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RISK OF SUBSEQUENT PRETERM DELIVERY FOLLOWING C-SECTION BIRTHS

by
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ABSTRACT
OF THE THESIS OF

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Title: Risk of Subsequent Preterm Delivery Following C-section Births

Background: Complications due to preterm birth (prior to 37 weeks of gestation) are the leading causes of deaths among children under 5 years of age. Factors known to increase risk include socio-demographics, maternal health status before and during pregnancy, obstetrics-related conditions, and environmental factors such as climate change and air pollution. The association between prior C-section and preterm delivery in subsequent births remains inconclusive in the published literature.
Aim: This study aims to: 1) examine the association between C-section deliveries and subsequent preterm births, controlling for major predictors of preterm birth. 2) examine the association between increasing numbers of prior C-sections and odds of preterm birth.
Methods: A case control study was conducted. The population includes women who gave birth between 2009 and 2019 in hospitals enrolled with National Collaborative Perinatal Neonatal Network. Cases included 12,049 pregnant mothers who gave birth prior to 37 gestational weeks with para>0. Controls included 48,196 mothers who had delivered post 37 gestational weeks with para>0. Cases and controls (1:4 ratio) were frequency-matched on newborn year of birth and gender and maternal place of residence. Case status was handled as a categorical variable representing stages of preterm birth ("extremely preterm birth", "very preterm birth", and "moderate to late preterm birth"). The two main exposures included presence of a previous C-section and number of previous C-section births. Crude and adjusted odds ratios and their 95% confidence interval were estimated by multinomial logistic regression models adjusting for measured confounders.
Results: The odds of having undergone a previous C-section was 1.3 times more likely in cases with moderate-to-late preterm birth (32-<37 weeks) [adjusted OR=1.3, 95% CI (1.21 – 1.38)] than in controls (full-term birth) controlling for measured covariates. There was also a statistically significant increase in the odds of moderate to late preterm birth vs. full-term birth with increasing number of previous C-sections, controlling for measured covariates. This increase reached almost a 3-fold rise in odds when the number of previous C-sections was five or more in comparison to no previous C-section [adjusted OR=2.85, 95% CI (1.50 – 5.42)]. The odds of having undergone 5 previous C-sections was 5.25 times more likely in cases with extreme preterm birth (<28 weeks) [adjusted OR= 5.25, 95% CI (1.03-26.65)] than in controls (full-term birth), controlling for measured confounders.
Conclusion: C-section delivery in the first pregnancy is shown to be a significant risk factor for moderate to late preterm birth in subsequent delivery even after adjusting for other predictors of preterm birth. Findings emphasize the importance of restricting

elective C-section deliveries, particularly among mothers who are at risk of premature delivery.

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CHAPTER I

INTRODUCTION

A. Background and Problem Statement:

Preterm birth is defined as newborn birth prior to 37 completed weeks of gestation [1]. Complications due to preterm birth are the leading cause of deaths among children under 5 years of age [1]. Several factors known to increase the risk of preterm birth were identified including socio-demographics (such as socioeconomic status, maternal age, consanguinity, maternal educational level) [2, 3], maternal health status before and during pregnancy (such as preexisting chronic diseases, BMI, gestational hypertension, gestational diabetes) [4-6], obstetrics-related conditions (such as infections during pregnancy, vaginal bleeding, prenatal care) [1, 7, 8], as well as environmental factors (such as climate change, air pollution, extreme heat) [9]. The association between prior C-section and preterm birth has been confirmed in one meta-analysis [10] but not another [11] and therefore remains inconclusive. Further review of the original articles showed that many of the included studies did not control for major risk factors of preterm such as previous preterm delivery [12] or maternal behavior such as smoking [12], chronic conditions [10, 13], pregnancy complications [12-17] or even possible contextual factors such as consanguinity. In addition, all the studies on the association between multiple C-sections and preterm have considered preterm birth as a binary event (yes/no) without differentiating between all stages of preterm: extremely preterm (<28 weeks), very and moderate preterm (28-33), and late preterm (34-36).

Lebanon has a very high rate of C-section that increased from 18 percent in 2000 reaching 47 percent in 2017 and 49.5 percent in 2019 [18]. This marked increase reaching 169 percent is against the WHO recommendation for it to range between 10-15 percent as mentioned previously [18-20]. Preterm complications in Lebanon also contribute to almost 22% of child mortality aged 5 and below, slightly higher than that reported for the Eastern Mediterranean Region (EMR) [19].

B. Objectives:

Thus, this study aims to:

- examine the association between C-section deliveries and subsequent preterm births, controlling for major predictors of preterm birth.
- examine the association between increasing numbers of prior C-sections and odds of preterm birth.

C. Public Health Significance:

Understanding the association between previous C-section and subsequent preterm birth could encourage clinicians and parents to reduce the occurrence of elective and unnecessary C-section deliveries, particularly among mothers who are at risk of premature delivery. The risk of preterm birth should be considered as part of the clinical assessment during the C-section in the first pregnancy. In other words, in additional to short-term operative risks physicians should advise mothers considering an elective C-section for its adverse outcomes on their next pregnancy [10]. They should enhance delivery knowledge among mothers adhering to standard indications for C-section deliveries and encourage mothers with opportunities for vaginal delivery [10]. This can also help mothers create informed decisions about mode of delivery.

CHAPTER II

LITERATURE REVIEW

The World Health Organization (WHO) defines preterm birth as any childbirth occurring prior to 37 completed weeks of gestation (259 days) after the first day of the mother's last menstrual period (LMP) [6, 21]. It is not diagnosed by certain signs or symptoms but rather by the uncompleted weeks of gestation [21].

A. Classification of Preterm Birth

Several classification systems have been established for preterm birth to facilitate surveillance and enable standardized regional and global data comparisons [21]. Preterm birth can be classified based on gestational age (GA), mode of preterm birth, etiology, or pathophysiological pathways [21]. Preterm classification based on gestational age includes four categories: extremely preterm (<28 weeks), very preterm (28 -<32 weeks), moderate preterm (32-<34 weeks), and late preterm (34 - <37 incomplete weeks) [22].

The method of calculation of gestational age is vital in classifying prematurity. The gold standard method for gestational age assessment is early pregnancy ultrasound measuring the fetus [21, 23]. Other techniques include the calculation from the first day of the last menstrual period, postnatal examination of the newborn, or a birthweight below 2500 g [23]. Infants born moderately or late preterm, between 32 and less than

37 weeks, make up to 85% out of 15 million preterm infants born yearly [24, 25]. 10% of preterm births occur between 28- and 32-weeks GA, while extreme preterm birth cases account for 5% of all pregnancies, and it varies slightly among regions [25, 26]. The classifications based on mode of delivery and pathophysiological pathways are interconnected and divided into two categories: spontaneous or provider-initiated [21, 23]. Spontaneous preterm may be either due to spontaneous labor or preterm pre-labor rupture of membranes that is considered the most frequent event leading to premature birth [21, 27]. However, provider-initiated may be due to maternal indications such as pre-eclampsia or eclampsia or due to fetal indications such as fetal distress or intrauterine growth restriction [21].

Among these factors, preeclampsia is the leading cause of provider-initiated preterm births. In mothers with preeclampsia, the gestational age recommended for a planned delivery is around 34 weeks [28, 29]. Even though provider-initiated preterm births account for 30% of all preterm births, this percentage differs between regions as it reaches 50% in many high-income countries [21, 30]. Provider-initiated preterm birth can be lifesaving for both the mother and the newborn in several cases such as placental abruption or fetal distress [31]. Thus, preterm birth can be considered an adverse outcome or a preferred outcome of pregnancy. For example, it would be an adverse outcome if the fetus doesn't complete in-utero growth. On the other hand, it is a preferred outcome when it is medically indicated avoiding a miscarriage or a worse scenario [21]. Even though there are multiple classification systems, the classification of preterm cases can be complicated as it may have many or non pre-existing pathological conditions [21].

B. Burden and Prevalence of Preterm Birth

Preterm birth has been considered a worldwide concern with a global incidence of approximately 15 million births per year [6]. It is the leading cause of deaths among neonates and children aged 5 years and below [1], accounting for 35% of neonatal deaths and 16% of deaths among children aged 5 years and below in 2019 [32]. Around 60% of these preterm births and 80% of complications due to preterm birth related deaths occur in South Asia and Sub-Saharan Africa [33]. Preterm births lead to unfavorable outcomes in different aspects including health, finance, and social and emotional statuses [22]. It does not only affect the newborn and the family but it also has an economic burden on societies [6]. The societal burdens mainly include the medical costs. For example, on average, a term infant stays at the hospital for one and a half day; while a preterm infant stays thirteen days [6].

Adverse outcomes of preterm births are exacerbated in low-middle income countries (LMICs), with evident inequalities in survival rates between low-income and high-income countries. Low-income countries lack available cost-effective care for infectious diseases, respiratory difficulties, and other conditions usually associated with prematurity [25]. For example, as more than half of infants born extremely preterm survive in high-income countries, around 90 percent of those and 50 percent of the infants born only moderately preterm die in low-income countries [25, 34].

The rate of preterm birth is increasing in almost all countries with reliable data. There are possible medical and social reasons for this increasing rate. Medically, better detection of GA through more accurate measurements increases the apparent incidence of prematurity. Socially, the increase in maternal age and maternal health problems globally have also the same effect [34]. In developed countries, the increase in provider-initiated preterm birth for improved management of high-risk pregnancies is one major reason for the increasing frequency of preterm birth [28]. However, in low-middle income countries, the highest preterm birth rates take place [28]. Most of these cases are spontaneous, and its avoidance can save over one million deaths every year [28].

C. Complications Due to Preterm Birth

Fetal development is a continuous process that achieves a major developmental milestone at 35 gestational weeks [27]. The lungs and the brain are late to mature [27]. Thus, although a preterm baby born at 22 to 25 weeks may survive, if cared for in the appropriate setting, there is still a risk of mortality mostly due to respiratory failure [27]. Also, the risk for neurodevelopmental disability is elevated if born before 26 GA [27]. More than one million children die every year due to complications of prematurity, while many premature survivors face multiple neonatal and long-term complications [25]. Neonatal complications associated with preterm delivery include low birth weight, visual and hearing impairment, hypothermia, hypoglycemia, intraventricular hemorrhage, chronic lung disease, respiratory stress syndrome, and hyperbilirubinemia [6]. Long-term illness includes neurodevelopmental impairment, cerebral palsy, retinopathy of prematurity, and cardiovascular diseases in adult life among others [6, 27]. These complications are associated with gestational age at birth. For example, for each additional gestational week prior to 38 weeks, morbidity rates almost double [35]. If an infant is born at 37 weeks of gestation, morbidity rate is shown to be 5.9 percent, much less than if born at 34 weeks at which morbidity rate is 51.7 percent [35]. Mortality is also related to gestational age at birth. For instance, the survival rate for a baby born prior to 22 GA weeks is null, increasing to 29 percent if born at 23 GA weeks, to 78 percent if born at 26 GA weeks and reaching 95 percent if born at 33 weeks [34]. Indeed, majority of complications and deaths due to premature birth occur among extremely and very preterm infants and the majority of death due to preterm birth occurs within the first week of age [35, 36]. However, late preterm infants in comparison with term neonates continue to have an increased incidence of mortality and morbidity [37]. The final gestational weeks, between 34 and 37 GA weeks, are vital for fetus' healthy weight gain and complete growth of several organ systems [27]. Morbidity due to late preterm birth include complications at birth such as respiratory distress, jaundice, and cerebral palsy [35, 38]. Also, infants born moderately preterm and late preterm have respectively 8 and 3 times the rate of newborn mortality in comparison with term infants [35].

D. Risk Factors for Preterm Birth

Since prematurity has such a huge burden on the family and the society as previously mentioned, several modifiable and non-modifiable risk factors have been studied and identified. Those include sociodemographic factors (e.g., socioeconomic status, maternal age, consanguinity) [2, 3], mother's health status (e.g., body mass index (BMI) and preexisting chronic diseases), father's chronic diseases [39], obstetric problems (e.g., cervical length, infection, multiple gestations, vaginal bleeding) [1, 7, 8], as well as environmental factors (e.g., climate change, air pollution, extreme heat) [9].

Sociodemographic factors include race, ethnicity, maternal age, socioeconomic status, maternal educational level, and consanguinity.

1. Maternal Race

One systematic review has shown that Black ethnicity in comparison with the White, Hispanic, and Asian ethnicities has an increased risk of preterm birth [40]. In one meta-analysis that includes over 26 million singleton births, White parents had the lowest odds of preterm birth (OR=1). The highest odds were when both parents were Black (OR=1.78) [41]. Also, the recurrence of preterm birth in a second delivery among Black women is higher than White women [42]. One explanation is that women's race affects the microbiome and the vaginal bacteria that can impact preterm birth [43].

2. Maternal Age

The frequency of preterm birth is also higher at the extremes of maternal age [3]. Pregnancy at adolescents and advanced maternal age is associated with an increased risk of preterm birth. In fact, nulliparous women younger than 18 year old had the highest risk [21]. Meanwhile, the lowest risk of prematurity was associated with a maternal age of 30 to 34 years [3].

3. Socioeconomic Status, Education Level, and Consanguinity

Preterm birth has also been associated with low socioeconomic status and low maternal educational level [21]. Potential explanations include disparities in accessibility and quality of care, psychosocial stress, poverty, lifestyle, and environmental factors [35]. Moreover, consanguinity is another potential risk factor for preterm birth. Infants of consanguineous parents in comparison with unrelated parents had a 1.6-fold increased risk of being born prematurely, at less than 33 weeks of gestation, compared to newborns of unrelated parents [2].

4. Mother's and Father's Health

Mother's health and obstetrics problems are other factors that have been associated with preterm birth. Preexisting chronic conditions such as hypertension and diabetes or pregnancy related conditions such as gestational diabetes, pre-eclampsia, or periodontal disease have been closely associated with preterm birth [21]. One study reported that women with diabetes mellitus are two times more likely to have late preterm birth [44]. Other conditions including low pre-gestation and gestational body mass index (BMI), obesity, and high gestational weight gain (GWG) also increase the likelihood of preterm birth [4, 45]. Lately, gestational weight gain and obesity during pregnancy are gaining more attention as factors for several adverse outcomes of pregnancy [46]. Gestational weight gain is defined as the amount of maternal weight gained between conception and delivery [46]. In 2009, the Institute of Medicine (IOM) articulated recommendations for healthy gestational weight gain, and it concluded that pre-pregnancy body mass index should be used to guide these recommendations [47].

Smoking during pregnancy is another major modifiable risk factor, similar to the use of illicit drugs such as alcohol and cocaine [21]. Cigarette smoking has a dose-dependent relationship with risk of prematurity. In other words, the incidence of preterm birth increases with the number of cigarettes that are smoked [27]. Heavy alcohol consumption during second and third trimesters was associated with a four-fold increase in risk of prematurity [48]. In one study, cocaine was identified in around sixty percent of women who had a preterm birth and a positive toxicology test [49].

Although preterm birth is often linked solely to maternal factors [50], one retrospective cohort study has shown that if the father suffer from chronic conditions, such as hypertension, diabetes, hyperlipidemia, and obesity, he is more likely to have a preterm newborn [39].

5. *Obstetric Problems*

Obstetrics and pregnancy-related factors such as multiple gestations, vaginal bleeding [51], cervical length [52], placenta previa [53], placenta accreta [54], placental abruption [55] and infections during pregnancy have all been identified as risk factors for preterm birth. Multiple gestations constitute only three percent of all births annually; yet, it accounts for 17 percent of births prior to 37 weeks GA and 23 percent of births prior to 32 weeks GA [56]. Twins and higher number multiple pregnancies in comparison with singleton births have increased rate of late and moderate preterm birth [35]. Also, pregnancies that are conceived by assisted reproductive technology have been associated with preterm birth among singleton and multifetal gestation [35]. Congenital malformations are also associated with preterm births at which the risk for infants born earlier than 32 weeks of gestation was five times higher than term infants [35]. Another major factor associated with preterm birth is the volume of amniotic fluid, that plays a major role in fetal growth and development and in the protection against infections [27]. Oligohydramnios, a condition in which there is a low volume of amniotic fluid, is frequently caused by the preterm rupture of amnio-chorionic membrane. This preterm rupture is the most common event leading to prematurity [27]. On the other hand, an increase in the amniotic fluid volume, termed polyhydramnios, is associated with severe defects in the central nervous system that can also cause preterm birth [27]. Amniotic fluid constituents are also a factor affecting preterm births. Amniotic fluid contains equal proportions of organic material such as protein and inorganic salts [27]. The presence of blood, pus, or meconium in the fluid, indicates the presence of a disorder, which increases the risk of preterm birth [57]. Furthermore, infections during pregnancy such as urinary tract infection, chorioamnionitis, herpes, and syphilis have also been associated with preterm birth [21]. Urinary tract infection that is common among pregnant women is sometimes accompanied by asymptomatic bacteriuria that has been associated with increased risk of preterm birth [58]. Also, absence or inadequate prenatal care is another modifiable risk factor for preterm birth. However, it is hard to tell whether this association is a causal or it is an indicator for other risk factors that are also associated with preterm births [59].

Previous preterm birth is another major risk factor for the recurrence of preterm birth, and this recurrence usually occur at the same GA [60]. In one study, the frequency of recurrent spontaneous preterm birth (sPTB) was around 30 percent after one previous sPTB and higher after two sPTB [61].

Furthermore, psychological factors such as stress, depression, and anxiety also elevate the probability of preterm birth [62].

6. Environmental Exposures

Finally, common environmental exposures, such as heat and air pollution that are worsened by climate change are significantly associated with preterm birth [9]. Also, poor air quality has been associated with preterm birth across several countries [44]. For example, heavy metal pollutants found in air, food or drinking water increase the risk of preterm birth [44].

7. Genetics and Preterm Birth

Genetics also plays an important role in preterm birth. Zhang et al identified several genes like AGTR2, WNT4, ADCY5 and more that are associated with different stages of preterm birth [63].

Although several factors mentioned, are not modifiable, understanding these risk factors is vital for targeting interventions especially among mothers who are at increased risk of preterm birth.

E. Cesarean Section

The etiology of spontaneous preterm birth remains incompletely identified, despite the various risk factors found. This has been illustrated in an individual participant data meta-analysis that included around four million singleton births in five high-income countries. In that study, around 65% of preterm cases had none of the known risk factors [21]. Literature reflects some controversies about possible risk factors such as prior cesarean section.

Cesarean section (C-section), an obstetric procedure, is performed to deal with dystocia and pregnancies of high risk [64]. There are several medical indications for a C-section including chorioamnionitis, umbilical cord prolapse, uterine rupture, fetal asphyxia, and fetal acidosis [65]. Thus, C-section has greatly reduced newborn and maternal mortality [66]. The rate of C-section has been shown to increase with an increase in mother's age [67], higher education [67], premature rupture of membranes [68], infections and bleeding during pregnancy [69, 70], chronic conditions [69, 70], multifetal gestations [27], and with an increased BMI [69]. One review in Germany has concluded that there is a risk of rare and serious outcomes of a vaginal delivery after C-section including an elevated rate of perinatal deaths and hypoxic brain damage [65]. Thus, another reason for the increase in C-section rate is a previous C-section.

World Health Organization (WHO) states that C-section rates should not exceed 10-15% per 100 live births, to optimize maternal and neonatal outcomes [71, 72]. Still, according to the WHO global survey, C-section rate varies considerably across geographical regions between 10% and 50% [73]. Also, in the last decades, C-section rates increased to reach around 30% of all births in high income countries [71]. This increase in the rate of cesarean section may be affected by several factors [65]. These include medical, social, cultural, and legal aspects that change the patients and doctors' perspective and attitude towards C-section [65]. In other words, several countries have changed the indications for C-section. Indications, nowadays, not only include physical factors but also psychosocial factors such as anxiety about the delivery, tokophobia that is defined as fear of spontaneous childbirth, or even mother's willingness of a C-section without any medical indication, also known as elective C-section [65]. Elective C-section has been the most cited indication for the increasing incidence of C-sections globally [65]. In other words, it is presumed that this high number of cesarean sections is electively planned without a vital maternal or fetal medical need. However, the rate of elective C-section varies globally among countries. For example, 0.5% of all births in Romania were elective C-section, unlike Cyprus that had a rate of 38.8% [18]. This rise can be linked to an increase in both primary and repeat cesarean section [18]. Thus, this increase in cesarean section rates has been a major public health concern, as there are health burdens associated with this increase. Although beneficial in many cases, cesarean births are shown to be associated with adverse effects on mothers and infants. Several investigations have shown that a prior C-section can increase the risk of maternal complications such as bleeding, intrauterine infection, ectopic pregnancy, and uterine rupture [19, 74]. Also, the increasing rate of C-section was associated with increasing risk of small bowel obstruction [75], placenta previa and abruption [11], and even severe acute maternal morbidity [76]. All of these adverse outcomes are believed to affect subsequent pregnancies as well. In additional to maternal complications, children delivered by C-section have an increased risk of altered immune development [76], increased risk of asthma [11], admission to neonatal intensive care unit [77, 78], respiratory distress syndrome, transient tachypnea of the newborn (TTN) [65], and even stillbirth [11]. Moreover, increasing in the number of previous C-sections has been shown to lead an increase in the risk of intra-operative and post-operative adverse outcomes. These outcomes include severe adhesions, placenta previa, placenta accreta, and cesarean hysterectomy [79]. One study that has illustrated this association by comparing the risk of adverse outcomes among mothers who had single or two previous C-sections. It showed that gestational age at birth, birthweight, and APGAR score were all statistically significantly lower among the group of mothers who had two previous C-sections in comparison to mothers who had only one [80]. It also showed that the most important reason behind this increased risk with increasing number of C-sections was placenta accreta [80]. Thus, an increasing number in prior C-sections was a risk factor for several maternal and fetal adverse outcomes.

F. Controversy and Gaps in Literature

The association between prior C-section and preterm delivery has been confirmed in one meta-analysis [10] but not another [11] and therefore remains inconclusive. The latter meta-analysis was conducted in 2018 including one randomized controlled trial and 79 cohort studies from high income countries to describe the long-term risks and benefits of C-section [11]. Although it was established in that meta-analysis that pregnancy after C-section was associated with increased risk of placenta previa, placenta accreta, and placental abruption, all of which known as risk factors for prematurity, the study concluded that previous mode of delivery is not associated with preterm birth [11]. However, the first meta-analysis, conducted in 2019, that included ten cohort studies involving ten million pregnant women from high-income countries concluded that there is 12 percent increase in the risk of preterm births (RR=1.12) [10]. Further review of the two meta-analyses [and their original articles] showed that many of the included studies did not control for major risk factors of preterm births such as previous preterm delivery or maternal behavior such as smoking [12], chronic conditions [10, 13], pregnancy complications [12-17], use of assisted reproductive technology [15, 81], pre-pregnancy BMI [82], neonatal birth defects [83], and none has controlled for possible contextual factors such as consanguinity. Thus, the conclusions of the included studies differed as some have confirmed the association between previous mode of delivery and preterm births, while others declined or even concluded that previous C-section can decrease the risk of preterm in subsequent delivery [10, 74]. In addition, most of the studies on the association between multiple C-sections and preterm have either considered preterm birth as a binary event (yes/no) without differentiating between all stages of preterm or only studied that association between late preterm and prior C-section. Finally, none of the studies have investigated the association between number of previous C-sections and preterm stages.

G. Preterm Birth in Lebanon

In 2019, the population size of Lebanon was estimated to be around 6.7 million including Lebanese, Syrian and Palestinian refugees and the population growth rate is estimated 1.4 [84]. According to data from National Collaborative Perinatal Neonatal Network (NCPNN), around 8.8% of 80,000 babies are born prematurely every year in Lebanon [85]. In 2011 alone, 4290 infants were born moderate to late preterm births in Lebanon [86]. In one study in Lebanon that included 137 neonatal deaths among refugees, sixty-one percent of the neonates were premature of which 10 percent were extremely preterm [87]. The GA ranged between 20 and 40 weeks and the average GA was 34 weeks [87]. Moreover, Lebanon has a very high rate of C-section that increased from 18 percent in 2000 reaching 47 percent in 2017 and 49.5 percent in 2019 [18]. This marked increase reaching 169 percent is against the WHO recommendation for it to range between 10-15 percent as mentioned previously [18-20]. In Lebanon, between 2001 and 2017, elective C-section deliveries constituted around 9.7% of all deliveries and 25.2% of all C-section deliveries [18]. Also in 2018, the infant mortality rate and the mortality among children aged 5 years and below was 7.4 and 9.4 per 1000 live births respectively [84]. Preterm complications in Lebanon contribute to almost 22% of child mortality aged 5 and below, slightly higher than that reported for the Eastern Mediterranean Region (EMR) [19]. Only one single-center study in Lebanon has investigated the link between prior C-section and preterm birth [12], and while the study found an increase in the rate of preterm in conjunction with the number of C-section, it did not investigate stages of preterm delivery or control for major risk factors such as previous preterm delivery or smoking status or consanguinity among others.

H. Prevention

In order to understand preterm birth epidemiology and develop proper health policies, having representative data and estimates of national preterm cases is vital [21]. Surveillance and epidemiological studies are crucial to assess the contribution of preterm birth in infant mortality and morbidity, identify mothers at high risk, guide obstetric practices, and plan appropriate strategies to reduce morbidity and mortality related to preterm birth [21, 32]. It is also vital to achieve the Sustainable Development Goal (SDG) 3.2 that aims to stop preventable deaths of newborns and children aged five years and below by 2030 [32]. Knowing that preterm birth is a major contributor and the leading cause of death among this age group, reducing preterm birth is crucial to achieving SDG 3.2 [32]. To reach this goal, WHO and the United Nations Children's Emergency Fund (UNICEF) have formulated the "Every Newborn Action Plan" that sheds the light on the important of improved measurement of preterm birth [32]. Also in 2012, WHO and partners were committed to conduct research into the causes of preterm birth and effectiveness of intervention and prevention strategies [34].

I. This Study

The association between previous mode of delivery and risk of preterm birth in subsequent delivery remains inconclusive. This relationship is affected by many confounders and other factors (such as sample size and biases) that may have affected the quality and conclusions of the published studies. This study aims to investigate the association between previous C-sections and stages of preterm birth [extremely preterm birth, very preterm birth, and moderate to late preterm birth], using a nationally representative sample of live births from multiple hospitals in Lebanon controlling for major risk factors of preterm delivery that were not adjusted for in previous published studies such as consanguinity, previous preterm birth, and chronic conditions. This study will also assess the association between multiple previous C-sections and the risk of preterm birth.

J. Research Questions

The research questions that this thesis aims to answer are the following:

1- What is the magnitude of the association between a prior c-section and preterm birth in a subsequent delivery, controlling for major confounders including socio-demographic variables of the mother and father (consanguinity, maternal age, education level), health status of the mother (chronic conditions, pre-gestational BMI, gestational weight gain, pregnancy complications such as preeclampsia, gestational diabetes, urinary tract infection during pregnancy), health habits (smoking and narghile use during pregnancy), obstetric history (previous PTB, vaginal bleeding), and other clinical healthcare variables (prenatal care, birth defects of newborn)?

2- Is a high-level repeat c-section associated with higher odds of preterm in a subsequent delivery controlling for the previously mentioned confounders? Do multiple c-section deliveries increase the odd of extremely preterm in a subsequent delivery controlling for the previously mentioned confounders?

K. Hypotheses

- The odds of having a previous C-section are higher among women who had preterm birth in the subsequent delivery controlling for measured confounders.
- The odds of preterm birth are higher as the number of previous C-section increases.
- The odds of extremely preterm birth are higher with greater number of previous C-sections.

CHAPTER II

METHODOLOGY

A. Study Design and Data Source

This was a case control multicenter study designed to examine the association between preterm delivery and prior C-section in Lebanon. The data source was the National Collaborative Perinatal Neonatal Network (NCPNN), which collected data on deliveries and newborns from enrolled hospital since 1998. The dataset included in the current analysis spans from 2009 until 2019, which includes 230,000 pregnant mothers who gave birth in that period.

The NCPNN network, established in 1998 in Lebanon, is a hospital-based surveillance system that compiles data on all live births and stillbirths occurring at least at 20 weeks of gestation, as well as neonates born in non-NCPNN member hospitals and transferred within 28 days of life to a member hospital [18]. Current NCPPN database is on over 325,000 coupled mothers and their newborns from a total of 33 hospitals. Member hospitals are located in different geographical areas in Lebanon reflecting the various socio-economic, cultural, religious, and regional settings. NCPNN data on all mothers and their newborns is collected prospectively by trained research assistants or local nurses through direct interviews with mothers after birth as well as from obstetric and nursery charts. The completeness and quality of database is periodically assessed and is communicated with member hospitals for improvement [18]. NCPNN aims to help fill the need for improved health indicators, particularly in maternal and neonatal health, with the target to improve maternal and newborn outcomes.

B. Study Population and Sampling:

All mothers who gave birth between January 2009 and December 2019 were included, regardless of nationality. We excluded 1,080 women with missing data on previous mode of delivery and we compared the included and excluded samples (see Supplementary Appendix).

The control group included 48,196 mothers who delivered post 37 weeks of gestation and have para>0 in their last pregnancy. Cases included 12,049 mothers who gave birth prior to 37 weeks of gestation and have para>0 in their last pregnancy. Cases and controls were frequency matched on year of birth of the newborn, gender of the newborn, and place of residence of the mother at time of childbirth. The case to control ratio was 1:4 to maximize study power.

C. Concepts and Measures:

The main outcome measure in this study in this study is *preterm birth* which was assessed based on gestational age. Gestational age in completed weeks was calculated using an ultrasound examination of the fetus during the first of early second trimesters or using the last menstrual period. Cases were further divided into subgroups based on their gestational age in weeks, as per the WHO classification: extremely preterm birth (<28 weeks), very preterm birth (28-32), and moderate to late preterm birth (32 - <37 weeks); controls included non-premature babies (>=37 weeks) [76].

The main risk factor in this study is the presence/absence of a prior C-section birth (yes/no), further categorized into the number of previous C-section births (initially a continuous variable - categorized such that the last category includes five or more previous C-sections).

Several sociodemographic characteristics of the mother were considered in the analyses as potential confounders. The mother's age, which was continuous, was recoded as such: younger than 18 years old, 18-29 years, 30-39 years, and above 40 years, according to the March of Dimes classification and Silva et al. approach [88, 89].

Mother's educational level was also measured categorically: illiterate, knows how to read or write, elementary school, intermediate school, secondary school, technical school, undergraduate university degree, and graduate university degree. The group of mothers who have an "undergraduate university degree" was taken as the reference category.

Consanguinity was also measured as a binary variable (yes/no).

Other variables that were included in the analyses were related to obstetrics and health status of the mother or the baby.

Pre-pregnancy BMI was computed using pre-pregnancy weight and height. Those were extracted from the medical records when available or recorded as self-reported throughout the interviews with the mothers. Following classifications, BMI was classified into four categories: underweight (BMI less than 18.5 kg/ m2), normal weight (between 18.5 kg/ m2 and 25 kg/ m2), overweight (between 25 kg/ m2 and 30 kg/ m2), obese (more than 30 kg/ m2) [90].

Gestational Weight Gain (GWG) was calculated as the difference between weight at delivery and pre-pregnancy weight using the approach of Abdulmalik et al [45]. The result was then recoded into insufficient, adequate, or excessive for each BMI category according to the 2009 Institute of Medicine (IOM) recommendations on weight gain during pregnancy [91, 92]. Adequate GWG was characterized as a weight gain during pregnancy of 12.5-18 kg among underweight mothers, 11.5-16 kg among mothers with a normal BMI value, 7-11.5 kg among overweight mothers, and 5-9 kg among obese mothers [45]. Excessive GWG was classified as a weight gain during pregnancy of more than 18 kg, 16 kg, 11.5 kg, and 9 kg among underweight, normal weight, overweight, and obese mothers respectively [45]. While insufficient GWG was defined as a weight gain of less than 12.5 kg, less than 11.5, less than 7 kg, and less than 5 kg, among underweight, normal weight, overweight, and obese mothers [45].

Number of gestations was classified into four categories: single, twins, triplets, or more than triplets.

Presence of any chronic condition was a variable created (yes/no); if mothers had any of the health conditions present, then they were considered to have one or more chronic conditions: hypertension, heart disease, asthma, hypothyroidism, hyperthyroidism, epilepsy, anemia, hemoglobinopathies, or diabetes.

Presence of a previous preterm birth was measured as a binary variable (yes/no).

Amniotic fluid was classified into clear and normal volume, bloody, pus, meconium, oligohydramnios, and polyhydramnios.

Other binary measures (yes/no) included: urinary tract infection during pregnancy, bleeding during pregnancy, gestational hypertension, gestational diabetes, use of assisted reproductive technology, birth defects, cigarette smoking during pregnancy, argileh smoking during pregnancy, and prenatal care.

D. Statistical Analysis:

All data management and analyses were conducted using SPSS statistical software version 25. and Stata 16.0. Hypothesis tests were two-sided, and statistical significance was determined at an alpha level of 0.05.

We initiated our analysis by appending data files, specifically data collected in 2017, 2018 and 2019 to the 2009-2016 NCPNN-D dataset. Following the data management and re-coding, as described above, exclusion criteria was applied, mainly excluding women with missing data on "presence of previous C-section". The excluded women were then compared to those included in the study on the main outcome and all measured confounders to assess for possible selection bias.

A subset of the data was created including only the above-mentioned measures of interest. Following data management, cases and controls were frequency matched. The final dataset included all cases frequency matched to controls on a ratio of 1:4.

The first step of analyses entailed exploratory data analyses, examining the distribution of the measures. Descriptive analysis was conducted on all variables. Frequencies and relative frequencies (valid percentages) were derived for each categorical variable. Summary statistics are also presented separately for cases and controls (as shown in table 3).

Then, bivariate analysis was conducted to examine the association between the main exposure (C-section births) and all possible confounders (presented in table 4), as well as between the latter and the main outcome: case-control status (table 5).

The assumption of proportional odds did not hold for most of the unadjusted and adjusted odds ratios (p-value>0.05) and thus, ordinal logistic regression was only considered when the assumption held. Simple binary logistic regression as well as multinomial logistic regression models were run (latter when preterm birth was considered categorically). Unadjusted odds ratios, their 95% confidence intervals, and p-values are reported. All potential confounding variables were associated with both the main exposure and the main outcome (p-values are ≤ 0.2) and were thus controlled for in the regression analyses. Adjusted odds ratios and their 95% confidence interval were estimated by multinomial logistic regression adjusting for all confounders.

E. Ethical Considerations

Data Collection for the NCPNN database is IRB approved; oral consent was obtained from each participating mother. This study was granted ethical approval by the Institutional Review Board of the American University of Beirut (Reference: SBS-2022-0027), considering that it deals with secondary data analysis of de-identified datasets.

CHAPTER III

RESULTS

In this chapter, the findings of the study will be presented. We will start by presenting the descriptive statistics. Then we will present the bivariate association between the main independent variable, presence of previous C-section, and the various measured independent risk factors being controlled for as potential confounders. Finally, the adjusted and unadjusted associations will be provided for the association between C-section and preterm birth stages, controlling for the measured confounders (in case of the adjusted models).

A. Sample Characteristics

Table 1 provides a description of the characteristics of mothers with preterm births (cases) and those with full-term births (controls). A total of 12,045 cases of mothers who had a preterm birth in their last pregnancy were included in the study; in parallel, 48,196 controls of mothers who had a full-term birth in their last pregnancy were included (ratio 1:4).

Mothers with full term birth (controls) and preterm birth (cases) were compared as can be seen in Table 1.

- *Socio-demographics:*

Table 1 compares full term (controls) and preterm (cases) newborns on several sociodemographic characteristics. All associations were statistically significant (alpha=0.05).

As can be seen, mothers who had a preterm birth (cases) were more likely to be at extreme of ages (below 18 years-old or 40 years and above) (7%) than mothers who had a full-term birth (controls) (5%).

- *Maternal Health and Lifestyle During Pregnancy and Obstetrics-Related Conditions:*

In terms of maternal health and obstetrics-related conditions, mothers who had a preterm birth were more likely to have had at least one previous C-section (39%) than mothers who had a full-term birth (30%). Mothers with preterm birth versus mothers with full-term birth were more likely to have chronic conditions (10% vs. 7%), urinary tract infection during pregnancy (16% vs. 15%), vaginal bleeding during pregnancy (12% vs. 4%), gestational hypertension (5% vs. 2%), gestational diabetes (5% vs. 2%) and oligohydramnios or polyhydramnios amniotic fluid (6% vs. 2%). Also, mothers who had preterm births were more likely to have a healthy BMI and an adequate gestational weight gain (20% and 25% respectively) in comparison to mothers who had a full-term birth (9% and 15% respectively).

Moreover, mothers who had a preterm birth in their last pregnancy versus mothers who had a full-term birth were more likely to have reported a previous preterm birth (13% vs. 4%), had multiple gestations in their last pregnancy (18% vs. 2%), have smoked cigarette during their last pregnancy (9% vs. 7%), and have used an assisted reproductive technology (7% vs. 1%). Cases who experienced preterm birth were more likely to give birth to newborn with a birth defect (5%) versus controls who experienced a full-term birth (1%).

Table 2 compares the characteristics of cases (mothers who had a preterm birth) by stages of preterm birth. All associations were statistically significant (alpha=0.05). Among cases of preterm (N=12,049), 520 (4.32%) were extremely premature, 825 (6.85%) were very premature, and 10,704 (89.83%) were moderately to late premature.

- *Socio-demographics:*

As can be seen, mothers who had an extreme preterm birth were more likely to be below 18 years or above 40 years (8%) in comparison with those with very preterm (7%) and moderate to late preterm birth (7%). They were also more likely to have lower level of education (56%) versus mothers who had very preterm birth (46%) and moderate to late preterm birth (40%). Mothers who had extreme preterm birth were also more likely to have consanguineous marriages (25%) versus those who had very preterm birth (22%) and moderate to late preterm birth (16%).

- *Maternal Health and Lifestyle During Pregnancy and Obstetrics-Related Conditions:*

Mothers who had a moderate to late preterm birth were slightly more likely to have had a previous C-section (39%) as compared to mothers who had an extreme or very premature birth (36% and 38% respectively). They were more likely to have 3 or more previous C-sections (6%) versus mothers who had a very preterm birth (3%) and extremely preterm birth (4%). Also, mothers who had a moderate to late preterm birth versus mothers who had very preterm birth and extremely preterm birth were likely to have an overweight or obese BMI (69% vs. 65% vs. 64% respectively).

Mothers who had a very preterm birth were more likely to have multiple gestations: twins, triplets, or more (27%) versus mothers who had moderate to late preterm birth (17%) and mothers who had extremely preterm birth (21%). They were also more likely to have a chronic condition (13%) versus mothers who had moderate to late preterm birth (9%) and mothers who had extremely preterm birth (11%). Moreover, they were more likely to have a urinary tract infection during pregnancy (25%) versus mothers who had moderate to late preterm birth (16%) and mothers who had extremely preterm birth (16%). Also, mothers who had very preterm birth compared to mothers who had moderate to late preterm birth and extremely preterm birth were more likely to have gestational hypertension (12% vs. 5% vs. 6% respectively), gestational diabetes (6% vs. 5% vs. 2% respectively), and oligohydramnios or polyhydramnios (11% vs. 6% vs. 9% respectively). Mothers who had a very preterm birth were also more likely to have used an assisted reproductive technology in their last pregnancy (15% compared to mothers who had moderate to late preterm birth (6%) and those who had extreme preterm birth (12%).

Mothers who had an extremely preterm birth in comparison to mothers who had very preterm birth and moderate to late preterm birth were more likely to have an insufficient gestational weight gain (51% vs. 34% vs. 26% respectively), previous preterm birth (21% vs. 19% vs. 12% respectively), vaginal bleeding during pregnancy (29% vs. 21% vs. 10% respectively), and have a newborn with birth defects (15% vs 13% vs. 4% respectively).

Table 1: Distribution of Independent Variables and a Comparison Between Women with Term and Preterm Birth

	Term Newborns (37 weeks GA>) N = 48,196 (80%) n (%)	**Preterm Newborns (<37 weeks GA) N=12,049 (20%) n (%)**	**p-value**
Socio-demographics			
Year of Birth of the Newborn			
2009	4,687 (9.72)	1,019 (8.46)	
2010	5,220 (10.83)	1,258 (10.44)	
2011	5,489 (11.39)	1,364 (11.32)	
2012	6,101 (12.66)	1,523 (12.64)	
2013	6,026 (12.5)	1,322 (10.97)	
2014	5,123 (10.63)	954 (7.92)	<0.001
2015	4,355 (9.04)	1,028 (8.53)	
2016	3,990 (8.28)	758 (6.29)	
2017	3,027 (6.28)	758 (6.12)	
2018	2,805 (5.82)	737 (6.12)	
2019	1,371 (2.84)	497 (4.12)	
Gender			
Male	24,168 (51.02)	6,511 (55.22)	<0.001
Female	23,203 (48.98)	5,279 (44.78)	
Governance			
Beirut	5,354 (12.62)	1,497 (13.51)	
Mount Lebanon	18,682 (44.03)	4,943 (44.62)	
Bekaa	1,073 (2.53)	329 (2.97)	<0.001

Baalbeck-Hermel	1,828 (4.31)	639 (5.77)	
North Lebanon	7,569 (17.84)	2,022 (18.25)	
Akkar	3,583 (8.44)	905 (8.17)	
South Lebanon	805 (1.9)	217 (1.96)	
Nabatiyeh	2,730 (6.43)	334 (3.01)	
Outside Lebanon	804 (1.89)	192 (1.73)	
Mother's Age			
Below 18 years	135 (0.28)	48 (0.40)	
18-28.11 years	18,207 (37.80)	3,839 (31.86)	<0.001
29-39.11 years	25,174 (52.26)	6,794 (56.39)	
40 years and above	2,027 (4.21)	768 (6.37)	
Mother's Educational Level			
Illiterate	1,158 (2.60)	344 (3.15)	
Knows how to read or write	1,395 (3.13)	449 (4.11)	
Elementary	4,574 (10.26)	1,161 (10.63)	
Intermediate	9,940 (22.29)	2,475 (22.66)	
Secondary	8,013 (17.97)	1,702 (15.59)	<0.001
Technical school	4,840 (10.85)	1,048 (9.60)	
Undergraduate university	10,550 (23.65)	2,851 (26.11)	
Graduate University	4,130 (9.26)	890 (8.15)	
Consanguinity			

No	37,788 (83.18)	9,432 (83.09)	0.008
Yes	7,642 (16.82)	1,920 (16.91)	
Maternal Health and Lifestyle and Obstetrics-related Conditions			
Previous C-sections			
No	33,699 (69.92)	7,392 (61.35)	<0.001
Yes	14,497 (30.08)	4,657 (38.65)	
Number of Previous C-sections			
None	33,699 (69.92)	7,392 (61.35)	<0.001
1 previous C-section	9,239 (19.17)	2,545 (21.12)	
2 previous C-sections	3,924 (8.14)	1,434 (11.9)	
3 previous C-sections	1,063 (2.21)	519 (4.31)	
4 previous C-sections	223 (0.46)	129 (1.07)	
5 or more previous C-sections	48 (0.1)	30 (0.25)	
Pre-pregnancy BMI			
Underweight [b]	1,486 (3.08)	451 (3.74)	<0.001
Healthy Weight [b]	4,496 (9.33)	2,363 (19.61)	
Overweight [b]	25,712 (53.35)	5,575 (46.27)	
Obese [b]	12,239 (25.39)	2,654 (22.03)	
Gestational Weight Gain (GWG)			
Insufficient GWG [c]	12,783 (26.54)	3,358 (27.87)	<0.001
Adequate GWG [c]	7,280 (15.12)	3,015 (25.02)	
Excessive GWG [c]	14,091 (29.26)	2,711 (22.50)	

Previous Preterm Birth			
No	46,055 (96.31)	10,306 (87.18)	<0.001
Yes	1,763 (3.69)	1,516 (12.82)	
Number of Gestations			
Single	46,452 (98.06)	9,556 (81.56)	<0.001
Twins	757 (1.60)	1,933 (16.50)	
Triplets	33 (0.07)	181 (1.54)	
More	41 (0.09)	26 (0.22)	
Cigarette Smoking During Pregnancy			
No	44,398 (92.70)	10,708 (90.60)	0.001
Yes	3,496 (7.30)	1,111 (9.40)	
Argileh Smoking During Pregnancy			
No	43,686 (91.19)	10,858 (91.95)	0.007
Yes	4,223 (8.81)	950 (8.05)	
Prenatal Care			
No	1,039 (2.18)	351 (3)	<0.001
Yes	46,654 (97.82)	11,332 (97)	
Chronic Conditions			
No	44,839 (93.08)	10,873 (90.30)	<0.001
Yes	3,331 (6.92)	1,168 (9.70)	
Urinary Tract Infection During Pregnancy			
No	40,735 (84.93)	9,889 (83.76)	0.002
Yes	7,226 (15.07)	1,917 (16.24)	

Vaginal Bleeding During Pregnancy			
No	45,908 (95.78)	10,410 (88.19)	<0.001
Yes	2,021 (4.22)	1,394 (11.81)	
Gestational Hypertension			
No	47,302 (98.73)	11,136 (94.56)	<0.001
Yes	610 (1.27)	641 (5.44)	
Gestational Diabetes			
No	46,763 (97.61)	11,231 (95.45)	<0.001
Yes	1,146 (2.39)	535 (4.55)	
Amniotic Fluid			
Clear and normal volume	32,521 (91.23)	7,957 (89.79)	<0.001
Meconium	1,723 (4.83)	348 (3.93)	
Pus	2 (0.01)	2 (0.02)	
Bloody	10 (0.03)	6 (0.07)	
Oligohydramnios	909 (2.55)	380 (4.29)	
Polyhydramnios	481 (1.35)	169 (1.91)	
Assisted Reproductive Technology			
No	44,880 (99.22)	10,337 (92.92)	<0.001
Yes	353 (0.78)	788 (7.08)	
Birth Defects			
No	44,632 (98.85)	10,569 (94.63)	<0.001
Yes	520 (1.15)	600 (5.37)	

[b] For the BMI, underweight (BMI less than 18.5 kg/ m2), normal weight (between 18.5 kg/ m2 and 25 kg/ m2), overweight (between 25 kg/ m2 and 30 kg/ m2), obese (more than 30 kg/ m2).

[c] For Gestational Weight Gain, GWG: adequate: 12.5-18 kg among underweight mothers, 11.5-16 kg among mothers with a normal BMI value, 7-11.5 kg among overweight mothers, and 5-9 kg among obese mothers. Any weight gain less than the lower limit mentioned in each category is considered as insufficient GWG and any weight gain above the upper limit mentioned in each category is considered excessive GWG.

Table 2: Comparison Between Women with Different Stages of Preterm Birth

Independent Variables	**Extremely preterm (<28 weeks GA) N= 520 (0.86) n (%)**	**Very preterm (28-32 6/7 weeks GA) N= 825 (1.37) n (%)**	**Moderately to Late Preterm (33-36 6/7 weeks GA) N= 10,704 (17.8) n (%)**
Socio-demographics			
Newborn's Year of Birth			
2009	66 (12.69)	77(9.33)	876 (8.18)
2010	66 (12.69)	89 (10.79)	1,103 (10.3)
2011	62 (12.69)	87 (10.55)	1,215 (11.35)
2012	62 (11.92)	99 (12)	1,448 (13.53)
2013	93 (17.88)	110 (13.33)	1,320 (12.33)
2014	59 (11.35)	113 (8.61)	1,150 (10.74)

2015	52 (10)	71 (8.61)	831 (7.76)
2016	47 (9.04)	69 (8.36)	912 (8.52)
2017	15 (2.88)	38 (4.61)	705 (6.59)
2018	10 (1.92)	34 (4.12)	693 (6.47)
2019	8 (1.54)	28 (4.61)	451 (4.21)
Newborn Sex			
Male	296 (60.66)	444 (56)	5,771 (54.91)
Female	192 (39.34)	349 (44)	4,738 (45.09)
Governorate of Residence			
Beirut	88 (17.53)	91 (11.61)	1,318 (13.46)
Mount Lebanon	271 (54)	328 (41.84)	4,344 (44.36)
Bekaa	21 (4.18)	35 (4.46)	273 (2.79)
Baalbeck-Hermel	24 (4.78)	74 (9.44)	541 (5.52)
North Lebanon	49 (9.76)	124 (15.82)	1,849 (18.88)
Akkar	28 (5.58)	81 (10.33)	796 (8.13)
South Lebanon	10 (1.99)	16 (2.04)	191 (1.95)
Nabatiyeh	3 (0.6)	20 (2.55)	311 (3.18)
Outside Lebanon	8 (1.59)	15 (1.91)	169 (1.73)
Mother's Age			
Below 18 years	4 (0.77)	8 (0.97)	36 (0.34)
18-28.11 years	195 (37.5)	284 (34.42)	3,360 (31.39)
29-39.11 years	272 (52.31)	460 (55.76)	6,062 (56.63)
40 years and above	39 (7.5)	48 (5.82)	681 (6.36)

Mother's Educational Level			
Illiterate	17 (3.7)	31 (4.15)	296 (3.05)
Knows how to read or write	28 (6.09)	39 (5.22)	382 (3.93)
Elementary	76 (16.52)	98 (13.12)	987 (10.16)
Intermediate	134 (29.13)	173 (23.16)	2,1680 (22.32)
Secondary	54 (11.74)	98 (13.12)	1,550 (15.96)
Technical school	30 (6.52)	77 (10.31)	941 (9.69)
Undergraduate university	91 (19.78)	171 (22.89)	2,589 (26.65)
Graduate University	30 (6.52)	60 (8.03)	800 (8.24)
Consanguinity			
No	363 (74.69)	614 (78.22)	8,455 (83.87)
Yes	123 (25.31)	171 (21.78)	1,626 (16.13)
Maternal Health and Obstetrics-related Conditions			
Pre-pregnancy BMI			
Underweight [b]	20 (3.85)	43 (5.21)	388 (3.62)
Healthy Weight [b]	142 (27.31)	194 (23.52)	2,027 (18.94)
Overweight [b]	224 (43.08)	372 (45.09)	4,979 (46.52)
Obese [b]	97 (18.65)	163 (19.76)	2,394 (22.37)
Gestational Weight Gain (GWG)			
Insufficient GWG [c]	267 (51.35)	279 (33.82)	2,812 (26.27)

Adequate GWG [c]	159 (30.58)	248 (30.06)	2,608 (24.36)
Excessive GWG [c]	52 (10)	155 (18.79)	2,504 (23.39)
Previous Preterm Birth			
No	392 (79.35)	650 (80.95)	9,264 (88.02)
Yes	102 (20.65)	153 (19.05)	1,261 (11.98)
Number of Gestations			
Single	372 (77.99)	566 (72.75)	8,618 (82.38)
Twins	89 (18.66)	165 (21.21)	1,679 (16.05)
Triplets	12 (2.52)	32 (4.11)	137 (1.31)
More	0	10 (1.29)	16 (0.15)
Previous C-sections			
No	335 (64.42)	520 (63)	6,537 (61.07)
Yes	185 (35.58)	305 (37.6)	4,167 (38.92)
Number of Previous C-sections			
None	335 (64.42)	520 (63)	6,537 (61.07)
1 previous C-section	108 (20.77)	179 (21.7)	2,258 (21.09)
2 previous C-sections	56 (10.77)	100 (12.12)	1,278 (11.94)
3 previous C-sections	12 (2.31)	20 (2.42)	487 (4.55)
4 previous C-sections	5 (0.96)	5 (0.61)	119 (1.11)
5 or more previous C-sections	4 (0.77)	1 (0.12)	25 (0.23)
Cigarette Smoking During Pregnancy			
No	441 (88.91)	697 (87.13)	9,570 (90.94)

Yes	55 (11.09)	103 (12.88)	953 (9.06)
Argileh Smoking During Pregnancy			
No	454 (91.72)	730 (91.02)	9,674 (92.04)
Yes	41 (8.28)	72 (8.98)	837 (7.96)
Prenatal Care			
No	22 (4.48)	23 (2.94)	306 (2.94)
Yes	469 (95.52)	758 (97.06)	10,105 (97.06)
Chronic Condition			
No	462 (89.02)	719 (87.36)	9,692 (90.59)
Yes	57 (10.98)	104 (12.64)	1,007 (9.41)
Urinary Tract Infection During Pregnancy			
No	418 (84.44)	602 (75.16)	8,869 (84.39)
Yes	77 (15.56)	199 (24.84)	1,641 (15.61)
Vaginal Bleeding During Pregnancy			
No	356 (71.34)	630 (78.55)	9,424 (89.73)
Yes	143 (28.66)	172 (21.45)	1,079 (10.27)
Gestational Hypertension			
No	464 (94.5)	702 (88.19)	9,970 (95.04)
Yes	27 (5.5)	94 (11.81)	520 (4.96)
Gestational Diabetes			
No	482 (98.17)	747 (94.08)	10,002 (95.43)
Yes	9 (1.83)	47 (5.92)	479 (4.57)
Amniotic Fluid			

Clear and normal volume	322 (81.52)	491 (83.36)	7,144 (90.68)
Meconium	34 (8.61)	30 (5.09)	284 (3.6)
Pus	0	0	2 (0.03)
Bloody	1 (0.25)	2 (0.34)	3 (0.04)
Oligohydramnios	31 (7.85)	51 (8.66)	298 (3.78)
Polyhydramnios	7 (1.77)	15 (2.55)	147 (1.87)
Assisted Reproductive Technology			
No	397 (88.03)	625 (84.69)	9,315 (93.75)
Yes	54 (11.97)	113 (15.32)	621 (6.25)
Birth Defects			
No	358 (84.63)	644 (86.91)	9,567 (95.62)
Yes	65 (15.37)	97 (13.09)	438 (4.38)

[b] For the BMI, underweight (BMI less than 18.5 kg/ m2), normal weight (between 18.5 kg/ m2 and 25 kg/ m2), overweight (between 25 kg/ m2 and 30 kg/ m2), obese (more than 30 kg/ m2).

[c] For Gestational Weight Gain, GWG: adequate: 12.5-18 kg among underweight mothers, 11.5-16 kg among mothers with a normal BMI value, 7-11.5 kg among overweight mothers, and 5-9 kg among obese mothers. Any weight gain less than the lower limit mentioned in each category is considered as insufficient GWG and any weight gain above the upper limit mentioned in each category is considered excessive GWG.

B. C-section, preterm birth, and the measured confounders:

Prior to examining the association between our main exposure variable (C-section birth and outcome (preterm birth), the association between each of the two variables was examined against all measured confounders. In the case of C-section deliveries, bivariate associations were examined; in the case of preterm births, the independent association between each of the measured covariates was assessed using regression analyses (controlling for C-section birth). The findings are presented in tables 2s and 3 respectively. All variables with a p-value of 0.2 or less were included in the final models examining the association between preterm birth and C-section.

a. Association Between C-section Birth and Measured Confounders:

Table s2 (see Supplementary Appendix) shows the association between our main risk factor (presence of previous C-section) and the other measured variables that were controlled for in the adjusted models (if p-value≤0.2). Prior C-section had a significant association with all the variables (p-value<0.05). The distribution of previous C-section was almost equal among male and female newborns. The percentage of mothers having previous C-section was increasing between 2009 (28%) and 2019 (37%). 36% of mothers aged 40 years and above and 20% of mothers aged below than 18 years had a prior C-section. Mothers who had a prior C-section constituted 34% of those with obese BMI and 31% of those with excessive gestational weight gain. Around 40% of mothers who had a previous preterm birth, or have a health problem including chronic conditions, gestational hypertension, gestational diabetes, vaginal bleeding during pregnancy, or used assisted reproductive technology had a prior C-section. Also, around 30% of mothers who had an abnormal level of amniotic fluid including oligohydramnios and polyhydramnios and 33% of those who experienced a urinary tract infection during pregnancy had a prior C-section. Regarding the mother’s behaviors, 36% of mothers who smoked cigarettes, 37% of those who smoked argileh, and 29% of those who didn't have prenatal care had a prior C-section.

b. Association Between Preterm Births and Measured Confounders:

The group "term birth" is taken as the reference category. Table 3 shows the unadjusted and adjusted associations between preterm stages and all independent variables. Most of the variables had a significant association with all stages of prematurity that are "extremely preterm", "very preterm", and "moderate to late preterm" except for consanguinity, the presence of urinary tract infection during pregnancy, arghile smoking during pregnancy, and prenatal care. Consanguinity was significantly associated with "extremely preterm birth" [Adjusted OR=1.68, 95% CI (1.36 – 2.06)] and "very preterm birth" [Adjusted OR= 1.38, 95% CI (1.16 – 1.63)] while urinary tract infection was significantly associated only with "very preterm birth" [Adjusted OR= 1.84, 95% CI (1.57 – 2.17)]. Meanwhile, arghile smoking during pregnancy was only significantly associated with "moderate to late preterm birth" [Adjusted OR=0.88, 95% CI (0.81 - 0.95)]. Prenatal care was significantly associated with "extremely preterm birth" [Adjusted OR=0.47, 95% CI (0.31 – 0.73)] and "moderate to late preterm birth" [Adjusted OR=0.73, 95% CI (0.65 – 0.84)]. Mothers aged below than 18 years were 4 times more likely to have a very preterm birth in comparison with full-term birth, versus those aged between 29 and 39 [Adjusted OR= 3.9 95% CI (1.89 – 8.03)]. The odds of delivering very preterm birth or moderate to late preterm birth in comparison to term birth increased by approximately 2-folds in mothers who had a chronic condition, a urinary tract infection and vaginal bleeding during pregnancy, gestational diabetes, and smoked cigarettes during pregnancy. Mothers who had a previous preterm birth showed an increased association with extreme preterm birth rather than moderate to late preterm birth in comparison to term birth. In comparison with those who had a full-term birth, the odds of experiencing an extreme preterm birth for mothers who had a previous preterm birth is almost 7 times more likely than those who didn't have a previous preterm birth [Adjusted OR= 6.76, 95% CI (5.4-8.46)]. While the odds of experiencing a moderate to late birth for mothers who had a previous preterm birth is almost 4 times more likely than those who didn't have a previous preterm birth [Adjusted OR= 3.45, 95% CI (3.19 - 3.72)]. Moreover, mothers who have triplets in comparison to single newborns were 47 times more likely to deliver very preterm birth [Adjusted OR=47.1, 95% CI (31.94-69.42)]. This odd is much higher than the odds of delivering moderate to late preterm birth [Adjusted OR=11.24, 95% CI (8.5 – 14.85)]. Also, the odd of delivering very preterm has a 23-fold increase among mothers who have used an assisted reproductive technology [Adjusted OR=22.69, 95% CI (18.09 – 28.44)] while the odds of delivering moderate to late preterm has an 8-fold increase among those who have used assisted reproductive technology [Adjusted OR= 8.38, 95% CI (7.34 – 9.57)].

Table 3: Unadjusted and adjusted odds ratios and their 95% CI of preterm stages with possible confounders using multinomial logistic regression

	Extremely Preterm (<28 weeks GA) Unadjusted OR (95% CI) Adjusted OR† (95% CI)	Very Preterm (28-31 6/7 weeks GA) Unadjusted OR (95% CI) Adjusted OR† (95% CI)	Moderate to Late Preterm (32-36 6/7 weeks GA) Unadjusted OR (95% CI) Adjusted OR† (95% CI)
Socio-demographics			
Newborn's sex			
Male	Ref	Ref	Ref
Female	0.68 ((0.56 – 0.81)** 0.68 (0.56 – 0.81)**	0.82 (0.71 – 0.94)** 0.82 (0.71 – 0.94)**	0.86 (0.82 – 0.89)** 0.86 (0.82 – 0.89)**
Mother's age			
Below 18 years	2.77 (1.03 – 7.55)* 2.83 (1.04 – 7.74)*	3.80 (1.84 – 7.83)** 3.9 (1.89 – 8.03)**	1.45 (0.9 – 2.1)* 1.47 (1.01 – 2.13)*
18-28.11 years	Ref	Ref	Ref
29-39.11 years	1 (0.84 – 1.21) 0.99 (0.83 – 1.19)	1.17 (1.01 – 1.36)* 1.15 (0.99 – 1.34)	1.30 (1.25 – 1.37)** 1.29 (1.23 – 1.35)**
40 years and above	1.80 (1.27 – 2.54)* 1.77(1.24 – 2.5)*	1.52 (1.11 – 2.07)* 1.49 (1.09 – 2.03)*	1.82 (1.66 - 2)** 1.8 (1.63 – 1.97)**
Mother's educational level			
Illiterate	1.70 (1.01 – 2.87)* 1.71 (1.02 – 2.89)*	1.65 (1.12 – 2.43)* 1.67 (1.13 – 2.46)*	1.04 (0.91 – 1.19) 1.05 (0.92 – 1.21)
Knows how to read or write	2.34 (1.52 – 3.57)** 2.35 (1.53 – 3.61)**	1.72 (1.21 – 2.45)* 1.76 (1.23 – 2.5)*	1.11 (0.98 – 1.26) 1.13 (1 – 1.28)*
Elementary	1.92 (1.42 – 2.62)** 1.93 (1.42 – 2.62)**	1.32 (1.03 – 1.7)* 1.33 (1.03 – 1.7)*	0.88 (0.81 – 0.95)* 0.88 (0.81 – 0.96)**
Intermediate	1.56 (1.19 – 2.04)* 1.56 (1.21 – 2.06)*	1.07 (0.87 – 1.33) 1.08 (0.88 – 1.35)	0.88 (0.83 – 0.95)** 0.89 (0.84 – 0.96)*

Secondary	0.78 (0.56 – 1.09)	0.75 (0.57 – 0.97)*	0.78 (0.73 – 0.84)**
	0.78 (0.56 – 1.09)	0.76 (0.59 – 0.97)*	0.79 (0.74 – 0.85)**
Technical school	0.72 (0.74 – 1.09)	0.98 (0.75 – 1.29)	0.8 (0.73 – 0.86)**
	0.72 (0.47 – 1.09)	0.97 (0.74 – 1.28)	0.79 (0.73 – 0.86)**
Undergraduate university	Ref	Ref	Ref
Graduate University	0.84 (0.56 – 1.27)	0.89 (0.66 – 1.21)	0.79 (0.72 – 0.86)**
	0.84 (0.56 – 1.28)	0.89 (0.67 – 1.21)	0.79 (0.73 – 0.86)**
Consanguinity			
No	Ref	Ref	Ref
Yes	1.68 (1.36 – 2.06)**	1.38 (1.16 – 1.63)**	0.95 (0.89 -1)
	1.68 (1.36 – 2.06)**	1.38 (1.16 – 1.63)**	0.95 (0.89 – 1)
Maternal Health and Obstetrics-related Conditions			
Pre-pregnancy BMI			
Underweight [b]	0.43 (0.27 – 0.68)**	0.67 (0.48 – 0.94)*	0.58 (0.51 – 0.66)**
	0.44 (0.27 – 0.7)*	0.69 (0.49 – 0.97)*	0.59 (0.52 – 0.67)**
Healthy Weight [b]	Ref	Ref	Ref
Overweight [b]	0.28 (0.22 – 0.34)**	0.34 (0.28 – 0.39)**	0.43 (0.4 – 0.46)**
	0.28 (0.23 – 0.35)**	0.34 (0.29 – 0.41)**	0.43 (0.41 – 0.46)**
Obese [b]	0.25 (0.19 – 0.33)**	0.29 (0.25 – 0.38)**	0.43 (0.41 – 0.46)**
	0.25 (0.19 – 0.33)**	0.31 (0.21 – 0.39)**	0.43 (0.4 – 0.46)**
Gestational Weight Gain (GWG)			
Insufficient GWG [c]	0.96 (0.78 – 1.16)	0.64 (0.54 – 0.76)**	0.61 (0.58 – 0.65)**
	0.98 (0.8 – 1.19)	0.65 (0.55 – 0.78)**	0.62 (0.59 – 0.66)**
Adequate GWG [c]	Ref	Ref	Ref
Excessive GWG [c]	0.17 (0.098 – 0.19)**	0.32 (0.24 – 0.37)**	0.49 (0.47 – 0.53)**
	0.14 (0.12 – 0.23)**	0.33 (0.26 – 0.39)**	0.50 (0.47 – 0.53)**
Chronic condition			

No	Ref	Ref	Ref
Yes	1.66 (1.26 – 2.19)**	1.95 (1.58 – 2.4)**	1.40 (1.29 – 1.51)**
	1.63 (1.24 – 2.15)**	1.91 (1.55 – 2.36)**	1.38 (1.28 – 1.49)**
Birth defects			
No	Ref	Ref	Ref
Yes	15.58 (11.80 – 20.58)**	12.93 (10.27 – 16.28)**	3.93 (3.45 – 4.47)**
	15.21 (11.51 – 20.01)**	12.59 (10 – 15.87)**	3.86 (3.39 – 4.39)**
Previous Preterm Birth			
No	Ref	Ref	Ref
Yes	6.78 (5.43 – 8.49)**[a]	6.15 (5.12 – 7.38)**[a]	3.56 (3.29 – 3.83)**[a]
	6.76 (5.4 – 8.46)**	5.94 (4.95 – 7.14)**	3.45 (3.19 – 3.72)**
Number of Gestations			
Single	Ref	Ref	Ref
Twins	14.68 (11.52 – 18.7)**	17.89 (14.83 – 21.58)**	11.96 (10.94 – 13.07)**
	14.64 (11.49 – 18.66)**	17.84 (14.79 – 21.53)**	11.93 (10.91 – 13.04)**
Triplets	20.25 (10.91 – 37.58)**	46.58 (31.61 – 68.63)**	11.14 (8.44 – 14.72)**
	20.46 (11.02 – 37.9)**	47.1 (31.94 – 69.42)**	11.24 (8.5 – 14.85)**
More	5.55 (2.03 – 15.19)*	4.56 (1.85 – 11.26)*	0.66 (0.35 – 1.23)
	5.3 (1.94 – 14.5)*	4.35 (1.79 – 10.75)*	0.63 (0.33 – 1.18)
UTI during pregnancy			
No	Ref	Ref	Ref
Yes	1.04 (0.81 – 1.32)	1.86 (1.58 – 2.19)**	1.04 (0.98 – 1.1)
	1.03 (0.8- 1.3)	1.84 (1.57 – 2.17)**	1.03 (0.97 – 1.09)
Vaginal Bleeding during pregnancy			
No	Ref	Ref	Ref

Yes	9.12 (7.47 – 11.13)** 9.02 (7.38 – 11)**	6.2 (5.21 – 7.38)** 6.09 (5.12 – 7.26)**	2.6 (2.41 – 2.81)** 2.57 (2.38 – 2.77)**
Gestational hypertension			
No	Ref	Ref	Ref
Yes	4.51 (3.03 – 6.7)** 4.43 (2.98 – 6.6)**	10.38 (8.25 – 13.06)** 10.13 (8.05 – 12.75)**	4.04 (3.59 – 4.55)** 3.97 (3.52 – 4.47)**
Gestational diabetes			
No	Ref	Ref	Ref
Yes	0.76 (0.39 – 1.47) 0.75 (0.39 – 1.45)	2.57 (1.9 – 3.47)** 2.49 (1.85 – 3.38)**	1.95 (1.75 – 2.18)** 1.91 (1.72 – 2.14)**
Amniotic Fluid			
Clear and normal volume	Ref	Ref	Ref
Meconium	1.99 (1.39 – 2.84)**	1.15 (0.79 – 1.67)	0.75 (0.66 – 0.85)**
Pus	-	-	4.55 (0.64 – 32.32)
Bloody	10.09 (1.28 – 79.12)*	13.25 (2.89 – 60.62)*	1.37 (0.38 – 4.96)
Oligohydramnios	3.44 (2.37 – 5)**	3.72 (2.76 – 4.99)**	1.49 (1.31 – 1.71)**
Polyhydramnios	1.47 (0.69 – 3.12)	2.07 (1.23 – 3.48)*	1.39 (1.15 – 1.68)*
Assisted reproductive technology			
No	Ref	Ref	Ref
Yes	17.29 (12.77 – 23.41)** 17.08 (12.62 – 23.13)**[a]	22.99 (18.34 – 28.82)** 22.69 (18.09 – 28.44)**[a]	8.48 (7.42 – 9.68)** 8.38 (7.34 – 9.57)** [a]
Cigarette Smoking During Pregnancy			
No	Ref	Ref	Ref
Yes	1.58 (1.19 – 2.1)*	1.88 (1.52 – 2.31)**	1.26 (1.17 – 1.36)**

	1.57 (1.18 – 2.08)*	1.84 (1.49 – 2.27)**	1.24 (1.15 – 1.34)**
Argileh Smoking During Pregnancy			
No	Ref	Ref	Ref
Yes	0.93 (0.67 – 1.29)	1.02 (0.79 – 1.3)	0.9 (0.83 - 0.97)*
	0.92 (0.67 – 1.26)[a]	0.9 (0.78 – 1.27) [a]	0.88 (0.81 - 0.95)*[a]
Prenatal Care			
No	Ref	Ref	Ref
Yes	0.47 (0.31 – 0.73)*	0.73 (0.48 – 1.12)	0.73 (0.65 – 0.84)**
	0.47 (0.31 – 0.73)*	0.73 (0.48 – 1.12)	0.73 (0.65 – 0.84)**

† association adjusted for "previous C-section" taking those who had a "term" birth as the reference category
*p-value<0.05; **p-value < 0.001
[a] For this particular analysis, the assumption of proportional odds held. The results as per the ordinal logistic regression are as follows: OR (95% CI) for previous preterm birth = 3.91 (3.64 – 4.19)**, aOR (95%) for assisted reproductive technology= 9.3 (8.29 – 10.42)**, aOR(95% CI) for arghile smoking during pregnancy= 0.89 (0.83 - 0.96)*
[b] For the BMI, underweight (BMI less than 18.5 kg/ m2), normal weight (between 18.5 kg/ m2 and 25 kg/ m2), overweight (between 25 kg/ m2 and 30 kg/ m2), obese (more than 30 kg/ m2).
[c] For Gestational Weight Gain, GWG: adequate: 12.5-18 kg among underweight mothers, 11.5-16 kg among mothers with a normal BMI value, 7-11.5 kg among overweight mothers, and 5-9 kg among obese mothers. Any weight gain less than the lower limit mentioned in each category is considered as insufficient GWG and any weight gain above the upper limit mentioned in each category is considered excessive GWG.

C- Association Between C-section and Preterm Birth, Controlling for Measured Confounders:

Table 4 presents the unadjusted and adjusted association of preterm stages and previous C-section and number of previous C-sections. There was a significant association between prior C-section and moderate to late preterm births. Also, the number of previous C-sections was significantly associated with moderate to late preterm birth only and not extreme preterm or very preterm birth. Even after adjustment, the odds of having undergone a previous C-section was 1.3 times more likely in cases with moderate-to-late preterm birth (32-<37 weeks) [adjusted OR=1.3, 95% CI (1.21 –

1.38)] than in controls (full-term birth) controlling for measured covariates. There was also a statistically significant increase in the odds of moderate to late preterm birth vs. full-term birth with increasing number of previous C-sections, controlling for measured covariates. This increase reached almost a 3-fold rise in odds when the number of previous C-sections was five or more in comparison to no previous C-section [adjusted OR=2.85, 95% CI (1.50 – 5.42)]. There was a dramatic increase in odds of moderate to late preterm as compared to term deliveries when the number of previous C-sections exceeded 3 [adjusted OR= 2.78, 95% CI (2.03 – 3.82)] with 4 previous C-sections as compared to an [adjusted OR=1.74, 95% CI (1.46 – 2.08)] with 3 C-sections. Moreover, there was a significant association between extreme preterm birth and number of previous C-sections, when the number was 5 or more. The odds of having undergone 5 previous C-section was 5.25 times more likely in cases with extreme preterm birth (<28 weeks) [adjusted OR= 5.25, 95% CI (1.03-26.65)] than in controls (full-term birth), controlling for measured confounders.

Table 4: Unadjusted and adjusted odds ratios and their 95% CI of preterm stages with previous C-section and number of previous C-sections, using multinomial logistic regression

Variable	**Extremely Preterm** **(<28 weeks GA)** **Unadjusted OR (95% CI)** **Adjusted OR† (95% CI)**	**Very Preterm** **(28-31 6/7 weeks GA)** **Unadjusted OR (95% CI)** **Adjusted OR† (95% CI)**	**Moderate to Late Preterm** **(32-36 6/7 weeks GA)** **Unadjusted OR (95% CI)** **Adjusted OR† (95% CI)**

Previous C-section			
No	Ref	Ref	Ref
Yes	1.14 (0.94 – 1.37) [a] 0.85 (0.63 – 1.14)	1.34 (1.15 – 1.55)**[a] 1.15 (0.92 – 1.43)	1.37 (1.31 – 1.43)**[a] 1.29 (1.21 – 1.38)**
Number of Previous C-sections			
None	Ref	Ref	Ref
1 previous C-section	1.19 (0.95 – 1.49) 0.94 (0.67 – 1.31)	1.32 (1.10 – 1.57)* 1.16 (0.89 – 1.49)	1.27 (1.20 – 1.34)** 1.18 (1.09 – 1.27)**
2 previous C-sections	1.08 (0.77 – 1.51) 0.59 (0.32 – 1.08)	1.28 (1.01 – 1.67)* 1.06 (0.72 – 1.57)	1.29 (1.19 – 1.39)** 1.25 (1.12 – 1.40)**
3 previous C-sections	1.04 (0.57 – 1.90) 0.74 (0.29 – 1.89)	1.37 (0.89 – 2.11) 1.10 (0.56 – 2.14)	1.73 (1.53 – 1.95)** 1.74 (1.46 – 2.08)**
4 previous C-sections	2.24 (0.92 – 5.48) 1.74 (0.41 – 7.35)	2.07 (0.97 – 4.42) 0.65 (0.09 – 4.77)	2.64 (2.11 – 3.30)** 2.78 (2.03 – 3.82)**
5 or more previous C-sections	4.19 (1.01 – 17.29)* 5.25 (1.03 – 26.65)*	1.38 (0.19 – 10.03) 1.75 (0.21 – 14.31)	2.84 (1.77 – 4.56)** 2.85 (1.50 – 5.42)**

† association adjusted for maternal age, maternal education, consanguinity, previous preterm birth, cigarette smoking, argileh smoking, prenatal care, vaginal bleeding during pregnancy, UTI during pregnancy, presence of any chronic condition, gestational hypertension, gestational diabetes, pre-pregnancy BMI, gestational weight gain, birth defects, number of gestation, use of assisted reproductive technology, year, sex of the baby, governorate, and volume and state of amniotic fluid taking those who had a "term" birth as the reference category

*p-value<0.05; **p-value < 0.001

[a] For this particular analysis, the assumption of proportional odds held. The results as per the ordinal logistic regression are as follows: OR (95% CI) for previous C-section= 1.31 (1.27 – 1.36)*

CHAPTER V

DISCUSSION

A. Summary of Key Findings

This retrospective multicenter population-based study addresses important gaps in the published literature focused on examining the association between previous C-section and preterm birth, controlling for the possible confounding effects of other predictors and the association between previous C-section or multiple previous C-sections and preterm birth stages (extremely preterm, very preterm, moderate to late preterm birth). Certainly, majority of complications and death due to preterm birth occur among extremely and very preterm infants [36]; thus, it is important to examine the association between prior C-section and the stages of preterm birth and not only the presence of preterm birth. Moreover, several risk factors (i.e., potential confounders) were not included in some previous studies [12-17]. These covariates include medical variables such as chronic conditions, gestational hypertension, gestational diabetes, level of amniotic fluid, and birth defects for the newborn, demographics such as age of the mother, educational level, and consanguinity, and behaviors such as cigarette smoking and prenatal care.

Previous studies on the effect of prior C-section on preterm birth in subsequent pregnancies appear to be inconclusive. Our findings support the link between C-section and preterm birth which was the conclusion of one meta-analysis [10] but not the other [11]. Our findings show that prior C-section increases the odds of moderate to late preterm birth in subsequent pregnancy by almost 1.3 folds, controlling for the previously mentioned covariates. In addition, an increasing number of previous C-section seems to be linked to higher odds of moderate to late preterm birth (vs. full term birth). The dose-response relationship between moderate to late preterm birth and number of previous C-sections was the highest related to having five or more previous C-sections (versus zero previous C-sections). Additionally, there was a 5-fold increase and a statistically significant association between extremely preterm birth and the number of previous C-sections when the mother experienced five or more C-sections.

Similar to our findings, Kennare et al found that there is a strong link between preterm birth and previous C-section when taking preterm birth as a dichotomous variable (yes/no). [93]. Congruent with our results, Ramadan et al have found that beyond the fourth C-section, there is a sharp increase in the odds ratio of preterm birth, keeping in mind that preterm birth was taken as a dichotomous variable (preterm birth vs. full-term birth) [12]. However, their reference group was mothers who had one previous C-section and not zero previous C-sections as in our study.

Nevertheless, some of the previous studies did not find an association or have even found that prior C-section is a protective factor against preterm birth respectively [11]. For example, Huang et al have found that prior C-section is not significantly associated with subsequent preterm birth after excluding mothers with chronic health problems or previous preterm birth (adjusted OR=1) [81]. They believed that mothers who were excluded are more likely to have a trial of labor; thus, making previous C-section group comparable to the previous vaginal delivery group with respect to the impact on subsequent delivery [81]. On the other hand, Jackson et al have found that C-section delivery is associated with a decrease in the risk of preterm birth after adjusting for age, smoking, alcohol, socioeconomics, and BMI [74]. However, the latter believed that this finding is explained by the fact that mothers included are generally healthy with high socioeconomic status; thus, they are at low risk of preterm birth in comparison to the general population [74].

The mechanism for this association and the pathogenesis of subsequent preterm birth in women who experience a C-section remain unclear. Possible reasons may be the potential change in the uterine structure or the intrauterine microenvironment by previous C-sections, cervical trauma, or unintentional incision into the uterine cervix during the prior C-sections, and thus increasing the risk of subsequent preterm birth [10]. Another possible reason may be related to the uterine scarring after previous C-section. Thus, it is important to address the interpregnancy interval that may affect the healing of this scar. Moreover, adhesions created by prior C-sections are believed to reduce the utero-placental function and disturb the blastocyst implantation creating sub-optimal conditions for fetal growth [10]. Moreover, several risk factors for preterm birth are also associated with C-section. In other words, factors such as higher pre-pregnancy body mass index, advanced maternal age, chronic conditions (such as hypertension and diabetes mellitus), and obstetrics (such as preeclampsia) which may be indications for C-section in the first pregnancy can also be risk factors for preterm birth in next pregnancies [10, 94].

Other secondary important finding of our study includes a significant positive association between consanguinity and preterm stages specifically extremely preterm birth and very preterm birth as well as a significant association between consanguinity and our main exposure which is previous C-section. Also, 9,562 (17%) of the participants had consanguineous marriage. It is worth noting that our study is the first study to control for consanguinity.

Additionally, the results of our study are consistent with previous literature that examined the association between several modifiable and non-modifiable risk factors and preterm birth. The modifiable factors include maternal age and education, prenatal care, and smoking during pregnancy. Understanding the association of these modifiable factors with preterm birth can help in identifying those who are at higher risk of preterm birth among mothers who had a previous C-section. For example, our findings support other published studies that concluded that the risk of preterm birth is higher among adolescents and mothers at advanced age [3, 21, 95]. Also, our findings have shown that mothers with low educational level (including illiterate mothers and mothers who know how to read and write) are more likely to have a preterm birth than mothers who have a university degree [21].

Another major modifiable risk factor associated with preterm birth is the cigarette and arghile smoking. Our findings were supported by Golderberg et al who found out that tobacco users have almost a 2-fold increase in the odds of having extremely preterm and very preterm births [96].

Absence of prenatal care is known to be another risk factor for several adverse outcomes including preterm birth. Our study has shown that the risk of very and moderate to late preterm birth is lower in mothers who had prenatal care compared to those who didn't. Prenatal care is vital to determine possible birth defects of the newborn. Our study showed that mothers who gave birth to a newborn with a birth defect were 15 times more likely to delivery extremely premature, 13 times more likely to deliver very premature, and only 4 times more likely to deliver moderate to late premature births. These findings are supported by Honein et al who found that birth defects were over five times more likely among mothers who had a very preterm birth [97].

Pre-existing health problems including hypertension and diabetes mellitus and pregnancy-related health problems including gestational hypertension and diabetes are all known risk factors for preterm birth. Literature has shown that hypertension is associated with a 3-fold increase in the risk of preterm birth and diabetes mellitus is associated with a 4-fold increase in the risk of late preterm birth [98, 99]. In this study, mothers suffering from a chronic condition (including hypertension, diabetes, heart disease, asthma, hypothyroidism, hyperthyroidism, epilepsy, anemia, or hemoglobinopathies), are 2 times more likely to have extremely and very preterm birth compared to term birth. Furthermore, in our study, mothers who had a urinary tract infection during pregnancy were 2 times more likely to deliver very preterm which is also supported by other studies [100].

Finally, multiple gestations status is a major risk factor for preterm birth, resulting in approximately 19% of all preterm birth per our study, a finding that is consistent with other studies stating that multiple gestations result in 15-20% of all preterm birth [96]. Multiple gestations status is usually also associated with the use of assisted reproductive technology that is another factor for preterm birth. In our study, mothers who used an assisted reproductive technology were found to be 17 times more likely to delivery extremely preterm and 23 times more likely to delivery very preterm birth.

Identifying the association between these maternal health problems with preterm birth can reiterate the importance of screening for risk factors of preterm deliveries specially among mothers who had a prior C-section.

Even though there was a statistical significance between all measured covariates and preterm birth, we believe that there may be associations that are not clinically significant. The sample size we had is large enough to detect even the smallest difference between cases and controls. Also, the association between pre-pregnancy BMI and gestational weight gain and preterm birth may have been affected by the fact that mothers who had a preterm birth were more likely to have several risk factors such as previous preterm birth and chronic conditions. These mothers may have been asked by their physicians to have a healthy pre-pregnancy BMI and an adequate gestational weight gain. Therefore, reverse causality is one hypothesis for our results showing that mothers who had a preterm birth were more likely to have a healthy pre-pregnancy BMI and adequate GWG in comparison to mothers who had a full-term birth.

B. Limitations and Off-setting Strengths

The study is not void of limitations. First, data on the clinical reasons behind previous C-sections (whether it was elective or medically indicated) is not available. Similarly, data on whether the preterm birth was spontaneous or iatrogenic was not available. Preterm birth is a syndrome that is not always feasible to distinguish between spontaneous from medically indicated [82]. Nonetheless, we took the clinical indication for the preterm birth into account by adjusting for the presence of several medical conditions.

The second limitation is the use of self-report data which may have introduced information bias (reporting bias, recall bias). However, NCPNN collects its data cross-sectionally by professionals through direct interviews with mothers after birth and from medical records, thus reducing this non-differential bias.

Third, residual confounding due to unmeasured confounders (i.e., interpregnancy interval that may impact uterine scar healing), or covariates with imperfect measurement is always a possibility; nonetheless, this study controlled for a great number of confounders, including important independent predictors of preterm births

The final limitation is that cases with missing data on the main exposure (i.e., previous C-section) were excluded. There was a significant difference in the distribution of several risk factors in the included and excluded samples (table s1). While for many variables that were clinically different (such as pre-pregnancy BMI, gestational weight gain, previous preterm birth, smoking during pregnancy, and birth defects), the differences were mostly very negligible though statistically significant due to the large sample size. In any case, since those excluded were more likely to have some of the known predictors, it is likely that our effect sizes are biased towards the null.

The study also has several offsetting strengths, which include the large number of cases and controls, representing social, religious, socioeconomical, and geographical region diversity. We also had rich data on clinical and social variables that enabled us to adjust for important confounders mentioned previously. These confounders include medical, sociodemographic, and behavior variables. Our study is the first study to assess the association between prior C-section and preterm birth controlling for consanguinity. Also, to our knowledge this is the first study that has examined the association between preterm stages and increasing number of previous C-sections.

C. Implications of the Study

Understanding the association between previous C-section and subsequent preterm birth could encourage clinicians and parents to reduce the occurrence of elective and unnecessary C-sections, particularly among mothers who are at risk of premature delivery. As mentioned previously, C-section constituted almost 50% of all deliveries in Lebanon in 2019 [18]. Moreover, elective C-section births constituted around 10% of all deliveries and 25% of all C-section deliveries [101]. Although, data on the distribution of previous C-sections were elective or medically indicated are unavailable, we can assume that around 25% of previous C-sections were elective. Thus, at least 20% of previous C-sections could have been prevented; thus, decreasing the risk of preterm birth in subsequent births. Therefore, risk of preterm birth should be considered as part of the clinical assessment during the C-section in the first pregnancy. In other words, in additional to short-term operative risks physicians should advise mothers considering an elective C-section for its adverse outcomes on their next pregnancy. Furthermore, quantifying the risk of subsequent preterm birth following C-section births could help identify mothers at risk of preterm birth and may benefit from screening and intervention methods. For instance, trauma to the cervix and myometrial scarring during C-section birth are considered indications to spontaneous and medically indicated preterm birth respectively [102]. Thus, understanding the association between prior C-section and preterm birth can encourage obstetricians to screen mothers at risk of preterm birth and thus provide proper management. These screening interventions include assessment of uterus, cervical length scan, and screening for asymptomatic bacteriuria [103]. For example, current guidelines in England include that all women who had a previous second stage C-section should do a single cervical length scan; however, this is not considered an evidence-based intervention [102]. Thus, further research is required to confirm appropriate management and intervention strategies.

D. Further work

In my future research, the classification of preterm birth stages and number of previous C-sections will be altered when investigating the association between preterm stages and subsequent preterm birth. For example, number of previous C-sections will be classified such that the last category includes three or more previous C-sections. Although there isn't a limit for number of C-sections, experts recommend a maximum of three [104]. Thus, our aim will be to assess the relationship of "3 or more previous C-sections" and subsequent preterm birth. Also, late premature infants constitute the majority of preterm cases [105]. Therefore, in order to measure the association between late preterm birth and prior C-section, preterm birth stages will be classified as "extremely to very preterm birth", "moderate preterm birth", "late preterm birth", and "full-term birth". Moreover, we will adjust for the impact of hospital on C-section and preterm birth to control any institutional difference or difference in policies among hospitals.

E. Conclusion and Recommendations

C-section birth in the first pregnancy is shown to be a significant risk factor for preterm birth in subsequent delivery even after controlling for history of previous preterm birth and other important risk factors. These results can play a role in the prediction of patients at risk of preterm birth; thus, clinicians and parents would aim to address potential existing risk factors to reduce perinatal mortality. It can also help create informed decisions about mode of delivery. Further studies should evaluate the possible causative agents for this association including incision placement, placental dysfunction, intrauterine microenvironment, taking into consideration the interpregnancy interval.

APPENDIX

SUPPLEMENTARY MATERIAL

Table s1: Distribution of Independent Variables Comparing the Included Sample and the Excluded Sample with Missing Values on "Previous C-section"

Independent Variables	% In Total Sample N = 60,245	% In Excluded Sample N = 1,080	p-value
Sociodemographic			
Newborn Sex			0.459
Male	51.84	53	
Female	48.16	47	
Governorate of Residence			<0.001
Beirut	12.92	6.82	
Mount Lebanon	44.31	35.64	
Bekaa	2.53	7.33	
Baalbeck-Hermel	4.48	11.51	
North Lebanon	17.84	22.3	
Akkar	8.37	9.16	
South Lebanon	1.92	1.22	
Nabatiyeh	5.76	3.67	
Outside Lebanon	1.85	2.34	
Mother's Age			<0.001
Below 18 years	0.3	0.46	
18-28.11 years	36.61	36.39	
29-39.11 years	53.17	48.7	
40 years and above	4.65	3.98	
Mother's Educational Level			<0.001
Illiterate	2.67	4.8	
Knows how to read or write	3.27	6.29	
Elementary	10.28	13.6	
Intermediate	22.31	25.6	
Secondary	17.54	14.97	
Technical school	10.64	8.69	
Undergraduate university	24.21	19.89	

Graduate University	9.09	6.17	
Consanguinity			0.001
No	83.23	79.03	
Yes	16.77	20.97	
Maternal Health and Obstetrics-related Conditions			
Pre-pregnancy BMI			<0.001
Underweight [b]	3.23	2.31	
Healthy Weight [b]	11.01	32.13	
Overweight [b]	52.12	41.76	
Obese [b]	24.85	17.59	
Gestational Weight Gain (GWG)			<0.001
Insufficient GWG [c]	26.89	22.41	
Adequate GWG [c]	16.77	35.28	
Excessive GWG [c]	28.01	22.31	
Previous Preterm Birth			<0.001
No	94.57	88.24	
Yes	5.43	11.76	
Number of Gestations			0.001
Single	94.83	92.55	
Twins	4.51	7.16	
Triplets	0.37	0.2	
More	0.11	0.1	
Cigarette Smoking During Pregnancy			<0.001
No	92.34	88.26	
Yes	7.66	11.74	
Argileh Smoking During Pregnancy			0.036
No	91.37	89.26	
Yes	8.63	10.74	
Prenatal Care			0.001
No	2.31	4.06	
Yes	97.69	95.94	
Chronic Condition			0.879
No	92.53	92.42	
Yes	7.47	7.59	
Urinary Tract Infection During Pregnancy			<0.001
No	84.77	80.28	
Yes	15.23	19.72	
Vaginal Bleeding During Pregnancy			0.482
No	94.29	93.74	
Yes	5.71	6.26	
Gestational Hypertension			0.103
No	97.92	97.1	
Yes	2.08	2.9	

Gestational Diabetes			
No	97.17	98.17	0.052
Yes	2.83	1.83	
Amniotic Fluid			
Clear and normal volume	90.97	89.6	0.451
Meconium	4.66	4.3	
Pus	0.01	0	
Bloody	0.04	0	
Oligohydramnios	2.88	3.88	
Polyhydramnios	1.45	2.22	
Assisted Reproductive Technology			
No	97.96	98.61	0.141
Yes	2.04	1.39	
Birth Defects			
No	98.05	95.66	<0.001
Yes	1.95	4.34	

[b] For the BMI, underweight (BMI less than 18.5 kg/ m2), normal weight (between 18.5 kg/ m2 and 25 kg/ m2), overweight (between 25 kg/ m2 and 30 kg/ m2), obese (more than 30 kg/ m2).
[c] For Gestational Weight Gain, GWG: adequate: 12.5-18 kg among underweight mothers, 11.5-16 kg among mothers with a normal BMI value, 7-11.5 kg among overweight mothers, and 5-9 kg among obese mothers. Any weight gain less than the lower limit mentioned in each category is considered as insufficient GWG and any weight gain above the upper limit mentioned in each category is considered excessive GWG.

Table s2: Association Between Previous C-section and Measured Confounders

	N	Previous C-section %	p-value
Socio-demographics			
Gender			
Male	9,634	31.97	0.071
Female	8,716	31.13	
Governance			
Beirut	2,249	33.15	
Mount Lebanon	7,685	33.02	
Bekaa	432	32.48	
Baalbeck-Hermel	959	40.74	
North Lebanon	2,849	30.3	<0.001
Akkar	981	22.31	
South Lebanon	346	34.26	
Nabatiyeh	762	25.17	
Outside Lebanon	294	30.22	
Mother's age			
Below 18 years	35	19.66	
18-28.11 years	6,245	28.84	<0.001
29-39.11 years	10,580	33.65	
40 years and above	986	35.83	
Mother's educational level			
Illiterate	386	26.44	
Knows how to read or write	419	23.42	
Elementary	1,743	31.04	<0.001
Intermediate	3,471	28.47	
Secondary	3,083	32.17	
Technical school	2,027	34.88	
Undergraduate university	4,572	34.57	
Graduate University	1,687	33.97	
Consanguinity			
No	14,899	32.06	0.001
Yes	2,838	30.31	
Maternal Health and Obstetrics-related Conditions			
Pre-pregnancy BMI			
Underweight [b]	507	26.52	
Healthy Weight [b]	1,639	25.17	<0.001
Overweight [b]	9,286	30.11	
Obese [b]	5,065	34.45	

Gestational Weight Gain (GWG)			
Insufficient GWG [c]	4,569	28.74	<0.001
Adequate GWG [c]	2,766	27.9	
Excessive GWG [c]	5,185	31.31	
Chronic condition			
No	16,985	31.04	<0.001
Yes	1,626	36.81	
Birth defects			
No	17,186	31.64	<0.01
Yes	400	37.04	
Previous Preterm Birth			
No	17,065	30.60	<0.001
Yes	1,421	44.39	
Number of Gestations			
Single	17,209	31.25	<0.001
Twins	911	34.81	
Triplets	74	34.91	
More	23	34.85	
UTI during pregnancy			
No	15,576	31.23	0.008
Yes	2,925	32.65	
Vaginal Bleeding during pregnancy			
No	17,199	31.02	<0.001
Yes	1,290	38.43	
Gestational hypertension			
No	17,961	31.22	<0.001
Yes	507	41.42	
Gestational diabetes			
No	17,765	31.12	<0.001
Yes	718	43.15	
Amniotic Fluid			
Clear	13,444	33.75	<0.001
Meconium	336	16.47	
Pus	2	50	
Bloody	9	56.25	
Oligohydramnios	358	28.39	
Polyhydramnios	198	31.23	
Assisted reproductive technology			
No	17,062	31.43	<0.001
Yes	472	41.84	
Cigarette Smoking During Pregnancy			
No	16,884	31.03	<0.001
Yes	1,631	36.13	
Argileh Smoking During Pregnancy			

No	16,650	30.93	<0.001
Yes	1,869	36.74	
Prenatal Care			0.007
No	381	28.14	
Yes	18,024	31.55	

[b] For the BMI, underweight (BMI less than 18.5 kg/ m2), normal weight (between 18.5 kg/ m2 and 25 kg/ m2), overweight (between 25 kg/ m2 and 30 kg/ m2), obese (more than 30 kg/ m2).
[c] For Gestational Weight Gain, GWG: adequate: 12.5-18 kg among underweight mothers, 11.5-16 kg among mothers with a normal BMI value, 7-11.5 kg among overweight mothers, and 5-9 kg among obese mothers. Any weight gain less than the lower limit mentioned in each category is considered as insufficient GWG and any weight gain above the upper limit mentioned in each category is considered excessive GWG.

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