THE ASSOCIATION BETWEEN EARLY MENARCHE AND PRETERM BIRTH

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ABSTRACT

Exploring healthcare outcomes throughout a female's reproductive life is an important area of research that is in need of more investigation. Specifically, there is a limited body of evidence available that explores the association between early reproductive behaviours and future pregnancy outcomes. Yet there is increasing evidence that points towards a relationship between the age at menarche and an increased risk for preterm birth. Therefore, this thesis explored the relationship between early age at menarche and the risk of preterm birth among a cohort of Canadian women. Responses from the Ontario Birth Study, a retrospective pregnancy-based cohort study, was used for the analysis. Summary statistics and a multivariable logistic regression were conducted, adjusting for covariates. Overall, 17% of the sample experienced early menarche. Additionally, 4.2% of all survey participants experienced a preterm birth. In total, 7.0% of women who experienced an early age at menarche went on to deliver preterm. The unadjusted association between early menarche and preterm birth was statistically significant; however, after adjusting for all covariates, the relationship was no longer significant. Significant determinants of a preterm birth included women who had any hypertensive disorders throughout their pregnancy, had fetal complications, or any placental issues prior to delivery. Conversely, those in the highest income group were at a decreased risk of a preterm birth. Recognizing risk factors is an important step to aid healthcare providers mitigate the risks associated with preterm birth. Future investigations are needed to probe deeper into the field and tease out social and environmental intricacies.

DEDICATION

To my vivacious and unwavering grandparents

To my backbone: Amma, Appa, and Akshitha

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LIST OF ABBREVIATIONS

PTB: Preterm Birth

OR: Odds Ratio

aOR: Adjusted Odds Ratio

CI: Confidence Interval

OBS: Ontario Birth Study

GA: Gestational Age

IVF: In vitro fertilization

IUI: Intrauterine insemination

BMI: Body mass index

SPSS: Statistical Package for the Social Sciences

LSQ1: Lifestyle Questionnaire 1

LSQ2: Lifestyle Questionnaire 2

LSQ3: Lifestyle Questionnaire 3

SOGC: Society of Obstetricians and Gynaecologists of Canada

ACOG: American College of Obstetricians and Gynecologists

EXTENDED INTRODUCTION

Reproductive Adversity, Preterm Birth & Consequences

Reproduction, or the creation of life, is often regarded as one of the most important biological processes known to humankind. Although the process of pregnancy is essential to the survival of humans, many pregnancies around the world endure some sort of complication or adversity.[1,2] Pregnancy complications alone affect millions of families worldwide, which ranges in severity and outcomes.[3,4]

Preterm birth (PTB), or delivery of the fetus between 20 to before 37 weeks of gestation, is one of the world's leading pregnancy complication and the number one leading cause of neonatal mortality globally.[5] Delivering a baby preterm is associated with negative early and late-life outcomes for the baby and their parents. Children born preterm experience longer hospital admissions,[6] have an increased risk of sensory deficiencies,[7] neurodevelopmental disorders,[8] physical impairment,[9] as well as behavioural and emotional difficulties.[10,11] As adults, preterm infants are more likely to develop chronic diseases including heart disease,[12] hypertension,[13] and type 2 diabetes.[14] Not only do these babies face long-term consequences, their parents and extended family also experience negative health and emotional effects following a preterm and unexpected delivery. Parents of preterm children report developing signs of posttraumatic stress disorder following the birthing process and continue to experience these symptoms after their children are discharged from the Neonatal Intensive Care Unit.[15] Moreover, the effects of preterm delivery on parental stress is exacerbated by caesarean section and the limited contact with their baby after birth.[16] Increased feelings of anxiety, depression, and extreme fatigue are also noted among these parents, which are linked to poor pregnancy

recovery and signs of delayed infant development.[17] An investigation by Wolke et al. (2014) argues that parents of preterm infants are less likely to initiate early contact with their children which can lead to a disorganized and detached parenting attachment style.[18] Similarly, a study conducted by Henderson et al. (2016) reported that mothers of preterm infants develop fewer positive feelings towards their baby, which adversely affects the later life development of the child.[15]

Due to the many consequences of PTBs, the prevention of preterm labour has been a topic of interest for several decades. Despite the years of research behind the determinants of PTB, it remains increasingly prevalent in both developing and developed nations and is the cause for many neonatal hospitalizations globally.[5,19] PTB is a challenge for scientists and clinicians, however the primary cause of a preterm delivery has yet to be clearly outlined.[20,21] Cases of PTBs are difficult to assess, wide ranging, and postulated to be underrepresented due to the nature of pregnancy care and data collection around the world.[21,22] A systematic review published in *The Lance Global Health* estimated that close to 15 million infants were born premature in 2014.[22] Of all PTBs in 2014, 81% of deliveries were attributed to women delivering in Asia and sub-Saharan Africa. However, on a global scale, over 90% of all available data on prematurity comes from middle-and higher-income countries, whom only account for less than 5% of the world's births.[22] Therefore, cases and severity of PTBs are estimated to be much higher than currently projected.

To date, the literature and knowledge surrounding PTB and all associated outcomes are assessed through experimental and observational studies. Given that the prognosis and pathways of preterm labour are largely complex, clinicians often rely on external symptoms and previously identified risk factors to assess the probability of PTB from pregnancy to pregnancy. Therefore,

more studies on PTB and any associated factors is vital to reduce the existing burden of PTB on the healthcare system and on families.

Menarche, Trends & Importance of Timing

Menarche, the first mensural cycle, experienced by a female can often act as a key developmental marker for physical, nutritional, and reproductive health.[23] Unlike other developmental and pubertal features that may appear gradually, menarche is a sudden event that marks the start of puberty.[24,25] The onset of menarche can also be considered one of the initial signs of possible fertility and can act as a good predictor of future obstetrical health.[25] Unfortunately, although a good predictor of female health, menarche, specifically the timing of menarche, is generally a discrete event which is underreported and overlooked by the medical community as an indicator of health.[26]

The timing of menarche varies between most females, with many experiencing their first menstrual period between ages 10 to 16.[27,28] The worldwide average age of menarche is difficult to estimate accurately and varies significantly by geographical region, race, and ethnicity.[28] However, the study of menarche has garnered attention from researchers as there is a general decline in the average age around the world, with more females reporting earlier ages at menarche compared to previous decades.[29] Plenty of drivers, including genetic and environmental factors, are proposed to explain this shift in timing; however, there is mixed consensus surrounding the primary influencing factors driving early menarche.[25,29] Remarkably, research suggests that the average age at menarche is observed to be generally lower in countries located in the Global North, compared to the countries in the Global South. Investigations in Canada, England, and the United States show the average age of menarche to be 12.7 years,[30]

12.7 years,[31] and 12.3 years respectively.[32] When observing countries in the Global South like India,[33] Vietnam,[34] and Ethiopia,[35] age of menarche ranges from 13.8 years to 15.8 years. The reason for this downward trend in developed countries is unknown, although factors such as industrialization, nutrient-poor foods, and sedentary behaviors are identified to play an important role.[29] With age at menarche being studied across the globe, investigations have signalled that an early age at menarche may be a negative predictor for later life events.[25,36,37]

Females who experience an earlier age at menarche are more likely to be at risk for developing poor health conditions such as cardiovascular disease,[38] type 2 diabetes,[39] and cancer.[36] Early menarche is also associated with a higher risk of asthma,[40] obesity,[41] substance use,[42] and mood disorders including psychosocial disorders, antisocial behaviours, bipolar disorders, depression, and increased levels of anxiety among women worldwide.[42–44] A meta-analysis by Baams and colleagues (2015) found that an early age at puberty is also associated with risky sexual behaviours, such as no contraception use, higher likelihood of contracting sexually transmitted diseases, and unwanted pregnancies.[45] Additionally, the life history theory notes that in poor and stressful environments, early menarche may be a sign of earlier mortality, and subsequently the body signals early reproduction to maximize the potential to procreate prior to a fatal event.[46] Following that hypothesis, independent studies by Jacobsen et al. (2007) and Tamakoshi et al. (2011) both observed that early menarche is correlated with an increased all-cause mortality among women.[47,48]

Significance of Early Menarche & Preterm Birth

As menarche is essentially the very first sign of reproductive potential, it can be hypothesized to have an effect on later-life reproductive outcomes. With many poor later life

outcomes associated with an early age at menarche, it is important that more research is done to assess how early age at menarche plays a role in reproduction. Moreover, given the upward trend in PTB and the downward trend in age at menarche across the globe, it is also important to assess the impact that the time of menarche may have on the timing of birth. Additionally, using data from Canada would provide insight on the trends that may be occurring among a specific demographic in the Global North, whom seem to be experiencing more PTBs all while experiencing a steeper decline in average age at menarche. It is important to add possible risk factors to the literature, as PTB mechanisms and pathways are unclear and are continuously changing.

Framework

Based on the literature, the life history theory is gaining traction among the public health community for exploring variations among human behaviours and outcomes.[49] The life history theory seeks to explain how evolutionary forces, such as natural selection, shape the reproductive and survival strategy of individuals during intense periods of stress and potential danger. This theory was originally developed to predict the interactions and trade-offs between biological traits that contribute directly to birth and death.[49] A review conducted by Ellis (2004) proposed that under the life history theory of reproduction, the timing of pubertal maturation may be considered a trade-off in reproductive strategies under stressful and potentially harmful environments.[50] As such, under risky circumstances, earlier age at menarche and early reproductive development may promote immediate and short-term reproductive success. Although accelerated reproduction may result in a higher quantity of offspring, they are often lower in biological fitness due to insufficient resource allocation.[50] Equally, in safer and less

stressful environments, late reproductive maturity would favor long-term and resource intensive reproduction that results in less offspring with a higher biological fitness.[50] Therefore, there is reason to believe that early-life triggers may affect age at menarche and consequently PTB.

The life history theory also postulates a potential trade-off between maternal and fetal success, making PTB unavoidable for mothers at all age ranges.[49] For younger-aged mothers, nutritional energy and growth-related biological resources would be in direct competition with the fetus, making it difficult for both mother and baby to receive equal resources. However, among relatively older-aged mothers, pregnancy may be in direct competition with natural senescence and may cause the body to divert energy towards itself to ensure self-preservation during a resource depleting period.[49] In essence, the life history theory can be used as an important model to help incorporate biological, evolutionary, and environmental conditions in the study of reproductive behaviours and potential.

MANUSCRIPT

Examining the Association Between Early Menarche and Preterm Birth: A Retrospective Cohort Study

ABSTRACT

Background: Preterm birth (PTB) is the main cause of perinatal mortality and morbidity globally, where 60-80% of deaths in infants are related to premature delivery. Menarche is a discrete event that is linked to poor pregnancy outcomes. However, evidence for a significant association between early menarche and PTB is mixed and limited. Therefore, the main objective of this study was to determine if early age at menarche is associated with PTB.

Methods: Secondary data analysis was conducted using data from the Ontario Birth Study (OBS) that included a cohort of women who delivered at Mount Sinai Hospital in Toronto, Canada. Inclusion criteria required participants to answer two lifestyle questionnaires between 2013 and 2019. Exclusion criteria included women with non-viable pregnancies, known fetal abnormalities, multiple gestation, delivery prior to 20 weeks' gestation, a stillbirth, previous PTB, missing gestational age (GA) at delivery, and missing age at menarche. The main outcome, PTB, was defined as neonatal delivery from 20 weeks gestation up to and including 36 weeks and six days at gestation. The main exposure, age at menarche, was assessed by the following question from the questionnaire: "How old were you when you had your first menstrual period?" Covariates were adjusted for and categorized in the following groups: Maternal Sociodemographic, Health, and Clinical Pregnancy Factors. A multivariable logistic regression

was conducted to assess the effect of early menarche on the risk of PTB adjusting for all covariates.

Results: The prevalence of early menarche in the OBS was 17% and the overall risk of PTB was 4.2%. Overall, 7.0% of the women who had early menarche went on to experience a PTB in their current pregnancy, compared to 3.7% of women who experienced a later age at menarche. The unadjusted association between early menarche and PTB was statistically significant (OR: 1.98, 95% CI: 1.11-3.54); however, after adjusting for all covariates, the relationship was no longer significant (OR: 1.68, 95% CI: 0.84-3.36). Significant predictors of a PTB included women who experienced any hypertensive disorders and those who had fetal or placental complications prior to delivery. Women in the highest income group were significantly at a decreased risk of a PTB compared to the rest of the population.

Conclusion: Results can be used as a baseline in investigating the intricacies between early reproductive factors and later life pregnancy outcomes, which may be important to the future of maternal and infant health.

INTRODUCTION

Every expecting family hopes for a relatively smooth experience during pregnancy, however a significant proportion of pregnancies experience an adverse maternal or fetal outcome.[19] Pregnancy related complications range in severity and vary between every individual.[3,51] Globally, preterm birth (PTB) is one of the most commonly seen pregnancy complications.[5] PTB, or birth before 37 weeks of gestation, occurs in approximately 5-13% of pregnancies worldwide affecting almost 15 million infants.[5,52–54] PTB is the main cause of perinatal mortality and morbidity across the globe, where 60-80% of deaths in infants are related to PTB complications.[53,55] Hospitalization in a neonatal intensive care unit is estimated to cost $1500 per day, and total neonatal care for preterm infants approaches $8 billion per year in Canada.[6,56,57] This represents a significant financial and social burden to caregivers and the Canadian healthcare system.[56,57] There is no single etiological pathway that predicts who will experience a PTB. Instead, healthcare professionals rely on clinical signs and symptoms such as abdominal cramping, premature rupture of the membrane, pelvic pressure, backache, and dilated/shortened cervix to diagnose potential preterm labour.[58–60] The etiology of PTBs is not completely understood, but is known to be multifactorial. Previous research across various countries suggests that risk factors for PTB include sociodemographic characteristics, behavioral factors, and aspects of obstetric history.[53,61,62]

Menarche, or the age at first menstrual period, is identified as an indicator of puberty that can help determine future health risks.[23] Associations with early age of menarche are studied across the globe, with many studies linking early menarche to adverse health outcomes.[63–66] Global investigations note an alarming trend of a decreasing average age of menarche over the

past century.[25,67] More importantly, research has observed that females who reside in the Global North currently experience menarche at significantly younger ages in comparison to their counterparts in the Global South.[30–32] Early menarche is linked to negative later life outcomes including a higher risk of developing breast cancer,[36,68,69] cardiovascular disease,[38,70] type 2 diabetes,[39,71] and asthma.[40,72] An earlier age at menarche is also linked to poor pregnancy outcomes including low birth weight,[73] spontaneous abortion,[74] and ectopic pregnancy.[75] Previous studies suggest that early menarche is associated with PTB risk factors such as obesity,[41,76] infections,[77,78] and psychological stress.[79,80] Biological investigations have linked early menarche to higher estradiol levels,[81,82] elevated C-reactive protein levels,[83] and high blood glucose levels in adulthood,[37,84] all of which are associated with an increased risk of PTB.[85–88]

The life history theory as a framework for pregnancy and other reproductive outcomes is growing in popularity over the last several decades. It is an evolutionary perspective that is used to explain the idiosyncrasies among key life stages, including birth, reproduction, and death.[73] Additionally, the life history theory makes use of both physiological and environmental viewpoints in order to evaluate potential outcomes. Due to the downward trend of age at menarche and higher incidence of PTB, the life history theory may be an important tool to examine whether negative health outcomes may be an evolutionary adaptive trait and also a biologically predictive one.[89] A key area of the life history theory is the idea of a biological trade-off between maternal and fetal resources.[89] This may be particularly interesting to explore, as reproductive behaviours often come in direct competition with the biological potential of both mother and fetus. Additionally, the life history theory postulates that early and later life environmental triggers may play a role in maladaptive behaviours like early menarche and PTB,[73] which is also a noteworthy concept to consider throughout this investigation.

To date, there is only a few studies worldwide which have assessed the association between menarche and PTB. An American case-control study conducted by Berkowitz in 1981, examined a group of 488 mothers who delivered at Yale-New Haven Hospital for one year. Although women who experienced a PTB reached menarche at a younger age, the results were not significant.[90] A subsequent investigation published in 1998 by Hennessy and Alberman in the United Kingdom found that teenage mothers who experience late menarche were more likely to experience PTB (OR: 1.51, 95% CI: 1.1-2.1).[91] Although these results are critical to the understanding of menarche's role in PTB, this study neglected to adjust for any covariates and failed to include mothers over the age of twenty.[91] A more recent study from China conducted by Li et al. (2017), examined a group of 11,016 births to study the relationship between menarche and PTB. They concluded that women who had early menarche (≤11 years) were 1.67 times more likely to experience PTB compared to those who experienced menarche at age 13 (OR: 1.67; 95% CI: 1.18, 2.36).[92] However, this study failed to adjust for noteworthy clinical pregnancy variables, including placental issues or fetal complications prior to delivery. The results of all of these studies are inconclusive and exhibit mixed results, therefore the relationship between early menarche and PTB is in need of additional investigation. It is important to consider whether menarche should be considered an essential health measure when screening for potential pregnancy complications, as there is a gap in the current literature. Therefore, the objective of this investigation is to determine if early age at menarche is associated with PTB in a cohort of women delivering in Toronto, Canada.

METHODS

Study Design & Participants

Data from the Ontario Birth Study (OBS) was used for this study. The OBS is an open longitudinal pregnancy cohort study initiated in 2013 at Mount Sinai Hospital in Toronto, Canada. The data collected by the OBS is used by researchers interested in exploring pregnancy and any related conditions. More details about the OBS can be found on their website.[93]

The OBS has data collection scheduled to coincide with routine pregnancy care to minimize the burden of research activities on participants. Pregnant women were approached at their first ultrasound or first antenatal appointment by trained research staff who recruit participants that fit the inclusion criteria. For women who consented to participate in the OBS, lifestyle questionnaires, diet history questionnaires, biospecimens, and clinical delivery data were collected as a part of the study during routine antenatal appointments. Lifestyle questionnaires were distributed during three time periods. Lifestyle questionnaire 1 (LSQ1) was completed between 12-16 weeks of gestation, lifestyle questionnaire 2 (LSQ2) was given to participants between 28-32 weeks, and lifestyle questionnaire 3 (LSQ3) was completed at the 6-10 weeks postpartum period. All lifestyle questionnaires were administered to participants in their choice of paper or web-based format. If the participant chose to complete the questionnaires on the paper-based form, trained research staff input the data into REDCap (version 8.10.2.), a secure and electronic data capture tool hosted at Mount Sinai Hospital.[94] For the current study, data from both LSQ1 and LSQ2, along with clinical delivery data, were used.

Inclusion criteria for the OBS included women who were less than 17 weeks gestational age (GA) at recruitment, over the age of 18, spoke and understood English, were able to provide

signed informed consent, and were planning to have their antenatal care and birth at Mount Sinai Hospital. Inclusion criteria for the current study included any OBS participant who answered both LSQ1 and LSQ2 between 2013 to 2019. Exclusion criteria for both the OBS and this study included the following conditions: a non-viable pregnancy, a fetus with a known significant abnormality associated with a low probability of survival, had multiple gestation, recalled a previous PTB, delivered prior to 20 weeks' gestation, had a fetal demise or stillbirth, did not report an age at menarche, or had missing information on GA at the time of birth.

Main Outcome Variable

The main outcome of this study was PTB. PTB was defined as neonatal delivery between 20-weeks gestation (140 days) up to and including 36 weeks and six days of gestation (258 days), which was obtained from the clinical delivery data. The definition of PTB was derived from the guidelines endorsed by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG).[95,96] The GA for the OBS participants was defined by using the dating ultrasound, and if unavailable, the last menstrual period.

Main Exposure Variable

The exposure for this investigation was age at menarche. The participants were asked about their age at menarche in LSQ1 with the following question: "How old were you when you had your first menstrual period?" For this investigation, age at menarche was dichotomized to 'early menarche' or 'not early menarche'. Consistent with previous literature, early menarche was defined as one (1) standard deviation less than the mean age at menarche in the study

sample.[55-57] Those who answered, 'don't know', 'prefer not to answer', or 'never had a mensural period' were excluded from the analysis.

Covariates

A complete list of covariates that have been identified as potential predictors of PTB were adjusted for in this study. These covariates were categorized in the following groups: 'Maternal Sociodemographic Factors' (including age, ethnicity, marital status, education, employment, and income); **'**Health Factors' (including pre-pregnancy BMI, pre-existing diabetes, gestational diabetes, hypertensive disorders of pregnancy, infection during pregnancy, emotional health, smoking during pregnancy, and alcohol use during pregnancy); and **'**Clinical Pregnancy Factors' (including IVF/IUI pregnancy, parity, previous pregnancy loss <20 weeks GA, fetal complications [including fetal anomaly, isoimmunization/alloimmunization, intrauterine growth restriction, large for GA, oligohydramnios, and polyhydramnios], and placental complication [including placental abruption, placenta accrete, increta, percreta, and previa]).

Statistical Analysis

Summary statistics and bivariable associations between the main outcome and exposure variables were conducted. A logistic multivariable regressions analysis was performed to control for covariates. The multivariable model adjusted for all maternal sociodemographic factors, health factors, and clinical pregnancy factors. Both unadjusted and adjusted Odds Ratios (ORs and aORs, respectively) along with the 95% Confidence Intervals (CIs) were reported. In addition, several potential interaction terms were investigated including a) age at menarche and

parity, b) age at menarche and pre-pregnancy BMI, c) age at menarche and pre-existing diabetes, d) age at menarche and gestational diabetes, and e) age at menarche and hypertensive disorders of pregnancy. Statistical significance for all analyses were set at alpha < .05 for a two-tailed test. All analyses were conducted using The Statistical Package for Social Science (SPSS) version 24.0 (IBM Corp, Armonk, NY, USA) and Stata Statistical Software version 13.0 (StataCorp, College Park, TX, USA).

Research Ethics

Research ethics approval for this investigation was obtained from York University's Research Office, alongside Mount Sinai Hospital's Research Ethics Board, approved on October 8th, 2019 for a one-year period for data analysis.

RESULTS

Between 2013 and 2019, the OBS enrolled 2,711 women. Approximately 30% of the respondents enrolled in the OBS did not complete either LSQ1 or LSQ2 and were considered missing for the analysis. Additionally, after all other study specific exclusions an additional 23% of the sample was excluded. Overall, a sample of 1,413 women were included in this analysis. The average age at menarche for the study sample was 12.7 years old. The prevalence of early menarche for women in the OBS was 17% and the overall risk of PTB was 4.2%.

Frequencies, along with unadjusted logistic regressions, are displayed in Table 1. Among women with early menarche, 7.0% went on to experience a PTB in their current pregnancy compared to the 3.7% of women who had a later age at menarche. Prior to adjusting for covariates, those who had early menarche were almost two times more likely to experience a PTB, compared to women who had a later menarche (OR: 1.98, 95% CI: 1.11-3.54). Additionally, women who reported their marital or relationship status as single accounted for 1.8% of the study respondents; however, 15% of these single mothers experienced a PTB compared to the 4.0% of women in a relationship (Table 1). Women above age 40 also experienced a higher rate of PTB (6.2%) compared to women in any other age category. Smoking during pregnancy (< .04%) was removed from the analysis due to low sample size.

Results displayed in Table 2 outline the adjusted logistic regression and the various covariates associated with PTB. After adjusting for maternal sociodemographic, health factors, and clinical pregnancy factors, early menarche was 1.68 times more likely to result in a PTB; however, the relationship was no longer statistically significant (aOR: 1.68, 95% CI: 0.84-3.36). Additionally, women who reported a household income in the second highest income bracket

[$100,000-149,999] were more than 2.5 times more likely to have a PTB compared to those in the highest household income [> $150,000] (aOR: 2.54, 95% CI: 1.27-5.06). Among health factors, women who experienced any hypertensive disorders during pregnancy showed a strong statistical association with having a PTB h compared to women who had no hypertensive issues throughout their pregnancy (aOR: 3.77, 95% CI: 1.51-9.41). For clinical pregnancy factors, women who had fetal complications prior to delivery had significantly greater odds of PTB (aOR: 2.37, 95% CI: 1.12-5.02) compared to pregnancies with no fetal complications. Further, women who had placental complications had 3.5 times greater odds of a PTB, compared to their counterparts (aOR: 3.50, 95% CI: 1.26-9.97). All interaction terms were not significant ($p > .05$).

DISCUSSION

The current study aimed to assess the association between early menarche and PTB among the participants of the OBS. This study is among the first to explore the association of early reproductive markers and PTB while adjusting for key maternal sociodemographic, health, and clinical pregnancy factors. When examining the association between early menarche and PTB, 7.0% of women who experienced early menarche went on to have a preterm delivery. The crude association between early menarche and PTB was statistically significant; however, after controlling for all associated covariates, the relationship between early menarche and PTB was positive but no longer significant. Characteristics of women who had a PTB include those who experienced any hypertensive disorders during their pregnancy, and women who had fetal or placental complications prior to their delivery. Moreover, mothers who belonged to the highest income group were at a decreased risk of a PTB. These findings contribute and add to the broader knowledge about the effects of early reproductive factors on later-life pregnancy outcomes.

Results from this investigation are distinctive from the findings of other studies that sought to examine the relationship between early menarche and PTB. A recent analysis conducted by Li et al. (2017) found that among a sample of Chinese women enrolled in the Healthy Baby Cohort study, those with early menarche were at a significantly greater risk of experiencing a PTB, even after adjusting for some confounding variables.[92] These finding were inconsistent with the results of the current study, which may be attributed to the contrast in sample size used in both investigations. The Healthy Baby Cohort included over eleven thousand women, which may allow it to better represent the study population, give it more statistical

power, and reduce the margin of error. Additionally, the ethnic profiles of both cohorts were pointedly dissimilar as the Healthy Baby Cohort had a higher number of Chinese-Asian women compared to the OBS which is represented by a larger number of White-North American women. This may be interesting to note, as White women have historically experienced lower levels of PTB compared to women of colour. Moreover, Li et al. (2017) categorized early menarche into 5 different categories, while this study dichotomized age at menarche, which may have led to differences in the final results. Conversely, an American study conducted in 1981 noted similar results to the ones found in the current investigation. Berkowitz (1981) observed that women who delivered preterm at Yale-New Haven Hospital reached menarche at a younger age; but, the results were not significant.[90] The ethnic profile and socioeconomic conditions of that study were similar to the sample in the OBS; however, that investigation took place approximately four decades prior and represented a relatively younger cohort of women. Therefore, it may be difficult to draw parallels with the changes in demographics and environmental factors that have occurred over time.

In regard to maternal sociodemographic factors, women in the highest income bracket [> $150,000] had a reduced risk of PTB compared to all other categories (Table 2). Income, whether it be at the community, neighbourhood, household, or individual level, is used to illustrate disparities among mothers experiencing poor pregnancy outcomes in several countries.[97–100] Among women delivering in British Columbia, those in the highest income quintile had a lower risk of delivering preterm infants.[101] Additionally, an investigation by Luo and colleagues (2006) found similar results in Quebec, noting that individuals and neighbourhoods with a lower socioeconomic status are more likely to experience negative pregnancy outcomes.[99] Interestingly, many of the studies investigating individual measures of

socioeconomic status and birth outcomes are conducted in the United Kingdom and the United States, where rates of income disparities and access to basic healthcare varies greatly from the Canadian population.[97,100,102] Regardless, on a global scale, the consensus surrounding the role of income and PTB is mixed, with many postulating that the role of income in predicting pregnancy outcomes is intricate and needs further exploration.

Among health and clinical factors, having any hypertensive disorder during pregnancy, a fetal complication, or a placental complication prior to delivery were factors associated with a higher risk of experiencing a PTB. These predictors are iatrogenic, or medically indicated, and considered by the prenatal healthcare provider in the event of the rapidly declining health of the mother or the fetus.[103] Hypertensive disorders in pregnancy, especially preeclampsia, is not fully understood by the medical community and global efforts to treat and prevent these disorders show limited potential.[104,105] Therefore, in the case of a severe and uncontrollable progression of the disorder, early delivery is the only definitive treatment to end the threat of maternal-fetal morbidity and mortality.[106] For women who develop preeclampsia and are able to manage with mild symptoms, delivery is recommended at 37 weeks of gestation.[103] However, for women who progress to severe preeclampsia, delivery at any GA is recommended.[106] A study conducted by Barton et al. (2011), highlighted that over 25% of women with stable or mild gestational hypertensive complications had iatrogenic and elective preterm deliveries, with rates of prematurity expected to rise in groups of women with a more severe diagnosis.[107] Fetal complications including fetal asphyxia, intrauterine growth restriction, fetal anemia, oligohydramnios, and fetal chromosomal abnormalities are shown to increase the risk of premature deliveries.[103,108] Moreover, placental complications throughout pregnancy including placenta accrete, placenta increta and percreta, placenta previa, vasa previa, and placental

abruption is noted to increase the likelihood of medically indicated preterm deliveries to prevent the risk of maternal hemorrhaging and fetal death.[103]

In regard to both early age at menarche and PTB, much of the literature suggests that early life circumstances have a key role in determining the timing of reproductive events. Previous literature notes that increased access to highly processed foods, urbanization, and sedentary behaviour during childhood is associated with an early age at menarche.[24] Additionally, girls who report undergoing early life emotional trauma, paternal absence, and sexual assault also are at a higher odds of experiencing menarche at earlier ages.[24] Many of the same childhood factors associated with early menarche are also associated with the risk of adverse pregnancy outcomes. Therefore, it is important to assess the ongoing social effects that mothers undergo over their lifetime to get a comprehensive view of the social experiences shaping both early and later life reproductive outcomes. Given that sociodemographic factors are often intertwined with other early life factors, many studies have found it increasingly difficult to evaluate the underlying relationships between sociodemographic circumstances and both early and later life reproductive events.[109,110] Therefore, future research should strive to incorporate early childhood exposures when evaluating the impact of early reproductive markers and subsequent pregnancy outcomes.

PTB and its associated perinatal morbidity and mortality has become a leading issue in the field of obstetrics. In an attempt to lower the rates of PTB, many researchers have sought to identify the pathophysiological, environmental, and social factors that play a contributing role. Although the results of this study add to the body of literature surrounding the effects of early reproductive factors and PTB, this study is subjected to a few limitations. The OBS relies partially on self-reported data and is therefore subject to recall bias, especially in relation to

recalling the exact age at menarche. Additionally, 30% of women enrolled in the OBS were excluded from the analysis due to missing LSQ1 and LSQ2 questionnaire information, which leaves a chance for selection bias. After analyzing the respondents and non-respondents, it was apparent that single women, those with a higher BMI, who had infections throughout their pregnancy, used assisted reproductive technology, or experienced fetal complications were significantly more likely to not complete their questionnaires prior to delivery (Table A1). Therefore, caution should be exercised while generalizing these results to the entire population. It may also be plausible that non-respondents, most of whom are considered at high-risk for preterm birth would have delivered early. If non-respondents were included in the analysis, it may have changed the overall results. Additionally, as this study did not consider any live births prior to 20 weeks' gestation, the analysis does not address all early deliveries, especially those that do not fall within the clinical guidelines of PTB. However, if early menarche is indeed associated with PTB it may be possible that delivery could have occurred prior to the 20-week gestational period. Despite these limitations, this study allows for a more in-depth investigation of different clinical pregnancy related covariates and considered a wider age range compared to the previously conducted research surrounding early menarche and PTB.

CONCLUSION

This is one of the few studies to explore the association between menarche and PTB while controlling for a wide range of maternal sociodemographic, health, and clinical pregnancy variables. This study illustrates a relationship between early menarche and the increased risk of a PTB on a crude level; however, this relationship became insignificant after adjusting for covariates. Given the number of pregnancies that result in a PTB, and the burden on both the families and the healthcare system, it is essential to investigate potential risk factors that can be used to screen and mitigate the potential challenges of PTB and associated adverse perinatal outcomes. Identifying predisposing risk factors is an important step to aid clinicians in assessing risk for patients and screen for on history and reassess throughout pregnancy. It is advisable that clinicians include a screening question about the age at menarche during adolescences and during routine pregnancy care to adequately collect more information in this field and gain a comprehensive view of a female's reproductive history. More studies are needed to expand the field of early reproductive factors and their effects on later life reproduction, specifically how different early life social environments may mediate these effects. Additionally, these results indicate that assessing the influence of early reproductive factors on later life reproduction may be an integral branch of perinatal health and reproductive potential in the future.

Table 1: Frequencies and unadjusted odds ratios (ORs) along with corresponding 95% confidence intervals (95% CIs) of experiencing a preterm birth, based on the Ontario Birth Study.

	N	%	% Preterm Birth	Unadjusted OR	95% CI
Early Menarche					
No	1172	82.8	3.7	1	
Yes	242	17.1	7.0	**1.98**	**1.11-3.54**
Maternal Factors					
Age					
18-29	159	11.2	3.1	1	
30-34	728	51.4	4.4	1.42	0.54-3.70
35-39	430	30.4	4.0	1.27	0.46-3.50
40+	96	6.9	6.2	2.03	0.60-6.84
Ethnicity					
White	993	70.2	4.1	1	
Other[1]	123	8.7	7.3	1.83	0.87-3.87
East, South, South East Asian	263	18.6	3.4	0.82	0.40-1.72
Black	34	2.4	2.9	0.7	0.09-5.27
Marital Status					
Cohabitating/Married	1385	97.9	4.0	1	
Single	26	1.8	15	**4.32**	**1.44-12.94**
Education					
Graduate degree	574	40.6	4.0	1	
Bachelors	623	44	4.3	1.09	0.62-1.92
Post-secondary Trade, Diploma, Certificate	167	11.8	4.8	1.21	0.53-2.75
Secondary or less	41	2.9	4.9	1.23	0.28-5.40
Current Employment					
Employed	1276	90.3	4.3	1	
Not Employed	129	9.1	3.1	0.71	0.25-2.00
Household Income ($)					
> 150,000	724	51.2	2.8	1	
100,000 – 149,999	339	24	6.8	**2.56**	**1.39-4.73**

50,000–99,999	212	15	5.2	1.93	0.91-4.09
<50,000	60	4.2	5.0	1.85	0.53-6.42
Health Factors					
Pre-pregnancy BMI					
Normal	940	66.4	3.6	1	
Underweight	67	4.7	2.2	0.44	0.06-3.31
Overweight	233	16.5	7.9	**2.31**	**1.25-4.25**
Obese	94	6.6	8.2	**2.73**	**1.21-6.12**
Pre-existing Diabetes[2]					
No	1381	97.6	4.2	1	
Yes	19	1.3	15.8	**4.27**	**1.21-15.07**
Gestational Diabetes					
No	1337	94.5	4.0	1	
Yes	78	5.5	7.7	1.98	0.82-4.76
Hypertensive Disorders					
No	1350	95.4	3.7	1	
Yes	65	4.6	15.4	**4.73**	**2.28-9.82**
Infection During Pregnancy[3]					
No	941	66.5	4.3	1	
Yes	474	33.5	4.2	0.99	0.57-1.72
Emotional Health					
No Emotional Concern	1309	92.5	4.1	1	
Emotional Instability	70	5	5.7	1.41	0.50-4.01
Alcohol Use During Pregnancy					
No	1120	79.2	4.2	1	
Yes	290	20.5	4.5	1.07	0.57-2.01
Clinical Pregnancy Factors					
IVF / IUI Pregnancy					
No	1265	89.4	4.0	1	
Yes	147	10.4	6.8	1.77	0.88-3.58

Parity					
Primiparous	1095	77.4	4.3	1	
Multiparous	306	21.7	4.2	0.99	0.53-1.85
Previous Pregnancy Loss					
No	955	67.5	4.0	1	
Miscarriage	260	18.4	4.2	1.07	0.53-2.12
Termination of Pregnancy	186	13.2	5.9	1.52	0.76-3.03
Fetal Complication[4]					
No	1270	89.8	3.6	1	
Yes	145	10.3	9.7	**2.84**	**1.52-5.31**
Placental Complication[5]					
No	1365	96.5	3.8	1	
Yes	50	3.5	17.6	**4.81**	**2.15-10.76**

[1]Includes those that identified as one or more of the following: Indigenous (First Nations, Metis or Inuit), Arab, Latin American/Hispanic, or Other

[2] Pre-existing diabetes includes Type 1 and Type 2 diabetes, diagnosed by a healthcare provide prior to pregnancy

[3]Includes one or more of the following prior to delivery: flu, pneumonia, diarrhea, sinusitis, ear infection, cold sore, mouth infection, or other infection/inflammatory condition during pregnancy

[4]Fetal complications includes one or more of the following prior to delivery: fetal anomaly, isoimmunization/alloimmunization, intrauterine growth restriction, large for GA, oligohydramnios, or polyhydramnios

[5]Placental complications includes having one or more of the following prior to delivery: placental abruption, placenta accrete, increta, percreta, and previa

Table 2: Multivariable adjusted odds ratios (ORs), along with corresponding 95% confidence intervals (95% CIs) of experiencing a preterm birth, based on the Ontario Birth Study.

	Adjusted OR	95% CI
Early Menarche		
No	1	
Yes	1.68	0.84-3.36
Maternal Factors		
Age		
18-29	1	
30-34	1.45	0.51-4.16
35-39	1.44	0.46-450
40+	1.11	0.23-5.33
Ethnicity		
White	1	
Other[1]	1.41	0.57-3.50
East, South, South East Asian	0.67	0.26-1.73
Black	0.56	0.06-5.35
Marital Status		
Cohabitating/Married	1	
Single	3.82	0.84-17.48
Education		
Graduate degree	1	
Bachelors	1.41	0.72-2.77
Post-secondary Trade, Diploma, Certificate	1.41	0.54-3.70
Secondary or less	1.13	0.20-6.56
Current Employment		
Employed	1	
Not Employed	0.95	0.31-2.94
Household Income ($)		
> 150,000	1	
100,000 – 149,999	**2.54**	**1.27-5.06**
50,000–99,999	1.82	0.75-4.41

<50,000	1.80	0.39-8.31
Health Factors		
Pre-pregnancy BMI		
Normal	1	
Underweight	0.48	0.06-3.85
Overweight	1.79	0.90-3.56
Obese	1.67	0.63-4.46
Pre-existing Diabetes[2]		
No	1	
Yes	1.93	0.20-18.77
Gestational Diabetes		
No	1	
Yes	1.33	0.44-4.03
Hypertensive Disorders		
No	1	
Yes	**3.77**	**1.51-9.41**
Infection During Pregnancy[3]		
No	1	
Yes	1.03	0.55-1.92
Emotional Health		
No Emotional Concern	1	
Emotional Instability	1.36	0.39-4.77
Alcohol Use During Pregnancy		
No	1	
Yes	1.37	0.67-2.80
Clinical Pregnancy Factors		
IVF / IUI Pregnancy		
No	1	
Yes	1.18	0.47-2.98

Parity		
Primiparous	1	
Multiparous	1.25	0.55-2.84
Previous Pregnancy Loss		
No	1	
Miscarriage	1.21	0.51-2.86
Termination of Pregnancy	1.38	0.58-3.29
Fetal Complication[4]		
No	1	
Yes	**2.37**	**1.12-5.02**
Placental Complication[5]		
No	1	
Yes	**3.50**	**1.26-9.97**

[1]Includes those that identified as one or more of the following: Indigenous (First Nations, Metis or Inuit), Arab, Latin American/Hispanic, or Other

[2] Pre-existing diabetes includes Type 1 and Type 2 diabetes, diagnosed by a healthcare provide prior to pregnancy

[3]Includes one or more of the following prior to delivery: flu, pneumonia, diarrhea, sinusitis, ear infection, cold sore, mouth infection, or other infection/inflammatory condition during pregnancy

[4]Fetal complications includes one or more of the following prior to delivery: fetal anomaly, isoimmunization/alloimmunization, intrauterine growth restriction, large for GA, oligohydramnios, or polyhydramnios

[5]Placental complications includes having one or more of the following prior to delivery: placental abruption, placenta accrete, increta, percreta, and previa

EXTENDED DISCUSSION

To outline, this thesis aimed to identify the relationship between an early reproductive behaviour and later life reproductive outcomes. More specifically, this thesis investigated the association between an early age at menarche and the risk of preterm birth (PTB) among a subpopulation of Canadian women. This study was based on a secondary analysis of a pregnancy-based cohort study, the OBS, conducted at Mount Sinai Hospital in Toronto, Canada. The current study is distinctive, as it adds to the body of literature surrounding reproductive behaviours while filling in the previously recognized gaps in the analysis. This thesis also presents a novel finding by identifying an approximate two-fold increase in PTB among women who experience early menarche; however, after adjusting for key variables this relationship remained positive but no longer significant. This extended discussion will probe deeper into plausible reasons for these findings and also discuss some future directions.

Early Menarche

The causes and effects of menarche can be classified as individually driven and dependent on a multitude of varying factors including genetics, the environment, and individual behaviour.[24,30] Moreover, the life history theory's evolutionary perspective may also have a role in explaining the declining age at menarche. Although research surrounding menarche's characteristics, behaviour, and global prevalence is a topic of interest, much of the etiology has largely remained unexplained and heavily debated among the scientific community.[25,78,111] Reproductive behaviours are associated with other biological events and are known to influence the timing of key life events, including fertility and menopause.[24,28,75] It is important to note that many direct

factors which play a role in promoting an early menarche are linked to predicting early initiation of labour, and consequently PTB.[19,109,112] Considering that many factors that drive reproductive behaviours are interconnected and follow a complex pathway, these factors may be the cause-and-effect for both early menarche and PTB. Below, two key factors that may play a large role in influencing both early menarche and PTB are outlined.

1) **Hormonal Activity**

The involvement in sex steroid hormones are frequently suggested to be a contributor of early menarche and the initiation of early labour, while also influencing other reproductive outcomes.[113,114] Given that estrogen receptors are expressed in many tissues, they are likely to regulate central and peripheral biological processes and disturb the function of the hypothalamus, pituitary glands, and gonads.[115] In regard to the age at menarche, an increase in neurological signals and neuropeptides from the hypothalamus alongside the peripheral gonadal signals have played a large role in the early initiation of puberty.[116] Moreover, researchers hypothesize that an earlier age at menarche exposes the uterus and cervix to a longer duration of simulation by female endogenous hormones, which has adverse effects on uterine function later in life.[117–119] Previous literature notes that the association between age at first menarche and a poor labour experiences, including preterm labour, operative delivery, and an incompetent cervix can be linked to a prolonged stimulation of the uterus by endogenous hormones.[120] Therefore, increased levels of estrogen in some women throughout their adolescence into their adulthood may be an important factor in monitoring the potential relationship between an early age at menarche and risk of premature labour.

2) **Stress**

Early life stress and childhood social environment are noted to play a role in female reproductive success.[46,98,121] Researchers have suggested that early menarche is often triggered in women who have stressful social and personal environments throughout their childhood. Women who have absent or abusive fathers, live in low-income neighbourhoods, or have faced sexual abuse are at more likely to experiencing an early age at menarche.[122,123] Additionally, the scientific community's consensus on stress during pregnancy is wide-ranging and extensive. A study by Cole-Lewis (2014) noted that changes in stress levels between the second and third trimester is associated with an increased chance of preterm delivery, after controlling for important covariates.[121] Studies on both objective and subjective levels of chronic and sudden stress highlight that unexpected events during pregnancy leads to poor overall reproductive outcomes.[2,124] Interestingly, research from Kuras et al. (2017) and Shonkoff et al. (2012) suggest that children that undergo early life stressors are more likely to express worsened physiological responses during stressful experiences in adulthood.[125,126] Therefore, it is possible that due to early life stressors, women may experience an earlier age at menarche and also develop a dysfunctional response to adulthood stressors that can worsen the body's response to pregnancy and signal early labour.[124,127]

Accounting for these covariates are considered confounding, as their effect on the causal pathway is still undetermined. Inevitably, if covariates such as hormonal activity and stress are directly present in the causal pathway for both early menarche and PTB, it may obscure the statistical significance when included in the overall model. This may be true for various other

factors accounted for in this model, therefore it is important to also consider the bivariate relationships seen throughout this investigation. Additionally, when examining both hormonal activity and stress, the life history theory is justified as it describes PTB as an evolutionary adaptive behaviour in the face of adverse physical and environmental settings. More importantly, it is essential to dedicate more effort in understanding the complex relationship between many of the covariates suggested in this thesis, and help identify coherent frameworks that incorporate the biological, social, evolutionary and epidemiological perspective.

Preterm Birth

Currently, PTB can be classified into two broad groups: idiopathic or iatrogenic. Globally, close to 70-80% of PTBs are considered idiopathic, while 20-30% of all preterm deliveries are classified as iatrogenic.[5,52,53] Idiopathic PTB can be defined as the spontaneous onset of labour which does not arise from a single known factor.[20] As such, idiopathic PTB can be a result of a premature rupture in the maternal amniotic membrane, an insufficient cervix, or may occur without a previously indicated cause.[128] Conversely, iatrogenic PTB is medically advised, often recommended for the safety of fetal or maternal health, and is a decision made cooperatively between the patient and their healthcare provider.[128] These medically indicated inductions often are preceded by poor health outcomes such as severe maternal hypertension, placental abruption, or intrauterine fetal restriction.[52,108]

It is important to note that the biological and etiological pathway for both idiopathic and iatrogenic PTB are vastly different and are accompanied by different risk factors. Moreover, the differences underlying the various subtypes of preterm labour are seen to vary dramatically across different populations, regions, and geographical areas.[52] Some common factors associated

with idiopathic PTB include maternal race, low socioeconomic status, and a short cervix.[53] However, iatrogenic PTB is usually associated with poor pre-pregnancy health status, multiple gestation, and older age.[54,103]

Previous literature has suggested that medically indicated (iatrogenic) PTBs are directly associated with an earlier menarche, potentially signalling a relationship between the two. A study conducted by Lakshman et al. (2009) on over fifteen thousand females, indicated that those with an earlier age at menarche were at a higher risk of developing hypertension throughout their lives, compared to those with a later age at menarche.[38] Additionally, among a group of women in the United States, early menarche was associated with a three-fold increased risk of experiencing preeclampsia compared to their counterparts.[129] This raises the belief that early menarche may have distinctive effects on iatrogenic and idiopathic clinical subtypes of preterm delivery, making it important to analyze each separately. This investigation grouped all PTB under one group rather than investigating the clinical subtypes individually, which may be the reason for muted significance after the final statistical analysis. It may be plausible that early menarche may have a heightened effect on one type of preterm delivery, and simultaneously show no impact on the other. These micro-differences between clinical PTB types may be difficult to observe and capture, which is why risk factors may be difficult to predict.

Future Directions & Implications

Both early menarche and PTB pose significant public health issues around the globe. Therefore, the results of this thesis add insight into the field of maternal-child health and widen the path for more in-depth exploration. By better understanding the associations and consequences of these results, we can easily implore new screening tools that incorporate early

life reproductive behaviours and life history traits to better predict and manage pregnancy outcomes. To state simply, capturing the age at menarche can be done easily in clinical settings by adding one additional question to the routine screening process. This information is simple to collect and may go on to have large impact in the field of future female reproductive research. Currently, pregnancy is viewed primarily in a clinical setting; however, the literature and trends observed in this study suggests that pregnancy should incorporate a wide range of childhood and life history considerations. The future direction of this research needs to address the lack of representation of remote and minority communities in pregnancy and reproductive research to be able to better evaluate the ethnic, racial, and cultural impacts of menarche on PTB. Additionally, future investigations should include an emphasis on the early life sociodemographic factors which may be contributing to earlier age at menarche and a shorter gestational period. Moreover, studies should aim to examine the individual relationship between the different clinical subtypes of PTB and their respective health outcomes, as both types of preterm deliveries are characterized differently and have dissimilar biological pathways. By incorporating a broader interdisciplinary scope to reproductive health, researchers may be able to capture details and narrow down specifics that may have been previously ignored.

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APPENDIX

Table A1: Comparing participants with missing and non-missing values in the lifestyle questionnaires in the Ontario Birth Study

	Missing Analysis		Not Missing		P-Value[1]
	N	%	N	%	
Early Menarche					
No	391	43.3	1172	56.7	0.69
Yes	81	9	241	17.1	
Maternal Factors					
Age					
18-29	58	6.4	159	11.3	0.18
30-34	260	28.8	727	51.5	
35-39	139	15.4	430	30.4	
40+	46	5.1	96	6.8	
Ethnicity					
White	331	36.6	992	70.2	0.45
Other[1]	47	5.2	123	8.7	
East, South, South East Asian	112	12.4	263	18.6	
Black	15	1.7	33	2.3	
Marital Status					
Cohabitating/Married	485	53.7	1383	97.9	**0.01**
Single	20	2.2	26	1.8	
Education					
Graduate degree	218	24.1	574	40.6	0.45
Bachelors	201	22.2	621	43.9	
Post-secondary Trade, Diploma, Certificate	65	7.2	167	11.8	
Secondary or less	16	1.8	41	2.9	
Current Employment					
Employed	452	50	1276	90.3	0.85
Not Employed	46	5.1	129	9.1	
Household Income					
> 150,000	252	27.9	724	51.2	0.36

100,000 – 149,999	104	11.5	337	23.8	
50,000–99,999	75	8.3	212	15	
<50,000	31	3.4	60	4.2	
Health Factors					
Pre-pregnancy BMI					
Normal	246	27.2	940	66.4	**0.01**
Underweight	13	1.4	67	4.7	
Overweight	59	6.5	233	16.5	
Obese	50	5.5	94	6.6	
Pre-existing Diabetes[2]					
No	496	54.9	1379	97.6	0.78
Yes	7	0.8	19	1.3	
Gestational Diabetes					
No	848	93.8	1335	94.5	0.21
Yes	56	6.2	78	5.5	
Hypertensive Disorders					
No	871	96.3	1348	95.4	0.25
Yes	33	3.7	65	4.6	
Infection During Pregnancy[3]					
No	866	95.8	939	66.5	**0.00**
Yes	38	4.2	474	33.5	
Emotional Health					
No Emotional Concern	94	10.4	1307	92.5	0.71
Emotional Instability	6	0.7	70	5	
Alcohol Use During Pregnancy					
No	88	9.7	1118	79.1	0.34
Yes	18	2	290	20.5	
Clinical Pregnancy Factors					

IVF/IUI Pregnancy					
No	846	93.6	1263	89.4	**0.00**
Yes	55	6.1	147	10.4	
Parity					
Primiparous	129	14.3	1093	77.4	0.67
Multiparous	369	40.8	306	21.7	
Previous Pregnancy Loss					
No	338	37.4	953	67.5	0.82
Miscarriage	89	9.8	260	18.4	
Termination of Pregnancy	71	7.9	186	13.2	
Fetal Complication[4]					
No	522	57.7	1268	89.7	**0.00**
Yes	100	11.1	145	10.3	
Placental Complication[5]					
No	590	65.3	1365	96.4	0.14
Yes	32	3.5	51	3.6	

[1]Includes those that identified as one or more of the following: Indigenous (First Nations, Metis or Inuit), Arab, Latin American/Hispanic, or Other

[2] Pre-existing diabetes includes Type 1 and Type 2 diabetes, diagnosed by a healthcare provide prior to pregnancy

[3]Includes one or more of the following prior to delivery: flu, pneumonia, diarrhea, sinusitis, ear infection, cold sore, mouth infection, or other infection/inflammatory condition during pregnancy

[4]Fetal complications includes one or more of the following prior to delivery: fetal anomaly, isoimmunization/alloimmunization, intrauterine growth restriction, large for GA, oligohydramnios, or polyhydramnios

[5]Placental complications includes having one or more of the following prior to delivery: placental abruption, placenta accrete, increta, percreta, and previa