Offering administration of uterotonic medication, such as oxytocin, to all woman after birth to reduce postpartum bleeding is promoted by professional organizations in the United States,(AWHONN, 2015) including American College of Nurse-Midwives (ACNM)(Main et al., 2015) and by the World Health Organization (World Health Organization, 2014). Administration of an uterotonic agent is considered an essential element of active management of third stage labor (AMSTL).

However, the necessity of administering prophylactic oxytocin administration to all women immediately after giving birth is controversial. ACNM supports clients' informed choice in this matter particularly for women without identified risk factors for PPH as noted in the National Partnership for Maternal Safety Consensus Bundle on Obstetric Hemorrhage report (Main et al., 2015). Yet, the consensus paper states that 40% of PPH may occur in low-risk women. The definition of low-risk, however, has not been clearly described. For example, 2 of the 3 studies cited for this statement did not evaluate use of intrapartum oxytocin in the assessment of risk for PPH (Dilla, Waters, & Yazer, 2013; M. S. Kramer et al., 2013), yet excessive or prolonged oxytocin use is a risk for PPH as noted in the California Maternal Quality Care Collaborative Obstetric Hemorrhage Toolkit, which is also cited by the National Partnership consensus report (Bingham, Melsop, & Main, 2010). In addition to a lack of definition for "low-risk", the terms, "excessive" and "prolonged", have not quantified in terms of dose or duration of oxytocin exposure during labor.

The risk of uterine atony in women who enter labor spontaneously and progress through labor without need for pharmacologic augmentation may not be the same as the risk of uterine atony in women whose labors are stimulated pharmacologically. Oxytocin is used during the first 2 stages of labor in nearly 50% of laboring women in the United States. While exact rates of augmentation are not readily available, the Listening to Mothers III Survey published in 2014, found that 31% of women self-reported oxytocin use for augmentation (Declercq et al., 2014). Reports of induction of labor are 23.8% nationally based on 2015 data (J. Martin et al., 2017).

The pharmacologic consequence of intrapartum oxytocin administration may be diminished uterine oxytocin receptor response to oxytocin (endogenous or exogenous) as demonstrated by studies of human myometrial tissue (Balki et al., 2013; Phaneuf et al., 2000)

and described in the article by Page et al in this issue (Page, McCool, & Guidera, 2017). This effect appears to be related to the dose and/or duration of intrapartum exposure and uterine tissue may take several hours to recover full oxytocin receptor function following exposure. Diminished uterine muscle oxytocin receptor response could in turn affect the risk for uterine atony during the immediate postpartum period (Balki, Ramachandran, Lee, & Talati, 2016). Therefore, a large number of women may be more vulnerable to PPH as a result of intrapartum management.

A number of studies report that risks for PPH increase following induction or augmentation of labor (Helman et al., 2015; Khireddine et al., 2013; M. S. Kramer, Dahhou, Vallerand, Liston, & Joseph, 2011; Wetta et al., 2013), although not all have found this association (Malabarey, Almog, Brown, Abenhaim, & Shrim, 2011; Sosa, Althabe, Belizán, & Buekens, 2011). In examining the relationship between intrapartum exposure to endogenous oxytocin and risk for PPH it is important to consider whether bleeding prophylaxis techniques such as AMTSL were employed in the care of these women. Sosa et al compared use of AMTSL (with oxytocin) to no AMTSL after induction or augmentation of labor and found that women, regardless of intrapartum use of oxytocin, had a reduced risk of an immediate postpartum blood loss of 500 mL or more, with AMTSL (Sosa et al., 2011). Rates of AMTSL were statistically similar between women undergoing spontaneous labor (30.3%) and those whose labors were induced or augmented (39.6%). Interestingly, the risk of a PPH greater than or equal to 1000 mL or a blood transfusion were not different by the third stage management approach. Intrapartum use of oxytocin also did not predict an increased risk of a PPH of 1000 mL or more after adjusting for covariates including parity, lacerations and retained placenta. This study's findings

demonstrate that AMTSL reduced the risk of a postpartum blood loss of 500 mL or more, but may not reduce risk for severe PPH and greater morbidity (Sosa et al., 2011).

The lack of a clear definition further complicates the assessment of risk for PPH. Because the definition of a PPH has traditionally been 500 mL or more following vaginal birth, research on interventions to limit or prevent excess blood loss (such as prophylactic oxytocin) often consider the intervention effective if it is successful in reducing postpartum blood loss to less than 500 mL. However, some researchers have noted that a 500 mL volume of bleeding immediately postpartum "is equivalent to the volume of a blood withdrawn at a routine blood donation"(Begley, 1990). Additionally, in healthy women, the normal expansion in blood volume (approximately 1250 mL) (Hytten, 1985) that occurs during pregnancy helps protect the woman against adverse effects of acute blood loss following birth. Larger amounts of blood loss, such as 1000 mL or greater are often grouped together in research outcomes with those having a blood loss between 500 mL and 999 mL. Yet 500 mL and 1000 mL may be two clinically significant different quantities that represent different biological risks to a woman. Thus, the prevalence and scope of the problem of PPH, if based on 500 mL or more, may represent, in part, a group of women experiencing physiologic blood loss, rather than a hemorrhage.

The need for a better definition of postpartum hemorrhage has been taken into consideration as one element within a broader initiative to standardize definitions of terms used in obstetrics. In 2014, the American College of Obstetricians and Gynecologists led the effort to standardize definitions for terms commonly used in obstetrics and gynecology research and practice. This effort, known as reVITALize has been endorsed by major women's health care organizations in the United States. ReVITALize refined the definition of early postpartum

hemorrhage as shown in Table 2.1 (American College of Obstetrics and Gynecology, 2014; Menard, Main, & Currigan, 2014).

When considering use of prophylactic oxytocin, the following questions are of import: 1) What is the evidence that prophylactic oxytocin is effective for women undergoing spontaneous labor and birth? 2) Do low-risk women having a spontaneous labor benefit from prophylactic oxytocin if the definition of PPH is expanded to 1000 mL or greater following a vaginal birth? 3) Are there any known or potential harms of prophylactic oxytocin? To begin exploring these questions we used random effects meta-analytics of data included in 2 recent Cochrane reviews and focused on samples of women who labored without intrapartum oxytocin.

Analysis

Effectiveness of Prophylactic Oxytocin for Women in Spontaneous Labor?

Two recent Cochrane reviews reported on the effectiveness of prophylactic oxytocin for prevention of PPH. One review by Westhoff et al analyzed RCTs that compared oxytocin administered after birth (intramuscular or intravenous) to no uterotonic or placebo (Westhoff et al., 2013), while the other by Begley et al examined RCTs reporting use of AMTSL compared to expectant or physiologic management (Begley et al., 2015). Westhoff et al concluded that women receiving oxytocin, compared to those who did not receive an uterotonic, were less likely to experience a blood loss greater than or equal to 500 mL or 1000 mL and less likely to have need for further uterotonic medication. However, there was no difference between groups in the likelihood of having a postpartum hemoglobin less than 9 gm/dL or a blood transfusion. Begley et al also reported reduced risk of bleeding greater than or equal to 500 mL or 1000 mL and additionally noted a reduced risk of blood transfusion and a low hemoglobin in the postpartum period associated with AMTSL. Of note, AMTSL protocols in the studies analyzed in these

meta-analyses utilized different pharmaceutical variations of the uterotonic agent including oxytocin, ergotamine, or a combination drug.

To test if prophylactic oxytocin was effective for women in spontaneous labor, we examined the inclusion criteria for the studies included in the 2 Cochrane reviews for the outcomes of risk associated with immediate postpartum blood loss of 500 mL or more, 1000 mL or more, blood transfusion, and need for further uterotonic treatment. While criteria varied, 2 studies in each Cochrane review excluded women who received oxytocin during labor (n=4) (de Groot, van Roosmalen, van Dongen, & Borm, 1996; Poeschmann, Doesburg, & Eskes, 1991; Rogers et al., 1998; Thilaganathan, Cutner, Latimer, & Beard, 1993). The other studies informing the Cochrane analyses that reported on these 4 outcomes either included induction/augmentation in the analysis or did not mention it specifically (n=6).

We analyzed the 4 studies that included women in spontaneous labor only by pooling the data for the 4 outcomes of interest using random effects meta-analytics (Stata 14.1, StataCorp, TX) (Table 2.2). Our analysis found a reduced risk of blood loss greater than or equal to 500 mL in women who received prophylactic oxytocin (alone or as part of a AMTSL package) compared to the women who did not receive prophylactic uterotonic medication (RR, 0.58; 95% CI, 0.35-0.98) but no reduction in the risk for blood loss of 1000 mL or more (RR,0.70; 95% CI, 0.42-1.17), blood transfusion (RR, 0.60; 95% CI, 0.12-2.81), or need for therapeutic uterotonic treatment (RR, 0.30; 95% CI, 0.08-1.1) in women given prophylactic oxytocin following spontaneous labor and birth. These results indicate that for women who are not exposed to intrapartum oxytocin, prophylactic oxytocin may reduce the amount of postpartum bleeding but not reduce the risk of a clinically significant PPH.

Two of the 3 studies weighed blood soaked pads one hour after birth. For these studies, mean blood losses were 548 mL ([standard deviation] SD, 376 mL) in the control group compared to 374 mL (SD, 279mL) in the oxytocin group (Poeschmann et al., 1991) and 520 mL (SD, 419 mL) in the control group versus 499 mL (SD, 454 mL) (de Groot et al., 1996). In the study by Rogers et al, the midwives estimated blood loss after birth (Rogers et al., 1998), and the mean blood loss was 336.5 mL (SD, 243.2 mL) in the control group and 268.5 mL (SD, 246.1 mL) in the oxytocin group.

The oxytocin medication preparations used in each of the four studies varied somewhat and included 5 U oxytocin with 500 mcg of ergometrine (Syntometrine) administered IM, oxytocin alone or oxytocin with ergometrine (dose unspecified), and 5 U oxytocin administered IM. Thus these results should be considered in light of the clinical and methodological heterogeneity among study designs, and the observed significant statistical heterogeneity noted between the studies in greater than or equal to 500 mL analysis (χ^2=8.06 (P = 0.02); I^2=75.2%) and the need for uterotonic treatment analysis (χ^2=22.64 (P < 0.0001); I^2=86.8%).

Discussion

The results of the 2 Cochrane reviews are cited as evidence supporting standard use of prophylactic oxytocin administration. The overall Cochrane results may not be generalizable to the subpopulation of women who experience spontaneous labor and birth. Although prophylactic oxytocin was shown to decrease blood loss, the clinical importance of this finding for low risk women is our next question.

Normal Blood Loss versus Postpartum Hemorrhage

Postpartum hemorrhage increases a woman's risk for postpartum complications such as need for blood products, extended hospitalization and in the severe cases, maternal mortality. But

the amount of postpartum blood loss that engenders these risks has been questioned. The reVITALize definition of PPH (≥ 1000 mL) is based on the immediate postpartum blood loss more consistently associated with signs or symptoms of hypovolemia after all modes of birth (vaginal or cesarean). The inclusion of signs and symptoms of hypovolemia in the reVITALize guidelines provides for a more rigorous determination of who may have suffered as a result of postpartum blood loss, rather than relying solely on the often subjective and quickly conjectured estimated blood loss to diagnose a PPH.

Considering that PPH identifies women at risk of further morbidity, having a 500 mL threshold for diagnosis may pathologize normal blood loss. Clinically, this threshold may lead to the underestimation of blood loss after a vaginal birth (subconscious or intentional) by the care provider. For the individual clinician, the diagnosis may trigger an audit or case review, particularly if occurring with high frequency or resulting in other morbidity.

The mean blood loss (mL) reported, and the method for assessing the blood loss, in the studies in this review highlights these points. In the 2 studies that calculated blood loss by weight, the mean blood loss in the control groups were both near 500 mL which may indicate that immediate blood loss of more than 500 mL may be a normal phenomenon. It also may support assertions that clinicians will under report blood loss when estimating.

If increased morbidity is more likely associated with immediate postpartum bleeding volumes of 1000 mL or more, then normal total blood loss can equal or exceed 500 mL. If up to 1000 mL can be tolerated physiologically (given the absence of signs of hypovolemia), then an intervention, such as prophylactic oxytocin, may not be routinely required to mitigate blood loss in otherwise healthy women.

Adverse Effects of Routine Prophylactic Oxytocin

Of the studies included in the analysis, 2 studies reported the role of prophylactic oxytocin on the incidence of nausea and vomiting, with conflicting findings (Poeschmann et al., 1991; Rogers et al., 1998). Other outcomes such as rates of retained placenta, manual removal of placenta, and having to return for care due to bleeding were increased in women in the intervention groups in 3 of the 4 studies analyzed, but the risk of these events occurring were not statistically significant (de Groot et al., 1996; Rogers et al., 1998; Thilaganathan et al., 1993).

Beyond the immediate recovery from birth, other less studied adverse effects of exogenous oxytocin are understudied, with very few studies examining third stage prophylactic oxytocin. The potential for adverse effects is based on the hypothetical potential for exogenous oxytocin to exert lasting effects on oxytocin receptor function throughout the body or alter feedback loops that trigger normal endogenous release of maternal oxytocin from the hypothalamus.

Evidence of oxytocin receptor changes, including desensitization (Balki et al., 2013) and downregulation of mRNA within human myometrial cells (Phaneuf et al., 2000) have been studied in response to dose and duration of intrapartum exposure, not postpartum administration. Diminished contractility of uterine tissue that had been treated with oxytocin for only 2 hours persists at least 90 minutes, demonstrating a lasting effect of receptor desensitization (Balki et al., 2013). These mechanisms of desensitization and down-regulation of the receptor for oxytocin may explain why women who have had intrapartum oxytocin administered are at increased risk for PPH. However, if bolus or intramuscular administration of oxytocin at higher doses (5U, 10U, 30U) used for postpartum prophylaxis or treatment of bleeding result in similar downregulation or desensitization is not known. Some animal research supports that higher doses of exogenous oxytocin desensitizes myometrial tissue from pregnant rats that are not related to

duration of exposure (Magalhaes et al., 2009). It is also not known if desensitization or downregulation occurs in receptors on other oxytocin responsive tissue (eg, breast) which might impact the function of that tissue (eg, lactation) (Erickson & Emeis, 2017)

Few human studies have examined the relationship between exogenous oxytocin given during the birth process on later oxytocin function or expression of other hormones (eg, prolactin) (Bell et al., 2014). One study, by Jonas et al, documented differences in maternal plasma oxytocin levels on the second postpartum day during breastfeeding (Jonas et al., 2009). The amount of oxytocin measured in these women negatively correlated to the amount of oxytocin administered during labor only (correlation with postpartum dose was not reported). Levels of prolactin in women receiving prophylactic oxytocin IM were also lower after 20 and 60 minutes of breastfeeding than women with intrapartum oxytocin or women without any oxytocin. This hormone difference was not studied in terms of correlation with bleeding or breastfeeding outcomes, however. Another study, by Gu et al, noted higher levels of maternal oxytocin at two months postpartum associated with higher combined intrapartum and postpartum administration. This finding was additionally associated with less exclusive breastfeeding (Gu et al., 2016). In addition, 2 other studies have related use of postpartum uterotonic medications to decreased early breastfeeding rates (as recorded at 48 hours postpartum in chart notes) (Jordan et al., 2009), decreased breastfeeding at 2 and 6 weeks postpartum compared to expectant management (A. Brown & Jordan, 2014). The precise mechanism for these findings is not yet known, but they deserve further exploration to determine if they are driven by postpartum blood loss, the effects of oxytocic medication, or other unknown variables.

Another speculative consequence of prophylactic oxytocin rests in the premise that normal blood loss after birth serves physiologic purpose during the course of a healthy birth. It

has been postulated that too little bleeding secondary to use of prophylactic oxytocin could be problematic, given the significant blood volume expansion of normal pregnancy (Goer & Romano, 2012). Is there an optimal amount of blood a woman should lose following birth? Would excess fluid or plasma volume pose a problem in the postpartum period? Research on the physiologic third stage of labor could explore concept this with outcomes such as postpartum edema or cardiovascular changes compared to women who receive prophylactic oxytocin.

Finally, standard use of prophylactic uterotonics like oxytocin may result in the loss of generational awareness by clinicians of normal physiologic postpartum bleeding. Knowledge of normal postpartum uterine contraction and bleeding patterns may be forgotten. In an effort to address a growing and consequential problem in maternity care, we may lose sight of when third stage labor is normal and as a result see quantities of physiologic bleeding or intermittent uterine tone (without bleeding) as problematic and requiring more uterotonic intervention.

The purpose of this analysis was to examine the effect of prophylactic oxytocin for prevention of PPH in women without intrapartum oxytocin exposure. Limitations of this analysis include the age of the studies included (1991-1998) as well as heterogeneity in study design (eg, dosage of prophylactic oxytocin, assessment of blood loss, treatment regimen). Furthermore, given that this was not an original literature search, the possible studies were those available at the time the Cochrane reviews were updated. The authors also utilized different search criteria and inclusion or exclusion parameters.

Conclusions

In the clinical scenario described here, the midwife administered oxytocin prophylactically to prevent PPH. The laboring woman may have appeared to have a higher risk for PPH due to a long induction, a moderately high dose of oxytocin, and a long second stage.

Her blood loss of 800 mL was considered a PPH by the standard definition, but not by reVITALize guidelines, given that she had no hemodynamic instability in the postpartum period. Other sources of bleeding (draining the placenta, bleeding lacerations) also contributed to the composite blood loss, which would not have been minimized by prophylactic oxytocin. Finally, her breastfeeding difficulties could have been attributed to a number of variables including nipple shape, infant latch characteristics, epidural use or length of labor—the role of oxytocin (prophylactic or for labor stimulation) is not well-studied.

Clinical decision-making in third stage labor occurs quickly. A practitioner needs to weigh antepartum and intrapartum risks, identify the source and significance of any bleeding and available resources in a matter of minutes. As such, routine administration of medications makes the job of the maternity care providers less speculative during the third stage—however, routine use of oxytocin may also be less individualized to the particular woman's needs, desires, and risks. The tension between evidence-based research on prophylactic uterotonic administration, women's desires to have individualized birth care, and the less explored realm of physiologic blood loss can cause conflict for practitioners. However, this analysis and discussion questions the clinical utility of prophylactic oxytocin particularly with the newly reconsidered parameters around blood loss in relation to signs and symptoms of hypovolemia. The effect of prophylactic oxytocin for women who are undergoing spontaneous labor needs further exploration in particular, as most studies reporting on blood loss and transfusion risk in the literature include women experiencing induction or augmentation of labor. Further meta-analytic and cohort studies controlling for intrapartum use of oxytocin may help address this question.

While reducing morbidity and mortality from PPH is a pressing goal, the question of universal application of prophylactic oxytocin should be considered in the context of the

available research, normal physiologic blood loss, and known or unknown harms. Like many obstetric practices that were universally applied (eg, “once a Cesarean” or routine episiotomy) only to be modified to a risk-based approach later as the adverse consequences became evident, women may benefit from further research given these considerations. Researchers can also study outcomes beyond blood loss and risk of transfusion to better understand the down-stream consequences of birth interventions. This is especially relevant given the updated definition of PPH and the limitations of generalizability to low-risk laboring women. In sharing decision making with women many factors need to be taken into consideration including a woman’s health status prior to birth, risk factors for excessive bleeding, shifting perspectives on what is normal blood loss after birth and what adverse effects are important to a particular woman’s health and experience.

Table 2.1: Definitions of postpartum hemorrhage

REVITALIZE INITIATIVE	TRADITIONAL DEFINITION
CUMULATIVE BLOOD LOSS OF ≥1000 ML OR BLOOD LOSS ACCOMPANIED BY SIGN/SYMPTOMS OF HYPOVOLEMIA WITHIN 24 HOURS FOLLOWING THE BIRTH PROCESS (INCLUDES INTRAPARTUM LOSS)	≥ 500 mL blood loss following vaginal birth or ≥ 1000 mL blood loss following Cesarean birth

Table 2.2: Bleeding outcomes of studies that included only women in spontaneous labor receiving third stage prophylactic oxytocin compared to control groups

	Oxytocin/ control (n)	≥ 500 mL blood loss n (%)	≥ 1000 mL blood loss n (%)	Blood transfusion n (%)	Further uterotonic treatment n (%)	≥ 500 mL loss blood loss RR (95% CI)	≥ 1000 mL blood loss RR (95% CI)	Blood transfusion RR (95% CI)	Further uterotonic treatment RR (95% CI)
Poeschmann et al (1991)									
Oxytocin	28	7(25)	2(7)	Not reported	0 (0)	0.60 (0.27-1.33)	0.57 (0.10-3.14)	not reported	17 (0.01-3.42)
Control	24	10 (42)	3 (12)	not reported	2 (8)				
De Groot et al (1996)									
Oxytocin	78	25 (32)	7 (9)	2 (3)	14 (18)	0.83 (0.57-1.22)	0.80 (0.34-1.87)	1.22 (0.21-7.16)	.99 (0.55-1.78)
Control	143	55 (38)	16 (11)	3 (2)	26 (18)				
Thialaganathan et al (1993)									
Oxytocin	103	not reported	not reported	1 (0.9)	1 (0.9)	not reported	not reported	2.63 (0.11-63.64)	.12 (0.02-1.00)
Control	90	not reported	not reported	0 (0)	7 (7)				
Rogers et al (1998)									
Oxytocin	748	51 (7)	13 (2)	4 (0.5)	24 (3)	0.41 (0.30-0.56)	0.66 (0.33,1.32)	0.20 (0.07-0.59)	.15 (0.10- 0.23)
Control	764	126 (16)	20 (3)	20 (3)	161 (21)				
					Pooled RR	0.58 (0.35-0.98)	0.70 (0.42-1.17)	0.60 (0.12-2.81)	0.30 (0.08-1.1)
					P- value	.04	.17	.51	.07
					Heterogeneity χ^2	8.06 (*P*= .02)	0.18 (*P*= .92)	4.41 (*P*= .11)	22.64 (*P*<.0001)
					I^2	75.2%	0.0%	54.7%	86.8%

Abbreviations: CI, Confidence Interval; RR, Relative Risk

Chapter 3: Physiologic Childbirth and Active Management of the Third Stage of Labor: A Latent Class Model of Risk for Postpartum Hemorrhage.

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Abstract

Background: Postpartum hemorrhage (PPH) is a threat to maternal mortality worldwide. Evidence supports active management of third stage labor (AMTSL) for preventing PPH. However, trials of AMTSL include women at varying risk levels, such as women undergoing physiologic labor and those with labor complications. Counseling women about their risk for PPH and AMTSL is difficult as many women who appear low-risk can still have PPH. **Methods:** This study uses outcomes of 2,322 vaginal births from a hospital midwifery service in the United States to examine risks for PPH and effectiveness of AMTSL. Using a latent class analysis approach, physiologic birth practices and other risk factors for PPH were analyzed to understand if discrete classes of clinical characteristics would emerge. The effect of AMTSL on the PPH outcome was also considered by class. **Results:** A four-class solution best fit the data, each class was clinically distinct. The two largest Classes (A and B) represented women with term births and lower average parity, with higher rates of nulliparity in Class B. Class A women had more physiologic birth elements and less labor induction or labor dysfunction compared to Class B. PPH and AMTSL use was higher in Class B. In Class B, AMTSL lowered risk for PPH. However, in Class A, AMTSL was associated with higher risk for PPH and delayed placental delivery (>30 minutes). **Discussion:** AMTSL may not be as beneficial to women undergoing physiologic birth. Other strategies for prevention of and etiology behind PPH in these women need further study.

4-5 keywords

Postpartum Hemorrhage

Physiologic Childbirth

Third Stage Labor

Oxytocin

Active Management of Third Stage Labor

Introduction

As all pregnant women are considered at-risk for postpartum hemorrhage (PPH), international health and professional childbirth organizations in the United States have called for the *universal* uterotonic medication use for PPH prophylaxis (AWHONN, 2015; Main et al., 2015; World Health Organization, 2014). These statements are based mostly on evidence showing lower PPH (500 mL or higher) rates when uterotonic medication (an important component of active management of third stage labor (AMTSL)) has been given following vaginal birth (Westhoff et al., 2013). This recommendation (Level of Evidence: 1A) (Hull & Lagrew, 2009) for PPH prophylaxis may be due to studies indicating rising PPH and uterine atony rates in developed nations (Callaghan et al., 2010; Grotegut, Paglia, Johnson, Thames, & James, 2011; M. S. Kramer et al., 2013; Wetta et al., 2013). Reasons identified for increased uterine atony include rising labor induction rates, prolonged labor, epidural analgesia, instrument-assisted vaginal birth, maternal obesity and higher intrapartum oxytocin dosage (Butwick et al., 2018; Callaghan et al., 2010; Grotegut et al., 2011; Kaelin Agten et al., 2017; Looft et al., 2017; Nyfløt, Stray-Pedersen, Forsén, & Vangen, 2017). Regardless of the call for universal AMTSL, both the statements from the Association of Women's Health, Obstetric and Neonatal Nursing and the National Partnership for Maternal Safety Consensus Bundle on Obstetric Hemorrhage support that women at low-risk for PPH can decline prophylactic oxytocin via informed consent. However, the characteristics of women at low-risk for PPH are not conveyed clearly by the statements. One estimate states 40% of PPH occurs in low-risk women

(Main et al., 2015). This lack of clarity can cause difficulties in counseling women who desire a low-intervention approach to birth and that informed consent is limited by gaps in knowledge.

Complicating the interpretation of studies reporting risks for PPH is an updated understanding of what amount of bleeding prompts the PPH diagnosis. The PPH definition has been revised by the American College of Obstetrics and Gynecology ReVITALize initiative (American College of Obstetrics and Gynecology, 2014). This revision expands the PPH definition for a vaginal birth to (combined intrapartum/ postpartum) blood loss totaling 1000 mL or greater, or hypovolemia symptoms accompanying any blood loss within 24 hours following birth. By expanding the definition, this statement indicates that normal physiologic blood loss is greater than previously thought with vaginal birth. Most research conducted prior to the 2014 revised definition consider the 500 mL or greater threshold, and therefore, report on data from some women who have blood loss volumes in the 500 mL to 999 mL range that would now be considered physiologic. Some studies on PPH prevention, when defined at 1000 mL or higher, have also found AMTSL or prophylactic oxytocin beneficial when compared to expectant management or placebo (Jangsten, Mattsson, Lyckestam, Hellström, & Berg, 2011; Westhoff et al., 2013). However, other studies have reported no difference between groups at the 1000mL threshold (Abdel-Aleem et al., 2010; de Groot et al., 1996; Poeschmann et al., 1991; Sosa et al., 2011), particularly among women who have had a physiologic labor (Begley et al., 2015) or labors not stimulated by exogenous oxytocin (Erickson, Lee, & Emeis, 2017).

The physiology of third stage labor relies intrinsically on the maternal oxytocin release following birth, as it is a dominant hormone for uterine contraction/ involution (Vannuccini et al., 2016). Maternal positioning and putting the baby to breast to stimulate oxytocin release may assist the physiologic third stage (Begley et al., 2015; Saxton et al., 2014; 2015). A physiologic

childbirth model was promoted and defined by the 2012 joint consensus statement of midwifery organizations in the United States (American College of Nurse-Midwives et al., 2012). The physiologic birth model emphasizes the importance of the innate biological forces of a woman's body as the basis for an evidence-based approach to safe low-risk birth. Included in the definition of normal physiologic childbirth is an expectation of physiologic postpartum blood loss as well as promoting delayed cord-clamping and early breast-feeding after birth (see Box 3.1). However, the definition or quantity of physiologic blood loss is not provided by the statement, nor does it address AMTSL / uterotonic medication use.

The purpose of this paper is to examine risk for total postpartum blood loss, PPH, and blood transfusion, and evaluate outcomes associated with AMTSL for women undergoing physiologic birth. This study employs a latent class analysis (LCA) procedure. LCA is a statistical technique, used to subdivide a population into naturally-occurring but previously unknown classes or groups to help predict outcomes like the risk for PPH (Lanza & Rhoades, 2011). It has been used in other scientific/ clinical fields, such as heart failure (C. S. Lee et al., 2014) and pelvic pain symptoms (Fenton, Grey, Tossone, McCarroll, & Gruenigen, 2015) in an attempt to identify distinct patterns within populations, rather than testing averages. To our knowledge, it has not been used to study PPH or other obstetric risk types. As maternal risk for PPH consists of many contributing characteristics, this approach allows for simultaneous consideration of multiple variables. This differs from multivariate regression models that consider the independent influence of each variable while holding covariates constant.

We hypothesize that in accordance with the normal physiologic childbirth model: 1. Women with higher rates of physiologic childbirth will have lower PPH rates and 2. AMTSL in

the third stage will not reduce postpartum blood loss outcomes for women with physiologic births.

Methods

De-identified data from a prospectively gathered birth repository attended by a nurse-midwifery faculty practice in the northwestern United States was analyzed. A waiver for Institutional Review Board approval was granted for this study. This repository contains detailed clinical outcomes for clients attended from 2012-2017. A data collection instrument was initiated at the first prenatal appointment for each client, updated during intrapartum admission, at discharge, and at a final six-week postpartum visit. Faculty and student nurse-midwives involved in the care completed the data collection. Each variable was defined on a datasheet, aiding accuracy of the data. Data were entered into REDCap software by paid support staff. Data verification took place prior to analysis, examining any discrepant and outlier blood loss data.

Outcome variables include blood loss at delivery, PPH defined as 500 mL or higher (to reflect the historic definition) as well as PPH 1000 mL or higher. Blood loss was reported by the attending CNM as either estimated or measured (if weighed). We used the higher of the two when both estimated and measured were listed. The time frame for totaling the blood loss varied depending on how long the CNM was present in the room prior to recording the total. General practice among attending CNMs was to remain present in the first 30-60 minutes after birth. Any later PPH within the first two hours postpartum (prior to transfer to the postpartum unit) would be reflected in the quantity of blood loss as well. Maternal hypovolemic symptoms were not recorded in the repository, though women with severe symptoms would have been offered blood transfusion. Blood transfusion was recorded on the instrument prior to patient discharge.

AMTSL was defined by the instrument as prophylactic oxytocin, controlled cord traction and uterine massage after placental delivery as needed. Another variable, "modified AMTSL," was defined in the instrument as oxytocin being given after the placenta was delivered, or no umbilical cord traction for expediting third stage. This was included due to individual practice variations in third stage management. Expectant management was considered the absence of either AMTSL or modified AMTSL. No data was collected in this dataset specific to further uterotonic treatment for heavier bleeding beyond the initial management of the third stage.

The sample was limited to live singleton, vaginal and instrument-assisted vaginal births, 34 or more weeks of gestation. Variables relevant to physiologic childbirth were identified in the dataset as presence, or absence, of: induction / augmentation methods, instrument-assisted delivery, estimated or measured blood loss, immediate skin-to-skin contact, early breastfeeding (within 30 minutes of birth), epidural or intravenous analgesia, episiotomy, cord-clamping timing, mother / infant separation, general diet during active labor and IV fluids use (see Table 3.1).

Covariates included maternal age, body mass index, pregnancy weight gain, race, ethnicity, parity, gestational age, antepartum anemia, vaginal birth after cesarean, labor duration, genital tract lacerations, obstetric complications (fetal intolerance to labor, intrauterine growth restriction, dysfunctional labor, chorioamnionitis, gestational hypertension, preeclampsia/eclampsia, diabetes), and newborn Apgar scores.

After descriptive and bivariate analysis, step-wise, forwards-backwards, generalized linear modeling (GLM) using a gamma distribution, determined physiologic childbirth variables and covariates significantly associated with blood loss using Stata SE 15.1 (College Station, TX). Gamma distribution was selected due to the significantly non-normal blood loss distribution

(right skew). Variables were included in the latent class analysis if the p-value was less than 0.2 in the stepwise GLM. Variables occurring at less than 5% of the sample were not included in the GLM due to difficulties in fitting LCA with low frequency data. Dropped from further analysis was the cord-clamping variable because these data were not collected prior to 2014. LCA was determined by best fitting structure comparing model fit parameters with MPlus 1.5(1) (Los Angeles, CA) using procedures described by Ram and Grimm (Ram & Grimm, 2009). Model fit was tested for 2-7 possible classes. Vuong-Lo-Mendell-Rubin likelihood ratio test, adjusted Lo-Mendell-Rubin LRT and bootstrapped LRT test were considered along with model convergence (entropy close to 1), class size (more than 5% in each group), and the correct class assignment probability (posterior probabilities over 0.8). With a latent model identified, regression using class assignment as the predictor was performed for blood loss, risk for PPH and blood transfusion outcomes in Stata. Interactions of the latent class with AMTSL on blood loss and risk for PPH were analyzed.

Results

After exclusions, 2,322 vaginal births were included in the GLM and 15 physiologic birth and covariate factors met criteria to be considered in LCA (Table 3.1). Sample mean postpartum blood loss was 390 mL (SD 295 mL) with a median of 300 mL. Rate of postpartum blood loss between 500-999 mL was n=345 (14.9%) and 93 women (4%) had 1000-2000 mL blood loss and 13 (0.6%) had higher than 2000 mL. There were 42 blood transfusions in the sample (1.8%). Management of third stage of labor were 24% (n=558) “expectant management”, 55.3% (n=1283) “AMTSL”, while 20.7% (n=481) were labeled “modified AMTSL.”

Latent Class Model.

Latent class analysis best fit the data with four classes. The classes represent 44.3%, 35.3%, 6.3% and 14.2% of the sample. Fit statistics are as follows: final classes all higher than 5% of the sample, Entropy = 0.823, Posterior Probabilities = 0.90, 0.89, 0.86, 0.92, Vuong-Lo-Mendell-Rubin LRT $p<0.00001$, Lo-Mendell-Rubin Adjusted LRT $p<0.00001$, bootstrapped LRT $p<0.00001$.

Table 3.2 describes the relative characteristics of each of the classes as well as third stage management, blood loss and PPH outcomes. Overall, the four groups are clinically distinct. Class A (44%) was termed the "physiologic" class, identified by term births, lower average parity (30% nulliparous) and low proportions of labor dysfunction or multiple lacerations needing suturing. Class A women also had more physiologic birth elements including low IV fluid administration, general diet in active labor, early breastfeeding and less oxytocin labor induction. Class B (35%), labeled the "dysfunctional" class, also included term births with low parity (76% nulliparous), but had higher induction rates, longer labors, more labor dysfunction, and more need for genital tract suturing, and lower proportions of the physiologic birth elements. Class C (6.3%), the "preterm" class, represented data from preterm births and had a higher percentage of women from non-European racial background, while Class D (14.2%), the "high multiparous" class, had more multiparous with greater than 3 prior births and Hispanic women. See Table 3.2.

Blood Loss and PPH Outcomes.

GLM and logistic regression using the latent class determination on blood loss and PPH outcomes is listed in Table 3.3. Women in the "dysfunctional" class had higher rates of, and risk for, blood loss, PPH and blood transfusion compared to women in the "physiologic" class (See Graph 3.1), whereas outcomes for "preterm" and "high multiparous" classes did not differ from

the “physiologic” class. Interactions with performance of AMTSL were conducted for the four outcomes as well (Table 3.3).

According to interaction analyses, quantity of blood loss and risk for PPH was differentially affected by class when considering the role of AMTSL. In the main effects, not using AMTSL for women in the “dysfunctional” class was associated with 70.3mL more bleeding (95% CI 29.4, 111.2) compared to the “physiologic” class. Risk for PPH (500mL or higher) was 87% higher (OR=1.87, 95% CI 1.3, 2.7) when not using AMTSL, in the main effects and the interaction term showed a 39% decrease in PPH for women in the “dysfunctional” class with AMTSL. In contrast, for women in the “physiologic” class, AMTSL may have had an adverse effect on blood loss outcomes. AMTSL used in the “physiologic” class was associated with higher total bleeding (60 mL) (95% CI 30.2 97.9) and increased risk for both PPH at $\geq$500mL (OR=1.96, 95% CI 1.41, 2.72) or $\geq$1000mL (OR=2.74, 95% CI 1.36 5.52). AMTSL did not influence risk for blood transfusion in any class.

Another driver of blood loss was tissue trauma, and need for suturing. Notably, “dysfunctional” class had the highest number of women needing 2 or more lacerations sutured (40%), and low numbers having no suturing needed (13%), which likely contributed to elevated blood loss in this class.

Post Hoc Analysis 1: Retained Placenta

While third stage length was an important driver of overall blood loss, in the sample, third stage over 30 minutes was infrequent (n=93/ 4%). In the “physiologic” class, third stage over 30 minutes was higher among women with AMTSL (n=20, 4.4%) than without (n=11, 1.9%, p=0.02). Post hoc interaction analyses (see Table 3.4) examined the role of AMTSL on a third stage lasting over 30 minutes within each class. Main effects showed that women in the

"physiologic" class were at higher risk for retained placenta *with* AMTSL. The interaction terms *(data not shown)* showed a non-significant reduced risk of retained placenta for the "dysfunctional" class and the "high multiparous" classes when AMTSL was used. Graph 3.2 displays the statistically distinct relationship between length of third stage and blood loss in the "physiologic" class, trend lines represent AMTSL and expectant management. The relationship between third stage length and bleeding quantity was stronger for women undergoing AMTSL in the "physiologic" class.

Role of Modified AMTSL Practice

As mentioned, midwives in the practice recorded if a modified version of AMTSL was performed at the birth. The effect of this alternative practice was controlled for in the model (Table 3.4). PPH risk (≥500 mL) for women in the "physiologic" class with AMTSL was 4.5 higher and 5.18 times higher for ≥1000 mL while controlling for modified AMTSL. Modified AMTSL was also independently associated with increased risk for PPH (≥500 mL). Interaction terms were non-significant (*data not shown*) but followed the trend for AMTSL in the "dysfunctional" class conferring lowering risk (OR 0.78, 95% CI 0.47, 1.27).

Discussion

The purpose of this study was to examine risk for postpartum blood loss, PPH and blood transfusion using a latent class analysis, and to test the role of AMTSL on the outcomes. Both hypotheses were supported by the results. 1) Women with higher rates of physiologic childbirth did have lower rates of PPH/ blood transfusion, and 2) prophylactic oxytocin in the third stage did not improve postpartum blood loss outcomes (blood loss, rates of PPH) for women with physiologic births. Unexpectedly, use of AMTSL for women undergoing a more physiologic and less complicated birth ("physiologic" class), was associated with higher risk for PPH as well as

higher odds for prolonged third stage labor. This association may be due to other risks present at birth for why AMTSL was performed (history of PPH), or it may be coincidental. For example, if women in the physiologic group were having heavily bleeding lacerations, AMTSL may have been administered but it would not be expected to minimize that source of bleeding.

There are several sources of postpartum bleeding and more than one of them may occur, resulting in a total blood loss that meets criteria for PPH. Assuming normal coagulation pathways, a retained placenta, uterine atony, and/or genital trauma all could potentiate blood loss. Partially mitigating some blood loss from uterine atony or expediting the third stage with AMTSL benefits women who are most at risk for cumulative PPH from complicated, prolonged labors. Women with complicated or prolonged labors are more at risk for bleeding through unreliable uterine contractility *and* through tissue trauma (instrumental vaginal birth, episiotomy, prolonged second stage and more severe lacerations) (Khireddine et al., 2013; Wetta et al., 2013). However, according to this data, for women undergoing a non-pathologic labor, who have been mostly orally nourished in labor and experienced minimal genital tract trauma, the role of AMTSL may be less beneficial, raise PPH risk. The role of AMTSL in increased length of third stage labor should be studied further for women at lower risk of PPH.

Conceptually, a physiologic blood loss should follow a normal physiologic birth, as introduced by the midwifery consensus statement. Normal blood loss depends heavily on adequate uterine contractility following birth. Yet, despite lower complicated birth rates and less genital tract trauma in the "physiologic" class, some women still experienced either a delayed placental delivery (3%, n=31) or PPH $\geq$1000 mL (3.6%, n=37). The possibility that prophylactic oxytocin or AMTSL can increase rates of retained placenta has been addressed in two Cochrane meta-analysis papers (Begley et al., 2015; Westhoff et al., 2013). Both reports found non-

significant increases in risk of manual removal of placenta with prophylactic oxytocin/AMTSL compared to no uterotonic or expectant management in randomized controlled trials. Of note, participants in these studies were of varied risk and intrapartum care (induction, augmentation). The mechanism for AMTSL to contribute to retained placenta is not clear. One hypothesis is that in the setting of a physiologically stimulated process, a supraphysiologic dose of synthetic oxytocin could lead to partial detachment or trapping the placenta with early cervical closure. Given these findings, clarifying risk for adverse outcomes by examining distinct groups of parturient women provides more nuanced understanding birth practices.

Other observational studies have noted increased PPH with AMTSL in low risk cohorts receiving institutional midwifery care. These studies report a physiologic approach to third stage labor management, including delayed cord clamping, draining of the placenta after cutting the cord, not administering routine uterotonic and use of gravity or gentle cord traction for placental expulsion. Rates of PPH $\geq$1000 mL were 2-fold higher in women having AMTSL in one study (Davis et al., 2012), and rates of PPH and manual removal of the placenta were increased with AMTSL in the other (Dixon et al., 2013). This points to the idea that not all interventions benefit all laboring women equally, even if randomized controlled trials show a mean difference. Using the latent class approach allows us to examine subgroups of women (rather than averages) and could help clinicians counsel women on their risks.

Most studies on AMTSL have not considered the role of early breastfeeding on third stage labor outcomes. Early breastfeeding promotes uterine involution through endogenous oxytocin release (Section on Breastfeeding, 2012; Yuko & Kataoka, 2017). In our study, women in the “dysfunctional” class had lower rates of early breastfeeding than the “physiologic” class and higher rates of PPH. This is consistent with a study that found a reduction of PPH with early

contact and breastfeeding among women. Interestingly, this paper also noted increased PPH when AMTSL was used as well (Saxton et al., 2015), A similar study, examined "psychophysiologic care" as (a hands-off approach to the third-stage while ensuring skin-to-skin and breastfeeding when possible) (Fahy et al., 2010) also reported low rates of PPH. For our data, however, an alternative explanation is that those already experiencing early heavy postpartum blood loss or undergoing significant laceration repair may have been unable to latch the infant within 30 minutes after birth, therefore the effect of early latching on reducing blood loss cannot be determined with certainty.

An assumption that birth care providers make in supporting a physiologic third-stage rests on the ability of the maternal posterior pituitary to secrete oxytocin after birth of the newborn. One study from 1988 challenged this premise using serial blood samples (obtained every 30 seconds from crowning of the fetal head until 15 minutes after birth) of 25 spontaneously laboring women (Thornton et al., 1988). Third stage management included immediate cord clamping and modified Brandt-Andrews technique. Ten women received an intramuscular injection of synthetic oxytocin and ergotamine immediately after birth and 15 women did not have the injection. Only 6 of the 15 expectantly managed women had a surge in their oxytocin levels that was "similar" to those who had injections. In all, the authors concluded that prophylaxis should be administered to all women as some did not surge after delivery. However, the rates of perineal trauma, epidural, skin-to-skin contact with baby or use of early breastfeeding following birth were not reported, and maternal positioning, or gravitational forces were not specified—which may impact third stage bleeding and oxytocin secretion. Further study should be considered to examine the physiologic third stage oxytocin secretion in the setting of early breastfeeding and delayed cord clamping.

Methods of prevention of PPH should be considered throughout labor and postpartum, not focused on the minutes between delivery of the newborn and placenta or the first PP hour. Attention to maternal nutrition and hydration will help support effective muscle contraction of the uterus ("Providing Oral Nutrition to Women in Labor: American College of Nurse-Midwives.," 2016). Minimizing use of synthetic oxytocin and considering decreasing or discontinuing use when active effective labor is established may help maximize oxytocin receptor availability such that women's uteri can respond to endogenous or exogenous oxytocin during the early postpartum period (Balki et al., 2016; Bor, Ledertoug, Boie, Knoblauch, & Stornes, 2016; Tran, Kanczuk, & Balki, 2017). Strategies for prevention or quick repair of genital tract trauma should be a priority (Aasheim, Nilsen, Reinar, & Lukasse, 2017); as it may be an overlooked driver of blood loss in the first minutes after birth (Girault, Deneux-Tharaux, Sentilhes, Maillard, & Goffinet, 2018). Finally, encouraging endogenous oxytocin release by assisting with early breastfeeding may be beneficial and deserves further study.

This study has several strengths including a large sample size and use of LCA for identifying risk using a clinically relevant phenotype of laboring women. Data was collected prospectively and included details of intrapartum care relevant to physiologic birth not always available. Limitations of this study are that it describes the population seeking midwifery care in the northwestern United States, limiting generalizability. Though the PPH rate was higher than other midwifery cohort studies (Dixon et al., 2013; Fahy et al., 2010), which may indicate higher risk parturient women. Other limitations include not having symptoms of hypovolemia in the data collection or total 24-hour blood loss, incomplete data on timing of cord-clamping nor the exact uterotonic administration timing. Finally, low rates of certain pregnancy / labor complications precluded them from inclusion in the LCA model. Replication of this study in

more diverse datasets would be useful for evaluating the spectrum of pregnancy-related complications on PPH outcomes.

In conclusion, risk for PPH is a multifaceted concept that deserves more attention through analyses that consider the distinctions between laboring women as well as intrapartum and physiologic birth characteristics. More research is needed on the effect of AMTSL and/or prophylactic oxytocin, particularly within the context of physiologic childbirth.

Box 3: Proposed Components of Physiologic Childbirth[24]

Normal physiologic childbirth: is one that is powered by the innate human capacity of the woman and fetus.

1. is characterized by spontaneous onset and progression of labor;
2. includes biologic and psychologic conditions that promote effective labor;
3. results in the vaginal birth of the infant and placenta;
4. results in physiologic blood loss
5. facilitates optimal newborn transition through skin-to-skin contact and keeping the mother and infant together during the postpartum period; and supports early initiation of breastfeeding.

The following factors disrupt normal physiologic childbirth:

6. induction or augmentation of labor
7. an unsupportive environment (ie, bright lights, cold room, lack of privacy, multiple providers, lack of supportive companions)
8. time constraints, including those driven by institutional policy and/or staffing
9. nutritional deprivation (eg, food and drink)
10. opiates, regional analgesia, or general anesthesia
11. episiotomy
12. operative vaginal (vacuum, forceps) or abdominal (cesarean) birth
13. immediate cord clamping
14. separation of mother and infant and/or
15. any situation in which the mother feels threatened or unsupported

Table 3.1: Generalized Linear Model Regression on Blood Loss

Physiologic Birth Factors	**n (%)**	**Full GLM model Coefficient (95% CI)**	**Stepwise GLM Coefficient (95% CI)**
Induction of labor	516 (22.26)		
*Oxytocin -	409	24.96 (-19.81, 69.73)	43.4 (8.9, 77.6)
Prostaglandin -	263	-29.64 (-79.94, 20.65)	
Mechanical -	145	-35.88 (-99.11, 27.35)	
Alternative methods -	22	n/a	
Multiple methods -	253	65.16 (-16.12, 146.44)	
Augmentation of labor	600 (25.8)		
Oxytocin -	388	-15.41 (-61.01, 30.2)	
AROM -	284	1.75 (-34.53, 38.03)	
Nipple stim/ambulation -	97	n/a	
Instrument assisted delivery	62 (2.7)	n/a	
Retained placenta (>30 minutes)	105 (4.5)	n/a	
Immediate skin to skin with infant	2194 (94.9)	17.4 (-39.56, 74.35)	
*Breastfeeding in 30 min after birth	1745 (75.15)	-36.72 (-69.04, -4.41)	-34.1 (-64.7, -3.4)
Umbilical cord clamping: <1 minute	315 (13.6)	n/a	
1-2 minutes	339 (14.6)		
>2 minutes	748 (32.2)		
Epidural	884 (38.1)	-12.67 (-42.6, 17.25)	
IM/IV medication for sedation or pain	760 (32.7)	11.83 (-13.95, 37.61)	
Episiotomy	84 (3.6)	n/a	
NICU admission or mother-infant separation	217 (9.3)	-18.24 (-59.65, 23.16)	
*Regular diet during active labor	796 (34.2)	-26.22 (-49.87, -2.57)	-26.1 (-49.3, -3)
*IV fluids during labor	1222 (52.6)	20.31 (-8.71, 49.33)	17.0 (-8.5, 42.6)
Covariate Factors	**mean (SD) / n(%)**	**Full GLM model Coef. (95% CI)**	**Stepwise GLM Coef. (95% CI)**
Age	30.6 years (5.1)	5.31 (-21.24 -- 31.86)	
BMI (pre pregnancy)	24.7 (5.2)	1.62 (-11.6 –14.8)	
*Total weight gain	30 (12)	-0.51 (-1.42, 0.4)	-0.6 (-1.5, 0.3)
*Weeks of gestation	39.9 (1.3)	7.39 (-1.56, 16.33)	7.7 (-1.2, 16.6)
*First stage labor 0-12 hours	1287 (55.43)	Ref	

	12-24 hours	590 (25.41)	15.47 (-12.8, 43.75)	18.0 (-7.8, 43.9)
	>24 hours	445 (19.16)	-0.15 (-34.93, 34.62)	
*Second stage labor	0-30 min	1029 (44.3)	Ref	
	30-60 min	395 (17.0)	41.34 (7.49, 75.2)	41.1 (10.1, 72.1)
	61-120 min	393 (16.9)	-3.36 (-37.06, 30.33)	
	121-180 min	232 (9.9)	54.91 (4.58, 105.24)	52.7 (6.7, 98.6)
	>180 min	273 (11.8)	10.5 (-35.77, 56.77)	
*Third stage	0-15 min	1984 (85.4)	Ref	
	16-29 min	245 (10.5)	6.19 (-29.41, 41.78)	
	≥30 min	93 (4.0)	217.36 (124.67, 310.05)	221.8 (129.2, 313.8)
	Apgar Score 5 min	8.8 (.6)	-4 (-22.31, 14.31)	
	*Newborn weight (grams)	3488 (455.7)	0.07 (0.04, 0.1)	0.07 (0.04, 0.1)
	*Not European Descent (ref European)	241 (10.7)	38.23 (1.17, 75.29)	37.6 (1.1, 74.2)
	*Hispanic/Latina (ref not)	428 (19.1)	41.09 (9.04, 73.14)	40.4 (9.4, 71.3)
	*Parity (prior to delivery)	0.92 (1.1)	-10.97 (-21.61, -0.32)	-10.0 (-19.7, -0.3)
	Antepartum Anemia	192 (8.3)	2.25 (-36.35, 40.85)	
	Gestational Diabetes	163 (7.0)	14.22 (-30.37, 58.82)	
	VBAC	226 (9.7)	13.89 (-27.72, 55.49)	
	*Dysfunctional labor	589 (25.4)	-21.16 (-64.52, 22.2)	-27.2 (-55.8, 1.4)
[t] *Laceration score	0	866 (37.3)	Ref	
	1	836 (36.0)	53.09 (25.95, 80.23)	55.2 (28.9, 81.5)
	2 or more	601 (26.1)	114.62 (80.73, 148.51)	118.2 (85.2, 151.2)

*indicates selected for LCA model

[t] laceration score: cumulative number of genital tract lacerations or episiotomy requiring suturing

Note: covariates left out of GLM model were variables < 5% of sample (fetal intolerance to labor, intrauterine growth restriction, chorioamnionitis, preeclampsia, gestational hypertension)

Table 3.2: Physiologic and Covariate Characteristics of Latent Class Assigment

Class		**A**	**B**	**C**	**D**	
	Sample	**Physiologic**	**Dysfunctional**	**Preterm**	**High Multiparous**	**A vs. B**
	Mean (SD)/ n(%)	Mean (SD)/ n(%)	Mean (SD)/ n(%)	Mean (SD)/ n(%)	Mean (SD)/ n(%)	*t-test*/χ^2 p-value
Class Membership	n= 2322	1028 (44.3)	819 (35.3)	146 (6.3)	329 (14.2)	
Parity (mean)	0.92 (1.1)	0.84 (0.7)	0.27 (0.5)	0.54 (0.7)	3.0 (1.1)	<0.00001
Category (Para) 0	1033 (44.5)	327 (31.8)	624 (76.2)	82 (56.2)	0 (0)	
1	777 (33.5)	549 (53.4)	176 (21.5)	51 (34.9)	1 (0.30)	
2-3	431 (18.6)	150 (14.6)	18 (2.2)	13 (8.9)	250 (75.9)	
>3	81 (3.5)	2 (0.2)	1 (0.1)	0(0)	78 (23.7)	
Gestational Age (weeks)	39.9 (1.3)	40.1 (1.0)	40.4 (1.0)	37.3 (1.3)	39.6 (1.2)	<0.00001
Total Weight Gained Pregnancy (lbs)	30 (12)	31.5 (11.2)	32.4 (12.1)	23.32 (11.7)	22.9 (11.4)	0.12
Newborn Weight (grams)	3488 (455.7)	3536.6 (417.8)	3564.4 (419.0)	2801.3 (349.9)	3480.2 (418.7)	0.09
Race (European/Caucasian)	2003 (89.3)	909 (91)	698 (88)	117 (82)	281 (91)	
No	241 (10.7)	91 (9)	96 (12)	25 (18)	29 (9)	0.04
Ethnicity (Hispanic/Latina)	428 (19.1)	108 (11)	89 (11)	36 (23)	195 (61)	0.83
No	1819 (80.9)	891 (89)	707 (89)	105 (77)	116 (39)	
Laceration/Episiotomy Score Index						<.0001
No suturing needed	866 (37.3)	425 (42)	102 (13)	63 (41)	276 (84)	
One repaired	836 (36.0)	367 (36)	378 (47)	46 (32)	45 (14)	
Two or more repaired	536 (23.0)	229 (23)	238 (40)	36 (27)	8 (3)	
First Stage						<.0001
Less than 12 hours	1287 (55.4)	816 (79)	188 (24)	81 (56)	202 (62)	
12-24 hours	590 (25.4)	182 (18)	286 (34)	40 (27)	82 (25)	
>24 hours	445 (19.2)	30 (3)	345 (42)	25 (17)	45 (13)	
Second Stage						<.0001
<30 minutes	1029 (44.3)	625 (60)	58 (8)	77 (52)	269 (83)	
30-60 minutes	395 (17.0)	216 (21)	118 (15)	24 (17)	27 (11)	
60-120 minutes	393 (16.9)	148 (15)	209 (25)	25 (18)	11 (3)	
120-180 minutes	232 (9.9)	37 (4)	180 (21)	10 (8)	5(1)	
>180 minutes	273 (11.7)	2 (1)	254 (31)	10 (6)	7 (2)	

Third Stage						0.14
<15 minutes	1984 (85.4)	885 (86)	687 (84)	118 (82)	294 (89)	
15-30 minutes	245 (10.6)	112 (11)	93 (12)	18 (12)	22 (7)	
>30 minutes	93 (4.0)	31 (3)	39 (5)	10 (6)	13 (4)	
Dysfunctional Labor Diagnosis	589 (25.4)	31 (4)	469 (56)	24 (16)	65 (20)	<.0001
No	1733 (74.6)	997 (96)	350 (44)	122 (84)	264 (80)	
IV Fluids during labor	1222 (52.6)	224 (23)	715 (86)	93 (62)	190 (58)	<.0001
No	1078 (46.8)	797 (77)	97 (14)	50 (37)	134 (42)	
Regular Diet in Active Labor	796 (34.2)	508 (49)	161 (21)	36 (25)	91 (28)	<.0001
No	1489 (65.2)	508 (50)	645 (79)	107 (75)	229 (72)	
Pitocin for Induction of Labor	409 (17.6)	97 (10)	198 (23)	41 (26)	73 (22)	
No	1913 (82.4)	931 (90)	621 (77)	105 (73)	256 (77)	<.0001
Breast Feeding in first 30 Minutes	1745 (78.6)	858 (87)	529 (68)	87 (63)	271 (87)	<.0001
No	475 (21.4)	130 (13)	251 (32)	52 (36)	42 (13)	
*Management of Third Stage						<.0001
Expectant	558 (24.0)	351 (34.1)	116 (14.2)	58 (17.6)	33 (22.6)	
Active Mangement	1283 (55.25)	453 (44.1)	546 (66.7)	201 (61.1)	83 (56.9)	
Modified Active Management	481 (20.7)	224 (21.8)	157 (19.2)	70 (21.3)	30 (20.6)	

*not included in latent model

Table 3.3: Blood Loss Outcomes by Class

		Physiologic Class 'A'	Dysfunctional Class 'B'	Preterm Class 'C'	High Multiparous Class 'D'
Blood loss (mL)	**Mean, SD**	367.3 (258.7)	440.5 (333.8)	350.5 (275.8)	356.5 (293.5)
	Coef. (95% CI)	Ref	73.1 (45.0, 101.2)***	-16.8 (-62.5, 28.8)	-10.8 (-44, 22.4)
≥500 mL PPH	**(n/%)**	178 (17.32)	198 (24.18)	21 (14.38)	54 (16.41)
	OR (95% CI)	Ref	1.52 (1.21, 1.91)***	0.80 (0.49, 1.31)	0.93 (0.67, 1.31)
≥1000 mL PPH	**(n/%)**	37 (3.6)	47 (5.74)	5 (3.42)	17 (5.17)
	OR (95% CI)	Ref	1.63 (1.04, 2.53)*	0.95 (0.36, 2.45)	1.45 (0.81, 2.62)
Blood transfusion	**(n/%)**	13 (1.26)	22 (2.69)	2 (1.37)	5 (1.52)
	OR (95% CI)	Ref	2.15 (1.08, 4.30)*	1.08 (0.24, 4.85)	1.20 (0.42-3.40)

Moderation of Blood Loss Outcomes by Latent Class with AMTSL

	Class	**Blood Loss Coef. (95% CI)**	**≥500 mL PPH OR (95% CI)**	**≥1000 mL PPH OR (95% CI)**	**Blood transfusion OR (95% CI)**
Main Effects:	Physiologic: A	Ref	Ref	Ref	Ref
Class	Dysfunctional: B	70.3 (29.4, 111.2)**	1.87 (1.3, 2.7)*	2.15 (0.95, 4.86)	1.26 (0.30, 5.33)
	Preterm: C	-22.8 (-83.4, 37.7)	0.83 (0.36, 1.89)	0.75 (0.09, 5.91)	1.37 (0.28, 6.58)
	Multiparous: D	-23.9 (-68.7, 20.8)	0.68 (0.36, 1.31)	1.51 (0.48, 4.77)	0.89 (0.10, 7.75)
AMTSL	(if Class A)	64.0 (30.2, 97.9)***	1.96 (1.41, 2.72)*	2.74 (1.36, 5.52)*	2.04 (0.66, 6.30)
Interaction	Physiologic: A	Ref	Ref	Ref	Ref
	Dysfunctional: B	-17.45 (-73.9, 39.0)	0.61 (0.38, 0.98)*	0.54 (0.21, 1.43)	1.58 (0.29, 8.35)
	Preterm: C	-3.7 (-92.7,85.1)	0.82 (0.29, 2.3)	1.14 (0.11, 11.7)	dropped collinearity
	Multiparous: D	3.58 (-61.5, 68.7)	1.3 (0.61, 2.8)	0.78 (0.20, 2.98)	1.25 (0.11, 14.9)

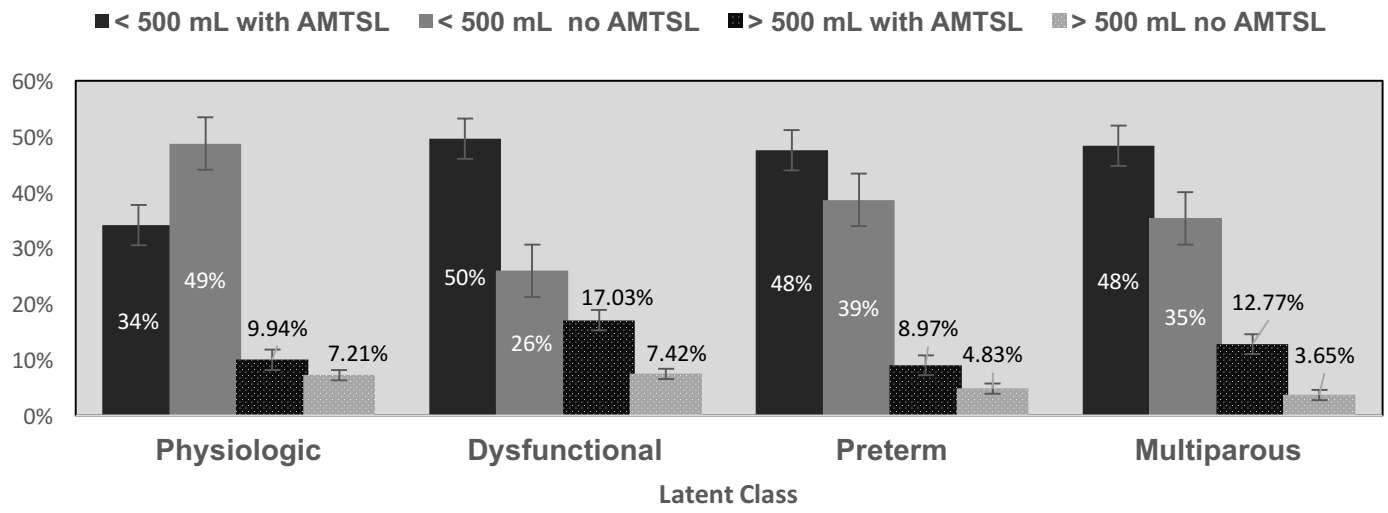
*p< 0.05, **p<0.01, ***p <0.0001

Table 3.4: Post Hoc tests

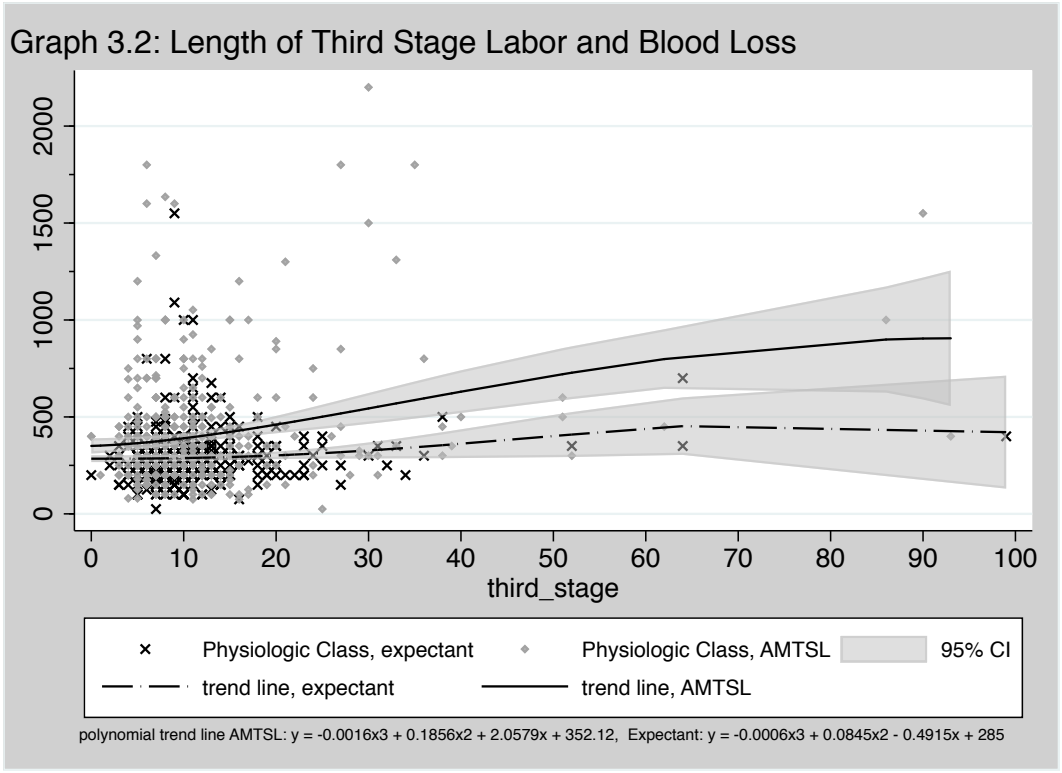
	Class	**≥500 mL PPH OR (95% CI)**	**≥1000 mL PPH OR (95% CI)**	**Blood transfusion OR (95% CI)**	**Third stage labor ≥30min**
Main Effects	Physiologic: A	Ref	Ref	Ref	Ref
	Dysfunctional: B	1.47 (0.99, 2.18)	1.71 (0.74, 3.90)	1.08 (0.25, 4.67)	1.55 (0.62, 3.91)
Class:	Preterm: C	0.71 (0.31, 1.67)	0.67 (0.08, 5.28)	1.37 (0.09, 6.87)	2.37 (1.0, 5.58)*
	Multiparous: D	0.53 (0.27, 1.03)	1.23 (0.38, 3.93)	0.78 (0.09, 6.87)	1.23 (0.33, 4.45)
AMTSL	(if Class A)	4.53 (2.94, 6.96)***	6.19 (2.36, 16.21)***	3.11 (0.76, 12.68)	2.36 (1.12, 4.99)*
Modified AMSTL	(overall effect)	4.83 (3.23, 7.25)***	4.28 (1.72, 10.72)**	2.34 (0.57, 9.60)	Not included

*p< 0.05, **p<0.01, ***p <0.0001

Graph 3.1: Blood Loss by Latent Class Assignment & Management of Third Stage (unadjusted for modified AMTSL)



Graph 3.2: Length of Third Stage Labor and Blood Loss



Chapter 4: Breastfeeding outcomes after oxytocin use during childbirth: an integrative review

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Precis

Limited research has found that oxytocin used in childbirth may affect breastfeeding. Given its extensive use during the birth process, this topic deserves further study.

Abstract

Introduction: Despite widespread use of exogenous synthetic oxytocin during the birth process, few studies have examined the effect of this drug on breastfeeding. Based on neuroscience research, endogenous oxytocin may be altered or manipulated by exogenous administration or by blocking normal function of the hormone or receptor. Women commonly cite insufficient milk production as reason for early supplementation, jeopardizing breastfeeding goals. Researchers need to consider the role of birth-related medications and interventions on the production of milk. This paper examines the literature on the role of exogenous oxytocin on breastfeeding in humans. **Methods:** Using the method described by Whittemore and Knafl, this integrative review of literature included broad search criteria within PubMed, CINAHL, Cochrane, Scopus databases. Studies published in English associating a breastfeeding outcome in relation to oxytocin use during the birth process were included. Twenty-six studies from 1978-2015 met criteria. **Results:** Studies were analyzed according to the purpose of the research, measures and methods used, results and confounding variables. The 26 studies reported 34 measures of breastfeeding. Outcomes included initiation and duration of breastfeeding, infant behavior and physiologic markers of lactation. Timing of administration of oxytocin varied. Some studies reported on low-risk birth, while others included higher-risk experiences. Fifty percent of the results (17 of 34 measures) demonstrated an association between exogenous oxytocin and less optimal breastfeeding outcomes, while 8 of 34 measures (23%) reported no association. The remaining nine measures (26%) had mixed findings. Breastfeeding intentions, parity, birth

setting, obstetric risk and indications for oxytocin use were inconsistently controlled among the studies. **Conclusion:** Research on breastfeeding and lactation following exogenous oxytocin exposure is limited by few studies and heterogeneous methods. Despite the limitations, researchers and clinicians may benefit from awareness of this body of literature. Continued investigation is recommended, given the prevalence of oxytocin use in clinical practice.

Keywords:

Oxytocin, Breastfeeding, Lactation, Drug effects, Labor (induced), labor (obstetric), labor stage (third), Active management third stage labor

Quick points

1) Oxytocin administration during childbirth is widespread, few studies have investigated the effects of this on breastfeeding, and most of these have not studied this relationship directly.
2) The effect of exogenous oxytocin on breastfeeding has been measured through infant breastfeeding behavior, physiologic lactation, maternal initiation, duration or exclusivity of breastfeeding.
3) While oxytocin administration has an important role in modern obstetric care, potential effects on lactation should be explored more, as the research on breastfeeding outcomes is incomplete.

Introduction

While increasing numbers of women are breastfeeding their newborns at birth, the ability to maintain breastfeeding may be affected by factors contributing to maternal milk production. This is reflected by the Centers for Disease Control and Prevention (CDC) 2016 Breastfeeding Report Card which shows that while 81.1% of women initiate breastfeeding after birth, only 44.4% of women are still exclusively breastfeeding at three months, falling to 22.3% of babies by the six-month target (Centers for Disease Control and Prevention, 2016). Common reasons for early cessation of exclusive or any breastfeeding is the perception of insufficient milk supply

(Kent et al., 2016; Stuebe et al., 2014) and the early introduction of formula (Chantry et al., 2014; Semenic et al., 2008). Therefore, factors that may influence physiologic milk production are compelling targets for translational research.

Understanding possible causes of suboptimal breastfeeding may have implications for improving maternal and infant health. Infants receiving formula or solid foods before six months of age are at increased risk for acute and chronic illnesses, as well as sudden infant death syndrome (Section on Breastfeeding, 2012). The number of infant deaths potentially preventable by meeting breastfeeding goals are estimated upwards of 700 annually (Bartick et al., 2016; Bartick & Reinhold, 2010). Furthermore, a growing body of literature is examining the long-term effect of breastfeeding on maternal health. Women who have no breastfeeding history have poorer indices of cardiovascular health in later life (Schwarz et al., 2010). Another study used a simulation model to estimate the impact of suboptimal breastfeeding on many maternal health outcomes, reporting a potential annual excess mortality of 3340 deaths and over 14 billion US dollars in costs due to premature death (Bartick et al., 2016).

Milk production and successful breastfeeding require oxytocin driven neuroendocrine pathways that are primed by pregnancy and the process of childbirth (Uvnäs-Moberg & Prime, 2013). Endogenous oxytocin function is essential for onset of lactation and milk ejection in mammals (Crowley, 2015). Manipulation of oxytocin in experimental animal models can lead to deficits in lactation, maternal behavior, and abnormal behavioral development of offspring (Hammock, 2015; Nephew & Murgatroyd, 2013). Oxytocin is commonly administered in modern obstetrics for labor augmentation, induction of labor, (J. A. Martin et al., 2011) and to minimize or treat uterine bleeding in the third stage of labor (World Health Organization, 2014). There is evidence that exogenous oxytocin can pass through the placenta and into fetal

circulation (Kenkel, Yee, & Carter, 2014). Therefore, depending on the timing of administration, this synthetic hormone and neurotransmitter could affect neonates as well as mothers.

The significance of these questions relates to the extensive use of oxytocin in practice. Estimates of induction of labor, typically involving exogenous oxytocin, range from 23-29% of births (Dublin et al., 2014; Osterman, 2015) but may be in the range of 31-42% in some settings, based on United States data (R. K. Freeman & Nageotte, 2007; Laughon et al., 2012). Among women who start labor spontaneously, augmentation of labor with oxytocin due to slow progress is also frequent, (R. K. Freeman & Nageotte, 2007) though exact national rates are not published. Epidural analgesia is also associated with induced and augmented labor, with more than 75% of women using an epidural undergoing induction or augmentation, according to 2008 CDC data (Osterman & Martin, 2011). During cesarean birth, accounting for 32.7% of births, (Osterman, 2015) oxytocin is administered after extracting the placenta to slow bleeding (World Health Organization, 2014). Finally, to help minimize bleeding, the World Health Organization (WHO) promotes prophylactic administration of oxytocin as the standard of care following vaginal birth (World Health Organization, 2014). It is also a mainstay treatment for postpartum hemorrhage.

Despite widespread use of oxytocin and importance of the physiology of oxytocin for successful lactation, clinical studies have rarely explored long term effects on mothers and babies, such as breastfeeding outcomes (Carter, 2003; Odent, 2013). The purpose of this integrative review is 1) to understand what breastfeeding outcomes (maternal or infant) have been reported following any clinical oxytocin administration and 2) any patterns in the published results to better inform future research.

Methods

An integrative approach described by Whittemore and Knafl (2005) informed the procedure for this review, as a preliminary literature search revealed significant heterogeneity in methods and outcomes among relevant studies (Whittemore & Knafl, 2005). We were unable to identify articles synthesizing the body of literature regarding oxytocin administration in humans and breastfeeding outcomes. The complexity of this question is owed both to the various indications and timing of oxytocin use during the birth process and also the multifactorial nature of breastfeeding and lactation research outcomes. In an effort to capture all possible oxytocin administration during the birth process, our review included intrapartum oxytocin and/or third stage labor administration. Breastfeeding outcomes were defined as any maternal and infant breastfeeding-related measure.

Literature Search

Due to the exploratory nature of this paper, the approach included broad search terms and no limits on publication date. We performed a Boolean search (as shown in Table 4.1) of PubMed Medical Subject Heading (MeSH) terms including: 1) oxytocin, labor (induced), labor (obstetric), labor stage (third) or epidural analgesia; and 2) breastfeeding, feeding behavior, lactation, or lactation (disorder), yielding 1847 results after limiting to human studies. A duplicate search in CINAHL yielded 268 citations ("infant behavior" substituted for "feeding behavior"). A total of 2115 abstracts (including duplicates) were scanned for inclusion by: 1) data-based studies published in English and 2) noting oxytocin administration and a breastfeeding outcome (maternal or infant). If a potential match did not mention oxytocin administration in the abstract, the full text was reviewed in detail. Induction of labor studies not evaluating oxytocin specifically were excluded, as well as studies assessing infant bottle feeding. The resulting group consisted of 26 studies published between 1978-2015.

Data Evaluation

Significant heterogeneity in the study objectives, design and outcomes complicated the evaluation of this body of literature. The majority of the studies were descriptive or secondary analysis reports (either prospective or retrospective), however one randomized controlled trial, two quasi-experimental studies and two case control studies also made up the sample.

While studies in this review considered oxytocin exposure during birth with at least one breastfeeding measure, most did not set out to study this relationship. Many noted the association between oxytocin and breastfeeding as a sub-analysis of the primary aim or as a covariate or control for another objective. We identified three groups of research objectives within the sample studies. Only nine studies examined the effect of oxytocin use on breastfeeding. Four studies examined factors (general health and obstetric) associated with delayed lactogenesis and poor breastfeeding generally. In these reports, use of oxytocin was among many variables considered. The largest group of studies, however, sought to understand broad outcomes of specific obstetric interventions: epidural (n=4), medication use (n=3), active management of third stage labor (AMTSL) (n=1), or as part of an induction of labor (n=5). These studies included a breastfeeding measure among other outcomes.

Time point of oxytocin administration varied among the studies, illustrated in Figure 4.1. The majority considered intrapartum oxytocin administration only. Four of these assessed the postpartum dose of oxytocin as well (Dozier et al., 2012; Gu et al., 2016; Jonas et al., 2009; Jordan et al., 2009). Another three studies mention that oxytocin was routinely given postpartum but was not included in the analysis in terms of exposure (García-Fortea et al., 2014; Marín-Gabriel et al., 2015; Olza-Fernández et al., 2012). Three other studies addressed the third stage issue generally by reporting “increased need for postpartum uterotonics” (ie, oxytocin and other

medications) (Dewey, Nommsen-Rivers, Heinig, & Cohen, 2003; Guerra et al., 2009; 2011), or commenting on the relationship of postpartum hemorrhage and breastfeeding outcomes (Nommsen-Rivers et al., 2010).

Breastfeeding outcomes included maternal behaviors like initiation, duration of breastfeeding, measures of physiologic milk production (eg, hormones, lactogenesis), and infant breastfeeding behavior. A total of 34 measures in the 26 studies were examined in relationship to oxytocin use as illustrated in Figure 4.2. Some studies reported more than one outcome in the findings. Due to the variety of study objectives, methods, and outcomes used in the sample, rigor of the studies was not evaluated by a standardized rubric or score. Instead, we addressed quality of the studies by assessing and synthesizing themes that may introduce bias or limit generalizability.

Data analysis

Breastfeeding Outcomes

No primary study outcome associated oxytocin use with a more favorable breastfeeding outcome. Data were arranged into three categories 1) use of oxytocin (intrapartum and/or postpartum) and a less optimal breastfeeding outcome, 2) no association or 3) having mixed findings. Results were labeled mixed if they were the sub-analyses of the primary aim of the study or significance was seen in certain sub-groups of the sample (ie, primiparas). Of the 34 measures reported in the studies, 50% found oxytocin use was associated with a less optimal breastfeeding outcome (n=17). Mixed or qualified support of less optimal outcomes was reported by 26% (n=9) and 23% showed no differences in breastfeeding outcomes with oxytocin use or not (n=8). Table 4.2 lists the measures, statistical data, and information about the study design and limitations.

Initiation of Breastfeeding. Eleven studies examined associations between breastfeeding initiation and oxytocin administration; seven studies reported on initiation only (Guerra et al., 2009; 2011; Jordan et al., 2009; Prendiville, Harding, Elbourne, & Stirrat, 1988; Vogel, Souza, & Gülmezoglu, 2013; Wiklund, Norman, Uvnas-Moberg, Ransjo-Arvidson, & Andolf, 2007; Yudkin, Frumar, Anderson, & Turnbull, 1979). Initiation of breastfeeding was defined by various time points ranging from 10 minutes after birth through 7 days postpartum. An additional four studies reported duration measures as well as initiation measures of breastfeeding (A. Brown & Jordan, 2014; García-Fortea et al., 2014; Ounsted, Hendrick, Mutch, Calder, & Good, 1978; Out, Vierhout, & Wallenburg, 1988).

Four of these 11 papers were generated from large data sets and controlled for multiple covariates in their analyses (Guerra et al., 2009; 2011; Jordan et al., 2009; Vogel et al., 2013). Two noted delay in initiation of breastfeeding following induction of labor and elective induction of labor in Latin American countries (Guerra et al., 2009; 2011). Another reported lower breastfeeding rates at hospital discharge following AMTSL in the United Kingdom (Jordan et al., 2009). In this study, after controlling for multiple intrapartum factors, and examining a subgroup of women with low-risk, physiologic labors, AMTSL still associated with an approximate 7% reduction in breastfeeding at two days postpartum.

However, the study by Prendiville (1988), the only randomized controlled trial in the sample, did not find an association between AMTSL and breastfeeding at hospital discharge. This study is limited by a lack of fidelity to the randomization; only 403 of 849 participants allocated to physiologic management had it performed. In addition, the physiologic group was also more likely to put the baby to breast 10 minutes after birth per midwives' recommendation.

Brown and Jordan (2014) also did not find that AMTSL affected rates of breastfeeding initiation in a self-report study of breastfeeding and administration of postpartum oxytocin. However, they did report a reduction in duration of breastfeeding at both two and six weeks postpartum among participants who had AMTSL. The most often reported reasons for cessation were pain, difficulty, and embarrassment compared to women who had physiologic management. This study did not control for prenatal intentions to breastfeed.

Altogether, the definition of initiation of breastfeeding was variable however appeared to reflect the first several postpartum days. Five papers associated delayed initiation of breastfeeding with induction or augmentation of labor compared to spontaneous labor or no augmentation (postpartum use not reported) (García-Fortea et al., 2014; Guerra et al., 2009; 2011; Wiklund et al., 2007) or postpartum administration of oxytocin compared to expectant management (Jordan et al., 2009). Mixed findings were reported in three studies (Ounsted et al., 1978; Out et al., 1988; Vogel et al., 2013).

Duration of Breastfeeding. Eight studies examined duration of breastfeeding. This was defined as the time of breastfeeding cessation (Dozier et al., 2012), report of exclusive breastfeeding at three months after birth (García-Fortea et al., 2014; Olza-Fernández et al., 2012), at six weeks postpartum (A. Brown & Jordan, 2014; Rajan, 1994), or breastfeeding at 8 weeks (Gu et al., 2016; Ounsted et al., 1978; Out et al., 1988). Shorter duration or exclusivity of breastfeeding was associated with intrapartum oxytocin use by four studies compared to spontaneous labor (Dozier et al., 2012; García-Fortea et al., 2014; Gu et al., 2016; Olza-Fernández et al., 2012) and with postpartum use in the study by Brown and Jordan (2014). Two reports had mixed findings on duration of breastfeeding (Ounsted et al., 1978; Rajan, 1994). One paper reported no difference (Out et al., 1988).

The total dosage of oxytocin was examined in terms of duration of breastfeeding by two authors. Both Gu et al (2015) and Olza-Fernandez (2012) noted that higher levels of exposure to oxytocin during the birth process was associated with reduced exclusive breastfeeding at 2 and 3 months postpartum respectively. Additionally, the participants in the study by Dozier et al (2012) most likely to cease breastfeeding by one month postpartum were those with both epidural and oxytocin exposure during labor (HR, 1.34; 95% CI (1.00-1.79). Women with epidurals in this study were more likely to have oxytocin administered during labor (58.8% versus 38.3%, $P<0.01$). Breastfeeding was not analyzed by total dosage specifically in this study but this may imply that women with epidural had more need for oxytocin administration, possibly representing higher total dosage.

Physiology of Lactation. Eight studies examined breastfeeding as a measure of physiologic milk production. Six of these examined lactogenesis onset, consistently defined by maternal report of breast fullness by 72 hours postpartum (Chapman & Perez-Escamilla, 1999; Dewey et al., 2003; Kong & Bajorek, 2008; Matias, Nommsen-Rivers, Creed-Kanashiro, & Dewey, 2009; Mauri et al., 2015; Nommsen-Rivers et al., 2010). Three studies reported no association between lactogenesis and synthetic oxytocin use during labor (Chapman & Perez-Escamilla, 1999; Kong & Bajorek, 2008; Mauri et al., 2015). Three papers reported mixed findings (Dewey et al., 2003; Matias et al., 2009; Nommsen-Rivers et al., 2010). None of these studies' primary aim was to examine the role of synthetic oxytocin on lactogenesis; thus these findings were result of sub-analyses or covariate data. All of these studies were prospectively conducted and sampled mixed populations regarding modes of birth (vaginal, cesarean, instrument assisted) and use of analgesia. None reported information on postpartum oxytocin exposure.

Augmentation of labor with exogenous oxytocin (compared with no oxytocin) was associated with delayed lactogenesis in a bivariate analysis by Dewey et al (2003) ($P < .05$) but not in regression analysis. Matias et al (2009) found a marginal association with labor augmentation in bivariate analysis as well ($P < .10$) but adjusted analyses found only low Apgar score predicted delayed lactogenesis. Nommsen-Rivers et al (2010) found no difference in delayed lactogenesis oxytocin administration for induction or augmentation compared to women who had none. Postpartum oxytocin use was not considered by these studies, except as implied by Dewey et al (2003) noting that women receiving "postpartum hemorrhage medications" were more likely to have delayed lactogenesis (26% compared to 16%, P<.10).

The final two maternal studies examined physiologic response by measuring hormone levels in maternal plasma in relation to oxytocin use. Jonas et al(Jonas et al., 2009) examined physiologic response to exogenous oxytocin during birth via blood samples collected during a breastfeeding session two days postpartum. Maternal oxytocin and prolactin levels were measured, however, this was not reported in relationship to any clinical marker of lactation (ie, lactogenesis). They further demonstrated an inverse relationship (r=-.495, P=.019) between the total dosage administered during labor and level of oxytocin found in women's blood at 48 hours during breastfeeding (n=61). Prolactin levels in women who received third-stage prophylaxis with oxytocin (n=13) were lower compared to the 20 women who received no oxytocin.

Gu et al (Gu et al., 2016) measured exclusivity of breastfeeding as well the level of plasma oxytocin in maternal blood at two months postpartum. The authors found higher levels of oxytocin in women exposed to higher collective dosages of oxytocin (intrapartum and postpartum), which were also linked to higher likelihood of formula or non-exclusive breastfeeding at two months.

Infant Behavior. In relationship to oxytocin administration, authors examined pre-feeding behaviors (Bell, White-Traut, & Rankin, 2013), Primitive Neonatal Reflexes (Marín-Gabriel et al., 2015; Olza-Fernández et al., 2012), the Widström nine stages of instinctive newborn behavior after birth (Brimdyr et al., 2015), suboptimal infant breastfeeding behavior as measured by the Infant Breastfeeding Assessment Tool (Dewey et al., 2003; Matias et al., 2009; Nommsen-Rivers et al., 2010), and finally, the Premature Infant Breastfeeding Behavior Scale (Radzyminski, 2003).

Four infant studies reported a significant negative relationship between oxytocin used for induction or augmentation of labor and infant behaviors or feeding-related reflexes in healthy newborns. Three of these found higher dosages of oxytocin predicted lower infant behaviors (Bell et al., 2013; Brimdyr et al., 2015; Olza-Fernández et al., 2012), while one did not (Marín-Gabriel et al., 2015). Radzyminski (2003) reported that term infants undergoing oxytocin induced labor scored below the mean for breastfeeding behavior on the Premature Infant Breastfeeding Behavior Scale, however, no statistics were provided. In contrast, oxytocin exposure did not associate with differences between groups on the Infant Breastfeeding Assessment Tool when assessed during the first week (Dewey et al., 2003; Matias et al., 2009).

Questions about the generalizability of the infant-focused studies arise from the variation in the measurement of neonatal behavior. The Primitive Neonatal Reflex tool has not been widely used in clinical breastfeeding assessment (Marín-Gabriel et al., 2015), but these innate reflexes (eg, hand to mouth, finger flexion and extension, gazing, head turning, bobbing, sucking and swallowing) relate to behaviors necessary to locate the maternal breast, latch, and suckle unassisted. The study by Bell et al (2013) recorded “pre-feeding” behaviors, which are a subset of reflexes more associated with feeding (hand to mouth, rooting, sucking on hand). Brimdyr et

al (2015) video-recorded the first hour of skin-to-skin contact following birth and reported the Widström stages, which lead to unassisted suckling at the breast by the infant when placed skin-to-skin with the mother during this period. Conversely, the Infant Breastfeeding Assessment Tool is a validated measure that assesses an infant's breastfeeding mechanics (Dewey et al., 2003). This measure evaluates four behaviors: readiness, rooting, latching, and sucking on a 12-point scale, these measures were used for infants beyond the immediate birth period. While it may imply neurobehavioral organization, it is also influenced by positioning and maternal efforts to assist her infant, as the infants are not assessed for unassisted latching as during Widström stages.

Overall the body of literature reports breastfeeding outcomes from birth through several months postpartum including mothers' and infants' experiences. Notably, only three studies(Dewey et al., 2003; Matias et al., 2009; Olza-Fernández et al., 2012) measured both maternal and infant factors. While the results do demonstrate various statistical associations, generalizability of these findings may be affected by the aim of the study or limitations of study setting, sample and control of confounding variables.

Setting

The majority of studies originated in Western Europe and Australia (n= 15) and United States and Canada (n=8). A minority of studies were in the developing world (n=4). Three of these utilized large international datasets from the WHO Global Survey (Guerra et al., 2009; 2011; Vogel et al., 2013). Two of which, conducted by Guerra et al (2009, 2011), addressed two different questions within Latin America (induction of labor and elective induction of labor).

Five studies described "Baby-Friendly" or early skin-to-skin practices following birth (Brimdyr et al., 2015; Dozier et al., 2012; Jonas et al., 2009; Marín-Gabriel et al., 2015; Olza-

Fernández et al., 2012). In the report by Bell et al (2013) babies went to a warmer after birth, per hospital routine. This study utilized an open crib for observation of pre-feeding behavior at 40 minutes of life, in contrast to the other three early infant behavior studies that reported observations while baby remained in physical contact with the mother. Despite these differences, the infant behavior studies did report similar diminished feeding-related behavior associated with oxytocin use.

Setting of the studies is important as likelihood of use of exogenous oxytocin during birth and the promotion of early breastfeeding best practices would affect outcomes related to this study question. Studies observing low rates of induction or augmentation of labor (Guerra et al., 2009; 2011; Kong & Bajorek, 2008; Matias et al., 2009; Rajan, 1994; Vogel et al., 2013), using lower volumes of oxytocin for induction of labor (ie, 5IU/500mL) (Mauri et al., 2015), or those that do not report the percentage of the sample exposed (Chapman & Perez-Escamilla, 1999; Radzyminski, 2003) would be more difficult to compare to populations with higher rates. Newborns that had no or interrupted skin-to-skin time following birth may also have a different breastfeeding course than others. Standardizing these study elements would be important for interpreting the findings.

Sample

Parity. Many studies in this review did not control for parity and two did not report parity (García-Fortea et al., 2014; Rajan, 1994). Parity predicted not only breastfeeding differences (Chapman & Perez-Escamilla, 1999; Dewey et al., 2003; Mauri et al., 2015; Wiklund et al., 2007), but also risk of oxytocin exposure (Marín-Gabriel et al., 2015). Dewey et al (2003) noted use of oxytocin was greater for primiparous women than multiparous (38% versus 23%) though the variable was not included in the regression model of delayed lactogenesis with interactions of

parity. Interestingly, of the studies that found no association between exogenous oxytocin and suboptimal breastfeeding, all used a sample of women of mixed parity. However, two studies reported a significant effect of oxytocin on decreased expression Primitive Neonatal Reflexes (Marín-Gabriel et al., 2015) and breastfeeding initiation (Jordan et al., 2009) even after controlling for parity.

Intention to Breastfeed. Three studies linking oxytocin administration to poor breastfeeding outcomes did not report intentions to breastfeed among their samples, only initiation and duration (A. Brown & Jordan, 2014; García-Fortea et al., 2014; Gu et al., 2016). This factor introduces study bias, as women with strong intentions to breastfeed may persist if difficulties arise. Of the four studies which reported risks for delayed lactogenesis, only two recorded maternal intentions to breastfeed, which were inclusion criteria (Dewey et al., 2003; Nommsen-Rivers et al., 2010). A minority of studies examining interventions during birth on breastfeeding reported maternal intention to breastfeed(Kong & Bajorek, 2008; Mauri et al., 2015; Ounsted et al., 1978; Out et al., 1988; Yudkin et al., 1979) or breastfeeding confidence (Dozier et al., 2012), as such, the risk of bias in the findings for breastfeeding attrition should be considered with this limitation in mind.

Obstetric Risk Level. Twelve studies focused on a lower risk sample (vaginal birth, healthy newborns) versus higher risk (cesarean birth, preterm birth, neonatal intensive care unit (NICU) admission). Seven of the 12 low-risk studies' samples examined the role of synthetic oxytocin on breastfeeding as a primary aim, highlighting the outcomes of healthy, lower risk mothers, and babies born vaginally in relation to oxytocin exposure specifically. For example, the four infant behavioral studies examining feeding reflexes included healthy neonates (normal Apgar score and no NICU admission) born vaginally; all studies controlled for epidural use,

which was not significantly related to the neonatal behaviors except for the study by Brimdyr et al (2015). While using a lower risk sample reduces the risk of confounding variables contributing to the breastfeeding outcomes, it limits generalizability to more complex obstetric cases and surgical birth. However, differences noted among lower risk women in breastfeeding strengthen the possible association of exogenous oxytocin and suboptimal breastfeeding.

In contrast, the studies examining delayed lactogenesis, those using the Infant Breastfeeding Assessment Tool and outcomes of obstetric interventions included varied levels of obstetric risks for breastfeeding problems. The effect of this single intervention of oxytocin is therefore difficult to discern from the rest. Only three studies in these categories focused on low-risk vaginal birth (Dozier et al., 2012; Mauri et al., 2015; Wiklund et al., 2007). Several other studies in these groups reported low rates of oxytocin use (Dewey et al., 2003; Kong & Bajorek, 2008; Matias et al., 2009) or did not report the proportion of sample exposed (Chapman & Perez-Escamilla, 1999), which limit the interpretation of the findings.

Indications for Synthetic Oxytocin Use. Despite studies in this review stating that healthy or lower risk women participated, authors did not routinely report the indications for the use of oxytocin. Various labor-related factors may drive the use of oxytocin, such as use of epidural anesthesia or length of labor. Eight studies examined labor duration in relation to breastfeeding outcomes. Four of the eight associated longer labor with less optimal breastfeeding (Dewey et al., 2003; Nommsen-Rivers et al., 2010; Radzyminski, 2003; Wiklund et al., 2007). Notably, three of these studies grouped primiparous and multiparous women together for this analysis, and multiparous women are more likely to have shorter labors as well as less difficulty breastfeeding.

Epidural analgesia and oxytocin use are often correlated (Osterman & Martin, 2011). This finding may be due to the potential for epidural analgesia to lower endogenous oxytocin

levels in maternal circulation which may slow second stage labor (Anim-Somuah et al., 2011; Worstell, Ahsan, Cahill, & Caughey, 2014) or lead to other factors (eg fetal malposition) that may contribute to augmentation (Anim-Somuah et al., 2011; Rahm, Hallgren, Hogberg, Hurtig, & Odlind, 2002). Oxytocin-induced or augmented labor may be perceived as more painful, thereby women opt for neuroaxial analgesia (Glantz, 2005; Henderson & Redshaw, 2013). However, some research has not considered the specific role of oxytocin when studying the effect of epidural analgesia on lactation (Lind, Perrine, & Li, 2014).

Exogenous oxytocin may be useful in reducing risks associated with prolonged labor. Breastfeeding problems may also be associated with longer labors, but researchers should try to tease apart the role of oxytocin from labor duration. For example, Nommsen-Rivers et al (2010) reported an association between length of labor and prevalence of delayed lactation, women with spontaneous labors less than 14 hours long had significantly less delayed lactogenesis, 35.7% compared to 57% of women with labors over 14 hours. In contrast, women with oxytocin who labored less than 14 hours had 47.1% delayed lactogenesis compared to 40.1% of those who labored greater than 14 hours. However, the authors did not report the dose of oxytocin nor proportion of labor exposed to oxytocin, which limits the analysis. Finally, Matias et al (2009), looking only at primiparas did not find a relationship between long labor and delayed lactation. Second stage labor was also examined by six studies (Chapman & Perez-Escamilla, 1999; Dewey et al., 2003; Kong & Bajorek, 2008; Nommsen-Rivers et al., 2010; Rajan, 1994; Wiklund et al., 2007). Three reported less delayed lactation in women who pushed for less than 60 minutes compared to longer second stage (Chapman & Perez-Escamilla, 1999; Dewey et al., 2003; Kong & Bajorek, 2008), however, they included multiparous women in their analysis. Data by Rajan (1994) contrasted with other study findings; administration of oxytocin was

associated with higher bottle-feeding at six-weeks post-birth, but only when second stage was less than one hour compared with greater than one hour when receiving oxytocin.

The primiparas in the Jonas study that evaluated levels of endogenous oxytocin and prolactin (Jonas et al., 2009) had augmentation of labor due to slow or stalled labor. Therefore, the differences seen in blood levels of oxytocin may be attributable to other physiologic differences in the women who required oxytocin administration. However, in this small sample, third stage administration was prophylactic, and changes in prolactin following oxytocin administration in this group could be more directly linked to the drug itself. It is unknown if women requiring induction or augmentation of labor are innately different physiologically which may also impact breastfeeding.

Discussion

The purpose of this review was to conduct a thorough exploratory search for research on synthetic oxytocin and breastfeeding outcomes. No two studies were similar enough to provide results at the level of meta-analysis. Given the variations in study design, we cannot conclude that oxytocin use during the birth process contributes to altered breastfeeding outcomes. However, because many of the studies did show associations between exogenous oxytocin and less optimal breastfeeding outcomes, especially in lower-risk samples, this question deserves more research before ruling out the possibility of an effect.

Exposure to Synthetic Oxytocin

Augmentation of labor tends to occur when labor is already prolonged. Oftentimes synthetic oxytocin can be infused for many hours or days during a lengthy induction process. The availability of the oxytocin receptor in uterine tissue may be a function of duration and/or the level of oxytocin in circulation (Balki et al., 2013; Phaneuf et al., 2000). Whether oxytocin

receptors located in breast tissue respond similarly as those in uterine tissue has not been researched directly. However, use of oxytocin in this review was often reported as a binary outcome rather than a continuous outcome of dosage or duration. Study participants with minimal augmentation would have been grouped together with those having significantly longer exposure. Furthermore, study designs that do not adequately sample women exposed to oxytocin have more limited generalizability or power to detect a difference between groups. Consideration of the duration and dosage of oxytocin rather than a binary outcome may be more relevant to this line of research.

Measurement of Breastfeeding

As illustrated by this review, the measure of breastfeeding varies greatly. The only outcome reported with consistency was the maternal report of timing of lactogenesis. This measure has been linked to the increased likelihood of continued breastfeeding (Brownell, Howard, Lawrence, & Dozier, 2012). Maternal report of breast fullness is considered reliable and valid (Chapman & Perez-Escamilla, 2000). However, significant variation in the initiation and duration outcomes were a function of the design, feasibility of the studies, as well as the origin of the data (ie, medical records). The binary nature of the breastfeeding variable in many of the studies also cannot consider the women who are partially breastfeeding and supplementing formula or donor milk. Several studies measured breastfeeding duration via maternal report, one occurring five years after birth, leaving room for recall bias (García-Fortea et al., 2014). While some research has noted that early exclusive breastfeeding may predict longer term outcomes (Chantry et al., 2014), many of these studies did not include any longitudinal data.

Infant behavioral studies in this review, particularly those examining the primitive and feeding reflex behaviors of healthy newborns, did share similarities in design and findings. As explained

by the authors, the underpinnings of these designs rest on the potential for oxytocin to cross the placenta, and act within the brain of the newborn either indirectly through feedback mechanisms (afferent vagus nerve) or directly by possibly crossing the blood-brain barrier itself or as an effect of increased lactate levels (Brimdyr et al., 2015), all of which are hypothesized to alter the behaviors based on animal research models

(Bales et al., 2007; Hashemi et al., 2013)

Limitations

This review has clear limitations due to high variability within the reviewed studies' designs. It is also not exhaustive; many elements of statistical analysis and synthesis of other outcomes (eg, role of cesarean birth or postpartum hemorrhage) were outside the scope.

Research Implications

Broadly, this review highlights the paucity of literature on this topic, despite the known physiology of oxytocin and lactation, frequent use of the hormone in childbirth, and growing emphasis on improving breastfeeding. Addressing this gap is possible through two main lines of common maternal-infant research. First, many studies published on lactation outcomes do not address the role of oxytocin use during labor and birth or control for its use (Bai, Wu, & Tarrant, 2013; Lind et al., 2014). Secondly, studies of labor induction or AMTSL are commonly done to compare intervention protocols, yet they rarely report lactation outcomes. These studies often utilize larger sample sizes, more rigorous randomized designs and can control for more factors like parity or duration of labor, which would be helpful in addressing this question.

Several specific recommendations stem from this review. First, future lactation research regarding oxytocin should consider neonatal behaviors as well as maternal function. Differences in newborn behavior may manifest as maternal report of decreased milk supply or duration of

exclusive breastfeeding. Second, setting and selection bias should be considered including breastfeeding intentions of the participants and birth practices. Third, measurement of oxytocin used in labor should be more comprehensive, including indicated or elective administration, combined intrapartum and postpartum dosages, and those following cesarean birth. Fourth, better reporting on epidural use and timing of oxytocin administration, including the order and duration of events, would help address the temporal role of the two often concurrent interventions on subsequent outcomes. Finally, cumulative pharmacokinetic effects should be considered (dosage and duration). As research on oxytocin outside of childbirth have shown a dosage-response in terms of behavioral and biological effects,(Bales et al., 2007; S. M. Freeman et al., 2016) dosage-related (rather than binary) data would be more informative when characterizing exposure to oxytocin.

Clinical Implications

Use of synthetic oxytocin has an important place in modern midwifery and obstetric care as its use can reduce morbidity or mortality in the setting of prenatal complications, dystocia or during postpartum hemorrhage. We have reviewed and organized this body of literature to inform clinicians about existing research. We recommend counseling clients that there is no proven effect of this medication on lactation or breastfeeding outcomes but that research is incomplete. While the existing research does not provide a clear answer of the effects of oxytocin, care providers may want to be observant for breastfeeding challenges among women and newborns who received oxytocin. Including oxytocin exposure as part of a risk-assessment for suboptimal breastfeeding may allow for early intervention.

Conclusion

This paper is the first known review of literature reporting synthetic oxytocin administered during childbirth on breastfeeding outcomes. We used a comprehensive and integrative approach including data from studies examining other research questions. This strength, combined with inclusion of multiple breastfeeding outcomes (maternal and infant), adds needed complexity to the discussion of routine birth interventions and our knowledge about any lasting consequences.

Since oxytocin was first used clinically, in the early 1900s (Holmes, 1954), research has inadequately addressed the possibility of an impact on the human breastfeeding relationship. As lactation is an oxytocin-dependent process, the role of oxytocin administered during birth is worth considering when examining suboptimal breastfeeding outcomes. Mothers' perceptions of inadequate milk supply are a leading cause of supplementation or discontinuation of breastfeeding. These perceptions deserve validation by clinicians and researchers by examining the issue through a holistic lens that includes physiologic foundations to this problem.

Table 4.1: Search strategy for oxytocin use during birth and breastfeeding

Database	Search Terms (MeSH and keyword)	Results	Unique Studies Included
PUBMED	Oxytocin, labor (induced), labor (obstetric), labor stage (third), epidural analgesia AND Breastfeeding, Feeding behavior, lactation, Lactation Disorder	598	14
	Lactogenesis (keyword)	131	3
	Labor (induced) AND oxytocin	1118	4
CINAHL	Oxytocin, labor (induced), obstetric care, labor stage (third), epidural analgesia AND Breastfeeding, Infant behavior, lactation, Lactation Disorder	89	1
	Lactogenesis	54	1
	Labor (induced) AND oxytocin	125	0
Cochrane	Induced labor AND breastfeeding	13	0
	Active Management (third stage) labor	1	1
SCOPUS			1
Hand check of reference lists			1
			26

Table 4.2: Studies reporting an association between synthetic oxytocin use and a breastfeeding outcome

Author Location	Design	Measures	Results	Limitations
Gu et al 2015 Canada	**Oxytocin Time Point** Intrapartum and postpartum **Design** Prospective Longitudinal Baby-Friendly setting[1] Mixed parity sample	Self-report: Exclusivity of breastfeeding at 2 months Plasma oxytocin levels at 2 months	n=386 92% of women received oxytocin. **Duration** Exclusively breastfeeding mothers at 2 months postpartum had received significantly less oxytocin during labor (33 units) when compared to formula (44 units) or mixed feeding mothers (43 units) (after controlling for education level) (P<.0001) **Physiology of Lactation** Circulating oxytocin at 2 months postpartum was positively correlated to dosage given during birth. (Pearson, 0.16, P<.01)	Did not specify the rates of analgesia, mode of birth, indication for oxytocin use or neonatal problems Breastfeeding intention not reported Did not control for parity or other neonatal or obstetric issues in breastfeeding outcomes
Brimdyr et al 2015 United States	**Oxytocin Time Point** Intrapartum **Design** Prospective Comparative Baby-Friendly setting Mixed parity sample	Widström's 9 instinctive stages of neonatal behavior	n=63 84% of women having oxytocin with or without epidural **Infant Behavior** Infants born after exposure to oxytocin were less likely to suck in the first hour after birth. (P = .026). Dose dependent response. Groups examined with use of epidural, which also exhibited a main effect by dosage and was frequently interrelated with oxytocin use.	Breastfeeding intention not reported Duration of oxytocin exposure not analyzed in relation to infant behavior Duration of labor overall not controlled

[1] Baby-Friendly Initiative certification noted in study for research site

Author Location	Design	Measures	Results	Limitations
Marín-Gabriel et al 2015 Spain	**Oxytocin Time Point** Intrapartum **Design** Prospective Cohort Baby-Friendly Setting Mixed parity sample Breastfeeding intentions reported (inclusion criteria)	Primitive neonatal reflexes related to feeding on day 1-2 postnatal.	n=98 53 women received oxytocin, 45 women did not **Infant Behavior** Fewer reflexes noted in newborns exposed to oxytocin infusion compared to non-exposed, (β, -12.7; 95% CI, -25, -0.5). Adjusted for parity, labor difficulty, epidural use.	Nulliparas and epidurals were more common in the oxytocin group, though this was controlled in the analysis. Dose of oxytocin not reported
Mauri et al 2015 Italy	**Oxytocin Time Point** intrapartum **Design** Prospective Longitudinal Descriptive Mixed Parity sample	Self-report: timing and intensity of lactogenesis related breast symptoms	n=366 62.8% of women received oxytocin. **Physiology of Lactation** No association between oxytocin infusion alone and onset of lactation symptoms (HR, 1.06; 95% CI, 0.77, 1.45). Epidural related to oxytocin infusion (P<.001) and suboptimal breastfeeding at 20 days (P = .02).	Baby-Friendly not reported Skin-to-Skin not reported[2] Rooming-in not protocol Breastfeeding intention not reported Intrapartum oxytocin protocol lower than other studies: 5 units/500mL Oxytocin dose not recorded/reported
Brown & Jordan 2014 United Kingdom	**Oxytocin Time Point** Postpartum **Design** Retrospective Descriptive Mixed parity	Self-report: feeding method at birth, duration of breastfeeding.	n=288 84.1% of sample reported postpartum oxytocin administration **Initiation** No differences between active and physiologic third stage on breastfeeding after birth (OR .57; 95% CI, .23-1.42). **Duration** AMTSL associated with reduced levels of breastfeeding at 2 weeks (OR .35; 95% CI, 0.18-0.71) and 6 weeks (OR .38; 95% CI,0.19-0.78), but not at birth.	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention not reported Self-report of labor procedures subject to recall bias Could not control for all intrapartum synthetic oxytocin use.

[2] Skin-to-skin: specific practice of putting newborn on maternal abdomen/chest following birth

Author Location	Design	Measures	Results	Limitations
			90.2% of the formula feeding group at 2 weeks received AMTSL compared to 76.3% of the breastfeeding group. Relationship held when women with epidural and over 41 weeks were removed from analysis (to control for possible intrapartum exposure).	
García-Fortea et al 2014 Spain	**Oxytocin Time Point** Intrapartum **Design** Retrospective Descriptive Cohort (randomly selected) Parity not reported	Self-report breastfeeding status and duration of breastfeeding	n=316 59.8% women received oxytocin. **Initiation** synthetic oxytocin was associated with fewer reports of breastfeeding (63.5% of exposed group vs. 92.1% non-exposed). (RR, 1.45; 95% CI, 1.288-1.635). **Duration** For duration (n=237) Use of synthetic oxytocin (120/237) associated with average of 33 fewer days of breastfeeding.	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention not reported Parity not reported Medical record used for clinical variables. - Self-report (five years prior): breastfeeding status (study does not report which time point this report represents) and duration of breastfeeding (reported in days) Duration not specified as exclusive or partial breastfeeding Large proportion of sample was twin delivery (30.7%)
Bell, White-Traut, & Rankin 2013 United States	**Oxytocin Time Point** Intrapartum **Design** Prospective Descriptive Mixed Parity	Pre-feeding behaviors Neonatal Behavioral Assessment Scale 45m after birth	n=47 76.5% of women received oxytocin **Infant Behavior** Newborn behaviors in the exposed group were more likely to show low levels of feeding behavior compared to unexposed who had more high level prefeeding behavior (OR,11.5; 95% CI,1.8-73.3)	Infants went to a warmer following birth per hospital routine, skin-to-skin not routine Breastfeeding intention not reported

Author Location	Design	Measures	Results	Limitations
			Adjusted for labor length and epidural use	
Vogel, Souza, & Gülmezoglu 2013 16 Africa/Asian Countries	**Oxytocin Time Point** Intrapartum **Design** Retrospective Descriptive	World Health Organization Global Survey Initiation of BF <24 h – 7 days	n=192,538 11,700 (6%) induction with oxytocin **Initiation** Increased odds of not breastfeeding in first 24 hours in Asian sample (OR, 2.17; 95% CI,1.27-3.73. Also associated with increased risk of low Apgar, birth weight and ICU admission.	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention not reported Oxytocin effect not examined with controls for obstetric complications (per aim of study)
Olza Fernández et al 2012 Spain	**Oxytocin Time Point** Intrapartum **Design** Prospective Longitudinal Descriptive Mixed parity Skin to skin noted (not Baby-Friendly)**:**	Duration exclusivity at 3 months Primitive Neonatal Reflexes on 2nd day of life	n=20 100% received oxytocin for induction or augmentation. 100% had epidural. 30% forceps rate. **Infant Behavior** Negative association between rate of newborn sucking reflex after birth and dosage of oxytocin administered (*P*=.03). **Duration** Women exclusively breastfeeding at 3 months were exposed to significantly less oxytocin during birth (*P*=.04).	Breastfeeding intention not reported Small sample, pilot study All women had epidural, effect of epidural could not be controlled statistically
Dozier et al 2012 United States	**Oxytocin Time Point** Intrapartum and Postpartum **Design** Prospective Cohort Baby-Friendly in part of sample (controlled for in analysis) Breastfeeding goals and confidence reported	Secondary analysis of self-report and medical record data: duration at 2 months postpartum	n=727 50% of women received intravenous oxytocin 14.8% had intramuscular oxytocin. **Duration** Combination of epidural and intrapartum oxytocin had increased early cessation (HR, 1.34; 95% CI,1.00-1.79). Absence of epidural and oxytocin were most protective of ongoing breastfeeding. Women giving birth in a baby friendly hospital who had oxytocin IV were less	Postpartum dose not included in oxytocin exposure for analyses Indication for oxytocin use was not specified

Author Location	Design	Measures	Results	Limitations
			likely to have early breastfeeding cessation (HR, .67; 95% CI,.53-.86). Women giving birth in non-baby friendly hospitals who had oxytocin IV were more likely to have early breastfeeding cessation (HR, 1.50; 95% CI,1.25-1.80).	
Guerra et al 2011 8 Latin American countries	**Oxytocin Time Point** Intrapartum **Design** Retrospective Descriptive (secondary analysis)	World Health Organization Global Survey: Initiation of breastfeeding <24 h – 7 days	n=37,597 Subset of elective induction of labor compared to low risk spontaneous labor 4.4% oxytocin exposure for elective IOL **Initiation** Increased risk of delayed initiation (compared to first hour after birth) of breastfeeding adjusting for parity, mode of birth etc. (RR,1.59; 95% CI,1.24-2.05).	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention not reported Oxytocin effect not examined with controls for obstetric complications (per aim of study)
Nommsen-Rivers et al 2010 United States	**Oxytocin Time Point** Intrapartum **Design** Prospective Longitudinal Descriptive Primiparous Breastfeeding intention: inclusion criteria	Onset of lactogenesis-maternal report.	n= 431 56.6% of women received oxytocin for induction or augmentation Overall delayed lactogenesis rate 44.3% **Physiology of Lactation** Delayed lactogenesis not associated with oxytocin exposure Shorter labor predicted less delayed lactogenesis but only for non-oxytocin group.	Baby-Friendly not reported Duration of labor reported but not duration of oxytocin exposure, only if it was part of the labor Indications for labor induction or augmentation not reported
Matias et al 2009 Peru	**Oxytocin Time Point** Intrapartum **Design** Prospective Longitudinal Descriptive Baby-Friendly Primiparous	Onset of lactogenesis-maternal report. Researcher observation of breastfeeding behavior with Infant	n=156 2.3% induction of labor rate 15% augmentation of labor with oxytocin rate **Physiology of Lactation** Of the augmented group 30.4% reported delayed onset of lactogenesis compared to	Breastfeeding intention not reported Breastfeeding outcomes of women with labor induction not reported in table. Low number of women with oxytocin exposure for labor

Author Location	Design	Measures	Results	Limitations
		Breastfeeding Assessment scale. Infant weight loss.	15% of the non-augmented group (p=.1). Not associated with excess weight loss or suboptimal breastfeeding behavior.	augmentation (n=25)
Guerra et al 2009 8 Latin American countries	**Oxytocin Time Point** Intrapartum **Design** Retrospective Descriptive	World Health Organization Global Survey: Initiation of BF <24 h – 7 days	n=97,095 87% of inductions used oxytocin (11,077 total inductions). **Initiation** Induction associated with delayed initiation of breastfeeding until after the first day (RR,1.31; 95% CI,1.22-1.43) adjusted for multiple risk factors.	*see Guerra (2011)
Jordan et al 2009 United Kingdom	**Oxytocin Time Point** Intrapartum and postpartum **Design** Prospective data collection, secondary analysis Mixed Parity	Medical record: Initiation of BF by 48 hours	n=48,366 79% of women received uterotonic medication (oxytocin and/or ergometrine) in the third stage of labor 10% were induced with oxytocin **Initiation** Third stage labor uterotonic associated with reduced breastfeeding at 48 hours postpartum in all women (*P*<.001) and primiparous subset (*P*<.001) for IM or IV oxytocin and ergometrine. This controlled for other medications in labor, social class, parity, age and deprivation rank.	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention not reported Classification of women breastfeeding at 48 hours included women partially breastfeeding and excluded women who were expressing milk. Outcome variable of breastfeeding at 48 hours unclear if referring to entire 48 hours or just the last feeding at that time (i.e. discharge feeding diagnosis).
Jonas et al 2009 Sweden	**Oxytocin Time Point** Intrapartum and postpartum **Design** Prospective Descriptive Comparative	Oxytocin and prolactin levels during breastfeeding on 2nd day postpartum	n=63 **Physiology of Lactation** Prolactin levels peaked earlier (10 minutes) (*P*=.012) and were higher in the oxytocin intrapartum groups (*P*=.006) for up to 60 minutes (*P*=.0012).	No clinical measures of breastfeeding outcomes were linked to the hormone data to correlate clinical significance.

Author Location	Design	Measures	Results	Limitations
	Skin-to-skin reported, number of feeds during first 2 days not different between groups Breastfeeding intention reported		Negative correlation between amount of oxytocin during labor and median level of oxytocin in blood on second postpartum day (r_s= -.495, *P*=.019).	
Kong & Bajorek 2008 Australia	**Oxytocin Time Point** Intrapartum **Design** Prospective Descriptive Breastfeeding intention was reported	Onset of Lactogenesis-maternal report	n=75 6.7% of the sample received oxytocin for induction of labor. Postpartum use not reported. **Physiology of Lactation** Average time to onset of lactogenesis was 77.0 (34.7) hours for induction of labor with oxytocin (n=5), compared to 68.1 (22.8) hours for spontaneous labor (n=28) (*P*=.66).	Baby-Friendly not reported Skin-to-Skin not reported Sample receiving oxytocin small, underpowered for this comparison
Wiklund et al 2007 Sweden	**Oxytocin Time Point** Intrapartum **Design** Comparative Retrospective: matched control Mixed parity (analysis did control for parity, length of labor in regression analyses)	Initiation after birth, formula supplementation	n=702 54% of the women received oxytocin during labor. **Initiation** oxytocin administration associated with delayed initiation >4 hours of breastfeeding (OR, 3.28; 95% CI, .1.57-6.84) and giving artificial milk supplement (OR, 2.15; 95% CI, 1.28-3.61).	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention not reported
Dewey et al 2003 United States	**Oxytocin Time Point** Intrapartum (postpartum?) **Design** Prospective Longitudinal Descriptive Breastfeeding intention: inclusion criteria	Self-report onset lactogenesis Infant behavioral observation Infant Breastfeeding Assessment Tool	n=280 31% of the women received oxytocin for labor augmentation. No data on induction of labor **Physiology of Lactation** 32% of augmented group had delayed onset lactogenesis compared to 18% of non-augmented group (*P*<.05).	Baby-Friendly not reported Skin-to-Skin not reported Duration/dosage of oxytocin augmentation not reported. Comparison of lactogenesis outcomes from augmentation include women who had scheduled cesarean births (n =11)

Author Location	Design	Measures	Results	Limitations
			64% of the sample received "postpartum hemorrhage medications" which may have included oxytocin and 26% of this group had delayed onset of lactogenesis compared to 16% (*P*<.1). Multiple regression analysis was not significant for oxytocin **Infant Behavior** No differences in suboptimal infant breastfeeding behavior scores or weight loss of infant	which may affect the results
Radzyminski 2003 United States	**Oxytocin Time Point** Intrapartum **Design** Prospective Comparative Multiparous only	Preterm Infant Breastfeeding Behavior, Neurologic and Adaptive Capacity Score.	n=56 dyads Unknown percentage of sample receiving oxytocin **Infant Behavior** 6 infants scored below the mean for breastfeeding behavior, these had a higher incidence of labor induction	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention: not reported Data outcomes on breastfeeding behavior incomplete: percent not reported, no descriptive statistics.
Chapman & Perez-Escamilla 1999 United States	**Oxytocin Time Point** Intrapartum **Design** Longitudinal Prospective Descriptive Mixed parity	Self-report onset lactogenesis	n= 192 **Physiology of Lactation** Induction with oxytocin was not associated with delayed onset of lactogenesis in Chi square test	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention: not reported Number of women induced with oxytocin not reported—cannot make comparison to those not exposed.
Rajan 1994 United Kingdom	**Oxytocin Time Point** Intrapartum **Design** Descriptive Retrospective, secondary analysis	Self-report breastfeeding at 6 weeks	n=1064 18% of the sample reported oxytocin for induction of labor **Duration** Chi-Square analysis showed relationship	Baby-Friendly not reported Skin-to-Skin not reported Breastfeeding intention: not reported Statistical analysis not

Author Location	Design	Measures	Results	Limitations
			between oxytocin use and shorter duration of second stage (<1hr) was associated with reduced exclusive breastfeeding compared to women who had a longer second stage or were not receiving oxytocin. (*P*=.04)	robust. No regression analysis. Multiple Chi square tests cannot control for confounding variables.
Out, Vierhout, & Wallenburg 1988 Netherlands	**Oxytocin Time Point** Intrapartum **Design** Prospective Quasi-experimental with control group Mixed Parity Intention to breastfeed recorded at 36 weeks of pregnancy	Nursing staff report "any serious attempt" and self-report 3-4 days postpartum and at 6 months.	n=185 26% of the sample received oxytocin for induction and 16% for augmentation. **Initiation & Duration** More women decided not to breastfeed in the elective induction of labor group than the others. Rates of breastfeeding beyond initiation did not differ over the reported 1 and 2 month postpartum time points	Skin-to-Skin not reported Statistical analysis not robust. Did not control for confounding factors: duration of labor or parity.
Prendiville et al 1988 United Kingdom	**Oxytocin Time Point** Postpartum **Design** Randomized Trial	Medical records: Breastfeeding at discharge	n=1695 74% of sample received active management **Initiation** No difference between groups in breastfeeding at discharge (OR, .96; 95% CI, .77-1.19)	Skin-to-Skin: not specifically reported. Women in control group encouraged to put baby to breast in first 10 minutes after birth more than AMTSL group (225/849 vs. 63/846). Breastfeeding intention: not recorded Lack of fidelity to treatment group: only 403/849 in physiologic management had this performed compared to 840/846 in the treatment group. Breastfeeding outcome not examined by parity, oxytocin intrapartum

Author Location	Design	Measures	Results	Limitations
				exposure.
Yudkin et al 1979 United Kingdom	**Oxytocin Time Point** Intrapartum **Design** Retrospective Case Control Breastfeeding intention: recorded at first prenatal visit Mixed parity	Breastfeeding at discharge	n=400 185/200 induction group received oxytocin 18 of the spontaneous group had oxytocin augmentation **Initiation** Of the women intending to breastfeed during antenatal care 86% of the spontaneous group were breastfeeding at "discharge" compared to 82% of induction group.	Skin-to-Skin: not reported. Inconsistent outcome variable. Discharge outcome was "when records stop" which include some follow up postpartum care
Ounsted et al 1978 United Kingdom	**Oxytocin Time Point** Intrapartum **Design** Prospective Longitudinal Quasi-experimental with 3 induction methods and control group Primiparous only Breastfeeding intention recorded	Breastfeeding self-report at birth and 4 days later and at 2 months postpartum	n= 184 26% of women received oxytocin for induction of labor Intention to breastfeed ranged from 66-71% of each comparison group. **Initiation** Fewer mothers changed to bottle feeding in spontaneous labor group compared to all induction methods. **Duration** Oxytocin group alone were breastfeeding 37.1% at 2 months compared to 68% of the spontaneous group (NS $P<.1$)	Skin-to-skin: not recorded Statistical methods limited analysis of oxytocin group alone due to high number of cells in the Chi Square analysis. Did not control for multiple confounding variables like length of labor or neonatal issues.
Abbreviations: OR, odds ratio; HR, hazard ratio; RR, relative risk; AMTSL, active management of third stage labor; NS, non-significant.				

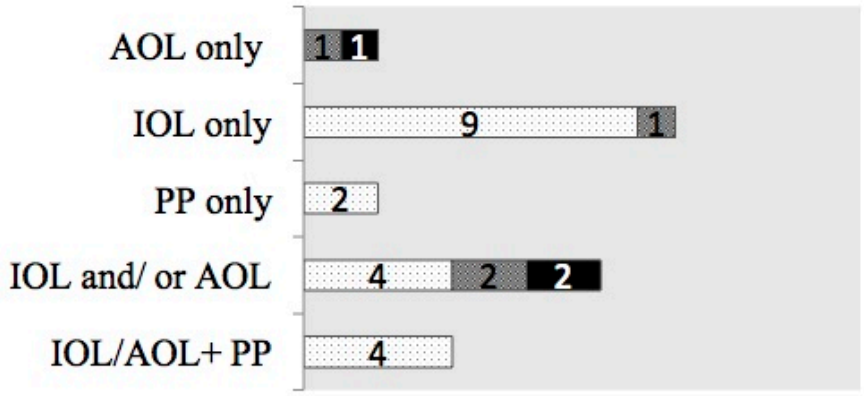

Figure 4.1: Number of studies by time point of oxytocin exposure and type of breastfeeding measures reported

Legend: AOL, Augmentation of Labor; IOL, Induction of Labor; PP, Postpartum Prophylaxis

Maternal measures of breastfeeding (Initiation or Duration of Breastfeeding, Physiology of Lactation)

Infant measures of breastfeeding (Infant Feeding Behavior)

Both maternal and infant measures

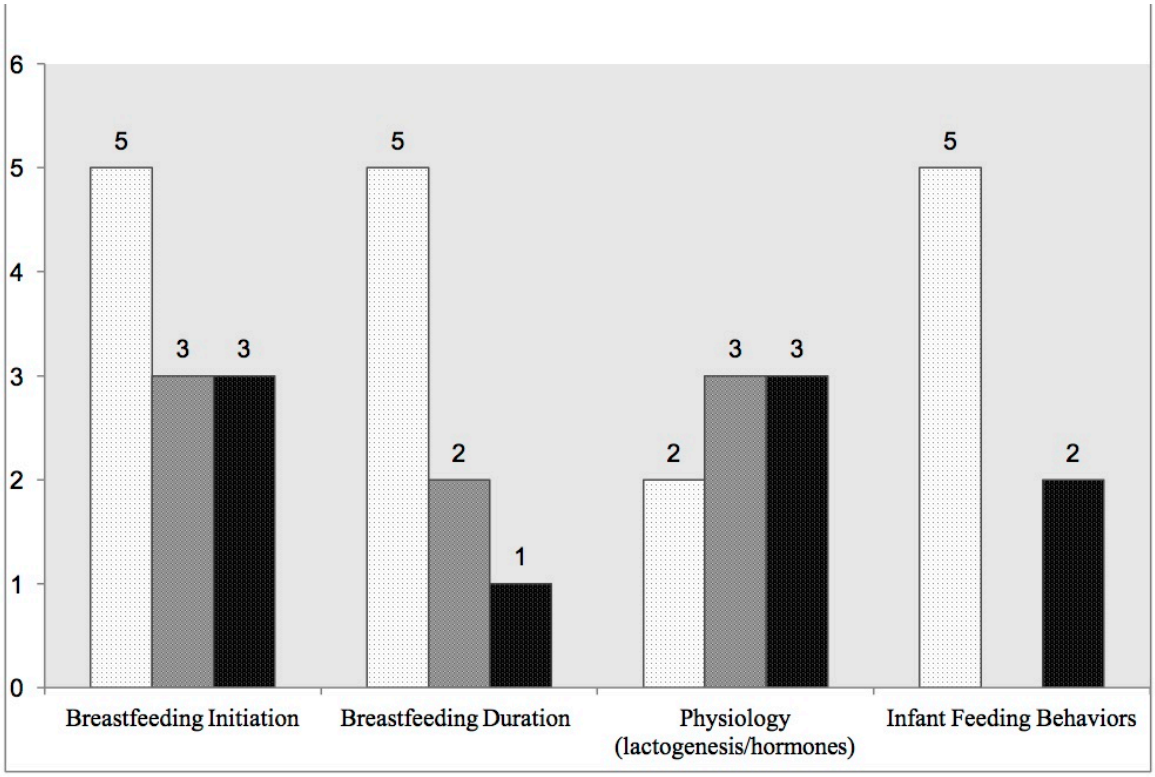

Figure 4.2: Number of measures by direction of findings reporting relationship between oxytocin use and breastfeeding outcomes

Legend:

Measures showing less optimal breastfeeding outcome with oxytocin use

Measures reporting mixed findings: less optimal outcome with oxytocin use in subgroup analysis

Measures reporting no association between oxytocin and breastfeeding

Chapter 5: Prolactin Response in Breast Feeding Women: Use of Synthetic Oxytocin During Childbirth and Newborn Weight Loss.

Authorship	**Elise N. Erickson** **TBD**
Journal	Breastfeeding Medicine
Journal Description	***Breastfeeding Medicine*** is a peer-reviewed interdisciplinary journal that will publish original scientific papers, reviews, and clinical case studies covering the epidemiology and physical basis for the benefits of breastfeeding, the pathophysiologic basis for the health consequences of artificial feeding, the impact of breastfeeding and lactation on physical and psychological health, indications and contraindications, and the effects of drugs on breastfeeding, as well as the broad range of social, cultural, and economic issues. Impact Factor: 1.438
Stage at dissertation defense	Planned for submission after defense in June 2018

- This manuscript represents a significant contribution to the Dissertation work.

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Introduction

Although women in the United States initiate breastfeeding at high rates (over 80%), but exclusive breastfeeding falls to 44% by three months postpartum (Centers for Disease Control and Prevention, 2016) which poses health risks to women and children. A commonly cited reason for supplementing breastmilk is the mother's report of inadequate milk production (Kent et al., 2016; Stuebe et al., 2014). While there are many known barriers to optimal breastfeeding, factors that influence the physiology of milk production are important considerations. Mammalian milk production relies on many elements, but oxytocin (OXT), a nonapeptide, produced in the hypothalamus and released into circulation via the posterior pituitary, is the primary hormone responsible for ejection of milk from breast gland lumen. Therefore, understanding variation in OXT function among women could be useful in identifying potential interventions or women at risk for suboptimal breastfeeding.

Additionally, OXT is an important trigger for prolactin (PRL) secretion from the anterior pituitary (Kennett & McKee, 2012). PRL, the primary lactagogue, is also necessary for milk production (Crowley, 2015). PRL, as reported in human studies, appears to follow a pattern of secretion in labor in that PRL falls during active and expulsive labor and rises after birth of the placenta and subsequent infant suckling (Rigg & Yen, 1977; Salamalekis, Pyrgiotis, Phoca, & Zourlas, 1991; Wladimiroff, Lo, & de Meijer, 1983). During human childbirth, the effect of peripheral synthetic OXT (synOXT) administration on subsequent neurohypophyseal hormone secretion has not been thoroughly examined. Some studies note that synOXT use during labor results in different patterns of PRL release during and after labor compared to those without synOXT, (Bremme & Eneroth, 1980; Haning et al., 1978; Jonas et al., 2009; Onur et al., 1989; Rae, Hollebone, Chetty, Clausen, & McFarlane, 2007), while other studies did not find a

difference in PRL with synOXT use (Haddad & Morris, 1983; Lao & Panesar, 1989). Whether PRL differences could lead to changes in lactation performance has not been examined. Many studies have linked synOXT administration to less optimal breastfeeding outcomes, but many they are limited by methodological issues and inadequate controls (Erickson & Emeis, 2017).

Until recently, it was not believed that peripheral synOXT could pass the blood-brain-barrier. Results from neuro-pharmacotherapuetic studies in primate models of high doses of peripherally administered synOXT have shown increased OXT levels in the cerebral-spinal fluid (CSF) after intravenous administration (S. M. Freeman et al., 2016). In another non-human primate study, researchers intravenously administered labeled (d5-deuterated) OXT and later identified the labeled peptide within the CSF, indicating passage in the CNS as opposed to feed-forward effect (M. R. Lee et al., 2017). When large doses of synOXT are administered intravenously, only small proportions appear to enter the CSF in non-human primates, but it appears to last for hours post administration, probably due to increased half-life in CSF (M. Lee, personal communication, April 19, 2018). Furthermore, work in other animal models suggest that peripheral administration of oxytocin agonists or antagonists can result in PRL change (Augustine et al., 2017; Briffaud, Williams, Courty, & Broberger, 2015; Kennett & McKee, 2012; Kennett, Poletini, Fitch, & Freeman, 2009).

In the United States, nearly 25% of labors are induced (J. Martin et al., 2017) and probably one third include augmentation of labor with synOXT (Declercq et al., 2014). In addition, prophylactic oxytocin in a bolus or injection is recommended for administration to women after birth to guard against postpartum hemorrhage (World Health Organization, 2014).

The purpose of this study is to examine maternal plasma OXT and PRL during the period of secretory activation (lactogenesis II) following low-risk spontaneous labor and birth in

healthy, nulliparous women and characterize its relationship to synOXT administered for third-stage labor hemorrhage prevention and to breastfeeding outcomes. The hypotheses for this biobehavioral pilot study were as follows:

1. Maternal plasma OT and PRL (change over baseline) by 5 days postpartum will be lower in women exposed to greater amounts of synOXT than those who did not receive the medication.
2. Breastfeeding outcomes will be less optimal in women with synOXT exposure including onset of secretory activation at more than 72 hours after birth, more neonatal weight loss, lower breastfeeding self-efficacy scores, or lower exclusive breastfeeding.

Methods

Inclusion/Exclusion

Institutional Review Board approval was granted for this protocol. Primiparous women aged 18-43 years who were intending to exclusively breastfeed who were also non-smoking and could read English were approached at a tertiary care center in the Northwestern United States following vaginal birth. Women were excluded if they had Cesarean or instrument assisted birth (forceps or vacuum), induced labor, pre-pregnancy body mass index greater than 40, suspected hypoplastic breast tissue, breast surgery involving areola, serious obstetric conditions (intrauterine growth restriction, severe hypertension, gestational diabetes requiring medical management) or personal history of uncontrolled or autoimmune thyroid disease or polycystic ovary syndrome. Women were also excluded if there was physical separation of neonate during the recovery period (e.g. NICU admission), greater than 1000 mL blood loss, blood transfusion or iron infusion therapy. Women who had augmented labor with oxytocin were included only if their exposure was less than or equal to 12 hours and no more than 20mU/minute maximum rate.

Procedure

A prospective, longitudinal, comparative design was used for this study. Power analysis was modeled after an published study of plasma OXT measured in maternal blood in the postpartum period in relationship to intrapartum use (Prevost et al., 2014). To detect a difference between OXT levels 200pg/ml (SD of 272.2) with significance level of .05 at 80% power, a sample size of 30 for each group was proposed (synOXT exposed/non-exposed).

Recruitment. In the first 24-48 hours following birth, women meeting study inclusion criteria were approached by study staff and informed consent obtained. Medical record information, birth experience information, and baseline psychometric surveys were administered including the Breastfeeding Self Efficacy Scale-Short Form (BSES-SF) (Dennis, 2003), Level of Breastfeeding Scale (Labbok & Krasovec, 1990), Edinburgh Postnatal Depression Scale (EPDS) and the Generalized Anxiety Disorder (GAD-7). Total oxytocin dose (intrapartum and postpartum) was calculated and recorded.

Each day after enrollment, until the follow-up visit, participants completed a journal including frequency of feeding at the breast and breast pumping, number of infant stools, level of breast fullness (timing of lactogenesis II measure) and infant. The journal also asked questions about breast symptoms, discomfort, measures to help breastfeeding (positions, devices, supplements) and infant behavior at the breast.

Follow-up Visit. On day 4-5 postpartum, women were asked to attend a research visit or an outpatient lactation support visit. Psychometric measures were administered for the second time. After getting settled comfortably, women breastfed during the visit when the baby showed feeding cues and venous blood samples were collected at Time 1 (within 1-2 minutes of latching the baby) and again at Time 2 (20 minutes later), at which time OT and PRL typically peak (Hill,

Chatterton, & Aldag, 1999). Infants were weighed prior to feeding and following each breast to estimate milk-transfer volume. Women were asked to feed their babies as desired and the duration of feeding recorded along with total infant weight change. The 12-point Infant Breast Feeding Behavior Tool was used to assess infant role in feeding. Blood was collected into a 6 mL EDTA tube at each draw, inverted several times and placed immediately into an ice bath. Samples were centrifuged following the 20-minute study period at 1,600 g for 15 min at 4 degrees Celsius. Immediately after the centrifugation, plasma supernatant was pipetted into two aliquot tubes per blood draw and stored in a -80° Celsius freezer. Women received a gift card as compensation for their time and effort.

Measures

Plasma PRL was assessed using an electrochemiluminescence immunoassay on a Roche cobas e411 automated clinical platform. The assay range is 1 – 10000 uIU/ml (0.0470-470 ng/mL). Plasma oxytocin was performed using enzyme immunoassay (EIA) methods (Carter et al., 2007; K. M. Kramer, Cushing, Carter, Wu, & Ottinger, 2004) from Arbor Assay (Ann Arbor, MI) and processed at the Kinsey Institute (Indiana University). Samples were not extracted, run in duplicate, with serial dilutions and with standardized controls for reliability and validity.

Breastfeeding Self Efficacy Scale-Short Form (BSES-SF): BFSE-SF is a reliable and valid 14-item measure to assess the confidence associated with many aspects of breastfeeding (Dennis, 2003). **Level of Breastfeeding:** Is a standardized scale to assess the amount of breastmilk/ breastfeeding being provided to an infant (Labbok & Krasovec, 1990). **Timing of Lactogenesis II:** Use of maternal report of breast fullness on a scale of 1-5 (1= no change, 5 = uncomfortably full) has been validated and considered reliable (Dewey et al., 2003). **Edinburgh Postnatal Depression Scale (EPDS):** Is a 10-item measure used to assess for postnatal

depression symptoms (J. L. Cox, Holden, & Sagovsky, 1987). Higher scores have also been linked to problems with breastfeeding (Dennis, 2003; Dennis & McQueen, 2009) and different patterns of oxytocin expression (E. Q. Cox et al., 2015; Gu et al., 2016) compared to asymptomatic women. **Generalized Anxiety Disorder (GAD-7):** A 7-item scale to specifically detect anxiety-related symptoms with high internal consistency (Spitzer, Kroenke, Williams, & Löwe, 2006). This scale, when tested with EPDS has been found to be more sensitive to anxiety than a high score on EPDS alone (W. Simpson, Glazer, Michalski, Steiner, & Frey, 2014).

Statistical Analysis

Exploratory and descriptive statistics were carried out using StataSE 15 (College Station, TX: StataCorp LLC). Between group comparisons using Fisher's Exact, Spearman rank correlation, Mann-Whitney tests and t-tests were conducted as appropriate. Statistical significance was determined using a $p < 0.10$ given the pilot nature of this study. Variables with statistically significant bivariate analysis were considered for multivariate regression on the plasma and lactation outcomes. Lastly, regression post estimation, model fit and effect size calculations were performed.

Results

From July 2016 to October 2017 inpatient postpartum records were screened for eligibility among newly delivered primiparous women who underwent spontaneous labor. We presented the study protocol to 77 women and 31 (40%) declined to participate. The most common reason for declining were feeling overwhelmed by the baby's needs or breastfeeding challenges (n=12). This recruitment difficulty, as well as limited numbers of women without synOXT exposure were barriers to achieving the target sample size of 60. Of the 46 women who enrolled in the study and completed baseline data, 35 attended the follow-up visit and plasma

measurement. Plasma samples were successfully obtained in 32 and 31 women at Time 1 and Time 2 respectively during the observed breastfeeding. Follow-up infant weight data was gathered from a combination of medical records, breastfeeding journal entries and in-person follow-up for a total of 38 of the 46 enrolled participants. After the enrollment period ended, 28.2% (n=13) of the sample had no postpartum synOXT exposure and 71.4% (n=33) had postpartum exposure. A total of 11 women had some intrapartum exposure for labor augmentation (23.9%), mean duration of exposure was 5.3 hours (SD 2.4 hours).

Table 5.1 presents the characteristics of the overall sample (n=46) as well as differences in the clinical and demographic variables of women who attended the follow-up visit by exposure to postpartum synOXT (n=35). Body mass index at delivery, total weight gain during pregnancy, use of intravenous fluids, and the primary care provider for birth differed between groups of postpartum synOXT exposure. The participants in the non-exposed synOXT group were all cared for by certified nurse-midwives. Baseline psychometric scores (EPDS, BFSE, GAD) did not differ between synOXT group (data not shown).

Hypothesis 1: Plasma PRL and OXT, Relationship to Postpartum SynOXT exposure

Prolactin. Women with postpartum synOXT exposure had lower PRL responses during breastfeeding (change in PRL over baseline) (Spearman Rho -0.40, p=0.03) (see Figure 5.1). PRL was highly positively correlated between the time points (Rho: 0.85, p=0.00001). Higher PRL was seen in women from a minority racial/ethnic background (Rho: 0.42, p=0.02). Age and PRL were inversely related (Rho -0.40, p=0.02). See Table 5.3 for plasma levels overall.

Oxytocin. Baseline and 20 min OXT levels did not significantly correlate with postpartum synOXT use, nor did OXT change during the feeding by group. In the whole sample, OXT at time 1 was inversely related to OXT response (-0.39, p=0.03). OXT was higher with

advancing maternal age (0.38, p=0.03) and inversely linked to BMI (-0.36, p= 0.04) and duration of active labor (-0.50, p=0.003). OXT at time 2 was higher if the baby was female (0.36 p=0.04). Trends toward higher OXT at time 1 were noted with longer third stage of labor, advancing gestational age but were non-significant with Spearman Rho.

Hypothesis 2: Early Breastfeeding Outcomes: Clinical, Demographic and Hormone Variables

Delayed Lactogenesis. Report of delayed lactogenesis onset (as reported in the breastfeeding journals) was not related to any of the examined clinical or demographic or plasma-level characteristics. During the follow up visit, volume of milk transfer was not different by postpartum synOXT exposure (see Table 5.2).

Neonatal weight loss. At 24 hours of life, babies whose mothers received postpartum synOXT had higher weight loss (-1.8% synOXT versus -3.01% without, p=0.07) but weight loss on follow-up day 4-5 did not differ. Babies born at an earlier gestational age had lost significantly more weight (Rho 0.43, p=0.003). Infants with the highest weight loss on day 4-5 received lower volumes of IV fluid (average 0.69 liters versus 1.4 liters t-test, p=0.04). Female newborns had higher weight loss on follow-up than males (average -6.05% vs. -3.81, t-test, p=0.03).

Breastfeeding self-efficacy scores. Postpartum synOXT exposure did not relate to BFSE scores across the study period (baseline, day 4/5), nor did it relate to change in score from baseline to follow-up. Higher maternal BMI at delivery predicted reduced breastfeeding self-efficacy across the study period (Rho = -0.39, p =0.01).

Exclusive breastfeeding. Rates of supplementation trended higher in women who had postpartum synOXT administered (n=5 vs. 1, p=0.14). Use of formula or donor milk supplements during the first 5 days of life also trended toward higher BMI (0.27, p=0.06).

Hormones and Breastfeeding Measures. Women a lower PRL response had infants that trended toward longer feeds during the study visit (Rho -0.35, p=0.05) and more breastmilk supplements during the 5 days after birth (Mann-Whitney z=1.89, p=0.05). Higher transfer of milk (40-100mL) over the study feeding was associated with lower baseline PRL levels (Rho= -0.35, p=0.04) and larger response in OXT (0.34, p=0.06). Women with the higher OXT quantile at time 1 had babies that had experienced less weight loss from birth at the follow-up visit (Spearman Rho= 0.38, p=0.03).

Multivariate Regression: Plasma Hormone Response and Infant Weight Loss.

Putting together demographic, clinical and plasma variables in multivariate regression was limited by the sample size to a few predictors in each analysis as to avoid oversaturation. We examined the role of postpartum synOXT on prolactin response (above median vs. below median) and if higher prolactin response predicts infant weight change, while controlling for significant covariates (see Table 5.4).

Prolactin Response. Postpartum synOXT was significantly associated with reduced odds of having PRL levels rise over the feeding period (OR 0.06, 95% CI, 0.005, 0.82). This remained after adjusting for intrapartum synOXT administration, baseline OXT levels and duration of observed feeding. Baseline PRL, age, race or BMI did not change the significance of postpartum synOXT on the outcome nor were they independently associated with PRL response.

Newborn Weight Change (Table 5.4b): We examined how PRL change may influence overall percentage of birthweight change on follow up day 4-5 while controlling for gestational

age, intravenous fluids and infant sex. Maternal high PRL response was associated with 3.19% higher percentage of infant birthweight (see Figure 5.2), while controlling for IV fluid, gestational age, newborn sex and baseline OXT. Effect size for this model was 0.37 (ω^2) with postpartum synOXT having partial $\omega^2 = 0.22$ (>0.14 large effect).

Post Hoc Models. To explore the mechanism through which PRL change may have been influenced by postpartum synOXT, we examined its role on both baseline OXT and PRL levels in two additional models.

Oxytocin. In the unadjusted regression, postpartum synOXT did not have an effect (p=1) on baseline OXT, but after adjusting for use of intrapartum synOXT, maternal age and BMI, the odds ratio for above median OXT increased to 3.58 (95% CI 0.43, 29.38, p= 0.23). Interestingly, intrapartum synOXT was associated with *lowered* odds of high OXT expression (OR 0.14, 95% CI 0.02, 1.18, p=0.07). Increasing maternal BMI was statistically associated with a 30% lower odds of higher OXT (0.70, 95% CI, 0.51, 0.95).

Prolactin. Women with postpartum synOXT had trends toward increased adjusted odds of higher PRL at baseline (OR 3.1, 95% CI 0.43, 29.38, p = 0.23). Minority race remained an independent predictor of higher PRL (OR 20.0, 95% CI 1.39, 288.54). Maternal age and BMI did not affect this model.

Discussion

The purpose of this study was to examine the role of synOXT given during the process of childbirth during the third stage of labor on expression of OXT and PRL 4-5 days later and its association with breastfeeding outcomes. While acknowledging a small sample and unequal group size, this pilot data demonstrates some interesting relationships that prompts further research. Hypothesis 1 and 2 are partially supported by the data, in that synOXT use was

associated with changes in PRL response and low PRL response was associated with infant loss of weight from birth.

Animal research and limited human studies have shown increases in PRL in response to exogenous synOXT, our data suggest a similar pattern. The use of the larger bolus/ injected dose of postpartum synOXT (10-40 Units) demonstrated a relatively higher maternal OXT and higher baseline PRL on day 4-5 postpartum when controlling for important factors. Conversely, the women who had *intrapartum* synOXT administration were less likely to have high OXT in plasma at baseline. It is possible that innate individual or situational characteristics of women requiring synOXT for labor stimulation could explain this finding (fatigue, stress, pain). However, Jonas et al (2009) also found a negative correlation between quantity of synOXT administered during labor and lower secretion of OXT on postpartum day 2. An alternative explanation is that longer exposure over time results in negative feed-back mechanisms that could decrease endogenous productions, but given our sample was restricted to spontaneously laboring women with minimal exposure, a role for low endogenous production (or genetic involvement) seems more likely.

Women with postpartum synOXT exposure were less likely to see a rise in the PRL over the feeding. This could be related to higher baseline PRL and a negative feedback process, though this process is not fully understood within lactating mammals (Grattan, 2015) as the usual dopaminergic regulation of PRL is blunted during lactation. It is also possible 20 minutes was not long enough to see the peak in PRL in these women, or that the peak occurred in the middle of the feeding and was resolving by the time the second blood sample was obtained. Regardless, the lack of response in PRL in these women was associated with more infant weight loss and higher supplementation. Similarly, Stuebe et al (2015) examined PRL response in 28 women

with established exclusive breastfeeding, finding a greater number of daily feedings predicted a higher PRL baseline and lower PRL response over the feeding (Stuebe, Meltzer-Brody, Pearson, Pedersen, & Grewen, 2015). In our data, in the early breastfeeding period there was no difference in the number of breast stimulations in the preceding days between synOXT groups, or between women with high/low PRL response.

Our findings should prompt further study to further examine the hormone response relationships in lactating women. If these findings are confirmed, further study of PRL response during a feeding could serve as a potential marker of suboptimal early milk production, or in the long-term, develop interventions for improving PRL response. While weight loss in breastfed infants is expected, excess losses drive decision making around supplementation, which may be an indicator of inadequate milk and / or a predictor of earlier cessation of exclusive breastfeeding in the long term(Section on Breastfeeding, 2012). Prior studies of human milk production and PRL levels have noted that mean levels increase over the feeding, which is shown in aggregate in this data as well (Hill et al., 1999).

The findings of increased maternal body habitus associated with lower OXT levels is of interest. Women with higher BMI may require higher doses of OXT during labor (Carlson, Corwin, & Lowe, 2017b; Maeder et al., 2017), possibly indicating a less robust OXT signaling. Alternatively, plasma OXT may have been lower in women with higher BMI due to more difficulties with feeding (lower self-efficacy), more supplementation which could be associated with lower OXT production. We did not find a difference in PRL or PRL response by body mass, as reported by other studies (Rasmussen & Kjolhede, 2004).

Intravenous fluids delivered to the laboring woman have been reported by other reports as a potential driver of newborn weight loss (Deng & McLaren, 2018), especially in high fluid

volumes (Watson, Hodnett, Armson, Davies, & Watt Watson, 2012). The comparison of synOXT on infant weight (which is often associated with intravenous fluid administration) has not been reported by other studies to our knowledge. In our data, after controlling for synOXT exposure (both intra and postpartum), IV fluids given to the mother were still significantly associated with less weight loss at 24 hours as well as day 4-5. Notably, 36% of the sample had no IV fluids administered.

The finding of a role of race/ethnicity on higher PRL levels at baseline was not expected. Few studies have considered racial background in reporting PRL values, however, one study found PRL did not differ by race in premenopausal, non-pregnant women (Pinheiro, 2005). However, PRL has been globally considered to be a marker of the stress response, particularly in the peripartum period (Torner & Neumann, 2002), and this relationship could be further investigated, particularly in terms of lactation outcomes for women of color and how the physiology of stress influences breastfeeding (Chen, Nommsen-Rivers, Dewey, & Lönnerdal, 1998).

Strengths and Limitations. Participants in this study were healthy, primiparous and underwent uncomplicated spontaneous births without hemorrhage and 50% had no pain medication administered and no mother-infant separation, which helps minimize alternative explanations for the findings. Over 30% of the sample was non-white, which allowed for better assessment of differences between women of different racial/ethnic backgrounds. However, the findings of this study are limited by a small sample, and that women declined to enroll in the study who were perceiving difficulties early on. Our sample is underpowered for determining precise differences between women who received postpartum synOXT or had physiologic third stage, and thus any significant findings or associations should be interpreted with caution.

Another limitation is only using two time points for plasma sampling, as OXT and PRL vary in patterns of secretion, including a third or fourth time point would provide more detail about the response over time and allow for better discrimination between groups. Including a baseline feeding in comparison to a post-lactogenesis time point, would have been another useful comparison.

Conclusions

This pilot study presents data consistent with other published literature that indicates synOXT administration given to women during birth has a role in postpartum secretion of hormones. Relationships between body composition or race on baseline hormone secretion is another contribution of this work. Determining the exact magnitude of synOXT on outcomes, relative to the complexity of the perinatal period will require further study. More work is needed on basic endocrine physiology of human lactation to better understand the effect of birth related intervention and individual variation in lactation function.

Table 5.1: Sample Demographic and Birth Related Variables. Comparison by synthetic oxytocin given during birth.

Participants Recruited (N=46)		Follow up Sample by use PP synOXT (n=35)		
Demographic variables	**N = 46**	**No postpartum synOXT (n =11)**	**Postpartum synOXT (n=24)**	**p-value Man-Whitney Spearman Rank**
Age	30.9 (4.8)	30.9 (5.1)	31.5 (3.9)	0.69
Race/Ethnicity: White/Caucasian Non-white	32 (69) 14 (31)	8 (72) 3 (27)	20 (83) 4 (16)	0.38
Gestational age	39.9 (.84)	40.0 (1.0)	40.1 (0.8)	0.9
BMI end of pregnancy	28.5 (3.7)	27.2 (2.1)	30 (4.1)	0.03
Marital status: Married or partnered	(45) 98%	11	24	
Total weight gained in pregnancy	31.7 (10.1)	25.9 (9.9)	34.8 (10.3)	0.03
Attended birth class	34 (73%)	8 (80)	21 (87.5)	0.46
Attended breastfeeding class	32 (69%)	8 (80)	16 (66.6)	0.36
Labor and birth variables				
Care provider in labor CNM MD	 33 (71.7%) 13 (28.3%)	 11 (100)	 15 (62)	 0.01
Latent labor (mean hours, SD)	13.2 (11.5)	12.8 (12.9)	15.2 (12.7)	0.37
Active labor (mean hours, SD)	5.4 (4.1)	4.4 (2.3)	6.2 (4.7)	0.43
Second stage labor (mean hours, SD)	1.9 (1.4)	1.5 (.9)	2.2 (1.7)	0.36
Third stage labor (mean minutes, SD)	9.6 (5.4)	11.45 (5.1)	9.4 (5.8)	0.09
Blood loss (mean mL, SD)	332 (120)	327.7 (159)	316 (90)	0.9
Epidural	20 (44%)	3 (27)	13 (54)	0.13
Fentanyl	12 (26 %)	1 (9)	7 (29)	0.19
IV fluid dose intrapartum (liters, SD)	1.1 (1.5)	0.59 (.8)	1.54 (1.3)	0.03
Postpartum (PP) management Any PP synOXT - AMTSL - PP synOXT (instead of or in addition to AMTSL)	 33 (71.7%) 28 (62.2%) 8 (17.4%)	 0/11	 24 / 24 20 4	
Methergine	2 (4%)	0	0	
Intrapartum Pitocin	11 (23.9%)	1 (9.09)	8 (33.3)	
Duration Intrapartum Pitocin	320 (144)	124	344 (132.6)	
Dose intrapartum Pitocin (mU)	301 (812)	25.5	555.9 (1070)	
Newborn variables				
Apgar >7 at 5 min	46 (100)	100	100	
Male sex of newborn	26 (57%)	4 (36.4)	16 (66.6)	0.09
Birthweight of newborn (mean grams, SD)	3394.3 (386.9)	3253.9 (301.9)	3500 (399.5)	0.06
Immediate skin to skin	40 (87%)	11 (100)	19 (82.6)	0.19
LATCH Score prior to discharge	7.7 (1.1)	7.6 (1.2)	7.5 (1.1)	0.78

Table 5.2: Early breastfeeding outcomes. Comparisons by level of synthetic oxytocin given during birth

	Follow up sample (n=35)	**No postpartum synOXT (n =11)**	**Postpartum synOXT (n=24)**	**Fishers Exact & Mann-Whitney**	**p-value**
Early Breastfeeding & Growth					
Day 2 & 3 (# breast feeding/ pumping)	22 (5.6)	23.2 (4.0)	21.4 (6.2)	M-W	0.31
Breast fullness (hours, SD)	62.4 (18.4)	60.6 (19.7)	62.9 (18.1)	M-W	0.77
% birth weight at 24 hours	-2.3%	-3.01 (1.85)	-1.8 (1.91)	M-W	0.07
Supplement in first 5 days	6 (17%)	1 (9.1)	5 (20.8)	Fishers	.37
Weight Change by day 4-5 **(total n= 38)**				Fishers	
over 5% loss	16 (50%)	5 (45.5)	11 (45.8)		0.64
over 7% loss	10 (26%)	1 (9.1)	7 (29.2)		0.19
Average % newborn weight change day 4-5	-4.5(3.6)	-4.5 (2.4)	-4.5 (4.1)	M-W	0.85
Milk transfer (ave. mL)	44.3 (23.2)	46.9 (18.1)	43.2 (25.4)	M-W	0.44
0-40mL	21 (60%)	6 (54)	15 (62)		
40-100mL	14 (40%)	5 (45)	9 (37)	Fishers	0.46
Feed duration (min)	25.5 (7.9)	26.1 (9.3)	25.3 (7.5)	M-W	1.0

Table 5.3: Day4-5 plasma OXT PRL between women who received postpartum synOXT

Plasma Outcomes	Overall sample Median (range) n	No postpartum synOXT	Postpartum synOXT	Rho	P value
PRL time 1	306.5 (77-652)	295.5 (197-652)	312 (77-452)	-0.07	0.69
	< median	6	10		
	> median	4	12		
PRL time 2	344 (166-650)	356.5 (206-650)	310 (166-519)	-0.24	0.18
	< median	3	13		
	> median	7	8		
PRL response	2 (-28- 228)	15 (-2-142)	-0.5 (-28-228)	-0.39	**0.03**
	< median	2	14		
	> median	8	6		
OXT time 1	1634 (1381.2-1867.8)	1651.8 (1485.6-1849.8)	1634.4 (1381.2- 1867.8)	0.04	0.84
	< median	5	11		
	> median	5	11		
OXT time 2	1695.6 (1452.6-1956.6)	1726.2 (1466.4-1883.4)	1695.6 (1452.6-1956.6)	-0.02	0.90
	< median	5	11		
	> median	5	10		
OXT response	85.2 (-174.6-429)	41.1 (-79-321.6)	98.7 (-174.6-429)	0.23	0.22
	< median	6	9		
	> median	4	11		

PRL, Plasma Prolactin; OXT, plasma oxytocin

Table 5.4a: Oxytocin and prolactin levels by obstetric, demographic and hormone patterns

Outcome	n	Predictors	Unadjusted ß /OR	95% CI	p value	Adjusted ß /OR	95% CI	p value
Model 1:	30	Postpartum SynOXT	0.10	0.01, 0.66	0.02	0.05	0.003, 0.71	0.03
Prolactin Response		Intrapartum SynOXT	0.45	0.09, 2.32	0.34	0.28	0.02, 3.33	0.31
(high vs. low)		High OXT Time 1 (vs. low)	0.24	0.05, 1.12	0.06	0.06	0.005, 0.78	0.03
		Duration of feeding	0.91	0.83, 1.02	0.09	0.89	0.78, 1.01	0.08
Model 2:	32	Postpartum SynOXT	1.00	0.22, 4.46	1	3.58	0.43, 29.38	0.23
Oxytocin Time 1		Intrapartum SynOXT	0.18	0.03, 1.08	0.06	0.14	0.02, 1.18	0.07
(high vs. low)		Maternal Age	1.11	0.93, 1.33	0.21	1.07	0.86, 1.34	0.52
		BMI at Delivery	0.72	0.53, 0.97	0.03	0.70	0.51, 0.95	0.02
Model 3:	32	Postpartum SynOXT	1.8	0.39, 8.21	0.44	3.09	0.43, 22.09	0.26
Prolactin Time 1		Intrapartum SynOXT	0.73	0.15, 3.45	0.69	1.42	0.18, 10.63	0.74
(high vs. low)		High OXT Time 1 (vs. low)	2.7	0.66, 11.62	0.16	5.20	0.75, 35.68	0.09
		Race (non-White vs. White)	9.00	0.93, 86.5	0.05	20.0	1.39, 288.54	0.02

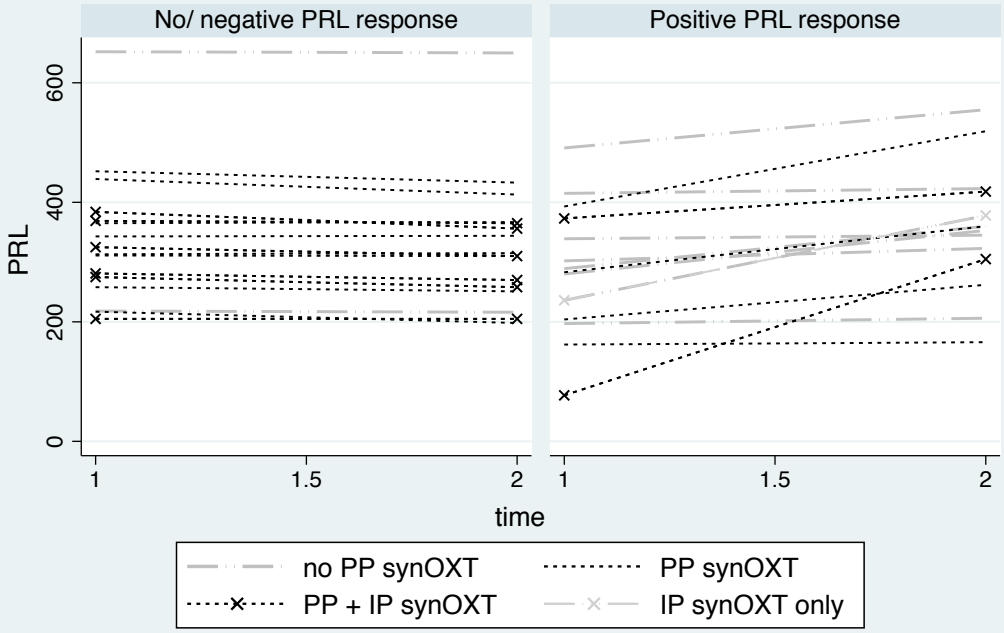
Model 1: $LR\chi^2$=17.25, McFadden R^2=0.42, Hosmer-Lemeshow p = 0.66, CCR= 77%, area under the curve = 0.88
Model 2: $LR\chi^2$=11.61, McFadden R^2=0.26, Hosmer-Lemeshow p = 0.20, CCR= 78%, area under the curve = 0.83
Model 3: $LR\chi^2$=9.77, McFadden R^2=0.22, Hosmer-Lemeshow p= 0.23, CCR= 75%, area under the curve = 0.79

5.4b: Newborn weight changes by clinical and plasma predictors

Outcome	n	Predictors	Unadjusted ß /OR	95% CI	p value	Adjusted ß /OR	95% CI	p value	Partial ω^2
Newborn		High PRL Response (vs. low)	1.55	-1.06, 4.16	0.23	3.19	0.91, 5.48	0.008	0.22
weight change	30	High OXT Time 1 (vs. low)	0.98	-1.62, -3.59	0.45	1.62	-0.60, 3.85	0.14	0.05
(% of birth		Intravenous fluids (Liters)	0.88	-.11, 1.87	0.07	1.02	0.15, 1.89	0.02	0.16
weight)		Gestational age (week)	2.04	0.74, 3.33	0.003	1.93	0.67, 3.20	0.004	0.26
		Female Sex (vs. male)	-2.34	-4.58, 0.10	0.06	-1.50	-3.59, 0.60	0.54	0.04

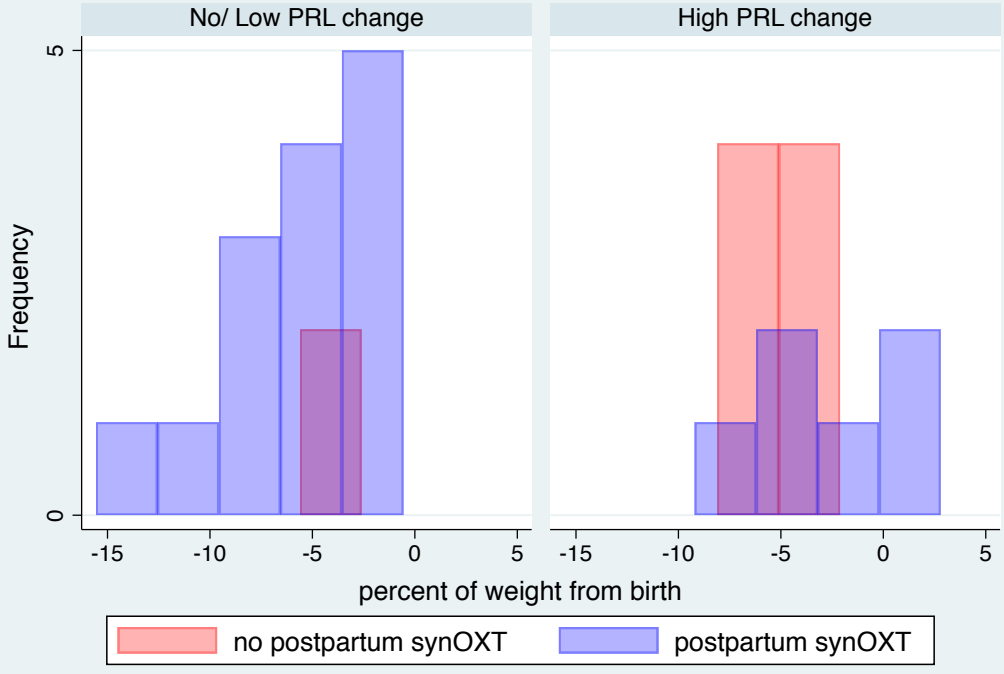
Adjusted R^2 = 0.38, ω^2= 0.37

Figure 5.1: PRL response to 20 min breast feeding by synOXT exposure



PP: postpartum, IP: intrapartum

Figure 5.2: Synthetic Oxytocin and % of birthweight, by maternal PRL change

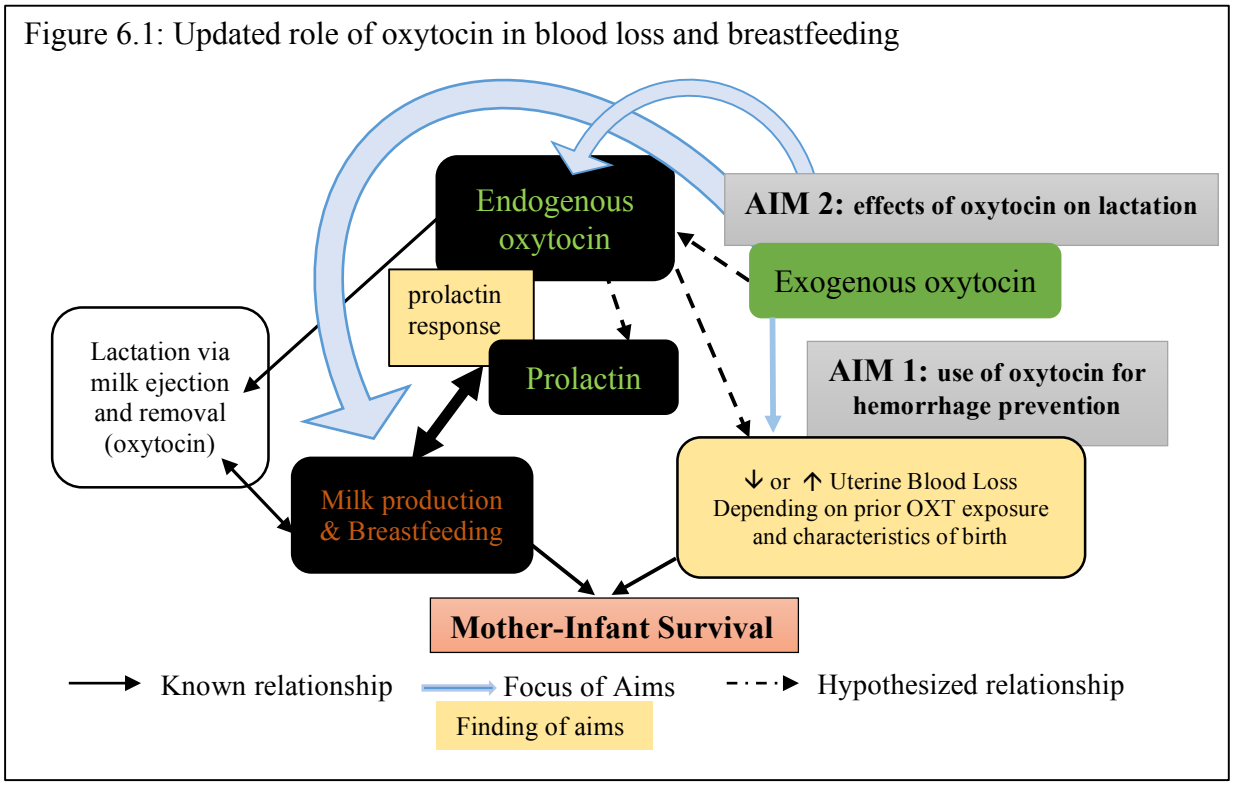


Chapter 6: Discussion, Summary and Implications

Discussion

The purpose of this program of research and dissertation was to examine the function of oxytocin from a pharmacologic and physiologic perspective, looking specifically at outcomes relevant to hemorrhage during the third stage of labor and breastfeeding/ lactation. This purpose was addressed via two specific aims (Figure 6.1): 1) investigating the premise for clinical oxytocin use in postpartum hemorrhage prevention, specifically in lower-risk populations, and 2) assessing downstream effects of oxytocin use during labor and birth on lactation hormones and breastfeeding outcomes. Four manuscripts were included in this body of work, two addressing each aim. One literature review paper and three data-based analyses were presented in the previous chapters. The manuscripts include a variety of methodological, statistical techniques and original prospective, longitudinal as well as cross-sectional data.

Figure 6.1: Updated role of oxytocin in blood loss and breastfeeding



Overview of Findings. Together, these four manuscripts promote the scholarly consideration that interventions performed with the goal of risk reduction may be in the best interest of some, but not all birthing women (see Table 6.1). The findings challenge the routine practice of oxytocin administration after birth as being universally beneficial and present the idea that active management of third stage labor (AMTSL) for women undergoing low-risk physiologically stimulated birth may contribute to delayed placental delivery possibly increasing postpartum bleeding or postpartum hemorrhage (PPH). In addition, we found that oxytocin administration after birth has potential to influence physiology important for establishing

Table 6.1: Summary dissertation findings

Aim	Key Findings
1: Investigate the premise for clinical oxytocin use in postpartum hemorrhage prevention, specifically in lower-risk populations	**1.** Women (lower risk) without oxytocin administered during the birth process did not experience reduction of PPH, less uterotonic treatment of bleeding or need for blood transfusion in randomized controlled trials of AMTSL (Chapter 2). **2.** Women with higher rates of physiologic childbirth had lower rates of postpartum hemorrhage/ blood transfusion (Chapter 3). **3.** Prophylactic oxytocin in the third stage did not improve postpartum blood loss outcomes (blood loss, rates of PPH) for women with physiologic births (Chapter 3). **4.** Use of AMTSL for women undergoing a more physiologic and less complicated birth, was associated with higher odds for PPH as well as for prolonged third stage labor (Chapter 3).
2: Assess downstream effects of oxytocin use during labor and birth on lactation hormones and breastfeeding outcomes.	**1.** Published literature on the role of oxytocin administration during birth on breastfeeding outcomes is limited overall by methodologic heterogeneity but also a limited number of studies addressing the association (Chapter 4). **2.** Of published studies, many report a possible negative influence of oxytocin with concerns for both maternal and infant biology/behavior (Chapter 4). **3.** In our prospective longitudinal study, women with postpartum synthetic oxytocin exposure were statistically less likely to experience a rise in PRL when feeding their baby (Chapter 5). **4.** A rise in PRL during breastfeeding was associated lower weight loss among newborn infants by day 4 to 5 (Chapter 5).

lactation, possibly through differing prolactin response in these women. This chapter will provide a synthesis of themes, conceptual and theoretical considerations, practice and research implications as well as strengths and limitations of the work. This chapter will provide a synthesis of themes, research and clinical implications, conceptual and theoretical considerations, as well as strengths and limitations of the work.

Patient centered risk-reduction. Addressing problems (such as PPH) in obstetrics will require developing multiple strategies that are focused on the specific etiology of the problem rather trying to treat the definition of the problem, e.g. trying to lower the estimated blood loss. The reasons prompting PPH may not be the same for women undergoing different birth experiences, therefore the solution needs to address the root of the problem.

Two of the analyses in this dissertation note a lack of efficacy of AMTSL on PPH for women undergoing physiologic birth. This finding presents both new questions and opportunities for clinicians and researchers. Women undergoing less labor interventions (IV fluids, oxytocin induction, augmentation) were less likely to have PPH, which offers the opportunity to reduce PPH through avoidance of elective (rather than medically indicated) intervention, particularly in a physiologic birth process.

However, prevention of PPH for women undergoing physiologic birth remains the key question. Given existing evidence that oxytocin receptor availability diminishes with longer exposure to exogenous oxytocin, one might predict that women without oxytocin stimulation would be very responsive to prophylactic oxytocin treatment (reducing uterine atony and PPH). However, this was not born out by the data in Chapters 2 and 3. The most obvious answer is that the cause of PPH following physiologic birth is not originating from uterine atony or lack of uterine tone, which is what prophylactic oxytocin will guard against. It may be that heavy

bleeding was predominantly coming from genital tract trauma, for which AMTSL would have no effect. Other cohort studies have also noted an increase in PPH in low-risk women who have had AMTSL performed. However, the association of AMTSL with higher risk of PPH as was seen in the latent class analysis (Chapter 3) is more difficult to explain without more detailed study of the third stage of labor practices.

Possible variations in practice of AMTSL (timing of administration of oxytocin, timing of umbilical cord clamping, draining the placenta prior to expulsion) are plausible contributors to the quantity of blood lost (Schorn, Dietrich, Donaghey, & Minnick, 2018). Oxytocin administration before or after placental expulsion was reviewed in a recent Cochrane meta-analysis finding no difference in PPH outcomes, though few studies have been conducted. Delayed cord-clamping (Mercer et al., 2017), as well as draining the cord after cutting shrinks the residual placental volume (Asicioglu et al., 2015) which may assist with physiologic placental separation, and this was not included the latent model. Obstetric practice has been moving away from immediate umbilical-cord clamping for years as benefits to newborn health for reduced anemia and improved developmental outcomes continue to be discovered in term and preterm infants (Mercer et al., 2017; 2016). If the absence of intervention for a normally transitioning newborn has benefits for the infant with physiologically increasing blood volume, this may benefit the mother as well by diverting blood within the placental bed. The role of delayed cord clamping on blood loss and PPH deserves further study.

The reasons for suboptimal breastfeeding outcomes also vary woman to woman, as is expected for a complex, biopsychosocial, two-person physiologic experience like lactation. Maternal and infant factors are both clearly important considerations. The literature review (Chapter 4) highlighted effects of synthetic oxytocin on both maternal and infant roles in the

breastfeeding relationship. Preventing attrition in breastfeeding also includes tracing back on an individual and sub-group level to identify areas for intervention. While not the focus of this study, breastfeeding outcomes could be examined through a latent class approach to identify the combinations of birth and co-morbid factors that underlie problems with meeting breastfeeding goals. Too often, as reported in the Chapter 4, the reasons for using synthetic oxytocin were not controlled for in the analysis linking breastfeeding difficulties with its use. However, knowing that oxytocin may be used even when a true problem has not been identified, or as prophylaxis for PPH is an important consideration when considering the findings as whole.

Physiologic knowledge incomplete. ***Third stage labor.*** Solving any clinical obstetric problem requires understanding the physiologic underpinnings of various etiologies of the issue and enquiry about how physiologic processes differ among groups of women. One possibility for why AMTSL was not effective in decreasing PPH for women undergoing physiologic birth may be due to pathways responsible for postpartum uterine involution are less dependent on oxytocin than previously believed. Another option is that there are a variety of physiologic pathways causing uterine contraction/ involution (prostaglandin, thrombin (Elovitz, Ascher-Landsberg, Saunders, & Phillippe, 2000; Sellers, Hodgson, Mitchell, Anderson, & Turnbull, 1982), which may represent variability in human survival strategies and/or genetic underpinnings. A third possibility is that bolus prophylactic oxytocin may be interpreted as a supra-physiologic quantity by the body and maternal brain which leads to a dysfunctional involution pattern rather than a coordinated one—causing partial detachment or entrapment of the placenta in some women.

Recently, differences in myometrial thickness (evaluated by ultrasound) was linked to various lengths and outcomes of third stage labor (PPH) and dysfunctional coordination of the regions of the uterus (Patwardhan et al., 2015). This study was designed to compare management

protocols but it could serve as a method for understanding more directly the effect of AMTSL on myometrial function. Another novel study used myographic sensors to detect electrical activity during the third stage of labor finding that women's 2nd and 3rd stage electrical activity was consistent across time despite the stage of labor (Rosen et al., 2013). The authors noted the electrical activity did not predict the length of the third stage but did not report on bleeding outcomes. However, this study demonstrates that similar levels of uterine electrical signaling during labor persist through the third stage. These studies allow for basic understanding of the third stage to continue and application of these non-invasive techniques may be useful for understanding physiologic third stage beyond the minutes and milliliters of blood loss by which it is currently defined.

Lactation. Physiology of typical onset of lactation and reasons for problems that arise are also limited by the lack of physiologic knowledge around milk-production and removal. Similar to the heterogeneity seen in understanding the physiology of third-stage labor complications, there are numerous contributors to suboptimal lactation outcomes. Some of these limitations are due to difficulties in accessing the study population (the newborn period being a vulnerable time), difficulties/discrepancies with hormone assays (oxytocin) (McCullough, Churchland, & Mendez, 2013), but also the fact that the basic anatomy of the breast was not well understood as recently as 2004 (E. Jones & Spencer, 2007). The discovery of the *lack of* lactiferous sinuses meant that copious milk is not sitting passively in breast tissue that the infant will remove through suction, but must be ejected/transported down the duct highlights the critical role of oxytocin in the breastfeeding process. Notably, oxytocin has been now labeled the most important galactokinetic hormone by modern authors (Crowley, 2015).

While human literature on oxytocin function and breastfeeding is limited, other mammalian models provide some added insight. It is noted that oxytocin receptor-deficient mice, for instance, could conceive and birth normal litters, but the pups perished following birth due to lack of milk ejection. This highlights the importance of oxytocin for the function of feeding offspring (Takayanagi et al., 2005). Oxytocin injection is performed on milk-producing cattle in the dairy industry for the purposes of getting more milk ejection and milk yield (Allen, 1990; Belo & Bruckmaier, 2010; Hameed et al., 2014). Through these practices, it has been noted that high levels of pharmaceutical oxytocin can lead to lower milk yields and higher sodium levels in milk (Allen, 1990), which may be evidence of a disruption of the tight junctions around milk ducts. Other studies have noted differences in other components of dairy milk produced after oxytocin injection (Dill, Lane, & Hartsfield, 1974; Hameed et al., 2014). However, these studies are done in mature milk-producing cattle and extrapolation beyond the basic pharmacologic principles is difficult to translate to humans who have yet to get their milk supply established. Our data did show that women with a larger increase in their oxytocin levels corresponded to larger volumes of milk expressed (>40mL) during the study visit. This one observed feeding did not, however, predict overall weight differences in the newborn. Nor was it related to synOXT administration—probably a single feed is not a useful proxy for milk ejection—thus the long-term implication of this phenomenon for human milk needs more study.

Theoretical and practical implications.

Normal Physiologic Childbirth. The frameworks used to develop and interpret these research questions were the "normal physiologic childbirth" model of care coupled with the broader "life history theory," which is a model for understanding forces of natural selection. The findings of these manuscripts are in line with the premise of the model of physiologic childbirth

which states that intervention in the absence of pathology during the physiologic process may present risks to the woman or baby. Considering the role of AMTSL (or prophylactic oxytocin) for reducing risk for PPH, the findings here demonstrate that risk was *not* reduced for women undergoing physiologically driven birth and it may have resulted in a prolonged placental delivery and increased blood loss. If prophylactic oxytocin could lead to a prolonged third stage of labor for some women, as the latent class analysis in Chapter 3 showed, it may be through disturbing the endogenous pathways/ feedback regulating existing oxytocin secretion in response to what may be a supra-physiologic dose of medication to some women.

The findings of Aim 2 also fit with the physiologic model. Some of the purported benefits of physiologic birth include the improved physiologic transition to breastfeeding, which has numerous benefits for the woman and her infant (Sakala, Romano, & Buckley, 2016). Our data show that women with less birth intervention had higher elevation in PRL and this was associated with less infant weight loss and less supplementation in the early breastfeeding period. Using this model of care allows for the consideration of the entire birth experience from the perspective of forces within the woman's body and with minimal interference. This research supports the idea that intervention in a normal physiologic process has potential to cause harm, e.g. PPH or breastfeeding difficulties.

However, a limitation of this model is that it does not address the reality that some women undergoing a normal physiologic childbirth will still develop problems and research should explore physiology and clinical practices for causes and solutions for women undergoing physiologic birth and those who have not—as they may be divergent. One could argue that much of the foundation for modern obstetrics is based on addressing problems for women undergoing non-physiologic childbirth—usually through surgical or pharmacologic strategies for

which the strategies may be quite effective. However, application of those strategies to all women may impose a burden of side effects that should be reserved for cases when benefits outweigh the risk.

Life-history theory. Physiology is the governing principle underlying all health and biological sciences. The mechanisms have been shaped by over several hundred thousand years of *homo sapien* evolution, which include processes selected for fitness and survival. While a grand theory, (and not readily testable by the methods of this dissertation) considering life-history theory in this body of work allows us the opportunity to consider the implications of intervention during birth on linked physiologic processes (birth and lactation, parenting etc.) as well as the reasons for why aberrations in the physiologic process arise from the evolutionary perspective. Life-history theorists support the inclusion of evolutionary medicine principles in understanding human health and disease as it may ultimately help determine *why* a phenomenon occurs, not simply the *how*, as physiologic understanding provides (Gluckman, Low, Buklijas, Hanson, & Beedle, 2011).

Life-history theory may also be useful in considering the broad role of obstetric medical intervention on genetic diversity in the patient population today as compared to 100 or 200 years ago. Should advocates of the normal physiologic childbirth model study the role of 'human or obstetric selection' (Mitteroecker, Huttegger, Fischer, & Pavlicev, 2016) on the physiology of childbirth? Will the idea of "normal" labor and birth change because humans are surviving from labor dysfunction? Are any underlying genetic contributions to those dysfunctions being passed along to the next generation? For example, mathematical models of the effect of increased use of Cesarean birth demonstrate that rates of cephalo-pelvic disproportion (i.e. the inability of the fetus to pass through the bony pelvis due to excessive size and/or overly restrictive dimensions

of the pelvis) have increased 10-20% due to reduced mortality from this condition (Mitteroecker et al., 2016).

The practical implication of this 'human / obstetric selection' idea is that Western society highly values human *survival* and has done so successfully. Considering life-history theory in this context will mean that we should consider the long-term associations of traits/phenotypes of women's pregnancies that have been complicated and/or involved medical intervention. This perspective on pleiotropic traits allows for more integrated understanding of health problems later in life as well as origins of some chronic diseases. From a global resource and health policy perspective, humankind should be prepared to care for downstream consequences of the success of higher rates of survival from pregnancy/birth. In the short term, better survival from birth may lead to lower fertility rates, which have already been seen globally (United Nations, Department of Economic and Social Affairs, Population Division*The impact of population momentum on future population growth.*, 2017).

However, some effects of successful perinatal care may not be seen until much later in life. For example, babies born with small-for-gestational age or low birth weight would likely have died in utero or shortly after birth in the past millennia. While survival represents a success in clinical obstetrics and neonatology, it presents challenges in later life as individuals born with low birth weight are at very high risk of later developing cardiovascular disease (Gluckman et al., 2011). Similarly, population-based studies have considered the link between development of autism with exposure to labor induction (Gregory et al., 2013). While this association does not demonstrate causality, shared mechanisms behind either obstetric complications or labor dysfunction may be also linked to development of autism. Another example is seen in the growing field of microbiome research and connections to autoimmune/atopic diseases in babies

born via Cesarean birth (Dahlen, Downe, Wright, Kennedy, & Taylor, 2016; L. Hanson & Vandevusse, 2013). While Cesarean birth can be life-saving for at-risk newborns, it may carry trade-offs for health and longevity later in life. In the same vein, if other obstetric intervention (synthetic oxytocin) designed to prevent mortality (e.g. postdates birth, labor dystocia, PPH) contributes to problems with other physiologic process for some women (e.g. PPH, lactation, mood etc.), experts should continue to think broadly about origins of health problems, to study these relationships and be prepared to support women and newborns appropriately if delayed problems present.

Approaches to Risk: 'maximin'. Another important consideration pertinent to PPH risk reduction is the general culture of risk within the modern obstetrics. This culture has been discussed as the 'maximin' approach in the literature (Brody & Sakala, 2013). This term, "denotes a method or strategy in game theory that maximizes the smallest gain that can be relied on in a situation of conflict." In obstetrics, 'maximin' means assuming/ imagining the worst possible outcome (usually fetal/infant or maternal death) is likely and then devising an approach to reduce that risk. Brody & Sakala also note the maximin approach usually leads to bundles of associated interventions, rather than single elements—this idea, now termed the "cascade of intervention" links proximal intervention with more distal events that together elevate risk.

The American College of Obstetricians and Gynecologists has recently addressed this concern of over-medicalized birth by highlighting the lack of strong evidence for many routine interventions (e.g. some labor induction and augmentation practices, pharmacologic pain relief, continuous fetal monitoring, maternal positioning in labor) for low-risk women (Committee on Obstetric Practice, 2017). In this document, the professional organization addresses the need for shared-decision making with women regarding previously standardized recommendations, given

lack of strong evidence for their benefit or evidence for possible harm with some practices.

While PPH outcomes were not the focus of the interventions discussed in the opinion piece, other studies do link obstetric practices (induced labor and synthetic oxytocin dose) to increased rates of PPH, particularly PPH associated with uterine atony (Callaghan et al., 2010; Grotegut et al., 2011). Certainly, the culture of risk in obstetrics is driven in part from fears and reality of litigation associated with poor perinatal outcomes (Barber et al., 2011; Clark et al., 2009). Regardless, some part of PPH as a phenomenon may be born out of the approach used to prevent other problems. As those strategies (induction, Cesarean) become more commonplace and the prevalence of PPH appears higher, the need for further intervention seems more universal and recommendations are applied to women without risk factors rather than scrutinizing the underlying causes.

Population versus individual risk reduction. A topic discussed in the broader epidemiologic literature is the comparison of population-level strategies versus strategies targeting individuals for risk reduction. The difference between these was classically highlighted by the late epidemiologist, Geoffery Rose, (Rose, 1985) as a paradox and the topic remains relevant in modern public health literature (Doyle, Furey, & Flowers, 2006). The population approach carries a higher chance of small inconvenience/ side effect for many in the population who may get relatively little-to-no benefit from a population level intervention. However, this strategy allows for the largest number of people to benefit from the intervention overall because it addresses the greatest number at relatively higher risk. Critics of the population approach note that its success may depend on the distribution of risk within the population, it could potentially exacerbate existing vulnerabilities and does not address the fundamental causes of the risk itself (Frohlich & Potvin, 2008). Another idea is that individuals may not view the benefits to others

(on a population level) as directly beneficial to themselves, as autonomous individuals have to weigh trade-offs and often view their own absolute risk/benefit as more important than relative risks to the population (C. Thompson, 2016). The absolute versus relative risk comparison resonates with dilemmas in communication of risk within the paradigm of shared decision making and preventing the rare but devastating outcome (Ecker & Minkoff, 2011).

Rose's paradox has not been widely studied in the context of obstetric risk prevention, but population wide intervention bears similarity to the 'maximin' approach offered by Brody which is focused on the relative risk. However, one could argue that preventive interventions in obstetrics are different than prevention of diabetes or hypertension in the general population as 1) childbirth is not an illness and 2) treatment and prevention in obstetrics are often the same intervention. Primary prevention of hypertension does not include prophylactically administering anti-hypertensive medication because one might develop high blood-pressure eventually. However, women are frequently offered induction of labor for problems that could develop based on criteria such as their age or estimated due date alone, bypassing the physiologic process which may confer benefits.

The normal physiologic childbirth model posits that considering all women to possess equal risk and applying interventions across the board will inherently lead to harm for some. i.e. making birth recovery, lactation, or transition to motherhood more difficult (American College of Nurse-Midwives et al., 2012). Linking this concept to life-history theory requires looking at intervention in physiologic birth from the 10,000-year view of future human evolution. Mechanisms leading women to the process of reproduction today have been maintained by natural selection because they are energetically beneficial to the species and enhanced fitness. From the life-history perspective, lactation is already energetically costly to the mother

(Muehlenbein, 2010) but in doing so it should confer maternal benefit over the short-term (pregnancy-spacing) and long-term (neoplastic, metabolic and cardiovascular) (Bartick et al., 2016).

Importance

Together, this program of research highlights the importance of physiologic methods and a broad view of the birth process for women and babies. This body of work represents unique inter-related contributions to the clinical literature and the knowledge base of physiology underlying the approach to low-risk physiologic birth. It will ideally serve as a platform for discussion about the modern medicalization of childbirth broadly and as a prompt to consider the role of specific practices on women's birth and postpartum experiences. It also introduces the use of the latent class analysis technique for examining the phenotype of birth experience and its relationship to PPH. This approach should be more widely applied in a prospective manner to determine if it could guide clinical decision making around PPH or other risk-avoidance interventions. We also provided, for the first time, pilot data showing that women's hormonal responses during feeding may be a driver of higher infant weight loss and that those responses may be partly informed by synthetic oxytocin used in the birth process. From the clinical view, this program of research can help birth attendants have a different appreciation of possible causes of PPH or ways to approach counseling for women at varied levels of risk. While the data on lactation are intriguing and worth further study, they are not conclusive enough to recommend against postpartum prophylaxis with synthetic oxytocin to avoid early breastfeeding difficulties, but care providers should not provide assurance that it has no effect either. Use of synthetic oxytocin can serve as an element of risk assessment in working with early lactating women. Finally, clinicians can consider this data in light of other studies showing that use of synthetic

oxytocin during birth does not appear to improve breastfeeding outcomes and that women undergoing physiologic birth may not have a great benefit from the practice for PPH prevention.

Summary and Implications

In summary, this set of manuscripts and studies details two phenomena not often studied contiguously, postpartum bleeding/postpartum hemorrhage and suboptimal breastfeeding outcomes. We examined these two pressing public health issues through the shared physiologic mechanism of oxytocin function. These manuscripts addressed the practice of preventing postpartum hemorrhage (PPH) by administering prophylactic oxytocin and highlighted the lack of effectiveness on women undergoing physiologically driven births using a meta-analysis of previously published randomized trials. Additionally, an original, contemporary dataset was used to demonstrate that clinically different phenotypes of women may have different risks for PPH and may not respond equally to prophylactic treatment. We studied the role of oxytocin given exogenously on breastfeeding through probing extant literature for relationships published over the last several decades. Finally, we demonstrated through a prospective, longitudinal pilot study that synthetic oxytocin given in the postpartum period may contribute to differences in early lactation performance by altering prolactin response and increasing risk for high infant weight loss.

Put together, these papers raise questions about the still undiscovered ways to evaluate risk and prevention strategies for women undergoing normal physiologic birth and if and how current methods could contribute to later postpartum difficulties with breastfeeding. In addition, this work highlights the need for a more personalized approach to obstetric care as current methods of avoiding risk appear to target the average woman's experience and risk, rather than understanding what is uniquely contributing to specific problems in certain sub-groups.

Limitations of the manuscript findings' have been described within each chapter. Overall, the strength of the conclusions detailed here are limited by sample selection bias intrinsic to cohort and observational studies. The latent class analysis was limited in external validity as it represented data from a cohort of women seeking midwifery care in Portland, Oregon. Particular limitations for the pilot data presented in Chapter 5 were unequal group sizes and attrition to follow-up. Yet, this data should be viewed in light of prior studies also demonstrating a more persistent effect of synthetic oxytocin on maternal physiology (Gu et al., 2016; Jonas et al., 2009) than previously appreciated and for the specific role of postpartum oxytocin on early breastfeeding rates (Jordan et al., 2009).

The implications of this work could impact research within nursing, midwifery, medicine, and physiology. It may prompt further use of latent models to study obstetric issues or consider the down-stream impact of birth related experiences. It will continue the conversation within the community of clinicians and scientists studying physiologic birth about the role of synthetic oxytocin among other routine experiences in modern childbearing.

While the introduction of synthetic oxytocin has been undoubtedly life-saving and risk-reducing for many women since it was derived in 1955, it should not go unnoticed that the now abundant use of the medication has changed the physiologic experience of childbearing for most women. Meanwhile, since the synthesis of oxytocin, advances in neuroscience, genomics and pharmacology have reported on the broad array of roles for oxytocin throughout the brain and body and the possibility that it has a more lasting effect than previously appreciated when given exogenously. It should give us pause and prompt curiosity that the natural experiment we have been conducting with women and their babies in the noble pursuit of risk-reduction could have more consequences than previously thought possible. To really solve the problems synthetic

oxytocin was designed to address, labor dystocia, preventing stillbirth and postpartum hemorrhage we need to prioritize physiologic inquiry of women's health and reproduction, childbearing and lactation. With the advance of precision medicine, targeted pharmacogenomics and personalized therapies across many disciplines, we have comparatively few tools available in obstetrics. By reframing the focus on the normal physiologic process as a continuum of evolutionary forces we can better understand where pathology truly exist and address intervention to those in need.

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Appendices

Appendix A: Consent Form and Minimal Risk Protocol for Chapter 5 Study

OREGON HEALTH&SCIENCE UNIVERSITY

IRB#: __00015142___

MED. REC. NO. _____
NAME _____
BIRTHDATE _____

Clinical Research Consent Summary

TITLE: Biobehavioral Lactation Outcomes Following Oxytocin Administration During Parturition

PRINCIPAL INVESTIGATOR Cathy L. Emeis, PhD,CNM (503) 494-3873

You are being asked to join a research study. You do not have to join the study. Even if you decide to join now, you can change your mind later.

1. The purpose of this study is to learn more about maternal hormone levels involved in lactation and their relationship to breastfeeding outcomes in women who received oxytocin as a part of their birth experience.
2. In this study, we will learn about the levels of two hormones, oxytocin and prolactin. We will study these levels in a mother's blood during the first week postpartum in women who received the medication Pitocin to prevent excessive bleeding after the birth of the placenta. We will also study these hormone levels in women who did not receive the medication Pitocin. We will compare these levels from the beginning of a breastfeeding session with hormone levels at the end of a breastfeeding session. We will also learn about women's experiences of breastfeeding and during the first four weeks following their birth. We want to learn:
    a. About the relationship between the synthetic form of the hormone oxytocin (commonly known as Pitocin) and the relationship to a mother's lactation hormones during the early days of breastfeeding.
    b. About the relationship between a mother's lactation hormone levels and breastfeeding experiences in the early days of breastfeeding.
    c. About the relationship of between a mother's lactation hormone levels in the early days of breastfeeding and her breastfeeding experiences at four weeks postpartum.
3. The OHSU School of Nursing is paying for this research study.
4. The length of this study is four weeks following the birth of your baby. There will be one visit for blood draws at the OHSU Lactation Clinic (or Women's Health Research Unit if Lactation Clinic is not available) during the first postpartum week , and a survey at four weeks.

5. There are risks involved in participating in the study. These are considered to be minimal risks.
6. If you agree, we will call you at 6 months to inquire about your breastfeeding status.

OREGON HEALTH&SCIENCE UNIVERSITY

IRB#: 00015142

MED. REC. NO. _____
NAME _____
BIRTHDATE _____

Clinical Research Consent and Authorization Form

TITLE: Biobehavioral Lactation Outcomes Following Oxytocin Administration During Parturition

PRINCIPAL INVESTIGATOR: Cathy L. Emeis, PhD, CNM (503) 494-3873

CO-INVESTIGATORS: Elise Erickson, MS, CNM (773) 354-5108
Laura Lallande, MS, CNM (503) 494-9397

FUNDED BY: OHSU School of Nursing

PURPOSE:

The purpose of this study is to measure the relationship between synthetic oxytocin given for the prevention of severe bleeding after birth and its effects on breastfeeding outcomes. Oxytocin is a hormone that makes the uterus have contractions during labor, it also helps the breast empty milk when the baby nurses.

You have been invited to be in this research study because you are breastfeeding.

The purpose of this study is learn about women who received synthetic oxytocin for prevention of severe bleeding after birth may have differences in hormonal responses to this medication and/or in their breastfeeding experiences.

There is a time commitment involved in participating in the study:

- 20-30 minutes: Survey questions at time of enrollment
- 10 minutes a day: Daily breastfeeding log on days 2-4 postpartum
- 1 hour: visit which includes blood draws to the lactation consultant on day 4-5 postpartum

- 20-30 minutes: Final survey completion at 4 weeks postpartum

Approximately 60-70 new mothers will be enrolled in the study. This study will be conducted at OHSU.

PROCEDURES:

There are three time periods for this study:
1. Hospital period: Baseline questionnaire will be completed before the participant is discharged from the hospital. These questionnaires are not a typical part of postpartum care. A follow-up visit with an OHSU Lactation Consultant during the first week postpartum will be made. (All breastfeeding mothers at OHSU are offered a visit with a lactation specialist).

2. The first week postpartum period: Daily completion of a one page breastfeeding journal and a visit to the OHSU Lactation Consultant. At this visit, participants will be asked to complete more questionnaires and have two blood draws, one at the onset of breastfeeding and the second blood draw after 20 minutes into the breastfeeding session. A small catheter (tube) will be inserted and remain in your vein for approximately 30 minutes. This catheter is a standard line used to prevent the need for a second needle stick. The remainder of the visit with the lactation consultant is standard care and will be directed by the participants and Lactation Consultant.

3. Four week postpartum follow-up survey: Completion of questionnaires by paper or electronic format, depending on participant preference. Participants will be asked at this time if they consent to being contacted at the six month period.

4. Optional Six month follow-up phone call: Participants will be contacted by the researchers and asked the following questions: 1) Are they still breastfeeding? 2) How much breastfeeding are they doing? 3) If they stopped breastfeeding, when did they stop and what was the primary reason for stopping.

Estimated Time Commitment for Study

	Hospital Day 1 or 2	Early days of Breastfeeding at home	Lactation Consultation Visit (Day 4-5)	4 Week Postpartum Survey	6 Months
Consent Discussion	X				
Questionnaires	x		x	x	
Breastfeeding log	X	x	X	X	
Outpatient Lactation Consultation Visit/ Blood samples *			X 2 Blood Samples		
Breastfeeding Status Check-in					X
Total time	20-30 minutes	10 min (daily)	60 minutes	20-30 minutes	5 minutes

*The total amount of blood to be drawn at this study is estimated to be 2.5 teaspoons.

This study will use four standard questionnaires that will be used to understand participants' mood, level of anxiety, amount and intensity of breastfeeding, and confidence for breastfeeding. A daily breastfeeding log (journal) has been developed by the researchers. It is estimated that the surveys, which will be completed 3 separate times, will take approximately 20-30 minutes (each time). The breastfeeding diary, which is to be done daily for approximately 4-5 days and once at 4 weeks postpartum, will take approximately 10 minutes.

We will collect information from your' medical record for the study. The following information will be collected: exact length of the pregnancy at the time of birth, type of delivery, preexisting medical conditions of mother and infant, treatments during labor and since birth, birthweight and weight of infant at hospital discharge, feeding record of infant.

ACCESS TO YOUR TEST RESULTS
The results of blood work are not intended for clinical use, thus we do not plan to share your results with you or your primary care provider.

The research questionnaires in this study may tell us that you are at risk for depression and/or anxiety. If we find out that you are at risk, we will contact you and refer you to your primary maternity provider. You would be responsible for all costs associated with any follow-up testing and medical care.

RISKS AND DISCOMFORTS:

We will draw blood from your hand or arm by inserting a small tube. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, an infection, or fainting. You may get an infection where the tube is placed. This would cause swelling, redness, and pain. You may bleed or get a bruise. There is a very small chance you may get a blood clot that could go to your lungs. These problems are very rare. If you have these problems, you will need medical care.

Some of these questions on the questionnaires may seem very personal or embarrassing. They may upset you. You may refuse to answer any of the questions that you do not wish to answer. If the questions make you very upset, we will help you to find a counselor.

BENEFITS:
You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future. Because you will be attending a visit with the lactation consultant, you may benefit from the additional breastfeeding guidance.

ALTERNATIVES:
You may choose not to be in this study.

CONFIDENTIALITY

We will take steps to keep your personal information confidential, but we cannot guarantee total privacy. Information from questionnaires, medical record data and blood specimens will be coded with a participant identification number only.

We will create and collect health information about you as described in the Purpose and Procedures sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.

The investigators, study staff, and others at OHSU may use the information we collect and create about you in order to conduct and oversee this research study.

We may release this information to others outside of OHSU who are involved in conducting or overseeing research, including:

- The Office for Human Research Protections, a federal agency that oversees research involving humans.

Those listed above may also be permitted to review and copy your records, including your medical records.

We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission.

Under Oregon law, suspected child or elder abuse must be reported to appropriate authorities.

When we send specimens or information outside of OHSU, they may no longer be protected under federal or Oregon law. In this case, your specimens or information could be used and re-released without your permission.

We may continue to use and disclose your information as described above indefinitely.

Some of the information collected and created in this study may be placed in your OHSU medical record. While the research is in progress, you may or may not have access to this information. After the study is complete, you will be able to access any study information that was added to your OHSU medical record. If you have questions about what study information you will be able to access, and when, ask the investigator.

COMMERCIAL DEVELOPMENT:
Blood samples or information about you obtained from you in this research may be used for commercial purposes, such as making a discovery that could, in the future, be patented or licensed to a company, which could result in a possible financial benefit to that company, OHSU, and its researchers. There are no plans to pay you if this happens. You will not have any

property rights or ownership or financial interest in or arising from products or data that may result from your participation in this study. Further, you will have no responsibility or liability for any use that may be made of your samples or information.

COSTS

Some of the services or items in this study are part of the regular treatment for your condition. These would be performed or used even if you were not in this study. The costs for these services or items will be billed to your insurance. You will be responsible for any costs your insurance does not cover. If you have any questions about these costs, or what out-of-pocket expenses you may be responsible for, contact your insurance company. If you are uninsured, you will be responsible for these costs. You will not be billed for the costs of any services or procedures that are required by the study but are not considered part of your regular treatment.

You may receive payment via a debit card. You will receive a $50 payment after completing the visit and blood draws with the lactation consultant at 4-5 days postpartum. You will receive the remaining $25 after we receive the final set of completed questionnaires at 4 weeks postpartum. There may be fees (for example, if the card is inactive for more than six months), which will be deducted from the balance on your card. Details on how to use the card and any fees are included in the separate card member agreement and FAQ sheet We may request your social security number in order to process any payments for participation.

LIABILITY:
If you believe you have been injured or harmed as a result of participating in this research and require treatment, contact Cathy Emeis, PhD, CNM at 503-494-3873 or Elise Erickson, CNM at 773-354-5108.

If you are injured or harmed by the study procedures, you will be treated. OHSU and the School of Nursing do not offer any financial compensation or payment for the cost of treatment if you are injured or harmed as a result of participating in this research. Therefore, any medical treatment you need may be billed to you or your insurance. However, you are not prevented from seeking to collect compensation for injury related to negligence on the part of those involved in the research. Oregon law (Oregon Tort Claims Act (ORS 30.260 through 30.300)) may limit the dollar amount that you may recover from OHSU or its caregivers and researchers for a claim relating to care or research at OHSU, and the time you have to bring a claim.
If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

PARTICIPATION:
If you have any questions, concerns, or complaints regarding this study now or in the future, contact Dr. Cathy Emeis, CNM, (503) 494-3873 or Elise Erickson, CNM at 1-773-354-5108
This research is being overseen by an Institutional Review Board ("IRB"). You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.

- You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, 7 days a week).

Your participation in this study is voluntary. You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study. [*If study has optional components, add:* Some parts of the study are optional. You can choose not to participate in some or all of the optional parts but still participate in the rest of the study.]

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. [*If study has optional components, add:* You can choose to withdraw from some or all of the optional parts of this study without withdrawing from the whole study.] If you choose not to join any or all parts of this study, or if you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study [*if study has optional components, add:* or change which parts of the study you are participating in].

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:
Cathy L. Emeis, PhD, CNM

Oregon Health & Science University

3455 SW US Veterans Hospital Rd

Mail code: SN-5S

Portland, OR 97239-2941

emeisc@ohsu.edu

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already acted based on your authorization. If you choose to withdraw from the study you will be compensated for the portion of the study you have completed.

If in the future you decide you no longer want to participate in this research, you can request that your blood samples and questionnaires be destroyed. However, if your samples are already being used in this project and if their withdrawal jeopardizes the success of the entire project, we may ask to continue to use them until the project is completed.

You may be removed from the study if the investigator or funder stops the study. We will give you any new information during the course of this research study that might change the way you feel about being in the study.

Your health care provider may be one of the investigators of this research study and, as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way involved in this project. You do not have to be in any research study offered by your health care provider.

The participation of OHSU students or employees in OHSU research is completely voluntary and you are free to choose not to serve as a research subject in this protocol for any reason. If you do elect to participate in this study, you may withdraw from the study at any time without affecting your relationship with OHSU, the investigator, the investigator's department, or your grade in any course.

SIGNATURES:

PARTICIPANT OPTIONS

The optional portions of this study are described in detail throughout this consent form and listed here as a summary. Please read the options and place your initials next to [*your choices/one of the choices below*]. You can still participate in the main part of the study even if you choose not to participate in the optional parts.

_____ I agree to receive a six month follow-phone call from the researchers.

Your signature below indicates that you have read this entire form and that you agree to be in this study.

We will give you a copy of this signed form.

Subject Printed Name	Subject Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date

Minimal Risk Protocol

1) **Protocol Title**

Bio-behavioral Lactation Outcomes Following Oxytocin Administration During Parturition

Specific Aims:

Aim 1: ***Determine the relationship between synthetic oxytocin (synOT) given as active management of third stage labor (bleeding prophylaxis) on maternal lactation hormones in the establishment phase of breastfeeding.*** Healthy primiparous women who underwent different synOT exposures will be invited to participate while inpatient following birth. Group 1: synOT injected intramuscularly or intravenously during third stage birth and Group 2: no active management given. During a 4-5-day postpartum outpatient lactation support visit, venous blood samples for OT and PRL will be obtained at both the **initiation** of a breastfeeding session and **20 minutes after the feed has started**, at which time OT and PRL typically peak. Rise of hormones from baseline to peak within individuals as well as intergroup differences will be analyzed.
Exploratory Aim1: Vasopressin will also be analyzed from plasma samples.

Aim 2: ***Characterize the relationship between exposures/experiences during birth and biomarkers to early breastfeeding outcomes***. Early breastfeeding outcomes include timing of lactogenesis onset, infant feeding behavior, breastfeeding self-efficacy (BFSE), level of breastfeeding (supplementation with formula or donor milk), infant weight loss/gain, and number of breastfeeds during the 4-5 days, as well as utilization of resources for breastfeeding support. Again, within participant (over time) and group differences will be considered. Lactogenesis onset when measured via maternal report is linked to copious milk production and considered valid.[26] BFSE is an experience and confidence influenced construct. Early low levels are linked to a shorter duration of exclusive breastfeeding and perception of low milk supply. Breastfeeding resource utilization is an index of women needing assistance with breastfeeding due to real or perceived problems. In addition, women will be asked to complete surveys of depression and anxiety to look for confounding aspects of mental health. The measures will be administered at recruitment and again at one week postpartum. A feeding log will be provided to record level of feeding during the first days postpartum, infant behaviors, use of additional resources, as well as timing of lactogenesis.

Aim 3: ***Characterize the relationship between early biomarkers, birth exposure of synOT and early breastfeeding experiences to breastfeeding outcomes at four weeks postpartum*.** Late postpartum breastfeeding outcomes include breastfeeding self-efficacy (BFSE), level of breastfeeding, infant weight loss/gain and utilization of resources for breastfeeding support. These surveys will be paper during the in person visits with the option of Internet or paper for the 4 week follow up.

HYPOTHESES

3. Maternal plasma OT and serum PRL (change over baseline) will be different at one week postpartum in women exposed to greater amounts of synOT than those who did not receive the medication.

4. Breastfeeding outcomes will be less optimal in women undergoing birth interventions than in women who receive no interventions (onset of lactogenesis < 72 hours, less neonatal weight loss, higher breastfeeding self-efficacy scores).

2) Study Design

PROTOCOL NOTE: Data collection for the lactation visit/blood sample component of the study was terminated in October 2017 with data collected on 35 participants. The protocol continues with collection of survey data only until a maximum of 70 participants have been enrolled. Compensation will be 50$ for the survey data – mailed gift card at completion of 4 weeks data as prior protocol states..

Design: Prospective comparative longitudinal.

Postpartum women meeting inclusion criteria will be allocated into the following groups based on the medication received during birth. The option to receive active management of third stage labor with synOT is typically presented during prenatal visits and also addressed during labor. Women in labor may opt to have this medication or not based on the process of shared-decision making.

Group 1: Active Management 3rd Stage	Group 2: Control
(n=30): Vaginal birth after spontaneous onset of labor, minimal synOT intrapartum exposure*, followed by active management of third stage labor w/ syn OT.	(n=30): Vaginal birth after spontaneous onset of labor, no intrapartum use of synOT, and expectant third stage
*Women without augmentation of labor are eligible, however if labor augmented, may participate in group 1 if exposure was <12 hours and synOT dose was <20 mu/min	

*The use of synOT to augment spontaneous labor is a common practice particularly with nulliparous women or after initiating epidural. The rationale for including women with some augmentation of labor is based on the low feasibility of finding 60 nulliparous women with no intrapartum oxytocin exposure who meet other study criteria within the study time line. The parameters of 12 hours and 20mu/min include women with a range of oxytocin exposure during labor but still exclude induction of labor.

3) Study Population

a. Number of Subjects

A total to 60 women will be sought for participation. However due to attrition, as this is a longitudinal study, we anticipate enrolling 70 women.

All women delivering their baby at OHSU hospital (approximately 200/mo) will be screened through medical record data for basic inclusion criteria. Further eligibility will be confirmed at the time of informed consent.

b. Inclusion and Exclusion Criteria

Study co-investigators, who are all OHSU clinical faculty members, Certified Nurse Midwives and active members of the medical staff, will screen individuals who have given birth within the last 24-48 hours from viewing the daily census on EPIC.

Women meeting basic inclusion/exclusion criteria will be asked for permission by their attending provider (CNM/MD) or the mother-baby registered nurse to present the details of the study and assess eligibility again.

Specific criteria are as follows:

Inclusion	Exclusion
Primiparous, healthy women following term birth	Induced labor, instrument assisted birth
Age 18-43	Thyroid disease: women with history of thyroidectomy or thyroid cancer. (Women with preexisting non-autoimmune thyroid disease, not needing medication or well-controlled on thyroid medication throughout pregnancy may be included)
Ability to speak and read English	Non-English speaking or reading
Spontaneous onset of labor and SVD	Known hypoplastic breast tissue in pregnancy
Postpartum blood loss $\leq$ 1000cc	History of breast surgery involving areola
Intention to exclusively breastfeed for 4 weeks	Pre-pregnancy BMI >40
Non-smoking	Serious obstetric conditions: IUGR, severe hypertension, preeclampsia, GDM requiring medical management or intrapartum chorioamnionitis (Women who were diagnosed with and/or treated for chorioamnionitis during labor that did not result in separation of mother and baby in the postpartum period (to NICU) may be included)
	NICU admission or mother/baby room separation (resuscitation)
	Blood products or IV iron due to excessive bleeding

At the time of in-person screening, the participant will be asked again for the above inclusion/exclusion criteria and if she does not meet these criteria or refuses participation, any screening documents will be destroyed at the conclusion of the study.

c. Vulnerable Populations

The postpartum mother is the subject of the study. However, the neonate will be included in the data collection for 1) infant weight at birth, discharge and at follow-up and 2) as part of the lactation clinical appointment as data collection on the mother takes place during breastfeeding.

The weight and participation in a breastfeeding session are standard elements of a lactation clinical visit and do not represent any added risk to the neonate him/herself.

d. Setting

The mother-baby unit on the 13th floor of OHSU hospital will be the site for initial recruitment and data collection following birth.

The outpatient follow up will occur at the OHSU Center for Women's Health outpatient lactation clinic will be the primary site for the early 4-5 day postpartum visit. An alternate site of the Women's Health Research Unit located in Multnomah Pavilion: Room 3309 will be utilized in the case of no available lactation clinic appointments or staff (sickness or other absence) in order to allow for data collection 7 days a week (Lactation clinic does not offer Sunday appointments currently).

The 4-week survey will occur online or on paper wherever the participant chooses to complete it.

e. Recruitment Methods

1. Study co-investigators, who are all OHSU clinical faculty members, Certified Nurse Midwives and active members of the medical staff, will screen individuals who have given birth within the last 24-48 hours from viewing the daily census on EPIC.

2. The overall "patient list" view on EPIC allows clinicians to view some basic clinical and demographic data. From this view Gravidity and Parity as well as mode of delivery can be assessed. Only charts of primiparous women age 18-43 with vaginal births will be examined further for inclusion based on medical history, intrapartum events and medications.

3. Only patients of the CNM Midwifery Service or the Generalist Obstetric Service will be approached for participation.

4. Women meeting basic inclusion/exclusion criteria from the medical chart review will be asked for permission by their attending provider (CNM/MD) or the mother-baby registered nurse to allow study personnel to present the details of the study and assess eligibility again.

5. Compensation for time and participation will include 50$ gift card at the in-person lactation visit and an additional 25$ at the end of the 1 month follow up survey.

f. Consent Process

1. Women who agree to discuss possible study participation will be presented with the details of the study in written and verbal format. The study will be explained including the tools for the at- home breastfeeding journal, the follow up visit including blood sampling and the four-week survey.
2. If the potential participant's birth was attended by one of the Co-Investigators (Emeis or Erickson) another Co-I will introduce the study information to minimize coercion or bias.

3. Questions will be answered thoroughly and to the satisfaction of the potential participant. Understanding will be gauged by a process of asking for questions as each phase of the study is explained.
4. After questions are answered and the woman provides written consent, the appointment for the follow up visit will be arranged. Again at this in person lactation visit, informed consent will be obtained verbally as part of the ongoing consent process
5. At the four-week time, the survey will be set up to ask for consent to continued participation in the study.
6. IF at any time the participant declines further participation, the woman will be asked for reasons for withdrawing from the study if she is willing to provide it and further contact/participation will cease.

g. Modifications to the Consent Process

1. Screening for potential participants will take place using the census on EPIC for the mother-baby unit using the "patient list" view which includes minimally available data without entering the chart to limit the number of charts opened or further screened.
2. Charts that are opened will be examined for exclusion criteria

Induced labor, instrument assisted birth
Thyroid disease: women with history of thyroidectomy or thyroid cancer. (Women with preexisting non-autoimmune thyroid disease, not needing medication or well-controlled on thyroid medication throughout pregnancy may be included)
Known hypoplastic breast tissue in pregnancy
History of breast surgery involving areola
Pre-pregnancy BMI >40
Serious obstetric conditions: IUGR, severe hypertension, preeclampsia, GDM requiring medical management or intrapartum chorioamnionitis (Women who were diagnosed with and/or treated for chorioamnionitis during labor that did not result in separation of mother and baby in the postpartum period (to NICU) may be included)
NICU admission or mother/baby room separation (resuscitation)
Blood products or IV iron due to excessive bleeding

4) **Procedures**

Baseline:

1. Once consent is obtained and questions answered the study will begin.
2. Baseline data will include filling out the
    a) Questions regarding initial breastfeeding experience after birth
    b) Breastfeeding Self Efficacy Scale
    c) Level of Breastfeeding Scale
    d) Edinburgh Postnatal Depression Scale (EPDS)
    e) GAD-7 Anxiety Scale
    f) The daily breastfeeding log for the first 24 hours of life
    g) Scheduling the 4-5 day follow up appointment
    (approximately 20-30 minutes of time at the initial contact with the participant)

Additional medical record data will be abstracted from EPIC and recorded on the protocol forms identified only by subject ID number for specific health/birth related information.

Daily breastfeeding journal (days 2-4):

1. Each day the participant will be filling out the 1-page journal (see attached forms) (10 minutes each day)

Follow up Lactation Visit:

1. Women will arrive with their babies to the outpatient clinical site designated by the lactation providers' schedules (or at the Women's Health Research Unit in the case of no available lactation schedule).
2. Standard instructions for these appointments is to bring the baby when he/she is hungry and ideally ready to feed.
3. They will be invited to get comfortable, and complete the follow-up survey data:
   Breastfeeding Self Efficacy Scale
   Level of Breastfeeding Scale
   EPDS
   GAD-7
   Final Breastfeeding Daily Journal Form
   While the mother is filling out these forms, the baby will be undressed and weighed
4. After 10 minutes of rest or when the participant feels ready. The blood collection catheter will be inserted for blood collection.
5. The hand/ wrist of choice will be cleansed with alcohol prep and a small gauge needle inserted and taped down.
6. When baby is ready to feed, the participant will be helped as needed with positioning and allow the baby to latch and breastfeed.
7. When latch is established, blood samples for Oxytocin and Prolactin will be drawn, and kept on ice or room temperature according to laboratory guidelines. The blood sample requires 5-6cc for the specimens.
8. A timer will be set at the point of the first draw and after 20 minutes into the feeding session the second blood sample will be collected for Oxytocin and Prolactin. If feeding stops prior to 20 minutes, the blood will be collected at 20 minutes. The mother may offer the other breast if desired at any time. The blood sample requires 5-6cc for the specimens.
9. The remaining time will be spent providing the usual advice and assistance that the lactation provider would do in any usual visit, including weighing the baby after the feeding.

(time of entire visit is about 1 hour, time for study data collection 30-40 minutes)

Four Week Follow Up Survey (survey text / email to participants in appendix)

1. Breastfeeding Self-Efficacy
2. Level of Breastfeeding
3. Infant Weight (self reported)
4. EPDS
5. GAD-7
6. Breastfeeding Assistance Utilized
7. Descriptor of infant behavior (taken from daily breastfeeding journal)
8. CTQ: Childhood Trauma Questionnaire and Recent Traumatic Events Scales

5) Data and Specimens

a. Handling of Data and Specimens

Data from surveys, medical record data and blood specimens will be recorded with participant ID number only.
The informed consent forms, journals and paper surveys will be kept in locked file cabinet in the office of Dr. Emeis until they can be entered into REDCAP software database.
Specimens will be centrifuged and stored in a -80 degree Celsius freezer with the Women's Health Research Unit.
Blood samples will be stored until the final samples are collected and can be processed as a batch for Prolactin by the OHSU Endocrine Lab at the Primate Center (approximately 1 year).
Blood samples will be shipped to Indiana University (Bloomington IN) for processing of Oxytocin and Vasopressin assays.
Study Co-I will be responsible for specimen collection, and transport to storage and finally to the primate center or Indiana University.
Transport will be done using biohazard containers that allow for specimens to remain frozen until analysis can take place.

b. Sharing of Results with Subjects

The results of the blood work are not intended for clinical use, thus these will not be shared individually with participants
Study results, after publication will be disseminated to participants who indicate they would like a copy at the conclusion of the study.
The prolactin/oxytocin levels obtained during this study are not for clinical diagnostic purposes and will not be shared.
In the event of high ratings on depression or anxiety scales or if any disclosure of self harm or homicidal ideation occurs, the the study investigator will ensure immediate safety of the mother and baby and then initiate a referral to their primary OB caregiver.

c. Data and Specimen Banking

Data and specimens will not be stored for future research.

6) Data Analysis

Using REDCap and STATA programs the data will be entered, cleaned, analyzed descriptively followed by linear/multiple regression models to answer study questions and address hypotheses. Logistic regression models may also be used depending on the nature of the variables. Consultation for statistical analysis is accounted for by the budget and will be provided by Dr. Nathan Dieckmann, PhD at the School of Nursing.

7) Privacy, Confidentiality and Data Security

1. Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information.
2. Electronic files for data analysis will contain only the subject code.

3. Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN)
4. The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff.
5. The key will be kept secure on a restricted OHSU network drive in a limited access folder.
6. Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study.
7. Study staff will be trained with regard to these procedures.
8. Paper files will be stored in locked filing cabinets in Dr. Cathy Emeis' office in a restricted access building at OHSU.
9. Electronic survey data will be stored in a web-accessible REDCap account housed on an OHSU secure server.
10. Access to data/specimens is restricted to study personnel.
11. Access to data requires OHSU ID/password authentication.
12. Specimens not processed or any residual blood specimen after processing will be disposed—approximately one year after the study begins enrollment.
13. Data/specimens released to other investigators will be labeled with only the code.
14. De-identified data obtained throughout the study will be kept in REDCap for three years after study completion at which point it will be deleted.
15. Consent forms and data abstraction forms will also be destroyed after three years.

8) Risks and Benefits

a. Risks to Subjects

1. Foreseeable Risks:
    a. Fatigue or emotional feelings may be experienced during survey data collection due to personal or embarrassing nature of questions which may be upsetting
    b. Pain related to venipuncture and insertion of catheter. Bruising, infection or fainting are also rare but possible risks due to venipuncture. Swelling at the site of insertion, erythema or pain can also occur. There is a rare risk of a blood clot from venipuncture with a catheter.
    c. Experience a mildly increased feeling of stress related to the heightened attention given to their breastfeeding experience.
    d. Time burden. Typically, women will participate in lactation visits when breastfeeding is not going well, however, all first time mothers are encouraged to have a lactation visit. If some participants are not in need of additional help, this visit may be an inconvenience.
    e. Breach of confidentiality.

2. Protection against risk:
    a. If subjects become fatigued, they can choose to delay or discontinue answering questions until they see fit to resume.
    b. If the Lactation Consultant/Advanced Practice Registered Nurse is unsuccessful on the second venipuncture attempt, every attempt will be made to find another qualified personnel to perform the venipuncture. The blood collection will also be stopped if the participant requests it.
    c. Women will be given a reminder phone call regarding the upcoming study appointment, participants have the opportunity to opt out at any time including cancelling the lactation outpatient appointment.
    d. To minimize risk to any subject confidentiality, all data will be coded with unique and anonymous alphanumeric identifiers. All electronic data will be collected and kept in password-protected databases and program files.

b. Potential Benefits to Subjects

1. Participants may benefit from a heightened awareness of the breastfeeding experience, as well as attention provided to the mother and/or baby during the individual lactation follow-up visit. The data collection tools used as in the breastfeeding journal may help the lactation provider better serve the patient with more complete record of breastfeeding than memory alone. This potential benefit is likely to be small and only last through the immediate follow-up period.
2. Because all subjects will be screened for depression and anxiety after birth and one week, postpartum; any concerning score would prompt a recommendation to follow up with the appropriate health care provider. This benefit may provide significant benefit if depression or anxiety is identified as women are usually screened between 2 and 6 weeks postpartum routinely.

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