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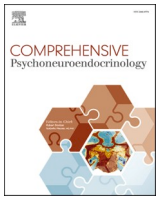

A prolonged latent phase: An early career in oxytocin during birth☆

1. Ghosts from the nursery

In the early 2000's, as a relatively new graduate Certified Nurse-Midwife, I worked with oxytocin daily in a busy southside Chicago hospital birthing unit. As a commonly used pharmacotherapy, I managed a steady stream of labors and births day and night using oxytocin for labor stimulation and for managing postpartum uterine bleeding following the delivery of the placenta. At the time, my knowledge of the function of endogenous oxytocin was limited to a cursory endocrine understanding of the infamous '*positive-feedback*' loop taught in all basic anatomy and physiology courses and of course also for milk-ejection. That is, with advancing cervical dilation more oxytocin is released by the maternal hypothalamus leading to more uterine contraction, greater cervical dilation and more oxytocin. Indeed, this belief that oxytocin is fundamental and necessary to maintain human labor, thus justifying administration to the majority of laboring mothers today in the United States, has become the lifeblood of my scientific career.

A chance stroll through a used bookstore on a chilly fall day in Chicago led me toward a new way of thinking about the birth process, maternal experiences, birth complications and the origins of behavior. Until this day, I already believed in the importance of the birthing process. As an undergraduate at the University of Michigan, a Women's Studies course on Women's Health taught by (now) renown Nurse-Midwife researcher, Dr. Lisa Kane Low [1], introduced me to women's reproductive health in a way that felt simultaneously grounding and horrifying. Using a feminist framework, I, alongside a hundred other 19-year-olds, absorbed the complicated history of current obstetric and gynecologic clinical practices with many misogynist or racist underpinnings [2–4]. We viewed videos of empowered births that challenged the dramatized childbirth narrative of mainstream media. We devoured papers on the historic exile of midwives in the early 1900s, who had been the shepherds of physiologic human birth for millennia. I was also inspired by my professor's research about birth companions (i.e., doulas) and how social support could positively change the course of a birth and safeguard this transformative time [5,6]. I eagerly gulped down this new knowledge, and I changed from whatever major I was planning to pursue that week of my sophomore year, to nursing; my path to become a nurse-midwife with an interest pregnancy research. I never looked back or regretted this choice.

However, about 7 years later, with a Bachelors and a Masters degree mounted to my wall,— a new, albeit circuitous, path to my sciencing life was cleared. The book I found that day within the dusty and worn stacks, Ghosts from the Nursery: Tracing the Roots of Violence (Kerr-Morse & Wiley, 1997) [7] stimulated an entirely new way of thinking about my role as a nurse-midwife in birth process, early brain development and maternal care through the lens of behavioral neuroscience. While this book did not mention oxytocin exactly, reading it led me to search the contemporary scientific literature about the neuroscience of maternal care, within which the study of oxytocin was ubiquitous [8–10]. In particular, I was struck by the revelation that oxytocin modulates the hypothalamic-pituitary-adrenal axis in such a way that confers protection and buffers against corticosteroids [11–13], and works to enhance opioidergic [14–16] signals broadly speaking. If oxytocin was a critical driver of the physiology of parturition, I thought, then why is it painful, stressful and scary for so many living through it?

Back at the bedside, I remember a 3:00 a.m. revelation: I might not *just* be ordering a uterotonic hormone when I started 30 Units of oxytocin in Lactated Ringers solution to stimulate a slow labor. The questions came quickly thereafter: *What did exogenous oxytocin do to the endogenous production? Were there any long-term effects of this medication? Do individuals who receive this medication in labor have better (or worse) lactation? Do they have different mood profiles after birth? Could this be linked to postpartum mood disorder and bonding? Why do some people seem to need a lot of this drug, while others do not? Why do some people seem to bleed more heavily after oxytocin use during labor? Why do people with continuous labor* support *seem to avoid having their labors slow down and seem to cope better—how was that physiologically possible? How could I go about studying all these questions?*

2. A foray into behavioral neuroscience

As it turned out, Dr. C. Sue Carter [17–19] was also in Chicago, at the University of Illinois Chicago, my alma mater for my Masters of Science

☆ The plan almost worked. In my first year, I wrote a National Science Foundation graduate research proposal for an Honorable Mention, then I wrote a National Institutes of Health (NIH) National Research Service Award (F31) through the National Institute of Nursing Research, which was awarded. It was also the early months of 2009 and the Great Recession had caused hardships across the lab. I had to work more than what a graduate stipend would provide to keep the condo where my husband (also a graduate student) and I lived, and there were no home buyers those days. Funding for science had been severely cut in 2008 and the downstream effect for the first-year graduate student was a vanishing number of available voles for experiments. I was told I could pivot and work on neurodegeneration or some other neurobehavioral outcome in another lab, but at the time, it did not make a lot of sense for a hopeful midwife scientist only interested in oxytocin-adjacent neuroscience. I declined the award.

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in nurse-midwifery. She was among the few professors who was kind enough to take the time to respond to a random email from a wide-eyed clinician with many questions. Before meeting Dr. Carter, I knocked on the virtual doors of biological anthropologists, endocrinologists, biopsychologists and others. She invited me to her office in 2007 and told me she had been wondering many of the same things about oxytocin for a long time and (as many people naturally do when speaking to a midwife) proceeded to tell me the birth stories of her own children. Dr. Carter, for most readers of this essay, needs no introduction, but it is worth stating that without her influence and willingness to listen to my ideas, I likely would never have meaningfully developed this line of inquiry. For those unfamiliar, Dr. Carter entered science through the field of zoology and was a pioneer in the use of *Microtus ochrogaster* (prairie vole) for studying sex differences, steroid hormones and neuropeptides like oxytocin. She has an encyclopedic memory and my meetings with her left me with pages of notes and scores of papers to read.

She told me to come and work in her lab as a graduate student and build the prairie vole model for labor induction so we could study effects of oxytocin on maternal behavior. I applied and was accepted into the graduate program in behavioral neuroscience. I attempted to find my place as a 28-year-old with a proper clinical career and a mortgage amid a cohort of younger biology majors. I transitioned to a part-time midwifery practice while learning in the lab and studied full-time. During the day, I attended lectures on electrophysiology, cell biology and learned skills like vole dissection and immunohistochemistry. At night and on the weekends, I cared for humans giving birth and their families, probably attending 5–10 births each month. I experienced episodes of imposter syndrome, an emotional break or two and on more than one occasion I fell asleep in the darkened classroom during neuroanatomy lecture (apologies to Dr. Wirtshafter).

Together with my lab mate, now *Dr.* William Kenkel, PhD [20], we established a protocol for timing the induction of ovulation [21] in the prairie vole female but not allowing them to mate by keeping the male and female separated across a cage with a pheromone-permeable barrier. We figured we would need to conduct timed mating in the afternoons in order to expect the parturition to occur in the day hours of the 21st day of gestation—otherwise we would risk pups arriving overnight and we would miss the opportunity to do oxytocin treatments. We then rehoused the female with her littermate (another female) in order to not lose the pregnancy (which could happen if housed solo) and to have a naïve female control group. The plan was to administer different dosages of oxytocin to the dam before giving birth, conduct various behavioral tests for those who delivered normally (both on dams and pups), and then gather tissues for later quantification of oxytocin receptor gene (*OXTR*) expression, receptor quantification and DNA methylation from brain, uterine, mammary and blood samples.

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3. A new path through the Willamette Valley

It took me 5 years to return to science. After questioning my career path and struggling with how to move forward mentally and physically, I left Chicago for a new start in the Pacific Northwest. However, finding a new sense of purpose by establishing a midwifery practice in a rural hospital in Oregon was tempered the next year by living through the loss of my only sibling, my brother, to suicide. Over the next couple of years, I managed to work with Dr. Carter and Dr. Aleeca Bell, PhD [22] (another midwife-turned oxytocin researcher) on a paper summarizing our current thinking about how important oxytocin was to factors beyond the birth process itself [23]. This first academic publication for me in 2014, kept my mind from drifting too far from science and felt like an achievement after several rough years.

Gradually, I found my way back to an academic environment in Portland, Oregon. Having a year of 'maternal experience' of my own with my new son and more years of clinical practice, I realized that I was not content in an exclusively clinical role. Having maternal experience with lactation was particularly powerful, which I felt as a potent mood regulator for myself [24,25]. As I was drawn back to studying oxytocin, I decided to directly focus on the health of individual humans giving birth. I made the very deliberate choice to pursue a PhD where I could ask questions relevant to the care of parturition and help move the science behind the art of midwifery forward. Fortunately, Oregon had the second highest rate of births attended by midwives in the United States, and Oregon Health and Science University was kind enough to let me work as a clinical instructor attending births while in the PhD program.

Getting a PhD in nursing is different than other disciplines of science or humanities. The 'apprenticeship' model is less common. Registered nurses or advanced practice nurses are skilled professionals with years of experience (and earning potential), thus stepping into a full time, fully funded (i.e., low-paid) role as a doctoral student to work with a principal investigator on their research is unlikely to attract many applicants. Instead, the process is highly self-directed and structured around principles of research design, methods, analytic skills and research critique. I found synergy with Dr. Cathy Emeis, PhD [26] who led the midwifery education division and was willing to take me on as an advisee. I brought my past experience, albeit abbreviated, in neuroscience to develop a line of study around how oxytocin given exogenously is related to both occurrence of postpartum hemorrhage and the physiology of lactation/breastfeeding.

4. Dot-to-dot: oxytocin function from labor to postpartum

My oxytocin-related research deepened and accelerated quickly, spurred by pep talks from Dr. Carter, who remained on my committee, and a healthy fear of failure. First I published an integrative review of the literature addressing one of those early questions that had come to me nearly 10 years prior, how does exogenous oxytocin given during the birth process influence or relate to later breastfeeding and lactation physiology and clinical outcomes? [27].

We found that most researchers were not directly reporting these outcomes, but among those that did, some consistent findings about differences in the newborn's early feeding cues or behaviors were diminished after birth involving oxytocin [28–30]. We found a few studies about postpartum oxytocin (given for preventing and treating bleeding), though the findings were inconsistent and methods varied greatly to limit comparability as well. Ultimately, the synthesis was that there were a limited number of studies addressing this difficult to study issue, though the effect on the infant was the most consistent line of study available. Another clear conclusion was that the use of oxytocin during labor and birth was difficult to separate from the rationale for the use of the medication; i.e. was the effect of postpartum oxytocin on lactation due to medication or the underlying condition of a long labor or postpartum bleeding/hemorrhage?

I thought this link needed to be further developed, thus, I conducted two studies examining effectiveness of oxytocin used prophylactically after delivery for preventing postpartum hemorrhage. I was specifically

interested in understanding if it would be efficacious among those without any oxytocin during labor for stimulating labor. Presumably, most of these labors proceeded without being prolonged or dysfunctional, thus would not we expect the uterine contractility to be maintained postpartum? Using a meta-analytic approach, we examined randomized controlled trials that only enrolled non-stimulated labors and examined postpartum hemorrhage following prophylactic oxytocin or non-pharmacologic third stage management. Interestingly, only a few RCTs from the 1990s have specifically studied individuals who labored without oxytocin stimulation and had a vaginal birth. Collectively, we found that neither clinically defined postpartum hemorrhage (1000 mL blood loss) or the need for a blood transfusion was reduced with prophylactic oxytocin [31].

The second study utilized the robust clinical dataset being gathered by the nurse-midwifery practice at Oregon Health and Science University on all births from 2012 [32]. I had recently been introduced to the latent mixture (latent class) analytic approach and felt it was highly relevant to the study of childbirth. Given the complexity and heterogeneity of factors that converge to determine the health and wellness of a mother and infant, I wanted to apply this technique to help discern clusters of people/births that were most similar together. In applying this approach, we expanded prior work in a meaningful way. Using these real-world data (not from an RCT), clusters of births that were more physiologically driven (i.e., few complications, little need for oxytocin in labor, etc.), prophylactic oxytocin after birth was not associated with reduced blood loss. We did see this effect among the labors that were more dysfunctional or complicated by longer, more stimulated labors. I began to think more deeply about what connects the progress of labor to the presence/efficacy of postpartum uterine contractions (with the proxy variable of postpartum hemorrhage) and the traits that could connect this often-seen clinical situation.

In addition to these cross sectional/secondary studies, I recruited participants who received little to no oxytocin during labor/postpartum and compared their levels of plasma prolactin, oxytocin and vasopressin to those who had labor/birth oxytocin in the first few days after giving birth. Dr. Emeis and I brought newly delivered mothers and babies back to the clinic and drew blood samples twice during breastfeeding or pumping. We examined infant weights before and after feeding to look at milk transfer during feeding, tracked infant weight gain trajectories, calculated oxytocin dosages and measured symptoms of problematic lactation. Amazingly, I somehow managed to birth my second son in the middle of running this study!

In the end, this pilot provided knowledge about maternal plasma levels of oxytocin and birth and lactation variables. A longer duration of labor was associated with lower plasma oxytocin postpartum (these people also needed augmentation in labor) and lower oxytocin was also associated with the infant experiencing a higher percentage of weight loss from birth [33]. Taken together, these findings stimulated the next set of studies designed to further understand how the function of oxytocin varies from person to person. Before we could understand how exogenous oxytocin influences birthing experiences and health, we would need to first clarify variability in the oxytocin system related to these complex findings.

5. Transition to a deeper understanding

A few days after my dissertation defense and graduation, I was able to convince a review committee of the merits of these questions as well, as I applied for an early career training award from the National Institutes of Health K12 Building Interdisciplinary Research Careers in Women's Health. Having experienced the destabilizing effects of loss of research funding, I decided the best way to approach this future work was to frame my work from the perspective of the things other people (and funders) care about first. While I was fascinated by the nuance of lactation physiology and postpartum experiences of mothers and infants, no one was funding that line of inquiry. Furthermore, the silos of oxytocin-related science meant that discoveries in prairie voles were not on the radar of clinicians. PubMed searches for oxytocin studies in obstetrics result in lists of studies about how quickly or concentrated oxytocin can be given before clinical harms outweigh perceived benefits (shorter duration of labor) [34–36]. Few clinical obstetric studies were concerned with questioning the longer-term effects of exogenous oxytocin or labor induction. In fact, I have noted that the mere mention of this hypothesis can cause discomfort or disbelief among some audiences. Given my focus on third stage labor and the potentially fatal condition of postpartum hemorrhage in my dissertation, this was the more strategic approach to continue my research career.

Finding Dr. Leslie (Les) Myatt [37], a reproductive biologist, at my institution turned out to be a lucky discovery. He had agreed to serve as my primary mentor and had decades of experience in crafting obstetric outcome and mechanistic grant proposals. My study centered on examining DNA methylation patterns in *OXTR* between births with postpartum hemorrhage and control births with normal bleeding. Dr. Jessica Connelly [38], epigeneticist and expert in regulation of *OXTR*, close colleague of Dr. Carter, also agreed to mentor me in addition to the Epigenetics Consortium Director at OHSU, Dr. Lucia Carbone [39].

The premise for this proposal drew from the numerous studies of *OXTR* in the psychological and behavioral neuroscience literature that consistently found variations in epigenetic regulation and *OXTR* expression and *OXTR*-linked behaviors and function [40–42]. No one had examined this variation in regard to the most famous positive feedback loop: oxytocin function during childbirth. Postpartum hemorrhage is thought to be most commonly caused by uterine atony [43], or an inability of the uterus to contract effectively after birth leading to excessive blood loss from the placental attachment site. Uterine atony often (though not exclusively) follows problematic labors or ones where oxytocin was needed to maintain labor [44]. Often the labor difficulties are thought to cause the postpartum hemorrhage because the uterine muscle (myometrium) is fatigued from a long labor or the receptors are desensitized to oxytocin by the end of the birth [45,46]. While this mechanism is valid, it may not be the only reason for poor contractility. As a discipline we have not spent nearly as much time considering the hypothesis, having fewer *OXTR* in myometrium (because *OXTR* is inaccessible) is a mechanism for labor dysfunction and postpartum problems.

Across the next 18 months we enrolled 119 participants but were unable to reach the goal of 200 due to the start of the SARS-CoV-2 pandemic. With modified operations in the health system, I was unable to get into the lab to train in pyrosequencing for assessing DNA methylation as planned [47]. A gap in funding in the summer of 2020 also sent me back to full-time clinical practice for 6 months and complicated an early research career by working full time while trying to finish the research I started and teaching remotely (while having my 2nd grader attend Zoom school down the hall).

As luck would have it, I had proposed some pandemic-proof aims as part of my fellowship training proposal. I continued descriptive data analyses in clinical datasets, examining hemorrhage outcomes by the duration of oxytocin used in hospital births [48,49] and availability of oxytocin in community births (homebirth/birth centers) [50]. These studies continued to support the idea that intrapartum oxytocin was associated with more hemorrhage, although plenty of less complicated births were vulnerable as well.

Over the next couple years, despite pandemic delays and challenges, with generous support from mentors, we were ultimately able to finish analyses and publish the findings of the postpartum hemorrhage case-control study. We demonstrated that not only was DNA methylation associated with greater oxytocin needs through labor and birth but that there was higher blood loss as well, but only in births where oxytocin was used in labor [51]. In a secondary study, we found that a commonly studied the single nucleotide polymorphism (rs53576) was also predictive of postpartum hemorrhage, particularly for those with *less* exposure to oxytocin during labor [52].

In some ways, it may appear that this combination of studies about how oxytocin administered in labor relates to postpartum uterine atony and hemorrhage contradict each other. On one hand, we see that people who have more physiologically driven births (no oxytocin stimulation) have less atony and postpartum hemorrhage overall, compared to those that experienced stimulated labors. But then, why would those without oxytocin in labor not be helped by prophylactic postpartum oxytocin? Presumably, the uteri of these individuals are ready to respond to the drug, not having been exposed for hours beforehand. One answer might be that the primary cause of hemorrhage for non-stimulated labors is something other than uterine atony. Perhaps, instead, excess bleeding from genital tract lacerations is the cause [53]; therefore oxytocin treatment would not be protective. Another possibility is that the person's *OXTR* genotype makes uterine atony more likely, as these individuals may not readily respond to exogenous postpartum oxytocin, even when labor was 'normal'.

Some might question, how could labor progress normally for these people with less-sensitive receptors or less-available *OXTR*? For this answer we turn back to the question of whether oxytocin is actually required for human labor at all. While there is knowledge of higher endogenous production of oxytocin during human parturition [54]; studies using *OXTR* knockout transgenic mice demonstrate that oxytocin is not needed for conception or birth [55,56]. What OXTR was needed for, however, in these studies, was milk production and maternal behavior and normal metabolic regulation (*OXTR* null mice develop obesity) [57]. A particularly curious case series of women with panhypopituitarism illustrate the closest evidence in humans to the genetic knockout papers [58]. While all 4 of these individuals experienced labor onset without functional maternal pituitary contribution they all had problems arise during the final moments of giving birth along with postpartum hemorrhage followed by inhibited lactation.

6. Chance discoveries and good timing

The fortunate accident of Sir Henry Dale's discovery in the early 1900s transformed obstetric care. His experiments with the pituitary *substance* demonstrated that it caused uterine contraction of the cat, irrevocably affixing oxytocin to childbirth [59]. However, we have come to appreciate now in the broader community of oxytocin scientists that oxytocin regulates physiology far afield from birth and lactation [60]. True, these experiments showed that oxytocin was sufficient for uterine contraction. Also true, without a reliable uterotonic medication, many more mothers and babies would die (and continue to die worldwide) from difficult labor, infection and hemorrhage [61]. However, I would hypothesize now, that this functionality may actually be a backup system for human birth, as one of many redundant mechanisms or pathways [62], in case problems occur in the functionality of other more dominant molecules. Functional progesterone withdrawal [63,64], the availability of prostaglandin receptors [65,66] (not to mention fetal signaling/HPA readiness [67,68]) might actually be the main actors in labor onset and progression. Oxytocin, on the other hand, might help keep the uterus from bleeding out after delivery—being released by the maternal hypothalamus at the pinnacle of pushing—and priming the myoepithelial breast tissue to pump.

However, these physiological considerations do not change the reality that oxytocin and oxytocin receptors are relied upon in nearly all labors in the United States via exogenous administration. Labor induction methods are used in nearly one-third of labors [69] and approximately a majority of labors that begin spontaneously are augmented with oxytocin [70–73]. Besides our studies, a growing number of reports link exogenous oxytocin use to postpartum hemorrhage [74–78] and reconsideration of how to define 'normal' labor progress from labor needing intervention [79–81]. The findings we reported from our case-control hemorrhage study along with all of the clinical data papers may hint at a confluence of effects: genetic and environmental. That is, that sensitivity to oxytocin treatment may be dependent upon DNA methylation, genetic susceptibility and pharmacologic exposures.

We have since doubled down on these interesting findings by submitting new grant proposals to study this phenomenon in larger and more generalizable samples. In sharing this work recently with clinical audiences, I find that they are hungry for 1) a deeper understanding of this hormone/medication that simply does not seem to work well for some people and 2) possible answers to intractable hemorrhage rates in many settings. However, as a profession we are reliant upon it, given obstetrics has so few tools for supporting or altering the physiology of labor and birth [82–84]. In these discussions, I relay that the hope, one day, is for clinicians to have useful biomarkers by which to better manage oxytocin in labor or to predict those likely to be less sensitive to treatment and experience postpartum hemorrhage. In addition, this work may allow us to better study causes or associations with differential DNA methylation. Maybe we may understand how early life experiences or other exposures may influence how oxytocin works in the context of birth, not just in the behavioral sciences.

It also happens to be a good time to be asking these questions. Addressing maternal morbidity and mortality in the United States has become a social, policy and funding priority with growing awareness of shameful and discouraging population trends of rising maternal deaths [85] and exacerbated disparities between racial groups and economic strata [86]. The increasing clinical practice trends toward more labor inductions occurring earlier in pregnancy [1] is also likely, in my review of the evidence, to do nothing to reverse climbing rates of postpartum hemorrhage and blood transfusion [77,87]. We have a long way to go to uncover answers to variability in birth outcomes and develop new tools in obstetrics and midwifery.

7. The fabric of maternal health

With the help of a 'Pathway to Independence' K99/R00 award I was able to make an important next step: in 2022 I joined the faculty of The University of Arizona in Tucson. Being at a large academic research institution has helped expand this work, to connect to a new enthusiastic network of collaborators in precision medicine, pharmacogenomics, physiology and data science—all of whom were not previously considering how their disciplines, tools and expertise related to maternal health. I am now one year into the growth of my own lab, Mechanisms Underpinning Maternal Health (MuMH). With a few new doctoral students, I hope to share a fondness for thinking about the ways the pieces of perinatal experiences and physiology thread together to influence the fabric of mother and infant health.

From where I sit now, despite challenges of being an outsider in a field or discipline, I find that it pays to be a little bit different or to challenge dogma. While it feels alienating and inspires fresh imposter syndrome to be sharing a unique perspective in a conversation, it can also distinguish oneself among a group of research ideas. Being a midwife trying to get a graduate degree in neuroscience had challenges, but I found that bench and behavioral scientists have been some of the most encouraging voices, both in real time and in my head, later, when the chorus of inner doubt sings loudly. Being a midwife trying to participate in an epigenetics class full of researchers and students takes courage to speak up and ask questions, but it also provides an opportunity to learn how to communicate to a non-clinical audience. But as hard as these experiences have been, being a nurse-researcher trying to draw on behavioral, genetic and epigenetic methods to examine current clinical canon has been the most developmentally significant. I had to learn how to explain mechanisms and methods for studying oxytocin (and other perinatal physiology concepts) to skeptical medical audiences/students—to convince them that studying nuance of minutia could be valuable to our practice and the families in our care. I have often found it the most challenging audience to be "different" within and the one to which I ultimately need to communicate most effectively if this line of inquiry will ever have a maternal health impact.

Through these experiences, I have realized that difference is

important, but difference needs to be balanced with accessibility. Learning to effectively translate a philosophy or disciplinary approach to another requires being accessible to others; i.e., being able to understand others and helping them to understand you and your viewpoints. The ability to translate your perspectives and knowledge is probably the most important skill I have learned and wish to share with students. In learning to do so, I believe we can remain self-aware, open to critique, willing to get it wrong sometimes and start over. The friends I have made studying oxytocin, teaching and practicing the art of midwifery have taught me this.

Declaration of competing interest

No conflicts to declare.

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