A Review of the Potential Therapeutic Application of Vagus Nerve Stimulation During Childbirth

By

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“A Review of the Potential Therapeutic Application of Vagus Nerve Stimulation During Childbirth,”
a thesis by Tanya Enderli

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Abstract

Title: A Review of the Potential Therapeutic Application of Vagus Nerve Stimulation During Childbirth

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The goal of this research is to show that transcutaneous Vagus nerve stimulation (tVNS) should be investigated as a possible modality for increasing endogenous release of oxytocin during childbirth. There have been many great advances made in the practice of modern obstetrics in the last century. The 1900s saw the discovery, isolation, and subsequent widespread use of the hormone oxytocin as an agent to prevent postpartum hemorrhage and to initiate or quicken labor during childbirth. There are significant risks to the fetus when synthetic oxytocin is used. While the medical administration of oxytocin during labor was being popularized, there was also research being conducted on its physiologic mechanism in labor. A popular idea is that uterine contractions initiate a positive feedback mechanism by triggering a neural pathway that stimulates the release of oxytocin from the
pituitary gland, and that the oxytocin then strengthens the contractions which leads to more oxytocin being released, and so on. The use of labor analgesia also became widely used in the 1900s, and by midcentury methods had been described for administering analgesics into the epidural space of the spinal cord. Currently, the epidural is considered the gold standard in labor analgesia. However, there is some evidence that epidural analgesia may inhibit the oxytocin release mechanism by blocking the neural input needed to stimulate it, as women who have had an epidural tend to require synthetic oxytocin infusion more often than women who have not. Research on women with complete spinal cord injury has shown that the Vagus nerves provide an alternate neural pathway from the female reproductive system to the area in the brain that stimulates oxytocin release. It has also been shown that electrical stimulation of the Vagus nerve increases plasma oxytocin levels. Implantable VNS systems are impractical for a single use in pregnant women and may be why VNS has not been explored in obstetrics. However, if a noninvasive transcutaneous method is found to elicit the same response as traditional VNS then it might provide a clinically relevant alternative to using synthetic oxytocin during labor.
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABVN</td>
<td>Auricular Branch of the Vagus Nerve</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic Hormone</td>
</tr>
<tr>
<td>ATN</td>
<td>Auriculotemporal Nerve</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-Brain Barrier</td>
</tr>
<tr>
<td>CA</td>
<td>Catecholamines</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CES</td>
<td>Cranial Electrotherapy Stimulator</td>
</tr>
<tr>
<td>CSS</td>
<td>Cervical Self-Stimulation</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotropin Releasing Hormone</td>
</tr>
<tr>
<td>DVN</td>
<td>Dorsal Vagal Nucleus</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>GAN</td>
<td>Great Auricular Nerve</td>
</tr>
<tr>
<td>IU</td>
<td>International Units</td>
</tr>
<tr>
<td>LON</td>
<td>Lesser Occipital Nerve</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NTS</td>
<td>Nucleus Tractus Solitarii</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomographic</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>PMA</td>
<td>Premarket Approval</td>
</tr>
<tr>
<td>PPD</td>
<td>Postpartum Depression</td>
</tr>
<tr>
<td>PNS</td>
<td>Peripheral Nervous System</td>
</tr>
<tr>
<td>PVN</td>
<td>Paraventricular Nucleus</td>
</tr>
<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
</tr>
<tr>
<td>SON</td>
<td>Supra-Optic Nucleus</td>
</tr>
<tr>
<td>STA</td>
<td>Superficial Temporal Artery</td>
</tr>
<tr>
<td>TENS</td>
<td>Transcutaneous Electrical Nerve Stimulator</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotropin Releasing Hormone</td>
</tr>
<tr>
<td>tVNS</td>
<td>Transcutaneous Vagus Nerve Stimulation</td>
</tr>
<tr>
<td>VIP</td>
<td>Vascular Intestinal Peptide</td>
</tr>
<tr>
<td>VNS</td>
<td>Vagus Nerve Stimulation</td>
</tr>
</tbody>
</table>
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Chapter 1
Introduction

1.1 Background of the Study

One of the most important, although in many ways poorly understood, events in human life is birth. A baby can be delivered either vaginally or by cesarean section, a surgical incision made directly into the uterus through the abdomen (Posner, Jones, Dy, & Black, 2013). There is a risk of morbidities or mortalities occurring in either mother or child for both methods of delivery (Posner et al., 2013), but the American College of Obstetricians and Gynecologists recommends vaginal delivery unless there are medical indications for cesarean (ACOG, 2013). Labor that lasts much longer than usual is referred to as labor dystocia, and can indicate the need for cesarean (Barber et al., 2011; Posner et al., 2013). Endogenous, or internal, oxytocin release is associated with a positive feedback mechanism called the Ferguson reflex where sensory input from uterine contractions stimulates the posterior pituitary gland to release oxytocin which then stimulates stronger contractions (Ferguson, 1941). Therefore, if labor dystocia is caused by insufficient uterine contractions, then synthetic oxytocin may be used to stimulate stronger contractions and thus prompt the progression of labor (Posner et al., 2013).
In normal childbirth, one of the issues of greatest clinical significance is the management of labor pain, as the majority of women experience moderate to severe pain during labor (Posner et al., 2013). There are several pharmaceutical treatments available to mothers in labor, but the current gold standard in pain control during labor is epidural analgesia (Posner et al., 2013). There has been some controversy about whether epidural analgesia affects the Ferguson reflex (Saunders et al., 1989), but when the nerves that convey the sensations that control the reflex are considered it is possible that it does (Goodfellow, Hull, Swaab, Dogterom, & Buijs, 1983). Actually, epidural analgesia use is associated with a longer labor (Alexander, Lucas, Ramin, McIntire, & Leveno, 1998; Leighton & Halpern, 2002b; Posner et al., 2013), and this may contribute to the higher rate of synthetic oxytocin infusions required for women who have received an epidural (Goodfellow et al., 1983; Leighton & Halpern, 2002a, 2002b; Zhang, Klebanoff, & DerSimonian, 1999).

Some evidence exists that indicates that oxytocin promotes mother-child bonding (Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Skrundz, Bolten, Nast, Hellhammer, & Meinlschmidt, 2011), but oxytocin is not known to cross the blood brain barrier (Altemus et al., 2004; Landgraf & Neumann, 2004; Skalkidou, Hellgren, Comasco, Sylvén, & Poromaa, 2012). Therefore, oxytocin that is not released by the pituitary gland, which includes synthetic oxytocin administered
during labor, is not believed to act on the brain (Altemus et al., 2004). Also, while the risks of using synthetic oxytocin are not generally life-threatening to the mother, there are some side effects related to its use that can be quite dangerous to the fetus (Posner et al., 2013). Another potential downside when comparing synthetic oxytocin administration to endogenous oxytocin release is that oxytocin is generally infused at a constant rate whereas oxytocin release from the pituitary gland occurs in a pulsatile manner (Simpson, 2011).

Recently, the Vagus nerve has been found to innervate the cervix of women (Komisaruk, Beyer-Flores, & Whipple, 2006; Komisaruk et al., 2004). In studies conducted on women with complete spinal cord injury (SCI) above the level of sensory input from the reproductive system it was found that cervical stimulation activated the area of the brainstem where Vagus nerve fibers enter, and if the woman reached orgasm it was also seen that the part of the brain that stimulates oxytocin release from the posterior pituitary was activated (Komisaruk et al., 2004). Research has also shown that electrical Vagus nerve stimulation (VNS) results in an increase of blood flow, indicating activation, to this region (Henry et al., 1998; Narayanan et al., 2002). However, there have not yet been any studies to determine if there is a potential clinical application of VNS to increase oxytocin release during labor.
1.2 Problem Statement

The current state of the art in labor pain management is epidural analgesia, which essentially functions as a nerve block for input from the reproductive organs to the spinal cord and brain (Posner et al., 2013). While the blocking of sensory input does produce analgesia, there is some evidence suggesting that women who receive epidural analgesia are more likely to require an infusion of synthetic oxytocin during labor (Alexander et al., 1998; Goodfellow et al., 1983; Leighton & Halpern, 2002a, 2002b; Zhang et al., 1999). The importance of oxytocin in childbirth cannot be understated, as it has a well-documented role in inducing uterine contractions (Caldeyro-Barcia & Poseiro, 1959; Dale, 1906; Den Hertog, De Groot, & Van Dongen, 2001; Ferguson, 1941; Magon & Kalra, 2011; Posner et al., 2013). Therefore, if medical interventions to control pain cause the blockage of the main pathway by which sensory input regulates endogenous oxytocin release, then any possible alternate nerve pathways should be assessed to determine their efficacy in stimulating this release.

It is now well established that VNS is an effective treatment for epileptic seizures (George et al., 1995; Woodbury & Woodbury, 1990; Zabara, 1992) and depression (Bajbouj et al., 2010; Christmas, Steele, Tolomeo, Eljamel, & Matthews, 2013; Daban, Martinez-Aran, Cruz, & Vieta, 2008; Eljamel, 2015). The VNS systems
that are currently approved by the Food and Drug Administration (FDA) consist of a device implanted under the skin with lead wires running from the device to the branch of the Vagus nerve in the neck (Howland, 2014). The invasive surgical implantation of a medical device to assess if it stimulates the release of oxytocin in childbirth would clearly be a laughable topic if it were to be presented to any Institutional Review Board, especially given the ready availability of synthetic oxytocin that can be used instead. However, it has been found that there is a branch of the Vagus nerve that extends to the external ear (Ellrich, 2011; Frangos, Ellrich, & Komisaruk, 2015; Howland, 2014), and that electrical stimulation to the skin over these nerves results in a response in the brain that is similar to direct VNS (Frangos et al., 2015; Kraus et al., 2013).

This method, called transcutaneous Vagus nerve stimulation (tVNS), has not been approved by the FDA, although tVNS systems have been approved of and are in use in Europe. However, tVNS is considered safe and well tolerated (Busch et al., 2013; Lehtimäki et al., 2013; Stefan et al., 2012), and tVNS of the Vagus branch in the external ear has even been performed using cranial electrotherapy stimulator (CES) units (Hein et al., 2013; Howland, 2014), which have been approved by the FDA for treating anxiety, depression, and insomnia. Given the fact that VNS has been shown to activate the region of the brain that stimulates oxytocin release and that tVNS offers a noninvasive alternative to implanted VNS systems, the goal of
this research is to present an argument for the potential application of tVNS in labor for increasing endogenous oxytocin release.

1.3 Objectives of the Study

This study will identify the anatomical structures, neural pathways, and endocrine factors relevant to childbirth. The development of the current understanding of each of these will be discussed throughout the review. A specific focus will be placed on the nervous system to establish the currently accepted understanding of sensory transmission during childbirth. The literature review will highlight medical interventions currently used in obstetrics as well as potential impacts they might have on the childbirth process.

Another goal of this study is to identify key points that need to be researched in order to determine the feasibility of using tVNS for increasing oxytocin release during childbirth. This will include a discussion on the lack of empirical data showing the safety of using VNS during pregnancy due to the exclusion of pregnant women from VNS studies. It will also propose which preliminary studies should be conducted in healthy humans to properly develop the technology before performing any trials on pregnant women.
1.4 Limitations of the Study

Currently, there is no evidence directly showing the involvement of the Vagus nerve in human labor and delivery. The lack of scientific evidence means that the entire concept of this thesis is theoretical. Functional magnetic resonance imaging studies on the female sexual response have shown that the Vagus nerves directly innervate the female reproductive system and facilitate orgasm in women with complete SCI (Komisaruk et al., 2004). Therefore, it has been assumed that the Vagus nerve might also play a role in facilitating the mechanical process of labor and delivery.

With the understanding that there is no published data on using VNS in any form as an application in labor and delivery nor any known laboratory research currently being conducted for this application, the argument presented in this thesis is therefore limited to a literature review of the physiology of the female reproductive system in both sexual response and childbirth, the involvement of the nervous and endocrine systems during labor and delivery, any medical interventions that might affect the role of these systems, the applications, methods, and effects of VNS, and any relevant research pertaining to childbirth as the basis for the reasoning behind the research goal. Every effort has been made to synthesize this research into a
logical argument, and discussions are presented in cases where the literature has been found to be contradictory of itself.
Chapter 2
Anatomy Review

2.1 Primary Anatomical Structures of Birth

It is well understood that to learn about labor and birth one must first know the parts that comprise the female reproductive system and what functions they perform in this process. Indeed, the first few chapters of one of the earliest published compilations of conventional knowledge on midwifery consist of a description of what the muscles and membranes of the body are followed by a detailed review of the anatomical structures of the female reproductive system (see Figure 1) (Hobby, 2009). The same format was used over 100 years later in one of the first textbooks on obstetric medicine, which begins with a comprehensive overview of the anatomy of the female reproductive system before listing the contents of the book itself (Mauriceau, 1697). Modern textbooks tend to follow the same format of reviewing female reproductive anatomy before presenting any other content (see Figure 2) (Dewhurst & Edmonds, 2007; Posner et al., 2013; Pritchard & MacDonald, 1976; Schumann, 1937), or may give a brief history of obstetrics followed by a review of the anatomy involved in childbirth (Bookmiller & Bowen, 1954), but it appears that in presenting any approach to childbirth authors feel that
it is first necessary to inform the reader of the relevant anatomy and physiology involved.

Figure 1 – Sixteenth Century Drawing of Female Reproductive System
(Hobby, 2009)
Anatomical terminology has changed over the centuries and the current understanding of the female reproductive system is much more complex than it was in the formative years of obstetric medicine, but little has changed in regards to agreement about the gross anatomical structures involved in childbirth.
Specifically, the uterus, cervix, and vagina are the main parts of the reproductive system that accomplish parturition, or birth, and thus comprise the birth canal (Schumann, 1937). It was known at least as early as the sixteenth century that the fetus is enclosed in the uterus during gestation and that the cervix, a narrow passage connecting the vagina to the uterus, remains tightly closed during pregnancy but during childbirth dilates many times its normal size until it is large enough to accommodate the passing of the fetus’ head out of the uterus and through the vagina for delivery (Hobby, 2009).
Chapter 3
Review of Childbirth Process

3.1 Overview of Parturition

Parturition is a complex event with many physiological and anatomical changes occurring over a relatively short time. The whole process is broken down into three stages of labor (Posner et al., 2013). Parturients are categorized as either nulliparas, if they have not given birth before, or multiparas, if they have (Posner et al., 2013).

By the start of labor the cervix should be ripe, which is defined as soft, shorter than 1.3 cm in length, easily admits a finger and is dilatable (Posner et al., 2013).

The period between onset of labor and full cervical dilation is the first stage of labor, and generally lasts between six to eighteen hours for nulliparas and two to ten hours for multiparas (Posner et al., 2013). The second stage of labor begins when the cervix is fully dilated and lasts until the baby is born, and the third stage of labor is the period between the expulsion of the baby from the birth canal and the delivery of the placenta (Posner et al., 2013).

The duration of the second stage of labor is largely dependent on parity and whether or not the mother received epidural analgesia, a nerve block for labor pain (Posner et al., 2013). Multiparous women with two or more previous births tend to
labor a quarter of the time as nulliparas, and women who have received epidurals tend to labor almost twice as long as women of the same parity who have not (see Table 1) (Posner et al., 2013). The duration of the third stage of labor is considered abnormal if it takes longer than thirty minutes (Posner et al., 2013).

Table 1 – Duration of Second Stage of Labor in Minutes (Posner et al., 2013)

| Parity | Epidural | | | No Epidural | | |
|---|---|---|---|---|---|
| | Median | IQ Range | Median | IQ Range |
| 0 | 82 | 45-134 | 45 | 27-76 |
| 1 | 36 | 20-77 | 15 | 10-25 |
| 2 | 25 | 14-60 | 11 | 7-20 |
| 3 | 23 | 12-53 | 10 | 5-16 |
| ≥4 | 22 | 9-30 | 10 | 5-15 |

*IQ, interquartile range (25%-75% of the population).*

3.2 The First Stage of Labor

The first stage of labor consists of three main phases: the latent phase, the active phase, and the descent of the presenting part (Posner et al., 2013). The latent phase begins with the mother feeling strong, regular contractions of the uterus that progressively get stronger and more coordinated (Posner et al., 2013). Also during this time the cervix is becoming softer, pliable, and elastic (Posner et al., 2013). The active phase begins when the cervix is dilated between 3 to 4 cm for nulliparas
and 4 to 5 cm for multiparas, and during this phase cervical dilation continues until it reaches about 10 cm, or full dilation (Posner et al., 2013). The descent of the presenting part refers to the descent of the fetus through the birth canal, and while it begins in the latent phase it mostly occurs when the cervix reaches full dilation and progresses into the second stage of labor (Posner et al., 2013).

### 3.3 The Second Stage of Labor

There are two separate phases in the second stage of labor, passive and active (Posner et al., 2013). In the passive stage, the cervix is fully dilated but the fetal head has not reached the pelvic floor and expulsive efforts have not yet begun (Posner et al., 2013). Once the fetal head is at the level of the pelvic floor or lower the active phase begins, in which the mother engages in pushing (Posner et al., 2013). As the mother pushes, the contractions push the baby lower in the birth canal until the head emerges from the vagina (Posner et al., 2013). After the birth of the head one final push delivers the shoulders, and generally the rest of the body then slides out without effort (Posner et al., 2013). After the baby is delivered, the umbilical cord is clamped and the second stage of labor ends (Posner et al., 2013).

### 3.4 The Third Stage of Labor

The third stage has two parts: separation of the placenta from the uterine wall and expulsion of the placenta through the birth canal (Posner et al., 2013). Placental
separation usually occurs within five minutes of the end of the second stage of labor (Posner et al., 2013). Expulsion of the placental is done by tractioning the cord while applying pressure to the uterus just above the symphysis pubis of the pelvis, a technique referred to as the Brandt-Andrews maneuver (Posner et al., 2013). The delivery of the placenta ends the third stage of labor, and thus completes the birth.

### 3.5 Birth by Cesarean Section

Cesarean section is a form of delivery where the fetus is removed from the uterus through a surgical incision in the abdomen (Posner et al., 2013). Current cesarean rates are between 25-30 percent (Posner et al., 2013), although the World Health Organization has suggested that the rate should be between 10-15 percent (WHO, 2015). There are a number of indications for cesarean section, such as fetopelvic disproportion, where the fetal head is too large to pass through the birth canal, malpresentation or malposition of the fetus, labor dystocia, or labor that lasts much longer than usual, previous cesarean surgery, and fetal distress (Posner et al., 2013). The fetal mortality rate in cesarean procedures is higher than that of vaginal delivery, but that is primarily attributable to the conditions for which the cesarean was indicated (Posner et al., 2013).
4.1 Nervous System Overview

The nervous system consists of a central nervous system (CNS) and a peripheral nervous system (PNS). The CNS includes the brain and spinal cord (Nathan, 1997), and the PNS is comprised of the cranial, spinal, and autonomic nerves ("Nervous System," 2016). The brain has several major divisions, including the cerebrum, basal nuclei, mid-brain, pons, cerebellum, and medulla oblongata ("Brain," 2010), and the spinal cord is a cylindrical structure that is continuous with the medulla oblongata and extends through the spinal column to give off the spinal nerves of the PNS ("Spinal cord," 2010).

These nerves include eight cervical nerves (C1-C8), twelve thoracic nerves (T1-T12), five lumbar nerves (L1-L5), five sacral nerves (S1-S5), and a coccygeal nerve (Co) (See Figure 3) (Netter, 2014). At about the level of L1 the spinal cord starts to branch out and separate into a bundle of the remaining spinal nerves, referred to as the cauda equina (Netter, 2014). The brain and spinal cord are protected by a sheath of three layers of tissue called the dura mater, arachnoid mater, and pia mater that collectively are referred to as the dural sac (Netter, 2014).
This sac also encases much of the cauda equina, but it terminates at about the level of S3 (Netter, 2014). There are also twelve cranial nerves, and with the exception of the hypoglossal nerve, or the twelfth cranial nerve, they all directly innervate the brain without any fibers passing through the spinal cord (See Figure 4) (Netter, 2014).
Figure 3 – Spinal nerve roots exiting the CNS (Netter, 2014)
Figure 4 – Motor and Sensory Distribution of the Cranial Nerves to the Brain (Netter, 2014)
4.2 The Spinal Cord

The spinal contains both white matter, which contains mostly myelinated neurons, and gray matter, comprised mainly of nonmyelinated neurons, arranged such that the gray matter has a shape somewhat like a butterfly and is surrounded by white matter (See Figure 5) (Nathan, 1997; Netter, 2014). Spinal nerves terminate and originate in the grey matter, with afferent, or sensory, input entering through the posterior portion, or dorsal horn, and efferent, or motor, output exiting through the anterior portion, or ventral horn (Nathan, 1997; Netter, 2014). The gray matter has been further compartmentalized into ten subunits, called laminae, that correspond to localized differences in cellular structure (Rexed, 1952). These subunits, commonly referred to as Rexed laminae, were first described based on anatomical findings in the cat, but have been used as a model to describe human anatomy and physiology, as well (Bonica, 1979; Schoenen, 1982).

![Diagram of Cross Section of Spinal Cord](Nathan, 1997)

Figure 5 – Diagram of Cross Section of Spinal Cord (Nathan, 1997)
4.3 The Autonomic Nervous System

Autonomic nerves are not under voluntary control, and can be further broken down into the sympathetic and parasympathetic nervous systems (See Figure 6 and Figure 7) ("Nervous System," 2016). However, the autonomic nerves are not entirely separate from the cranial or spinal nerves. Sympathetic input to the CNS is relayed first to sympathetic nerve ganglion and then to the spinal nerves via structures called white and gray ramus communicans (Netter, 2014). Parasympathetic nerves at the spinal nerve level, on the other hand, do not have rami communicans; rather they connect directly to the spinal nerves (Netter, 2014). Interestingly, a few of the cranial nerves, including the oculomotor, facial, glossopharyngeal, and Vagus nerves, are, in fact, part of the parasympathetic nervous system (Netter, 2014). Also, it has been established that emotions can influence the autonomic nervous system ("Nervous System," 2016). The sympathetic system tends to be activated by negative feelings such as rage and fear whereas the parasympathetic system regulates bodily functions while one is relaxed and peaceful (Nathan, 1997).
Figure 6 – Sympathetic Nervous System (Netter, 2014)
There are many substructures within the primary divisions of the brain that have specialized functions. One of these is the hypothalamus, which is found in the basal nuclei of the brain ("Brain," 2010). The hypothalamus is believed to be the structure that regulates the autonomic nervous system, and is the site that controls primitive physical and emotional behavior ("Hypothalamus," 2010). It also has

**Figure 7 – Parasympathetic Nervous System (Netter, 2014)**
centers that regulate metabolism, sleep, body temperature, and sexual function ("Hypothalamus," 2010). The primary nervous structures of the hypothalamus include the paraventricular, posterior, dorsomedial, supra-optic, ventromedial, arcuate, and mammillary body nuclei (Netter, 2014). Of these, it is the paraventricular nucleus (PVN), supra-optic nucleus (SON), and arcuate, or infundibular, nucleus which have neurons that project into the pituitary gland via the pituitary stalk, or infundibulum (See Figure 8) (Netter, 2014). The pituitary gland, while connected to the hypothalamus, is actually part of the endocrine system ("Pituitary gland," 2010). Endocrine involvement in parturition is discussed in Chapter 6.

Figure 8 – Diagram Showing Neural Projections of PVN, SON, and Arcuate Nuclei From Hypothalamus to Pituitary Gland (Netter, 2014)
Chapter 5
Innervation of Female Reproductive System

5.1 Background and History

The modern idea that the brain oversees voluntary motion and interpretation of sensory information was first proposed in a scientific sense by Galen (130 – 210 A.D.), whose experiments with nerves allowed him to identify both that there are separate nerve roots now known as the afferent and efferent nerves, and that damage to the spinal cord results in partial or total loss of their function (Riese, 1959). Regarding childbirth, Galen believed that labor was caused by the head of the fetus stimulating the nerves of the cervix and lower uterus as it began its descent through the birth canal, a possibility still accepted by modern medicine as a potential cause of the onset of labor (Schumann, 1937).

The nerves of the uterus, referred to as the womb, were described by Mauriceau as originating from the “sixth pair of the brain” and the spinal cord (Mauriceau, 1697). At the time, the sixth pair of nerves was used to describe the three cranial nerves now known as the glossopharyngeal, Vagus, and accessory nerves (Swanson, 2014). These are the ninth, tenth, and eleventh cranial nerves, respectively, but it is
only the Vagus nerve that has fibers that project inferior to, or below, the shoulder line in the human (See Figure 3) (Netter, 2014). As mentioned previously, the Vagus nerve is also one of the cranial nerves that comprises the parasympathetic nervous system (Netter, 2014). Interestingly, Mauriceau attributed the shared innervation of the sixth pair of nerves between the stomach and womb to nausea experienced during pregnancy and even suggested that vomiting during childbirth hastens delivery (Mauriceau, 1697). It does not appear that any modern research has been done to determine if there is any truth to that claim, but there are cases not related to childbirth where emesis can be induced or ceased by modifying Vagus nerve function (Lang, 1999).

Modern anatomy and obstetric textbooks do not acknowledge that the female reproductive system is directly innervated by the Vagus nerve. Some claim that labor is regulated exclusively by the sympathetic nervous system and spinal nerves (Pritchard & MacDonald, 1976; Schumann, 1937). Others only mention the parasympathetic system in discussions on topics not directly related to childbirth such as urinary incontinence (Dewhurst & Edmonds, 2007) Moreover, some textbooks do not even mention the nerves of the reproductive system except in discussing what nerves to apply a block to in labor analgesia and anesthesia (Posner et al., 2013; Pritchard & MacDonald, 1976). It was previously suggested that parasympathetic nerves may have afferent fibers that extend to the uterus (Moir,
1939; Robertson & Guttmann, 1963), and it is now shown in anatomy books that both afferent and efferent parasympathetic fibers do indeed innervate the lower uterus, cervix, and upper vagina (Netter, 2014). However, the pathway for this is believed to be associated only with the sacral spinal nerves and not the Vagus nerve (Moir, 1939; Netter, 2014). More recently, it has been shown that women with complete spinal cord injury above the level of T10, meaning that they receive no sensory input from the reproductive system through the CNS, are capable of experiencing an orgasm through mechanical stimulation of the vagina and cervix, presumably modulated by afferent Vagus nerve fibers extending from these structures (Komisaruk et al., 2004).

5.2 Sensory Nerves

Generally speaking, afferent nerve fibers of the female reproductive system include the pudendal, pelvic splanchnic, and hypogastric nerve bundles, which innervate the vagina, cervix, and uterus, respectively (See Figure 9) (Netter, 2014), although the afferent innervation of the cervix has been disputed (Bonica, 1979; Bonica & Chadwick, 1989; Komisaruk et al., 2004). Interestingly, sensory information from both the pudendal and pelvic splanchnic nerves enter the CNS through the second, third, and fourth spinal nerves of the sacrum, and the pelvic splanchnic nerves are also the route that parasympathetic nerve fibers follow to enter the spinal cord
Afferent input from the hypogastric nerve enters the sympathetic ganglia of the L2 and L3, and then travels through the ganglia to enter the spinal cord through T11 and T12 (Netter, 2014).

Figure 9 – Innervation of the Female Reproductive System (Netter, 2014)
5.3 Motor Nerves

Motor impulses to the female reproductive system are under both autonomic and voluntary control, but there is a discrepancy between the texts on what spinal nerves give rise to the efferent fibers that innervate uterus. It is stated in *Williams Obstetrics* that during labor motor impulses are transmitted by T7 and T8 (Pritchard & MacDonald, 1976), but in the *Atlas of Human Anatomy* it is shown that sympathetic motor fibers extend from the T11 and T12 to the uterus, parasympathetic motor fibers travel through the pelvic splanchnic nerves to the cervix and upper vagina, and motor fibers under voluntary control extend to the lower vagina and external female anatomy through the pudendal nerve (See Figure 10) (Netter, 2014). Both the pelvic splanchnic and pudendal nerves extend from S2-S4 (Netter, 2014).
Figure 10 - Neuropathways of Parturition (Netter, 2014)

5.4 Nerves That Transmit Pain During Labor

It has been reported throughout the last few decades that the nerves that transmit pain during childbirth include T10-L1 in the first stage of labor and S2-S4 in the
second stage (Bonica, 1970, 1979; Bonica & Chadwick, 1989; Brownridge, 1995; Nicolls, Corke, & Ostheimer, 1981; Pritchard & MacDonald, 1976). This is in direct conflict with the *Atlas of Human Anatomy*, which states that the pain from uterine contractions are transmitted through a number of nerves in the abdomen and pelvis and enter the CNS via T11 and T12, and that pain from cervical dilation and the upper vagina is conducted through the pelvic splanchnic nerves to S2-S4 (Netter, 2014). In fact, it has been noted that research has concluded that labor pain from cervical dilation is transmitted by T10-L1 and not S2-S4 as reported in anatomy books (See Figure 11) (Bonica, 1979; Bonica & Chadwick, 1989), and from this it has been assumed that the parasympathetic nervous system is not involved in transmitting pain signals during parturition (Brownridge, 1995; Rowlands & Permezel, 1998). Also, it has been suggested that the descent of the fetal head through the birth canal may cause pain to be referred through L2-S1 (Bonica, 1979; Brownridge, 1995).
Figure 11 – Nerve Pathways for Labor Pain (Bonica & Chadwick, 1989)
Chapter 6
Endocrine System Involvement in Parturition

6.1 Background and History

Towards the end of the nineteenth century, there was a rapid expansion of knowledge about the glands that secrete hormones, or chemical signals that are produced to effect the function of the organ it targets (Kleine & Rossmanith, 2016). Hormones are transported to the target organ through the bloodstream in what is known as the endocrine process (Kleine & Rossmanith, 2016). In childbirth, the primary hormones released are oxytocin, beta-endorphin, adrenaline and noradrenaline, and prolactin (Buckley, 2005). There is also a possible role of the hormones estrogen and progesterone in parturition, but their involvement is not well understood (Posner et al., 2013).

By the 1930s, the extent of knowledge regarding the role of the endocrine system on the reproductive system was limited to a few hormones secreted from the pituitary gland (See Figure 12) and the observation that the size of the thyroid, parathyroid, and adrenals increase during pregnancy (Schumann, 1937). It was known that the posterior pituitary had a pressor, or blood pressure-raising, effect on
the circulatory system, a water-retention effect on the kidneys, and an oxytocic action on the uterus while the anterior pituitary produced hormones for growth, metabolism, follicle ripening, milk production, and luteinization (preparation of uterus for pregnancy) (Schumann, 1937). While the pressor and antidiuretic effect of posterior pituitary extract had been described previously and are now attributed to the hormone vasopressin (Kleine & Rossmanith, 2016), the so-called oxytocic effect was discovered by Sir Henry Dale in 1906 when he noted that pituitary extract had a strong contractile effect on the uterus of a cat (Dale, 1906; Kleine & Rossmanith, 2016). This substance was named oxytocin, meaning “swift birth” in Greek (Magon & Kalra, 2011).

Figure 12 – Diagram Showing 1930s Understanding of Pituitary Involvement in Female Reproductive System (Schumann, 1937)
6.2 Hormones of the Posterior Pituitary

One of the places oxytocin receptors can be found in the body is on the uterus, and towards the end of pregnancy the number of uterine oxytocin receptors increases significantly so that by the start of labor there are 300 times the number of receptors found in the nonpregnant uterus (Tenore, 2003). The increased number of receptors increases uterine sensitivity to oxytocin, and oxytocin is believed to increase the excitability of the uterine muscle and thus causes it to contract (Posner et al., 2013). Endogenous oxytocin release can be stimulated by cervical dilation, sexual intercourse, emotional reactions, suckling, and certain drugs such as acetylcholine (Posner et al., 2013).

The origin of posterior pituitary hormones has not been well understood until the last several decades. In 1951, it was proposed that the posterior pituitary functions as a place to store, but not produce, vasopressin and oxytocin as had previously been believed (Bargmann & Scharrer, 1951; Kleine & Rossmannith, 2016; Scharrer & Scharrer, 1954). It was theorized that in the brain these hormones are produced by the PVN and SON of the hypothalamus, and then transported via a portal system to be stored in the posterior pituitary gland (Bargmann & Scharrer, 1951; Scharrer & Scharrer, 1954). This was substantiated in 1975 (Daniel & Prichard, 1975), and the hypothalamic-pituitary, or hypophyseal, portal system is now the accepted
model of posterior pituitary hormone release into the bloodstream (See Figure 13) (Kleine & Rossmanith, 2016). Interestingly, while the pituitary gland is continuous with the brain it actually sits outside the blood-brain barrier (BBB) (Nussey & Whitehead, 2001), a highly selective transport system that limits the passage of circulatory molecules to only those required by the brain to function properly (Montenegro & Juarez, 2012)
6.3 Hormones of the Anterior Pituitary

Unlike the posterior pituitary, the anterior pituitary is capable of producing hormones in addition to storing them, but in order to release them the portal system must deliver hypothalamic-releasing hormones from the hypothalamus to receptors.
on the anterior pituitary (Kleine & Rossmanith, 2016). There are four different hypothalamic-releasing hormones that affect the release of various anterior pituitary hormones (Kleine & Rossmanith, 2016). Of these, the ones involved in releasing hormones associated with childbirth are corticotropin releasing hormone (CRH) and thyrotropin releasing hormone (TRH) (Kleine & Rossmanith, 2016). A nonpregnant woman not under stress normally has CRH levels around 10-20 pg/ml, but a woman at full term pregnancy or in labor generally has a peak concentration between 1000-10,000 pg/ml, a level normally only reached in periods of stress (McLean & Smith, 2001). However, the stress response results in only a brief period of elevated CRH whereas in late term pregnancy and labor these levels are relatively constant (McLean & Smith, 2001).

Two of the pituitary hormones CRH stimulates the release of are beta-endorphin and adrenocorticotropic hormone (ACTH), which are both derived from the anterior pituitary hormone precursor proopiomelanocortin (Kleine & Rossmanith, 2016). Beta-endorphin is an endogenous analgesic, or pain suppressor, and ACTH acts on the adrenal glands (Kleine & Rossmanith, 2016). The adrenals are located on top of the kidneys, and when stimulated they glucocorticoids, mineralocorticoids, and the hormone adrenaline (Kleine & Rossmanith, 2016). Interestingly, animal studies have shown that there is a chance that oxytocin may also be associated with ACTH release during labor (Campbell et al., 1987; Link,
Dayanithi, Föhr, & Gratzl, 1992; Matthews, 1999), and therefore could be partially responsible for the adrenal response in parturition (Campbell et al., 1987; Gimpl & Fahrenholz, 2001). In fact, both human and rat studies have found oxytocin in the adrenal glands at much higher concentrations than in the plasma (Ang & Jenkins, 1984), and oxytocin is also known to enhance the effects of CRH (Gimpl & Fahrenholz, 2001).

Prolactin, another anterior pituitary hormone, is regulated by dopamine and is stimulated by TRH, oxytocin, vasoactive intestinal peptide (VIP), an intestinal neurotransmitter and neuromodulator, and possibly by a yet unidentified hypothalamic-releasing hormone (Kleine & Rossmanith, 2016). Interestingly, the lactotropic pituitary cells, which dopamine functions to suppress, release prolactin without stimulation if dopamine levels are low (Kleine & Rossmanith, 2016). Also, dopamine can inhibit prolactin release that is stimulated by the hypothalamic releasing hormone TRH, but not oxytocin or VIP (Kleine & Rossmanith, 2016). While prolactin has no mechanical role in childbirth, it does regulate milk production and helps to promote the mother-child bond (Buckley, 2005; Kleine & Rossmanith, 2016). Also, it has been shown that that prolactin stimulates the release of oxytocin and vasopressin in rats (Vega et al., 2010). However, at present there is no evidence that this also occurs in humans.
### 6.4 Hormones of the Adrenal Glands

Adrenaline and noradrenaline, as well as dopamine, are collectively referred to as the catecholamines (CA), or amino acid derived hormones (Kleine & Rossmanith, 2016). In fact, adrenaline is derived from noradrenaline, which is derived from dopamine (See Figure 14) (Kleine & Rossmanith, 2016). Noradrenaline and adrenaline control the sympathetic response to stress, such as increasing heart rate, constricting blood vessels, and increasing glucose availability (Kleine & Rossmanith, 2016). The primary difference between noradrenaline and adrenaline is that noradrenaline functions as a neurotransmitter that acts through nerve synapses while adrenaline is released into and acts through the circulatory system (Kleine & Rossmanith, 2016). It should be noted that increased levels of adrenaline and noradrenaline are normal during labor and help provide the energy needed for the final fetal expulsion efforts by the mother, but if the levels get too high due to maternal stress or discomfort they can interfere with oxytocin release (Buckley, 2005). When there are high levels of both oxytocin and CA the uterus will produce a few extremely strong contractions resulting in a quick birth, referred to as the fetus ejection reflex (Buckley, 2005; Odent, 1987).
6.5 Endocrine Role in Initiation of Labor

It cannot be definitively stated what initiates labor in humans. It has long been assumed that the fetus, not the mother, is responsible for the start of labor, and while this is well documented in sheep there is also evidence that this occurs in primates and may also be the case in humans (Challis, Matthews, Gibb, & Lye, 2000). Animal studies have shown that the fetus and placenta may release hormones that act on the maternal endocrine system to trigger the start of labor (Challis et al., 2000; Posner et al., 2013). There is some evidence that suggests
prostaglandin may play a role in the onset of labor (Challis et al., 2000; Posner et al., 2013; Tenore, 2003).

Prostaglandins are similar to hormones in that they are chemical messengers, but they have a more localized action and are primarily made by immune cells so they are not considered part of the endocrine system (Kleine & Rossmanith, 2016). Prostaglandins, as well as synthetic oxytocin, are used as pharmacological agents to induce labor (Posner et al., 2013; Tenore, 2003). Interestingly, endogenous oxytocin is not believed to be able to induce labor (Posner et al., 2013; Pritchard & MacDonald, 1976). It has been suggested that prostaglandin plays a major role in parturition (O'Brien, 1995), but at present knowledge of its function is limited to cervical ripening (Nair, Verma, & Singh, 2017). Although the exact role of oxytocin in childbirth is still being discovered, there is already an abundance of information available on its use in labor induction and augmentation.
7.1 Endogenous Oxytocin Release in Labor

It was first proposed in 1961 that oxytocin is released from the posterior pituitary during delivery as a result of a sympathetic nervous response activated by stretching of the lower birth canal (Goodfellow et al., 1983). Subsequently, multiple teams of researchers measured increased plasma oxytocin levels during labor that peaked in the second stage (Coch, Brovetto, Cabot, Fielitz, & Caldeyro-Barcia, 1965; Dawood, Raghavan, Pociask, & Fuchs, 1978; Goodfellow et al., 1983; Leake, Weitzman, Glatz, & Fisher, 1979). Evidence of this has also been shown in the rat, where it has been found that the amount of oxytocin stored in the posterior pituitary gland increases by 50% during pregnancy but is temporarily depleted postpartum, or following birth (Blanks & Thornton, 2003). Another interesting finding is that endogenous oxytocin has a pulsatile release profile, and that during labor and delivery the frequency and duration of the pulses increases (Fuchs et al., 1991).

There is also some evidence that the fetus may play a role in releasing oxytocin during parturition (Goodfellow et al., 1983). It has been shown that umbilical cord
blood from babies delivered vaginally has a significantly higher oxytocin concentration than from babies delivered by cesarean section (De Geest, Thiery, Piron-Possuyt, & Driessche, 1985). Some researchers have even theorized that the synthesis of mRNA encoding oxytocin within the uterus late in pregnancy may have a local hormonal effect that could be important in parturition (Mitchell, Fang, & Wong, 1998). Much more research needs to be done to learn the full extent of the involvement of these different endogenous sources of oxytocin release during parturition.

Besides the known effect of oxytocin to stimulate uterine contractions, it has also been found that plasma oxytocin levels during pregnancy have an effect on mother-child bonding and postpartum depression (PPD) (Feldman et al., 2007; Skrundz et al., 2011). Indeed, it has been reported that plasma oxytocin levels during pregnancy are negatively associated with the risk of developing PPD (See Figure 15), a condition that affects nearly one in five women after childbirth (Skrundz et al., 2011). One important point to note is that oxytocin does not cross the BBB (Altemus et al., 2004; Landgraf & Neumann, 2004; Skalkidou et al., 2012), so peripherally released oxytocin is not believed to act on the CNS (Altemus et al., 2004). However, peripheral oxytocin levels taken from plasma samples have been found to be significantly higher than CNS oxytocin levels measured from samples of cerebrospinal fluid in pregnant women compared to nonpregnant women.
(Altemus et al., 2004; Skalkidou et al., 2012). Interestingly, it has also been noted that PPD is associated with a marked decrease in hypothalamic-pituitary activity (Tsigos & Chrousos, 2002).

Figure 15 – Graph Showing Higher Plasma Oxytocin Levels in Pregnant Women Not at Risk for Developing PPD than in Women Who Are at Risk for PPD (Skrundz et al., 2011)

It does not appear that any research has yet been done to determine if there is a significant difference in CNS levels of oxytocin between pregnant women who are
at risk and not at risk for experiencing PPD. There has, however, been research published that women who suffered from a traumatic childhood, a group known to be vulnerable to depression, had significantly lower CNS levels of oxytocin than women who did not (Heim et al., 2009). The exact relationship between CNS oxytocin levels and depression, if there is one, remains to be seen (Altemus et al., 2004; Heim et al., 2009). Regardless, the BBB limits the oxytocin, as well as vasopressin, that is released in the CNS to the hypothalamic nuclei, and thus it is believed that it is these neurons that contribute to the emotional response of the brain to these hormones (See Figure 16) (Landgraf & Neumann, 2004).
Interestingly, both the PVN and SON have oxytocin receptors, and thus oxytocin released from these structures binds to them and stimulates further oxytocin release creating a positive feedback loop (Carson, Guastella, Taylor, & McGregor, 2013). During labor, it is believed that the first contractions of the uterus trigger a release of oxytocin from the PVN and SON which then binds to receptors both in the uterus and hypothalamus, and thus causes stronger contractions and greater oxytocin release, respectively (Carson et al., 2013; Neumann, Douglas, Pittman,
Russell, & Landgraf, 1996). However, evidence of this is currently limited to results of animal studies (Armstrong & Hatton, 2006; Kimura et al., 2003; Neumann et al., 1996), although the release of oxytocin during parturition is well known and is referred to as the Ferguson reflex (See Figure 17) (Carson et al., 2013; Ferguson, 1941). While Ferguson’s research was conducted on cats and rabbits, it has been demonstrated in humans, as well (Vasicka, Kumaresan, Han, & Kumaresan, 1978).

![Figure 17 – Diagram of the Ferguson Reflex (Everett, 1964)](image-url)
7.2 Pharmacologic Use of Oxytocin in Labor

Although oxytocin is not believed to be directly responsible for the initiation of parturition, it has been used in the management of labor for many years. In 1909, it was reported that posterior pituitary extract was effective in treating post-partum hemorrhage (Theobald, Graham, Campbell, Gange, & Driscoll, 1948), and because of this it remains current practice to administer 10 IU (International Units), or about 17 μg, of oxytocin via intramuscular injection during the third stage of labor (Posner et al., 2013). Oxytocin was isolated in 1926 (Kleine & Rossmanith, 2016), and by 1927 it had been used to treat prolonged labor (Theobald et al., 1948). However, the method of administration was not standardized until a slow drip intravenous method was developed in 1948 (Moir, 1964; Theobald et al., 1948), and prior to that there was a general fear of using oxytocin during labor due to a number of cases where women died after being given too large of a dose (Moir, 1964).

There are still some notable risks and side effects for using synthetic oxytocin, including tachysystole, or more than five contractions in ten minutes over a thirty minute period, uterine rupture, cervical and vaginal lacerations from the baby passing through too quickly, water intoxication, and premature separation of the placenta (Posner et al., 2013). Additionally, there is the possibility of loss of uterine
tone and postpartum hemorrhage after the oxytocin infusion is stopped (Posner et al., 2013). Oxytocin can also have damaging effects on the fetus, including loss of oxygen supply caused by contractions that last too long or are too hard or frequent, being forced through a pelvis that is too small for its head, and abnormal heart rate patterns (Posner et al., 2013). In fact, one of the indications for monitoring the fetal heart rate during labor is the use of synthetic oxytocin (Posner et al., 2013).

Currently, all medically administered forms of oxytocin are synthetic, and the preferred method of delivery is intravenous infusion (Posner et al., 2013). It is recommended that the dosage of synthetic oxytocin for labor augmentation be kept at a minimum, and therefore the infusion is generally started at a rate of 1 mU/min (1.7 pg/min) and increased gradually until regular uterine contractions are achieved (Posner et al., 2013). Generally doses of less than 10 mU/min are adequate to induce contractions, and for safety the maximum dose should not exceed 20 mU/min (Posner et al., 2013). In comparison, oxytocin secreted by the fetus and maternal posterior pituitary gland during the first stage of spontaneous, or non-induced, labor has a combined concentration between 5-7 mU/min (Simpson, 2011).

Also, it has been noted that while endogenous oxytocin is released in a pulsatile manner the infusion of synthetic oxytocin is generally administered at a continuous
rate (Simpson, 2011). The pulsatile nature of endogenous oxytocin release is believed to create a greater effect on uterine contractions with a lower amount of hormone than is required to get the same effect with synthetic oxytocin (Rooks, 2009). This has been demonstrated in an oxytocin challenge test, or pre-labor screening of the fetal heart rate during contractions utilizing pulsatile versus continuous oxytocin infusion, although notably the pulsatile method did take longer to produce the same strength of contractions as the continuous infusion (Perales et al., 1994).

Limited research has been done to determine if there is an advantage to using pulsatile instead of continuous oxytocin infusion during labor, but the data reported is inconsistent in terms of length of delivery and fetal morbidity (Cummiske, Gall, & Dawood, 1989; Tribe, Crawshaw, Seed, Shennan, & Baker, 2012). It has been proposed that a systematic review be performed to clarify any difference in safety or efficacy between pulsatile and continuous oxytocin infusion in labor (Kendrick & Neilson, 2015). There has been at least one review done to compare the safety and efficacy of high dose versus low dose oxytocin infusion in labor augmentation, but the authors excluded studies that used a pulsatile oxytocin delivery method (Wei, Luo, Qi, Xu, & Fraser, 2010).
Chapter 8
Epidural Analgesia: Uses and Effects

8.1 Background and History of Epidural Use

There has been some controversy in the past regarding the use of analgesics in labor. A number of physicians were initially skeptical of the idea after it was first reported that the use of ether, an anesthetic, was successful at relieving labor pain (Bookmiller & Bowen, 1954). There was also opposition from members of the clergy, whose resistance was largely due to the bible passage in the book of Genesis which, in reference to childbirth, states “In sorrow thou shalt bring forth children.” (Bookmiller & Bowen, 1954). Regardless, the use of labor analgesics persisted, and it is now widely considered inhumane to not offer pain relief during labor. This philosophy may contribute to the widespread use of labor analgesics, as a 2008 study of almost two million vaginal births across 27 states found that epidural and spinal anesthesia was used in 61 percent of all cases (Osterman & Martin, 2011).

Continuous caudal analgesia, a method of blocking pain by injecting an analgesic into the area just outside of the dural sac (See Figure 3), or epidural space, of the sacrum, was first described for use in labor almost halfway through the twentieth
century (Galley & Peel, 1944). This procedure focused on delivering an analgesic that would migrate through the space until it reached the level of L1, but it was specified that it should not go above that point or it could block the motor fibers supplying the upper segment of the uterus and affect contractions (Galley & Peel, 1944). It was later noted, however, that uterine contractions are largely controlled by hormones and that epidural blocks up to and including T2 do not interfere with uterine contractions, although blocks should not paralyze the voluntary muscles of the abdomen (Bromage, 1961).

8.2 Nerves Blocked by Epidural Analgesia

While the caudal method was effective at relieving childbirth pain, one of the disadvantages of its use was that it only blocked pain transmitted by S2-S4 in the second stage of labor (Bonica, 1970; Bromage, 1961). Instead, it was proposed that a more effective method is the lumbar epidural method in which the infusion needle is inserted into the L2 or L3 epidural space (Bromage, 1961). This method allows input to T11 and T12 to be blocked during the first stage of labor and S2-S4 to be blocked during the second stage (See Figure 18) (Bromage, 1961). It was specified that the patient be lying down when the epidural analgesics were administered during the first stage of labor so that the analgesic would only affect the upper thoracic nerves, and during the second stage another dose should be given with the
patient sitting upright so that gravity could help the analgesic migrate through the spinal canal to reach the sacral nerves (Bromage, 1961). In current practice it appears that the patient can either be side lying or sitting during either stage of labor to receive an infusion of epidural analgesia (Posner et al., 2013).

![Figure 18 – Schematic Of Sensory Input During Labor (Bromage, 1961)](image)

As mentioned previously, in the 1960s it was believed that epidural analgesia below T2 had no effect on uterine contractions produced by hormone release (Bromage, 1961). However, this has remained a controversial topic in obstetrics, and in fact there is even an inconsistency in reports from the same author. In 1970, John J. Bonica published an article comparing caudal to lumbar epidural anesthesia and concluded that one of the advantages of using a lumbar epidural during the first
stage of labor was that the Ferguson reflex, a significant posterior pituitary release of oxytocin during parturition, would not be blocked because the block would not affect S2-S4 (Bonica, 1970). However, the Ferguson reflex is believed to be caused by sensory input from the cervix as it dilates (Ferguson, 1941), and Bonica later asserted that the nerve supply to the cervix is provided by T10-L1 rather than S2-S4 (Bonica, 1979; Bonica & Chadwick, 1989).

It appears that the discrepancy this created in regards to the Ferguson reflex was not addressed. In fact, when the details of the findings of the cervical sensory pathway were reported only sympathetic pathways were mentioned (Bonica & Chadwick, 1989), and thus it has led some researchers to conclude that the parasympathetic nervous system, which the Ferguson reflex is associated with, is not involved in cervical labor pain (Brownridge, 1995; Rowlands & Permezel, 1998). The Ferguson reflex is still associated with the parasympathetic innervation of S2-S4 when the cervix is fully dilated (May & Leighton, 2007). However, the second stage of labor begins when the cervix reaches full dilation (Posner et al., 2013), and that is when the epidural block is applied to S2-S4 (Bonica, 1970; Bromage, 1961; May & Leighton, 2007).
8.3 Effect of Epidural Analgesia on Labor

Interestingly, it has been found that women who have received an epidural exhibit a lower level of uterine activity during labor than women who have not (Alexander et al., 1998; Bates, Helm, Duncan, & Edmonds, 1985), and the duration of the second stage is notably longer in women who have versus have not had an epidural (See Table 1) (Alexander et al., 1998; Cheng, Shaffer, Nicholson, & Caughey, 2014; Leighton & Halpern, 2002b; Posner et al., 2013). The duration of the first stage of labor might also be increased by epidurals (Alexander et al., 1998), although claims have been made that it does not (Leighton & Halpern, 2002b; Posner et al., 2013).

Also, there have been some studies that have associated epidural use with an increased risk of requiring oxytocin for labor augmentation (Alexander et al., 1998; Goodfellow et al., 1983; Leighton & Halpern, 2002a, 2002b; Zhang et al., 1999), and in fact some research has shown that women who receive epidural analgesia have decreased plasma oxytocin levels during childbirth compared to controls (Rahm, Hallgren, Högberg, Hurtig, & Odlind, 2002). It has even been reported that the use of epidural analgesia decreases uterine activity following labor induction with oxytocin (Alexander et al., 1998). It is unclear if the increased need for synthetic oxytocin with epidural analgesia is due to a blockage of the Ferguson reflex (Saunders et al., 1989), but given the nerves that the epidural blocks it is possible (Goodfellow et al., 1983).
Chapter 9
Studies on the Female Sexual Response

9.1 Oxytocin Release During Orgasm
Since the 1960s, there has been a growing body of knowledge on the
neuroendocrine effect of the human sexual response. In 1987, it was shown in both
men and women that plasma oxytocin levels increase during sexual arousal
(Carmichael et al., 1987). After a single orgasm oxytocin levels peaked in females
but continued to rise in males (See Figure 19) (Carmichael et al., 1987). It was
concluded that the secretion pattern of oxytocin might coincide with smooth muscle
contractions of the reproductive system during orgasm (Carmichael et al., 1987).
Interestingly, it had been written years earlier that oxytocin might be released
during the female sexual response and was noted that uterine contractions
following sexual activity in nonpregnant women occur more often during the
premenstrual phase, when the uterine tissue is most sensitive to oxytocin (Lloyd,
1964). It was also suggested that this could be a variation of the Ferguson reflex
found in parturition (Everett, 1964).
Figure 19 – Mean Plasma Oxytocin Levels at Baseline, Early, Middle, and Late Stages of Self Stimulation (SS), During Orgasm (OO), and 2 and 5 Minutes Post-Orgasm in Men (♂) and Women (♀) (Carmichael et al., 1987)

9.2 Orgasm in Women with Complete Spinal Cord Injury

One of the most recent discoveries in research on female sexuality is the ability of women with complete SCI above the level of sensory input from the reproductive system, believed to be T10 (Berard, 1989), to experience an orgasm. This phenomenon had been mentioned as early as 1975 (Cole, 1975), and subsequent reports of orgasm in women with complete SCI above the level of T9 followed (Kettl et al., 1991; Sipski & Alexander, 1993; Sipski, Alexander, & Rosen, 1995;
Whipple, Gerdes, & Komisaruk, 1996). It was shown in 1990 that the uterus of the rat is innervated by the Vagus nerve (Ortega-Villalobos et al., 1990), and it was later reported that it innervates the cervix, as well (Collins, Lin, Berthoud, & Papka, 1999). In a study published in 1997 it was suggested that the Vagus nerve might also provide an afferent pathway for genital sensation in humans (Komisaruk, Gerdes, & Whipple, 1997). It was hypothesized that this pathway might be responsible for the pain-attenuating effects produced by vaginocervical self-stimulation (See Figure 20) (Komisaruk & Sansone, 2003).

![Figure 20 – Hypothetical Alternative Reproductive System Afferent Pathway Mediated by the Vagus Nerve (Komisaruk & Sansone, 2003)]
Later, functional magnetic resonance imaging (fMRI) was used to show that the PVN of the hypothalamus is activated at the time orgasm is reported by women with complete SCI above T10 using cervical self-stimulation (CSS) (See Figure 21) (Komisaruk et al., 2004). It was stated that this activation is consistent with prior reports that oxytocin is released occurring during orgasm (Carmichael et al., 1987), as the PVN releases oxytocin from the posterior pituitary gland (Cross & Wakerley, 1977). In addition to the PVN, the Nucleus Tractus Solitarii (NTS) of the medulla oblongata, where the Vagus nerves project into the CNS, is also activated during CSS (See Figure 22) (Komisaruk et al., 2004). Vagal afferent fibers enter the NTS via the dorsal vagal nucleus (DVN) (Netter, 2014), and a direct pathway extends from the DVN to the PVN (See Figure 23) (Palkovits, 1999). Thus, the fMRI studies of orgasm in women with complete SCI provides evidence of a genital sensory pathway facilitated by the Vagus nerves (Komisaruk et al., 2006; Komisaruk et al., 2004).
Figure 21 – MRI and fMRI Evidence of Activation of PVN During Orgasm in Woman With Complete SCI (Komisaruk et al., 2004)

Figure 22 – fMRI Images Showing NTS Activation (arrows) During CSS (Komisaruk et al., 2004)
9.3 Orgasm During Childbirth

Perhaps one of the greatest paradoxes in childbirth is that it can be a pleasurable, and in some cases orgasmic, experience (Caffrey, 2014; Harel, 2007; Komisaruk & Whipple, 2011; Komisaruk, Whipple, & Nasserzadeh, 2009; Mayberry & Daniel, 2015; Postel, 2013). The possibility of this experience, termed birthgasm, has led to the development of a birth model referred to as Orgasmic Birth™, which consists
of a documentary film and book focused on describing pleasurable birth experiences and how to have one (Davis & Pascali-Bonaro, 2010; Pascali-Bonaro, 2009). Like other birthing methods that utilize relaxation and breathing techniques to reduce pain during labor (Bradley, 2008; Mongan, 2015), the Orgasmic Birth concept also focuses on empowering the expectant mother by teaching her to channel her pain and turn it into pleasure (Davis & Pascali-Bonaro, 2010; Pascali-Bonaro, 2009). One point worth noting is that models such as Orgasmic Birth tend to advocate a natural birth, which generally refers to a birth that occurs at home or in a midwife-assisted setting, rather than a medicalized birth that takes place in a hospital in the care of an obstetrician (Brubaker & Dillaway, 2009).

Data showing the efficacy of these methods in improving birth outcomes is questionable. For example, a comparison report on a method called HypnoBirthing® showed excellent outcomes in areas such as synthetic oxytocin infusion, episiotomy, and epidural rates compared to a national sample (Swencionis, Litman Rendell, Dolce, Massry, & Mongan, 2012). A major limitation of the study was that the HypnoBirthing data was collected from all HypnoBirthing parents who completed an optional online survey (Swencionis et al., 2012), but the data it was compared to had been adjusted to represent an accurate national profile based on age, ethnicity, parity, and birth method and attendant (Declercq, Sakala, Corry, & Applebaum, 2006). Overall, it appears that
there has been no solid empirical research conducted on the effectiveness of Orgasmic Birth or any other natural birth method. However, recent research conducted in a single hospital showed that mothers whose labors were attended by a midwife had almost half the cesarean rate of deliveries attended by a physician (Nijagal, Kuppermann, Nakagawa, & Cheng, 2015).

Although the success of Orgasmic Birth in producing a pleasurable childbirth experience is largely based on anecdotal evidence, it does highlight the importance in addressing the connection between childbirth and female sexuality. There are some authors who believe that the medicalization of childbirth has taken the intimacy and privacy out of the experience (Buckley, 2010; Mayberry & Daniel, 2015; Tew, 1998). There may also be a psychological explanation for the separation of sexuality and childbirth, as the personal experience of both might be influenced by culturally ingrained expectations in the individual of what should be felt or thought during the experience (Mayberry & Daniel, 2015; Wiederman, 2005). Regardless, the nerves that convey sensory input from the reproductive system to the CNS in the female sexual response are the same ones that transmit pain during childbirth (Giuliano, Rampin, & Allard, 2002; Netter, 2014), and while the Vagus nerves used to only be considered very likely to be involved in the female sexual response (Giuliano et al., 2002) there is now fMRI evidence to show that they are (Komisaruk et al., 2004).
Chapter 10
Vagus Nerve Stimulation

10.1 Overview of Vagus Nerve Stimulation

Electrical stimulation of the Vagus Nerve, referred to as Vagus nerve stimulation (VNS), is a FDA approved neurostimulation method (Kotagal, 2011). In 1997, VNS was approved for use in partial epilepsy (Kotagal, 2011), where seizures are localized in one area of the brain ("epilepsy," 2016), although the mechanism by which it reduces seizures is not yet known (McLachlan, 1997). Interestingly, positron emission tomographic (PET) studies have found that blood flow in the hypothalamus increases significantly both when the maximum or threshold level of stimulation is applied (Henry et al., 1998), and fMRI studies also showed increased blood flow in the hypothalamus with VNS being applied at 30 second rotating on and off intervals (Narayanan et al., 2002).

Originally, VNS clinical trials were only performed using patients twelve years of age and up, but its off label use has shown it to be effective in treating epilepsy in younger patients, as well (Kotagal, 2011). In fact, it has been shown that children under the age of twelve respond better to VNS implantation than children aged twelve or above do (Alexopoulos, Kotagal, Loddenkemper, Hammel, & Bingaman,
The safety of electrical stimulation in pregnancy has not been evaluated, and pregnant women have therefore been excluded from enrollment in studies that utilize it (Husain, Stegman, & Trevino, 2005; Sand et al., 1995). While this means that no data exists on the safety or efficacy of any electrical stimulation therapy in the pregnant population, there is case study evidence from a single patient who got pregnant and delivered a baby while receiving VNS that indicated that it was safe for both the patient and her baby (Husain et al., 2005). As an aside, the woman received an epidural during labor but it was not mentioned if she required synthetic oxytocin (Husain et al., 2005).

In addition to preventing seizures, VNS has also been found to improve the mood in epileptic patients that receive it (Elger, Hoppe, Falkai, Rush, & Elger, 2000). It has subsequently been approved by the FDA as a treatment for treatment-resistant major depression (Cristancho, Cristancho, Baltuch, Thase, & O'Reardon, 2011), and studies have found that in this group VNS has a response rate around forty percent after one year (Cristancho et al., 2011; Schlaepfer et al., 2008) and up to fifty percent after two years (Bajbouj et al., 2010). Researchers have also investigated the potential use of VNS in treating a variety of pathologies such as schizophrenia (Hasan et al., 2015), heart failure (De Ferrari et al., 2011), and migraine and cluster headaches (Mauskop, 2005).
Previously, research has also been conducted on the potential application of VNS as an analgesic (Komisaruk et al., 2006; Maixner & Randich, 1984; T. Ness, Fillingim, Randich, Backensto, & Faught, 2000; T. J. Ness, Randich, Fillingim, Faught, & Backensto, 2001; Randich & Gebhart, 1992). Interestingly, in rats vaginocervical stimulation has been shown to modulate pain following transection of all known genitospinal nerves with Vagus nerves left intact, but after the Vagus nerves were transected in the same rats this analgesic effect was diminished (Cueva-Rolón et al., 1996; Komisaruk et al., 2006; Komisaruk et al., 1996). Animal models are also revealing the potential role of VNS in treating intestinal inflammation (de Jonge et al., 2005; Han, Fink, & Delude, 2003; The et al., 2007; Van Der Zanden, Boeckxstaens, & De Jonge, 2009) and improving recovery from neurological injury (Ay, Napadow, & Ay, 2015; Ay, Sorensen, & Ay, 2011; Sun, Baker, Hiraki, & Greenberg, 2012). Clearly, there is a diverse range of conditions VNS can be applied to, but pregnancy does not appear to be one that has yet been seriously considered.

10.2 Methods of Vagus Nerve Stimulation

When VNS was approved by the FDA for treatment of partial epilepsy, the devices used in studies consisted of a surgically implanted stimulator with lead wires to left
branch of the Vagus nerve that passes through the neck (Henry et al., 1998; Howland, 2014; Narayanan et al., 2002; Schachter & Saper, 1998). Left VNS was also used later in the treatment of depression (Berry et al., 2013; Daban et al., 2008; Howland, 2014). The use of right Vagus nerve stimulation has generally been avoided due to the potential risk of unwanted cardiac side effects (Howland, 2014). However, there have been VNS devices designed for and implanted into the right cervical branch of the Vagus nerve specifically for the treatment of heart failure, an application which so far appears to be successful (De Ferrari et al., 2011; Howland, 2014).

Perhaps VNS implantation in pregnant women has not been given much scientific consideration because pregnant women, fetuses, and neonates (newborns) are given special research protections in the United States Code of Federal Regulations (OHRP, 2009), and because the FDA classifies implantable Vagus nerve stimulators as Class III medical devices, which require a premarket approval (PMA). Requirements of a PMA include non-clinical laboratory studies and clinical studies (FDA, 2016). Given that VNS implantation is an invasive procedure and it would be hard to justify the benefit of performing it for a single use in pregnant women, it is understandable that it has not been an area of research that has been actively pursued.
Recently, though, it has become known that there is a branch of the Vagus nerve that extends into the external ear in humans, called the auricular branch of the Vagus nerve (ABVN) (See Figure 24 and Figure 25) (Ellrich, 2011; Frangos et al., 2015; Howland, 2014; Peuker & Filler, 2002). It has also been shown through fMRI evidence that electrical stimulation of the outer ear results in a brain activation pattern similar to that found in direct VNS (Frangos et al., 2015; Kraus et al., 2013). Actually, transcutaneous Vagus nerve stimulation (tVNS), or electrical stimulation of the Vagus nerve through the skin, has already been developed and gammaCore® (electroCore LLC, Basking Ridge, NJ), a stimulator placed over the left Vagal branch in the neck, has been shown to be effective in relieving cluster headaches (Gaul et al., 2014). Similarly, NEMOS® (cerbomed, Erlangen, Germany), a tVNS system that stimulates the ABVN, has been found to be effective in treating epilepsy (Bauer et al., 2016).
Figure 24 – Diagram of Left Ear, Lateral View (Peuker & Filler, 2002)
Curiously, there are not currently any tVNS systems that have received FDA approval, although they would presumably be classified as a Class III device which would require clinical trial data for each intended labeled use, and in fact there are numerous clinical trials that are currently investigating potential applications for
tVNS (clinicaltrials.gov). Interestingly, there have been studies that have utilized a type of CES unit to stimulate the ear in the region of the ABVN (Hein et al., 2013; Howland, 2014). The FDA has classified CES units as Class III medical devices labeled for use in treating anxiety, insomnia, and depression, but unlike the implantable VNS devices they do not require a PMA prior to marketing. However, changing the labeled use of a CES unit would probably require a PMA, so clinical trials would be necessary regardless. There might be a better chance of tVNS being accepted in clinical trials on women giving birth though, as it is noninvasive and because several studies have noted that it is safe and well tolerated (Busch et al., 2013; Lehtimäki et al., 2013; Stefan et al., 2012).
Chapter 11
Discussion

11.1 Motivation for This Research

In many ways, the field of obstetrics has been completely revolutionized in the last hundred years. The twentieth century saw an unprecedented rise in the number of births that took place in a hospital, increasing from less than five percent in 1900 (Wertz & Wertz, 1989) to fifty-six percent in 1940 and ninety-seven percent in 1962 (NCHS, 1962). Note that the statistics for 1940 and 1962 did not include the nonwhite population, which consistently had lower rates of hospital deliveries (NCHS, 1962). However, this number continued to rise for the whole population and by the final years of the century ninety-nine percent of all births took place in the hospital (Rooks, 1997). With childbirth increasingly taking place in a medical setting, the 1900s also saw both the creation and widespread use of pharmacologic agents to induce or speed up labor and block pain from being experienced during labor and delivery.

In the mid-nineteenth century, the use of ether to control pain during childbirth was first described (Channing, 1848; Heaton, 1946). Chloroform was also used, and these anesthetics remained the only drugs used in obstetrics for a few decades.
In the last quarter of the nineteenth century, the drug nitrous oxide, an inhaled anesthetic, was introduced to obstetrics (Heaton, 1946). At the start of the twentieth century, a new form of pain control called twilight sleep, a combination of scopolamine hydrobromide and morphine sulfate, was used to produce amnesia and analgesia during the first stage of labor (Heaton, 1946; Rooks, 1997). In 1944, caudal analgesia, a method for inserting a needle into the epidural space of the sacrum for completely relieving pain during labor, was first described (Galley & Peel, 1944). However, the caudal method only blocked the nerves that convey pain during the second stage of labor, and in 1961 it was suggested that lumbar epidural analgesia, where the epidural needle is inserted at the lumbar rather than sacral level, is superior to caudal analgesia because it blocks pain transmitted during both the first and second stages of labor (Bromage, 1961).

In the decades that have passed since then, lumbar epidural analgesia has become the gold standard in labor analgesia (Posner et al., 2013). In fact, sixty-one percent of women received an epidural during labor in 2008 (Osterman & Martin, 2011). With such a large percent of the population now opting for epidural analgesia during labor, there should be an equally significant amount of research being conducted to determine exactly the effect, if any, that it has on labor. While a large amount of this research has been conducted to determine the pharmacokinetics of different analgesic drugs (D’angelo, Gerancher, Eisenach, & Raphael, 1998; Polley,
Columb, Naughton, Wagner, & van de Ven, 1999; Stienstra et al., 1995), there has also been a considerable amount of research to determine how epidural analgesia might affect the course of labor (Alexander et al., 1998; Bates et al., 1985; Goodfellow et al., 1983; Leighton & Halpern, 2002a, 2002b).

Studies on the effects of epidural analgesia on labor have found that women who have received an epidural have a decreased level of uterine activity even when labor was induced by oxytocin (Alexander et al., 1998; Bates et al., 1985), a longer second stage (Alexander et al., 1998; Cheng et al., 2014; Leighton & Halpern, 2002b) and possibly first stage of labor (Alexander et al., 1998), and an increased risk of requiring oxytocin for labor dystocia (Alexander et al., 1998; Goodfellow et al., 1983; Leighton & Halpern, 2002a, 2002b) compared to women who have not. It is particularly interesting that uterine activity is decreased following an epidural even if the labor was initiated with synthetic oxytocin. It is presumable that the Ferguson reflex (Ferguson, 1941) could be blocked by epidural analgesia (Goodfellow et al., 1983). The inhibition of uterine contractions following epidural analgesia when labor is induced by oxytocin supports the role of the CNS in the Ferguson reflex, as oxytocin does not cross the blood brain barrier (Altemus et al., 2004; Landgraf & Neumann, 2004; Skalkidou et al., 2012) so it could be possible that synthetic oxytocin acting on the uterus triggers the neural pathway to the PVN resulting in the release of endogenous oxytocin to carry on the progression of labor.
However, it does not appear that research has yet been done to validate this hypothesis, although it has been mentioned that the autonomic nervous system is influenced by both endogenous and exogenous oxytocin (Porges, 2011).

Modern obstetrics textbooks do not make a direct association between epidural use and increased oxytocin administration, but rather comment that epidural analgesia is known to prolong the second stage of labor (Posner et al., 2013). It might not be considered that important to obstetricians if oxytocin infusion is required to stimulate the progression of a labor that has slowed after an epidural has been administered, but unfortunately this perceived complacency has drawn criticism about the overuse of oxytocin (Clark, Simpson, Knox, & Garite, 2009; Rooks, 2009). In fact, over half of all paid obstetric litigation cases involve the misuse of oxytocin (Clark, Belfort, Dildy, & Meyers, 2008; Clark et al., 2009). It has been noted that in no other field are potentially harmful drugs administered for the convenience of the patient or practitioner (Clark et al., 2009). One thing that has not been attempted in the initiative to reduce dependence on synthetic oxytocin labor is to describe a method by which the mother’s own body can be used to stimulate an increase in plasma oxytocin levels.

Research in a separate but related field has shown that women with complete SCI above the level of spinal input of reproductive afferent nerves has shown that the
Vagus nerve provides an alternate sensory pathway in these women and even accommodates their ability to experience an orgasm through cervical stimulation (Komisaruk et al., 2006; Komisaruk et al., 2004). To eliminate the possibility that any genital sensations were transmitted through the spinal cord, the researchers only selected women for the study whose spinal cords had been completely severed as a result of gunshot wounds (Komisaruk et al., 2004). What they found in fMRI studies was that during cervical stimulation the NTS was activated in all women, and in women that reached orgasm the PVN was activated, as well (Komisaruk et al., 2004). This led the researchers to correlate this activation with the known release of oxytocin that occurs during orgasm (Carmichael et al., 1987; Komisaruk et al., 2004) However, this is not to say that for the Vagus nerve to stimulate the release of oxytocin one must first have an orgasm.

Actually, research done on blood flow within the brain during VNS has shown that the hypothalamus, where the PVN is located, exhibits a markedly increased blood flow when the Vagus nerve is stimulated (Henry et al., 1998; Narayanan et al., 2002). Electrical stimulation of the posterior pituitary gland has also been associated with oxytocin release and was part of the series of experiments conducted by Ferguson in his research (Ferguson, 1941). There is even evidence that VNS stimulates the release of both oxytocin and vasopressin in the brain (McEwen, 2004). With a seemingly apparent indication for the potential use of
VNS to stimulate oxytocin during parturition, it is something of a wonder that it has not been previously addressed in the literature.

One of the likely reasons that VNS has not yet been explored for use in obstetrics is the historically invasive nature of its use. The original VNS system consists of a programmable stimulation device implanted in the chest with lead wires leading to the cervical branch of the Vagus nerve located in the neck (Howland, 2014). This is suitable for applications where VNS is used to treat a chronic disorder, but even though a woman might experience childbirth more than once in her life it does not justify implanting a permanent device with the sole goal of reducing the need for synthetic oxytocin administration during childbirth. Also, in the one documented case of a VNS study subject becoming pregnant and delivering while receiving VNS a plan was developed to discontinue her VNS should any procedure utilizing electrocautery, such as cesarean section, be required (Husain et al., 2005). However, there has been a method of VNS developed more recently that noninvasively stimulates the Vagus nerve from outside of the body and if electrocautery were required the unit could be easily removed from the patient’s ear without any risk to interference with the devices’ programming.

This method, tVNS, produces a brain activation pattern like that of direct VNS when applied to the ABVN (Frangos et al., 2015; Hein et al., 2013). If further
research shows tVNS to have a physiologically identical response in the brain as implanted VNS it could be of significant clinical importance in stimulating endogenous oxytocin release during labor, especially in cases where women have complete SCI or have received epidural analgesia. The noninvasive nature and ready availability of stimulators that could be used for tVNS makes this both a practical and potentially cost-effective area of research, as well. If found to be effective, this technology could also save on delivery room and supply costs for parents.

For example, in 1994 the Washington Post ran an article on a couple’s itemized hospital bill which included a charge of almost $100 for synthetic oxytocin to induce labor (Evans, 1994). The Consumer Price Index from the Bureau of Labor Statistics was 143.6 in January 1994 (BLS, 1994) and 242.839 in January 2017 (BLS, 2017), indicating that oxytocin that cost $100 in 1994 would be almost $170 today. The CES units used one study on the effect of tVNS were the NET-2000 and NET-1000 (See Figure 26) (Auri-Stim Medical, Inc., Denver, CO) (Hein et al., 2013), and although the NET-2000 is no longer available the NET-1000 currently sells for $650 from the manufacturer. However, part of the expense of the NET-1000 is probably attributable to the fact that it also interfaces with smart devices as part of its function as a music therapy device. A design like the NEMOS (See Figure 27) would probably be much more cost effective than the NET-1000, as the
stimulator device is not integrated into the headset and therefore it would be feasible to have a stimulator as part of the available delivery room equipment and provide each patient that uses it with a new earpiece.

Figure 26 – The NET-1000 (left) and NET-2000 (right) CES units (From http://net1device.com)
11.2 Transcutaneous Vagus Nerve Stimulation

The foremost concern that needs to be addressed in any studies that lead to the development of a tVNS device for use in obstetrics is safety for both the mother and child. It is unclear why pregnant women have been excluded from studies involving electrical stimulation, other than the fact that no research exists to show that it is safe. This presents a matter of circular logic; the device is not used on pregnant women because it is unknown if such devices are safe to use during pregnancy so no studies are done on pregnant women, and as a result no data is available to determine if the device is safe for pregnant women. However, publications have also noted that there is no evidence that use of electrocautery is
suitable in pregnant women (Berghella, Baxter, & Chauhan, 2005; NCCWCH, 2004), yet it was used to perform cesarean sections several years earlier (Meyer, Narain, Morgan, & Jaekle, 1997) and it appears as though it is now commonly used in performing cesareans (Hofmeyr, Novikova, Mathai, & Shah, 2009).

Also, while CES and tVNS have not been evaluated for safety in pregnant women, similar devices called transcutaneous electrical nerve stimulator (TENS) units have been utilized during pregnancy (Keskin et al., 2012) and during labor (Augustinsson et al., 1977; Bundsen, Peterson, & Selstam, 1981) with no negative consequences. A later systematic review, however, concluded that TENS units had no measurable effect on relieving pain during labor (Carroll, Moore, Tramer, & McQuay, 1997). Regardless, the fact that multiple studies conducted using TENS units with electrodes placed much closer to the uterus than they would be with tVNS is ample evidence that studies on the safety and efficacy of tVNS should not pose an unnecessary risk to pregnant women.

While the single case study of a woman who went through pregnancy and childbirth during participation in a VNS study indicates that tVNS would probably not be harmful to the mother or child, this does not mean that studies should first be conducted on pregnant women. It has been reported that VNS stimulates the release of oxytocin in the brain (McEwen, 2004). First, research would need to be
conducted to determine if the release of oxytocin in the brain following VNS also causes a significant increase in plasma oxytocin levels of test subjects. If it does, then the temporal relationship between the VNS stimulation and plasma oxytocin levels would need to be evaluated to determine if they fit into the timespan necessary to be useful in labor.

After confirmation that VNS can significantly increase plasma oxytocin levels within the timeframe of a normal labor, then further analysis should be performed to determine the minimum, maximum, and optimal level of stimulation required to be effective as well as the minimum treatment time to be effective and if there is a maximum length of time were the effectiveness of the stimulation plateaus or ceases. Full technical information for the NEMOS tVNS system is not readily available, but is given for the NET-2000 stimulator in 510(k) documentation submitted to the FDA showing substantial equivalence to the Alpha-Stim® 100 (See Figure 28 and Table 2) (Electromedical Products International, Inc., Mineral Wells, TX).
Figure 28 - The Alpha-Stim 100 unit (left) and earclip electrodes (right) (from https://alleviahealth.com/product/alpha-stim-100/ and http://www.alpha-stim.com/product-category/alpha-stim-100/)
Table 2 – Comparison of Technical Details Between the NET-2000 and Alpha-Stim Devices (from http://www.accessdata.fda.gov/cdrh_docs/pdf6/K060158.pdf)

<table>
<thead>
<tr>
<th>Feature</th>
<th>NET-2000</th>
<th>Alpha-Stim 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Treats anxiety, depression, and insomnia</td>
<td>Treats anxiety, depression, and insomnia</td>
</tr>
<tr>
<td>Classification</td>
<td>CES, Class III Prescription, 882.5800</td>
<td>CES, Class III Prescription, 882.5800</td>
</tr>
<tr>
<td>Contraindications</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Power Source</td>
<td>9 volt battery</td>
<td>9 volt battery</td>
</tr>
<tr>
<td>510(k)</td>
<td>This submission</td>
<td>K903014</td>
</tr>
<tr>
<td>Size</td>
<td>3.25” x 2” x .14”</td>
<td>13.5cm x 6.4cm x 3.3cm</td>
</tr>
<tr>
<td>Weight</td>
<td>3 oz.</td>
<td>5.5 oz.</td>
</tr>
<tr>
<td>Current</td>
<td>0-600 microamperes</td>
<td>10-600 microamperes</td>
</tr>
<tr>
<td>Frequency</td>
<td>0.5, 1.5, 100 Hz</td>
<td>0.5, 1.5, 100 Hz</td>
</tr>
<tr>
<td>Waveform</td>
<td>Bipolar asymmetric rectangular waves 50% duty cycle, 0 net current</td>
<td>Bipolar asymmetric rectangular waves 50% duty cycle, 0 net current</td>
</tr>
<tr>
<td>Timer Treatment Settings</td>
<td>16.5 minutes</td>
<td>10, 20, 60 minutes and continuous</td>
</tr>
</tbody>
</table>

Both devices are classified as CES devices requiring a prescription, utilize a 9 volt battery for power, have a maximum current of 600 μA, produce frequencies of 0.5,
1.5, and 100 Hz, generate bipolar asymmetric rectangular waves, and have silver electrodes with self-adhesive pads and a conduction solution that are applied to the ear lobes. The only major difference between the two devices is the treatment time, which is 16.5 minutes for the NET-2000 and 10, 20, or 60 minutes for the Alpha-Stim 100. There is actually a wide degree of variability amongst the different manufacturers of devices that electrically stimulate the outer ear.

For example, in a study that used the NEMOS to show that the ABVN creates a similar brain activation pattern to that of direct VNS the participants were only given seven minutes of stimulation while fMRI scans were performed (Frangos et al., 2015). Interestingly, these scans showed that the NTS was activated during tVNS, but not the hypothalamus (Frangos et al., 2015). However, in the study that provided fMRI evidence of Vagus nerve involvement in conveying sensory information during cervical stimulation in women with complete SCI it was shown that the NTS was activated in all cases but the hypothalamus was only activated when women achieved orgasm (Komisaruk et al., 2004). Thus, the duration of the stimulation in the ABVN study may not have been long enough to elicit a response by the hypothalamus, but it does not rule out the possible activation of the PVN by tVNS.
Clearly, there is a large amount of research that needs to be conducted before any tVNS studies should be performed on pregnant women. It first needs to be established as a safe application in healthy humans and its efficacy in stimulating endogenous oxytocin release must be thoroughly documented. Special controls should also be used in developing any device to be used for tVNS studies to ensure a minimal electrical shock risk to the mother and fetus. If these studies are conducted and tVNS is found to have a viable application in obstetrics to increase endogenous oxytocin release it could be of great clinical importance in reducing the amount of synthetic oxytocin that is used in labor.
References


