Cesarean Delivery in Context

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Cesarean Delivery in Context

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Abstract

Vaginal delivery (VD) involves physical, biochemical, and microbe-related processes that interact synergistically to facilitate colonization of the newborn with beneficial microbes and prime healthy immune and stress responses. Cesarean delivery (CD or C-section) bypasses these critical changes, which can affect the child's long-term health concerning immunocompetency and the wide-ranging role of human microbial symbionts. Interventions that compensate for such bypassed changes during CD have the potential to minimize the long-term risk factors associated with this delivery mode. This literature review relates details of the evolution of human reproduction to an analysis of current challenges in reproductive medicine. I discuss factors that put a mother at higher risk for C-sections and synthesize emerging insight into components of the VD processes that work together to prepare the neonate for life outside the womb. This insight can also provide an educational tool to assist expecting and new parents in their decision concerning birth method. While CD is a powerful medical tool, expecting parents need to understand the potential long-term effects of CD and how one could minimize such effects when a CD is necessary.

Key Concepts:
Cesarean Delivery
Altered Gut Microbiome
Chronic Disease
1. Introduction

1.1. Goals

This thesis reviews the evolution of human reproduction and applies this understanding to an analysis of current challenges in reproductive medicine to make recommendations for how to overcome these challenges. I also aim to provide an educational tool that helps new and expecting parents understand that the process of labor is an essential step in preparing newborns (neonates) for life outside the womb. This thesis delves into the underlying mechanisms of labor and how the delivery process affects the newborn to prepare it for life after birth physiologically. I elucidate why these mechanisms of labor have been critical to human survival before modern medicine and technology. The focus of this thesis is a comparison of the impact of two different delivery modes, vaginal delivery (VD) versus cesarean delivery (CD or C-section). I discuss factors that put a mother at higher risk for C-sections and synthesize emerging insight into the physical, biochemical, and microbe-related processes that interact synergistically to facilitate neonate colonization with beneficial microbes, and prime healthy immune and stress responses. I describe how these critical changes are bypassed during a C-section and how that may affect the child’s long-term health. I use this insight to formulate possible interventions that compensate for changes bypassed during CD and that have the potential to minimize the risk factors associated with CD. Lastly, I identify areas for future research as well as any limitations of this paper.
1.2. The Advent of Cesarean Delivery

Successful reproduction is a key component in natural selection. The reproduction of humans evolved from that of non-human primate (NHP) relatives. During this process, anatomical changes took place in the pelvic region in bipedal hominids (upright-walking human ancestors) that affected the birth canal and delivery (Fig. 1). These changes were accompanied by a transition from solitary child delivery by the mother alone to assisted delivery with the help of a human assistant (Rosenberg & Trevathan, 2002). Such obligatory midwifery (Rosenberg & Trevathan, 2002) may be viewed as a prelude to the involvement of nurses and doctors in today’s birthing process and the field of modern reproductive medicine. The emergence of medical technology refined safe delivery methods to reduce birth fatalities of mother and child. The CD method did not gain popularity until the early 1970s (MacDorman et al., 2008). This thesis explores the relationship between the evolution of human reproduction and medical intervention, specifically the CD method.

2. Background on Evolution and History of the Birthing Process

2.1. Transition from Non-human Primates to Early Humans

Profound anatomical and physiological changes during the evolution of modern humans from non-human primates (NHPs) were accompanied by changes in the birthing process (Rosenberg & Trevathan, 2002). While current delivery methods are congruent with humans’ evolutionary changes (Fig. 1), key elements of the labor process (Table 1) are likely remnant from ancestors and have played a significant role in our reproductive success.
Figure 1. A simplified overview of the shift in delivery method from NHPs to human ancestors.

<table>
<thead>
<tr>
<th>Key Element</th>
<th>How</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of the stress response</td>
<td>Physical forces, maternal stress</td>
<td>Contributes to development &amp; maturation of inflammatory response, HPA-axis, immune response, and other organs including lungs</td>
</tr>
<tr>
<td>Microbiome acquisition</td>
<td>Exposure to maternal vaginal flora</td>
<td>Initial microflora colonization, lay foundation for a diverse microbiome, contributes to development &amp; maturation of the neonatal immune system</td>
</tr>
<tr>
<td>Development of neonatal immune</td>
<td>Fetal stress, initial microbiome</td>
<td>Prepare for future pathogen exposure, prevent autoimmune response</td>
</tr>
<tr>
<td>response/immunological memory</td>
<td>acquisition, naïve T cell to memory T cell transformation &amp; epigenetic modifications</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. The key elements of labor to prepare the neonate for life outside the womb. Definitions: The hypothalamic-pituitary-adrenal (HPA) axis is a core pathway of the human stress response. Naïve T cells are unspecific to foreign antigens. Memory T cells are specific to certain antigens. Epigenetic modifications are chemical modifications of the DNA that control gene expression and usage in a cell. In an autoimmune response, the body self-attacks healthy tissues.
The evolutionary change from NHP to human pelvic anatomy can be related to changes in the physical aspect of obstetrics. As bipedalism evolved, human ancestors’ shoulders broadened, and their brains increased in size. Human mothers who successfully birthed offspring after these changes would have had to have a concomitant difference in pelvic shape (Fig. 2; Rosenberg & Trevathan, 2002). Opposing pressures have selected for pelvic anatomy that maximizes the human ability to effectively walk upright while also allowing the delivery of healthy offspring (Gruss & Schmitt, 2015). Across all primates, the neonate’s cranium is largest in the anteroposterior direction, i.e., the front-to-back axis (Gruss & Schmitt, 2015; Rosenberg & Trevathan), and orients itself in line with the largest diameter of the birth canal (Gruss & Schmitt, 2015). The pelvic inlet (the upper limit of the pelvic opening) and outlet (the lower limit of the pelvic opening) of NHPs, especially monkeys, are generally more anteroposteriorly elongated, which allows the neonate to emerge with its face up. Without inhibition from broad shoulders in NHPs, rotation of the neonate is not necessary. During the delivery process, a non-human mother can reach down to scoop up her neonate and bring it to her chest to remove mucous and fluids from its airways (Rosenberg & Trevathan, 2002).

In contrast, the human maternal pelvic inlet is more transversely elongated, i.e., the side-to-side axis, whereas the outlet is anteroposteriorly elongated. Since the human neonate’s cranium is also widest along the anteroposterior axis, it must rotate to pass through both the inlet and the outlet, followed by the same rotation of the neonate’s broad shoulders. The result is a face-down emergence of the human neonate. This change in emergence direction poses a risk of damaging the neonate spinal column if the human mother were to attempt to assist in the delivery in the way NHP mothers do. These physical changes in the delivery process no
longer allowed the mother to assist in the delivery and likely favored involvement of a 
companion for birth assistance, which presumably reduced neonate mortality (Rosenberg & 
Trevathan, 2002). Over time, natural selection may have further favored assisted versus solitary 
deliveries, and social standards ensured obligatory midwifery as the beginning of interventions 
to increase birth success for mother and child.

![Anatomical differences between non-human primates (A) and humans (B) in the position of the neonate in the mother’s birth canal. The solid blue line is the maternal inlet, and the red dashed line is the maternal outlet. The solid blue oval depicts the neonate cranium. A. The maternal inlet and outlet are elongated along the same axis as the neonate cranium. This, along with narrow shoulders, allows for face-up neonate emergence without rotation. B. The widest points of the maternal inlet and outlet are perpendicular to each other, requiring both the neonate’s cranium and shoulders to rotate. This results in the neonate emerging face-down. Figure 2 is adapted from Rosenberg and Trevathan (2002).](image)

The assisted birth process described above still involved vaginal birth and the associated exposure of the neonate to physiological processes that prime the neonate’s immune system for life outside the womb. It was only after the advent of modern medicine and technology that sterile delivery by way of cesarean delivery became feasible. The physiological effects of sterile versus non-sterile delivery are examined in Section 3.2.
2.2. Brief History of Cesarean Delivery

Cesarean delivery is thought to have first been performed in Ancient Rome; one of the first successful records of CD in more recent times is from Switzerland in the late 1500s. It was not until the late 1800s that the procedure was performed in the US. The CD procedure was typically used to save the baby rather than the mother but was rarely performed due to its dangerous nature (Mandal, 2019). Approximately 80 years after the first successful CD in the US, CD rates began to increase rapidly, rising from 1 in 20 births in 1970 (Porreco and Thorp, 1996) to 1 in 3 births in 2017 (Martin et al., 2018).

Technological and medical advancements (Table 2) likely contributed to making CD more popular among doctors and their patients. The commercial introduction of electronic fetal heart rate (FHR) monitoring in the early 1970s provided a resource to detect fetal distress (Freeman et al., 2012); a positive correlation between electronic FHR monitoring rates and CD rates suggests that the advent of FHR monitoring was a contributor to the increasing CD-rate trend (Garite et al., 2000). Additionally, safety concerns of having a vaginal birth after a previous C-section pushed an increase in malpractice insurance premiums due to litigation risk. The risk for litigation heightened if a complication occurred during vaginal birth after C-section (VBAC) that might have been avoided with CD. This resulted in a positive relationship between CD rates and malpractice litigation pressure (Yang et al., 2009). Vaginal delivery after C-section is associated with maternal risks such as emergency CD, hemorrhaging, and uterine rupture, along with neonatal risks of suffocation and perinatal death (Ryan et al., 2018). Not surprisingly, VBAC rates exhibited a negative correlation with CD and malpractice insurance costs, i.e.,
increased litigation pressure reduced doctors’ margin for deciding between VBAC or CD. Thus, VBAC rates decreased as CD rates increased (Yang et al., 2009).

An important medical advancement to improve lung function and reduce respiratory distress syndrome (RDS) was the introduction of synthetic surfactant therapy post-birth (Horbar et al., 1993) and pre-birth administration of the steroids beta- and dexamethasone (Bloom et al., 2001) in the late 1980s and early 1990s. To reduce and prevent RDS, medical professionals utilized surfactant therapy to counteract the effects of deficiencies in natural surfactant production in the lungs, while beta- and dexamethasone activated specific lung-cell maturation. In conjunction with CD, these treatments provided medical tools to decrease neonatal morbidity and mortality in premature and near-term infants (Finer, 2004; Horbar et al., 1993).

<table>
<thead>
<tr>
<th>Event</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of electronic fetal heart rate monitoring device; early 1970s</td>
<td>detection of fetal distress</td>
</tr>
<tr>
<td>Post-delivery surfactant and pre-delivery steroid usage; 1980s-1990s</td>
<td>reduce mortality/morbidity from respiratory distress</td>
</tr>
<tr>
<td>Increase in medical/liability insurance; late 1990s, early 2000s</td>
<td>doctors increase cesarean delivery frequency &amp; decrease vaginal delivery after cesarean</td>
</tr>
</tbody>
</table>

Table 2. A summary of suggested driving forces in the initial observed increasing trend of CD frequency.

3. Pre- and Post-Cesarean Risk Factors

3.1. Pre-Cesarean Maternal Factors

Predisposing risk factors (variables that increase susceptibility to the procedure) for CD vary among individuals. They include a previous CD, maternal weight and age, existing and pregnancy-induced medical conditions, doctor and patient bias, and cultural standards (Table 3; Boerma et al., 2018; Chu et al., 2007; Magne et al., 2017; Ryan et al., 2018; Yerebasmaz et al.,
While the latter factors are not the only CD contributors, they will be the focus of the sections below.

### 3.1.1 Environmental Risk Factors

#### 3.1.2.1 Previous CD

After having had a prior C-section, mothers can either opt for VBAC or elective repeat cesarean section. A tear in the uterine wall (uterine rupture), most often at the incision site of a previous CD (Gregory et al., 1999), is one of the most serious risks associated with VBAC (Ryan et al., 2018). A previous CD is one of the highest – approximately 30% in the developed world – predisposing factors for women undergoing subsequent CDs (Boerma et al., 2018; Ryan et al., 2018). This trend contributes to increasing CD rates and is an obstacle for reducing CD rates in the future, given the extensive number of women who have previously had a CD (Boerma et al., 2018).

#### 3.1.2.2 Body Mass Index

Body Mass Index (BMI), calculated from one’s height and weight, is used as a measure of obesity. In general, an individual is considered overweight, obese, or very obese with BMIs of 25-29, 30-39, and 40+, respectively (Obesity Class BMI, 1998). Obesity rates in 2013 (National Conference of State Legislatures, 2014) and CD rates in 2012 by US state (Osterman & Martin, 2014) are highly congruent. A meta-analysis including 33 studies found that obese and severely obese women had approximately two and three times, respectively, higher risk of requiring a CD than normal-weight women (Chu et al., 2007). The latter authors concluded that a 1% decrease in obesity rates of birthing women could decrease the number of CDs in the US by approximately 16,000 per year. Support for this notion comes from an additional study
involving 2.2 million women in the US, where the risk of CD for overweight and obese first-time mothers was 1.3-2.2 times higher than that of normal-weight women (Declercq et al., 2015). While the underlying reasons for these increased risks require further investigation, one mechanistic explanation for a link between obesity and CD risk is chronic inflammation (Monteiro & Azevedo, 2010; Pawelec et al., 2014). Visceral (belly) fat cells produce large amounts of inflammation-promoting hormones; chronic inflammation is a major risk factor for a host of health problems, including high blood pressure, diabetes, and many other chronic diseases (Monteiro & Azevedo, 2010). Obesity is a topic of intense discussion in various medical fields outside of reproduction as a major risk factor for multiple health problems. In light of the correlation between obesity and CD risk, women beginning the family planning process should be counseled about this connection and encouraged to manage their weight to avoid chronic inflammation.

3.1.2.3 Medical Conditions and Complications

Medical conditions that predispose the mother to CD include conditions that have been linked to immune dysfunction and chronic inflammation, such as diabetes, sexually transmitted diseases like HIV (human immunodeficiency virus), and herpes (see Section 3.2.2.2.1 for further discussion of the link between diabetes, immune system dysfunction, and chronic inflammation). Additional conditions that increase CD risk include hypertension (high blood pressure), placenta previa (placenta covers all or part of the cervix and sits low in the uterus), multiparous births (delivering multiple babies), breech position (the fetus’ head is up rather than just above the cervix) and other abnormal fetal positioning, pinched or prolapsed umbilical cord (enters vagina before the baby), neonate defects like hydrocephalus (enlarged head from
fluid build-up on the braining), dystocia (abnormal labor progression due to, e.g., large neonatal size or small maternal birth canal), and ineffective contractions of the uterus and cervix (Barber et al., 2011).

3.1.2.4 Maternal Age

Typically, a woman over the age of 35 is considered to be of advanced maternal age (AMA). Over the last few decades, maternal age at primary (first) birth has increased (Mathews & Hamilton, 2016; Richards et al., 2016). A variety of risks for adverse pregnancy outcomes are associated with AMA, including an increased risk for CD (Kenny et al., 2013; Mathews & Hamilton, 2016; Richards et al., 2016; Rydal et al., 2019; Yerebasmaz et al., 2015). Factors that make CD necessary, such as obesity, preterm delivery, gestational diabetes mellitus, preeclampsia (high blood pressure during pregnancy), placental and uterine complications, and incorrect neonatal presentation, are all positively associated with AMA (Pawelec et al., 2014; Yerebasmaz et al., 2015). Although the underlying mechanisms for this association are unclear, the current literature offers some insight, describing that the propensity for chronic inflammation increases with increasing age (Khansari et al., 2009; Pawelec et al., 2014; see further discussion on the implications of chronic inflammation in Section 3.2.2.2).

3.1.2.5 Doctor and Patient Bias

Doctor and patient bias can increase the likelihood of CD due to multiple factors. From the patient’s perspective, fear of one or multiple aspects of labor and delivery can be a large driving force for an elective CD. First-time mothers often fear the pain associated with VD, along with the possibility of permanently altering physical appearance and continence (Magne et al., 2017). For mothers who previously had a negative experience with labor and delivery, opting
for an elective CD could result from fear of repeating the same negative experience. A doctor’s suggestion for elective CD may arise from the doctor’s personal views, national or institutional regulations, or aim to reduce chances of litigation in pregnancies with slight complications (Lobel & DeLuca, 2007; Ryan et al., 2018). Given that CD is more expensive than VD, doctors in private practice may, unfortunately, be more inclined to suggest the procedure despite lower-risk pregnancies due to the private clinic’s economic agenda to increase revenue (Magne et al., 2017).

3.1.2.6 Culture

Cultural standards and norms shape whether actions, including elective CD, are viewed as acceptable or expected (Teixeira et al., 2013). Although the World Health Organization (WHO) suggests that CD frequency should not exceed 15% of all deliveries, well-resourced and developed countries (e.g., US, Brazil, Chile, China, etc.) greatly exceed this threshold with CD rates at approximately 20-50% (Magne et al., 2017; Ryan et al., 2018; Sevelsted et al., 2015). For example, C-section rates in Brazil’s public and private sectors are 40-45% and 80-95%, respectively. Cesarean delivery is considered a cultural norm and an indicator of economic status for Latin Americans (Magne et al., 2017). If a culture views effects associated with VD, such as incontinence, vaginal tearing, residual pain in the vaginal area, and sexual issues associated with injury during VD, as highly undesirable, this can effectively drive a mother’s delivery method decision.

Additionally, modern women often place larger importance on furthering their education and establishing or advancing their careers before considering motherhood (Martenelli et al., 2018). Second marriages and improved contraceptives also allow women to
start or continue family planning at a more advanced age (Martenelli et al., 2018; Yerebasmaz et al., 2015). Social and cultural encouragement to achieve those goals before motherhood often overrides considering the risks associated with AMA discussed in Section 3.1.2.4.

3.1.2 Genetic Predisposition for CD

While research on genetic predispositions for CD is sparse, a mismatch between neonate size and maternal pelvis size, or fetopelvic disproportion (FDP), is one factor that has received attention. Comparison of a model to predict the likelihood of women born via CD having a CD with a data set on multigenerational epidemiological studies indicated that mothers born via CD due to FDP have about twice the risk of developing FDP in their pregnancy than those born vaginally (Mitteroecher et al., 2017). Before the advent of CD, neonates that were too large often would not survive if they could not fit through the mother’s birth canal. It is possible that removing this selective obstetric pressure through medical intervention by CD is contributing to larger offspring while allowing for mothers with smaller pelvises to reproduce.
<table>
<thead>
<tr>
<th>Category</th>
<th>Evidence</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous CD</td>
<td>Uterine rupture is a serious risk associate with VD after CD</td>
<td>Ryan et al., 2018</td>
</tr>
<tr>
<td>Previous CD</td>
<td>Previous CD is one of the highest attributing factors to subsequent CDs – accounts for ~30% in the developed world</td>
<td>Boerma et al., 2018; Ryan et al., 2018</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Congruent obesity and CD rates in the US between 2012 and 2013</td>
<td>National Conference of State Legislatures, 2014; Osterman &amp; Martin, 2014</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Obese and severely obese women had 2-3 times higher risk for CD compared to normal-weight women</td>
<td>Chu et al., 2007</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Overweight and obese first-time mothers had 1.3-2.2 times higher risk for CD compared to normal-weight women</td>
<td>Declercq et al., 2015</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Visceral fat cells produce pro-inflammatory hormones; chronic inflammation increases the risk for chronic conditions</td>
<td>Monteiro &amp; Azevedo, 2010</td>
</tr>
<tr>
<td>Medical Conditions &amp; Complications</td>
<td>Increased risk for CD associated with chronic conditions; placental, uterine, and umbilical complications; multiparous birth; incorrect fetal position; birth defects; &amp; dystocia</td>
<td>Barber et al., 2011</td>
</tr>
<tr>
<td>Maternal Age</td>
<td>Maternal age at primary birth has increased</td>
<td>Mathews &amp; Hamilton, 2016; Richards et al., 2016</td>
</tr>
<tr>
<td>Maternal Age</td>
<td>Risk for CD increases with increasing age</td>
<td>Kenny et al., 2013; Mathews &amp; Hamilton, 2016; Richards et al., 2016; Rydal et al., 2019; Yerebasmaz et al., 2015</td>
</tr>
<tr>
<td>Maternal Age</td>
<td>CD-related conditions that increase with age: obesity, preterm delivery, gestational diabetes mellitus, preeclampsia, placental and uterine complications, incorrect neonatal position</td>
<td>Pawelec et al., 2014; Yerebasmaz et al. 2015</td>
</tr>
<tr>
<td>Doctor and Patient Bias</td>
<td>First-time mothers fear pain and possible physical changes associated with vaginal delivery; higher cost of CD can influence private clinics to encourage CD to increase revenue; Brazil public sector CD rate is 40-45% and the private sector rate is 80-95%; CD is an economic status indicator in Latin America</td>
<td>Magne et al., 2017</td>
</tr>
<tr>
<td>Culture</td>
<td>Well-resourced countries exceed recommended 15% CD rate by WHO</td>
<td>Magne et al., 2017; Ryan et al., 2018; Sevelsted et al., 2015</td>
</tr>
<tr>
<td>Genetic Predisposition</td>
<td>Women born via CD due to fetopelvic disproportion (FDP) have about twice the risk of developing FDP in their pregnancy compared to women born vaginally</td>
<td>Mittoreoecher et al., 2017</td>
</tr>
</tbody>
</table>

Table 3. A summary of factors that predispose women to have a cesarean delivery.
3.2 Post-Cesarean Risks and Effects for the Neonate

As stated in the background section above, VD primes the neonate’s immune system (Table 1) to function in the outside world (Romero & Korzeniewski, 2013; Sandall et al., 2018; Yektaei-Karin et al., 2007). While CD is a powerful medical tool for difficult births that would otherwise be unsuccessful, it also compromises this essential priming of the neonate’s immune system. The sections below detail that this priming has both physical and biochemical aspects.

3.2.1 Priming the Neonatal Immune System

3.2.1.1 The Stress Response

The birthing process represents a stressful event not only for the mother but also for the neonate. Both the physical forces involved and exposure to maternal stress hormones have profound effects on the neonate’s immune system (Romero & Korzeniewski, 2013; Sandall et al., 2018; Yektaei-Karin et al., 2007), initiating a crucial physiological chain of events. Specifically, the inflammatory response generated by the stress of labor activates a myriad of neonate immune cells (Romero & Korzeniewski, 2013; Yektaei-Karin et al., 2007). Stress-hormone exposure is a significant component in the development and maturation of the neonate’s immune system, lungs, cells of the nervous system, other organs, and hypothalamic-pituitary-adrenal (HPA) axis or the central stress response system (Sandall et al., 2018) which is regulated by the central nervous system and orchestrates the immune response (Otmishi et al., 2008).

3.2.1.2 Microbiome Acquisition

Fetal stress during VD may play a role in the onset of innate immunity along with the requirement for exposure to microflora at the epithelial linings (organs’ outer surfaces) during
the birthing process (Yektai-Karin et al., 2007). Gut microbial health is a significant component of immune system development and maturation. A diverse, yet balanced gut microbiome is important for a healthy immune system that effectively fights pathogens while not attacking healthy body systems (Grölund et al., 1999; Jakobsson et al., 2014; Knight, 2014; Kuitunen et al., 2007; Romero & Korzeniewski, 2013). A neonate’s first exposure to the maternal vaginal microbiota during delivery provides the foundation for the development of a balanced gut microbial community and immune system (Romero & Korzeniewski, 2013). The initial post-birth intestinal microflora colonization appears to be crucial in the selection of which genera of bacteria will predominate in the microbiome in the long-term (Grölund et al., 1999).

3.2.1.3 Immunological Memory

In addition to the need for acquisition of the neonatal gut microbiota through exposure, immune system maturation involves the development of immunological memory. Exposure to microorganisms causes a transformation of naïve T cells unspecific to antigens to memory T cells that are specific to antigens. Subsequently, lasting immunological memory (Tough & Sprent, 1994) is formed in preparation for further pathogen exposure. This memory consists of lasting alterations in access for internal gene regulators to DNA sequences via epigenetic modification in gene expression (Romero & Korzeniewski, 2013). These epigenetic modifications can have life-long effects and even be passed on to future generations.
3.2.2 The Short- and Long-Term Impacts of Delivery Mode on the Offspring

Bypassing the critical changes that occur during VD can have adverse short- and long-term effects on the neonate. The sections below will discuss these effects (see Table 4) and the conditions to which infants born via CD are more susceptible (see Table 5).

3.2.2.1 Respiratory Function

Cesarean delivery is associated with negative neonatal respiratory function, specifically, an elevated risk for respiratory morbidity for elective CD when compared to either VD or emergency CD (Hansen et al., 2008; Zanardo et al., 2004). This risk decreased as fetal gestational age increased. It is thus possible that neonatal lung maturation requires physiological and hormonal changes associated with labor (Hansen et al., 2008). Elective CD is often scheduled to occur before the fetus is full-term, i.e., at a gestational age of 37-38 weeks (Salim & Shalev, 2010), which has an additional impact on lung development. Further research is necessary to explore if there are benefits of later-term elective CD in consideration of the known increased risk of complications associated with spontaneous labor before a scheduled CD (Salim & Shalev, 2010).

3.2.2.2 Immune Function and the Microbiome

The effect of delivery mode on the HPA axis mentioned in Section 3.2.1.1 is still being explored. It is, however, clear that compared to infants born via VD, infants born via CD exhibited lower cortisol reactivity before and after receiving their two-hour post-birth immunization shots (Chiș et al., 2017), highlighting the notion that CD is a low-stress delivery method for the neonate. Consequently, CD elicits a reduced inflammatory response from the neonate compared to VD (Yektaei-Karin et al., 2007). Therefore, one can conclude that such an initial hypo-inflammatory
response (Puff et al., 2015) is insufficient to solicit a healthy immune response in the neonate. A healthy immune response consists of transient activation of inflammation to fight injury or infection, followed by termination of inflammation when the threat has passed. Deficiencies in the immune response can lead to immune system dysfunction characterized by failure to terminate inflammation, or chronic inflammation, which compromises the ability to fight infection and leads to self-attack on healthy tissues, which is a form of autoimmunity (Adams et al., 2016; Otmishi et al., 2008). Chronic inflammation is a key root cause of most chronic disorders and diseases, including diabetes, heart disease, neurodegenerative diseases, depression, bipolar disease, schizophrenia, asthma, allergies, obesity, etc., which are today all recognized as pro-inflammatory diseases with an autoimmune component.

Furthermore, the impact of CD on the infant’s gut microbiome can last for six months to two years (Grönlund et al., 1999; Jakobsson et al., 2014), and possibly longer (Koenig et al., 2011). As previously stated, the effects on the gut microbiota are intertwined with effects on immunological health. Beyond the first few months of the colonization process, the predominating genera of bacteria remain rather constant (Grönlund et al., 1999). A lower bacterial diversity over the first two years after birth via CD was associated with lower levels of immune-response modulating hormones, such as Th1-associated chemokines (Jakobsson et al. 2014). Th1 cells (a class of helper T cells) are one of two major classes of immune cells and specialize in fighting pathogenic bacteria and viruses. The gut microbiota may impact Th1 cell maturation and, in turn, shape immune system reactivity (Emanuel & Hawarden, 2018). Lack of abundant microbial exposure in conjunction with a reduced neonatal stress response during CD
has been identified to increase the risk for chronic conditions such as diabetes, obesity, asthma, and allergies.

<table>
<thead>
<tr>
<th>Category</th>
<th>Evidence</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td>Respiratory Function</td>
<td>Poor neonatal respiratory function is associated with CD; elective CD has higher risk than emergency CD and VD</td>
<td>Hansen et al., 2008; Zanardo et al., 2004</td>
</tr>
<tr>
<td>Stress Response</td>
<td>CD infants had lower cortisol reactivity before and after two-hour immunization shots compared to VD</td>
<td>Chiș et al., 2017</td>
</tr>
<tr>
<td>Stress Response</td>
<td>Reduced inflammatory response observed in CD neonates compared to VD</td>
<td>Puff et al., 2015; Yektaei-Karin et al., 2007</td>
</tr>
<tr>
<td>Immune Function</td>
<td>Immune dysfunction can lead to chronic inflammation and autoimmune responses</td>
<td>Adams et al., 2016; Otmishi et al., 2008</td>
</tr>
<tr>
<td>Gut Microbiome</td>
<td>Gut microbiome of infants born via CD can be impacted for months to several years</td>
<td>Grölund et al., 1999; Jakobsson et al., 2014; Koenig et al., 2011</td>
</tr>
<tr>
<td>Gut Microbiome &amp; Immune Function</td>
<td>After CD, lower bacterial diversity in the first 2 years compared to VD associated with lower levels of Th1-associated chemokines</td>
<td>Jakobsson et al. 2014</td>
</tr>
<tr>
<td>Gut Microbiome &amp; Immune Function</td>
<td>Gut microbes can shape immune system reactivity by impacting Th1 cell maturation</td>
<td>Emanuel &amp; Hawarden, 2018</td>
</tr>
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Table 4. A summary of the adverse effects observed in infants born via cesarean delivery immediately after birth and within the first two years.

### 3.2.2.2.1 Type 1 Diabetes

Type 1 diabetes (T1D) is precipitated by the destruction of insulin-producing pancreas cells by a dysfunctional immune system (Eringmark Regnéll & Lernmark, 2013), which typically occurs in infants between nine months and two years of age (Puff et al., 2015). Referencing T-cells mentioned above, misrecognition of pathogenic antigens and self-antigens can elicit a severe inflammatory response, further amplifying the destruction of such pancreatic cells (Eizirik et al., 2009). There is evidence that CD increases the risk of developing T1D early in life (Algert et al., 2009; Cardwell et al., 2008), particularly in infants born via elective CD (Black et al., 2015).
Children with familial risk for T1D who are born via CD may have an increased susceptibility to developing T1D due to alterations in neonatal immunity (Puff et al., 2015).

3.2.2.2.2 Obesity

Overall, the available literature suggests that CD increases the risk of obesity. The gut microbiota is associated with digestion efficiency as well as the regulation of appetite and satiety, and thus food intake behavior (Knight, 2014). Moreover, inflammation contributes to adipose tissue enlargement and more efficient fat storage (Singer & Lumeng, 2017). The available studies disagree somewhat on the duration of the effect of CD on obesity. In one study, babies born via CD versus VD were found to have a higher risk of being overweight or obese into adulthood (Darmasseelane et al., 2014). Other studies focus on childhood and adolescent obesity only (Blustein et al., 2013; Keag et al., 2018; Pluymen et al., 2016). Some studies found an elevated risk only early in life (Pei et al., 2014; Sutherson et al., 2014). One study found no increased risk after accounting for confounding factors such as maternal socioeconomic status, race, age and weight, smoking and alcohol consumption, and physical activity (Barros et al., 2012). While more research is needed in this area to resolve these differences, it seems clear that CD has an impact on body weight.

3.2.2.2.3 Allergies and Asthma

Reduced microbial diversity in infants (Bisgaard et al., 2011) and the resulting delayed maturation of the immune system associated with CD is also suggested to increase the risk for developing atopic diseases such as food allergies, allergic rhinitis or inflammation due to airborne allergens (Bager et al., 2008; Jakobsson et al., 2014; Negele et al., 2004), and asthma.
(Keag et al., 2018; Riiser, 2015). This increased risk is highly pronounced in developed countries (Johnson & Ownby, 2017).

<table>
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<tr>
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<th>Evidence</th>
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<tr>
<td>Type 1 Diabetes</td>
<td>Destruction of insulin-producing pancreas cells typically occurs in children between 9 months and 2 years; children born via CD with familial risk for type 1 diabetes (T1D) were more susceptible to T1D</td>
<td>Puff et al., 2015</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>Children born via CD had higher risk of developing T1D in early life</td>
<td>Algert et al., 2009; Cardwell et al., 2008</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>Elective CD had particularly higher risk for T1D</td>
<td>Black et al., 2015</td>
</tr>
<tr>
<td>Obesity</td>
<td>Gut microbiota impacts digestion efficiency and food intake behavior</td>
<td>Knight, 2014</td>
</tr>
<tr>
<td>Obesity</td>
<td>Inflammation contributes to increasing size and storage of adipose tissue</td>
<td>Singer &amp; Lumeng, 2017</td>
</tr>
<tr>
<td>Obesity</td>
<td>Children born via CD had higher risk of being overweight or obese into adulthood compared to VD</td>
<td>Darmasseelane et al., 2014</td>
</tr>
<tr>
<td>Obesity</td>
<td>CD associated with higher risk for obesity in childhood and adolescence compared to VD</td>
<td>Blustein et al., 2013; Keag et al., 2018; Pluymen et al., 2016</td>
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<tr>
<td>Obesity</td>
<td>CD associated with higher risk for obesity in early life compared to VD</td>
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<tr>
<td>Obesity</td>
<td>No associated between CD and obesity when adjusted for confounding factors</td>
<td>Barros et al., 2012</td>
</tr>
<tr>
<td>Allergies &amp; Asthma</td>
<td>Higher risk for atopic diseases in children born via CD compared to VD</td>
<td>Bager et al., 2008; Jakobsson et al., 2014; Keag et al., 2018; Negele et al., 2004; Riiser, 2015</td>
</tr>
<tr>
<td>Allergies &amp; Asthma</td>
<td>Increased risk for atopic diseases is highly pronounced in developed countries</td>
<td>Johnson &amp; Ownby, 2017</td>
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Table 5. A summary of the evidence for conditions associated with cesarean delivery.

4. Further Discussion for Key Concepts

The reproductive process is not simple, and various factors are at work in determining which delivery mode a mother will undergo. While many of the pre- and post-cesarean factors are different, several of them have a commonality in key root causes. Immune dysfunction and
chronic inflammation are significant components of conditions to which offspring born via CD are susceptible as well as predisposing factors for women who require a CD. Today, antimicrobial hygiene products, processed foods, and high-stress environments and lifestyles are common. Chronic psychological stress is associated with abnormal immune responses and increased levels of inflammation (Ouakinin et al., 2018). Furthermore, the idea of the “Hygiene Hypothesis” (Okada et al., 2010), also acknowledged as the “Microbiota Hypothesis” or “Hygiene-Microbiota Hypothesis” (Johnson & Ownby, 2017), stresses the notion that the elimination of many pathogenic diseases and sterilization of microbes, both good and bad, in our environment is essentially increasing susceptibility to autoimmune conditions.

As the scientific community progresses in its understanding of the symbiotic relationship between humans and the microbes with which we have coevolved, it becomes increasingly clear that this relationship is, and has been, imperative to our health and survival. The findings of this review suggest that the processes of VD are evolutionary adaptations meant to lay the foundation for this symbiotic relationship and immune function to prepare the neonate for extrauterine life. A C-section foregoes a large portion of that preparation. It is strikingly clear that further research is needed in each area discussed above, as also stated by the majority of authors referenced in this review. Since a host of chronic diseases and disorders such as inflammatory bowel disease, multiple sclerosis, heart disease, colon cancer, depression, and autism, are recognized as involving an altered microbiome composition and immune system dysfunction (Bisgaard et al., 2011; Dietert, 2011; Knight, 2014), the risk for these conditions may also very well be impacted by delivery mode.
5. Recommendations for Public Health Interventions

The findings of this thesis can be used to formulate interventions that may ameliorate the negative impacts of CD. Such interventions include measures that could be taken immediately following a CD as well as long-term lifestyle management to balance the microbiome, immune function, and lower the risk for chronic conditions at the level of the individual and the community. These interventions could also have the potential to reduce factors involving
immune dysfunction and chronic inflammation that predispose women to require a C-section (Fig. 3).

5.2 At the Individual Level

5.2.1 Breastfeeding

There is evidence that breast milk is not sterile but passes on microbes to the infant; and that maternal diet can affect infant microbiome through breast milk (McGuire & McGuire, 2017). Breastfeeding has been shown to significantly impact infant gut microbial development in the first year of life and thus has long-lasting beneficial effects on microbiome maturation. Higher levels of bacteria taxa used in probiotic supplements, i.e., live microorganisms consumed to restore or improve the gut microbiota (Senok et al., 2005), have been found in exclusively breast-fed infants when compared to exclusively formula-fed infants (Bäckhed et al., 2015). For infants born via CD, breastfeeding during their first year, a crucial period of microbial changes (Knight, 2014), can aid in ameliorating the differences in infant gut microbes as a result of CD.

5.2.2 Diet, Physical Activity, and Stress Management

An abundance of literature demonstrates that a prudent lifestyle can drastically reduce the risk of several conditions related to gut microbiome dysbiosis and chronic inflammation. Perceived psychological stress can increase appetite and food consumption, reduce one’s drive to be physically active (Geiker et al., 2018), and negatively impacts the quality and quantity of one’s sleep patterns, all of which are associated with increased pro-inflammatory biological indicators (Kashani et al., 2012). Higher gut microbial diversity, reduced inflammation, and reduced insulin insensitivity has been associated with regular physical activity (Codella et al., 2018) and healthy
dietary patterns, such as diets rich in plant fibers (Doré & Blottierre, 2015), non-excessive caloric intake, and diets low in saturated fats (Conlon & Bird, 2015). There is an unmistakable cyclic relationship between these three lifestyle elements, highlighting the notion that these should not be treated as separate entities. Thus, combining a balanced diet, regular moderate physical activity, and stress management allows the synergy among these lifestyle factors to produce substantial benefits for small changes. Implementing these lifestyle changes could reduce the adverse effects experienced by children born via CD as well as contribute to improving chronic conditions that predispose mothers to a CD.

5.3 At the Community Level

5.3.1 Education for Health Care Providers and Expecting Parents

As ascertained via google searches with the key phrase “C-section risks,” the publicly available information on CD focuses on risks for mother and child during and immediately after the procedure itself and why it is beneficial to have a planned versus non-planned C-section. Very little information is presented regarding long-term risks for a child born via CD. This thesis provides a summary of physiological changes during the birthing process and could be used to educate health care providers and, after further condensation and adaptation, their patients. Even though more research is needed to further elucidate the mechanisms involved, I believe it would be beneficial to offer educational forums in hospitals for providers and for expecting parents beginning now.
5.3.2 Reduced Antibiotic Use

Antibacterial products are abundantly used in various aspects of our lives, for example, in the food we eat, residential and commercial sanitation products, and prescribed medical treatments. In developing countries where antibiotic use is common practice, 44-97% of hospital patients are prescribed antibiotics, even when it is unnecessary (Abdulah, 2012). This excessive use of antibiotics, particularly in young children whose microbial community is not yet stable and rapidly changing, is diminishing the symbiotic microbe population living on and within us. Overexposure to antibiotics can eliminate microbes that are essential to gut health and immune function (Eisenstein, 2016). Therefore, limiting the use of indiscriminately acting broad-band antibiotics would be an important step in promoting microbial health.

5.3.3 Social Justice: Avenues for Activity, Affordable Foods, Reduce Income-Related Stress

Social disparities in access to areas for physical activity and healthy foods, as well as low-income-related stress can predispose individuals to poor health outcomes. Focusing on socioeconomic status and low-income neighborhoods, perceived safety concerns, particularly in high-poverty neighborhoods, reduce residents’ usage of public parks and playgrounds, which are valuable areas given income restrictions on access to private wellness organizations (Han et al., 2018). Furthermore, compared to high-income individuals and families in the developed world who spend 10% of their income on healthy food, healthy food can cost low-income households up to 30% of their income (Ward et al., 2013). This food-cost disparity in conjunction with reduced access for physical activity often results in income-related stress, and the negative health implications identified in this review as being associated with insufficient exercise, unhealthy food consumption, and psychological stress. I firmly believe considerable
benefits in these communities could be manifested by improving social justice to give better access to safe playgrounds or recreational centers, affordable healthy food, and reduce stress related to food insecurity and low income.

6. Limitations of this Study

While aiming to be comprehensive, this review is not intended to be inclusive in an encyclopedic sense. Additional limitations include the fact that much of the available literature fails to specify elective versus emergency CD, length of labor to which the neonate was exposed, variables such as maternal weight, age, smoking habits, alcohol consumption, socioeconomic status, and family history of various medical conditions, all of which could affect the observed results. Additionally, many studies were conducted over a relatively short period and thus did not assess possible long-term effects of CD. Moreover, the study of the effects of the human microbiome on health is rapidly expanding, with new insight emerging every year. The current understanding of the effects of CD is likely to change as new technology and new knowledge continue to emerge. Further research is also needed to explore recommendations for ameliorating the adverse effects of CD before they can be widely recommended as safe. Section 7 below offers some specific recommendations for future research.

7. Future Research

7.1 Candidates for Priming the Immune System and Gut Microbiome

Future research should assess the impact of allowing a mother pre-CD to enter the active phase of labor (i.e., cervical dilation greater than 6 cm), during which the neonate is exposed to
messengers that prime the immune system in preparation for extrauterine life (Martikainen et al., 2017). While CD following spontaneous onset of labor may carry inherent risks (Salim & Shalev, 2010), incorporation of some labor into the plan for a scheduled CD may be beneficial for the neonate in the long term.

More research is also needed on how to promote a healthy microbiome in CD infants. Given the discussed essential role of the gut microbiome, infants born via CD may benefit from some probiotic and prebiotic supplementation (Kuitunen et al., 2009). Prebiotics, in contrast to probiotics, provide nutrients that support the gut microbiome; e.g., oligosaccharides like oligoglucosaccharides and oligofructosaccharides (Schrezenmeir & de Vrese, 2001; Senok et al., 2005) and may ameliorate gut microbial imbalance and its adverse effects (Tsai et al., 2019).

While the benefits of pre- and probiotics are still controversial, there are reported benefits of this type of supplementation for children born via CD (Kuitunen et al., 2009). In opposition to oral supplementation of pro- and prebiotics, it has been proposed that direct vaginal and rectal suppository of supplemental and nourishing microbes for the gastrointestinal tract microbiome would be the most effective (Lynch, 2019).

An alternative to the above pre- and probiotic supplementation could be vaginal seeding, a process that involves infusing gauze with maternal vaginal fluids used to coat newborns with the mother’s vaginal flora directly following a C-section (Committee on Obstetric Practice, 2017). Vaginal seeding resulted in partial microbiota restoration in infants born via CD in a controlled environment with mothers who tested negative for potentially dangerous and transferable infections (Domínguez-Bello et al. 2016). Patient interest in this process following CD is increasing (Committee on Obstetric Practice, 2017). In 2017,
Committee Opinion released by the American College of Obstetricians and Gynecologists cautioned against and did not recommend vaginal seeding outside of a research setting until the safety and efficacy of the procedure are further researched. The latter Opinion also stressed the need for briefing patients interested in this procedure on pathogenic transfer risks.

7.2 Mother-child Interaction

The quality of the interaction between mother and child after CD, and how it differs from that following VD also warrant future research. It has been observed that mothers after CD breastfeed less, if at all, and had lower satisfaction with their birthing experience and at home, and less home interaction with their infants (DiMatteo et al., 1996). Is it possible that impairment of mother-child interaction after CD may adversely affect a child’s health?

8. Conclusions

The purpose of this study was to analyze the current challenges in reproductive medicine through an evolutionary lens. I assessed the key elements of VD and the impact that CD has by bypassing those processes. The discussion of risk factors that predispose women to a C-section and the risks for offspring born via C-section highlighted the common issue of immune-incompetency and chronic inflammation primarily influenced by an altered gut microbiome. With this insight, I made recommendations for lifestyle management and areas of Public Health that require attention by the individual and the community.

Anatomical changes in human ancestors drove the advent of assisted birth and sparked some of today's reproductive medicine and medical care processes. Although assisted births led to medical procedures that reduce mortality rates, today’s sterile birth environments during CD
may inadvertently have removed an essential step that prepares the neonate’s immune system for the outside world. In an environment full of microbes and pathogens, early exposure to the maternal microbiome – as takes place during VD – is key to the neonate’s acquisition of the diverse microbiome required for a functioning immune system. While more research on the long-term impact of CD, and how to safely counteract its adverse effects, is necessary, it nevertheless appears prudent to limit CD to cases where the procedure is medically necessary for mother and child, and to avoid elective CD. New parents should be made aware of all risks and potential long-term effects of CD when making decisions about their upcoming birth.
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First and foremost, I would like to thank my family, my life partner, and my friends who have stood by me throughout each stage in my academic journey. They have continuously pushed me to keep going when I felt defeated in the face of adversity, self-doubt, and sheer exhaustion. Without these incredible people, I would not be the woman I am today, nor would I have achieved a fraction of my goals. I am and will be forever grateful to each and every one of them as my new chapter begins knowing that their love and support will not waiver.

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