EXTERNAL CEPHALIC VERSION BEFORE TERM AND PRETERM BIRTH

EXTERNAL CEPHALIC VERSION BEFORE TERM AND THE RISK OF PRETERM BIRTH

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2016) Hamilton, Ontario (Health Research Methodology)

TITLE: External Cephalic Version Before Term and the Risk of Preterm Birth

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NUMBER OF PAGES: xi, 56

ABSTRACT

External Cephalic Version Before Term and the Risk of Preterm Birth

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Background: External cephalic version (ECV) is an obstetric maneuver used to turn a fetus from breech (buttocks first) to cephalic (head first) presentation. A Cochrane Review suggests that beginning ECV earlier in pregnancy (before 37 weeks) compared to later in pregnancy (37 weeks onwards) is associated with a decreased likelihood of breech presentation and cesarean section; however, it appears to be associated with an increase in late preterm birth (PTB; <37 weeks).

Objective: To explore the association between early ECV and the risk of PTB.

Method: Secondary data analyses of the Early ECV Trials. 1765 women with low-risk breech pregnancies were enrolled with 749 receiving at least one ECV before term. Accounting for centre in our analyses, risk factors for PTB, including exposure to early ECV, were analyzed for their contribution to odds of PTB. Interactions between risk factors and early ECV were explored. Characteristics among women who received an ECV before term and delivered PTB (N=48) were described.

Results: Early ECV exposure was not an independent predictor of PTB; however, the interaction between early ECV and anterior placental location was a significant predictor, and associated with a two-fold increase in the odds of PTB (OR: 2.05; 95% CI: 1.12 – 3.71; p=.02). Compared to other women in the study, women with an ECV before term who delivered PTB (N=48) were more likely to have an anterior placenta (67% vs. 35%), and this proportion was even higher among women who delivered preterm and within 48 hours of early ECV exposure (75%).

Conclusion: Exposure to early ECV was associated with risk of PTB for women with an anterior placenta. The manipulation that occurs during an ECV may induce fetal distress in a preterm fetus and/or increase risk of uteroplacental hemorrhage for those with an anterior placenta. These biological pathways may be triggered and initiate PTB.

ACKNOWLEDGMENTS

There are a number of individuals who played an important role in helping to bring this thesis project to fruition. Thank you to my supervisor, Dr. Eileen Hutton, for your guidance and mentorship during the completion of this thesis. The passion, commitment, and dedication that you put into your work and research have been an inspiration to my own academic career. I would also like to acknowledge the support of my committee members, Dr. Lauren Griffith and Dr. Sarah McDonald, whose statistical and clinical expertise throughout this project has been much appreciated. Thank you to Julia, Rashid, and Samantha for your assistance with data management, and for generously providing feedback and support during this project.

I would also like to extend my gratitude to my friends who effortlessly act as a constant source of happiness and entertainment in my life. I appreciate your being there to ensure I exit academic mode and enter laughter mode. Thanks to Mom, Dad, and Brittany for always believing in me and taking such pride in everything I do, including my academic endeavors. Your love does not go unnoticed, and I am honoured to fill and maintain the position of nerdy little sister in our family. Last but certainly not least, I would like to thank Dr. Louis Schmidt and Dr. Ryan Van Lieshout who have graciously provided me with confidence and nurturance over the last few years, while continuing to supply me with encouragement and urging to always reach my full potential.

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LIST OF ABBREVIATIONS

TBT - Term Breech Trial

RCT - randomized controlled trial

NICU - neonatal intensive care unit

OR – odds ratio

RR – relative risk

CI – confidence interval

ECV – external cephalic version

EECV – early external cephalic version

PPROM - premature rupture of the membranes

HPA - hypothalamic-pituitary-adrenal

CRH - corticotropin-releasing-hormone

BMI – body mass index

PMR – perinatal mortality rate

GLMM – generalized linear mixed model

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis project encompasses the work undertaken during 7 months of research and collaboration.

I: INTRODUCTION

1.1. The Obstetrical Complication: Breech Presentation

1.1.1. Incidence of Breech Presentation

Typically, a fetus will present in a head-first (cephalic) presentation. Breech presentation occurs when a fetus is in a buttocks-first or feet-first presentation. There is a natural, gradual decline in the incidence of breech presentation as gestational age increases (1). At 28 weeks gestational age, approximately 22% of fetuses will present as breech (2). At 30 weeks gestational age, 15% of women have breech presentation, and by 37 weeks, this rate is reduced to approximately 3-4% of fetuses (3).

Although the incidence of breech presentation is relatively low, a baby in breech presentation results in a delivery that is more complicated than the birth of a baby in a cephalic presentation.

1.1.2. Delivery Options for Breech Presentation

There are different options for delivering a fetus that is in breech presentation. Over the past two decades, there has been a decline in vaginal breech delivery because of the associated complications and unfavorable neonatal outcomes (3). The results of the Term Breech Trial (TBT) supported this notion. The TBT was a large, multicenter, randomized controlled trial (RCT) completed in 2000, which compared planned cesarean section versus planned vaginal breech delivery in over 2000 women with singleton, breech presentation pregnancies (4). Results of this RCT suggested that perinatal mortality, neonatal mortality, and serious neonatal morbidity were significantly lower for the infants

of women randomized to the planned caesarean section group relative to the infants of women randomized to the planned vaginal delivery group (4). The authors of this trial suggest that although some of the morbidity and mortality in the planned vaginal group were indeed related to difficulty with the vaginal breech delivery, others were associated with complications that happened *during* labour. If women can avoid labour and vaginal breech delivery, there may be a reduction in the associated poor fetal outcomes. Overall, the authors of the TBT determined that in women with breech pregnancies, for every 14 caesarean sections done as opposed to breech vaginal delivery, one baby will avoid death or serious morbidity (4).

As a result of the TBT findings, cesarean delivery is now generally viewed as a safer option than vaginal delivery for fetuses in breech presentation. While evidence from the TBT suggests that women with a fetus in breech presentation are more likely to have decreased morbidity with delivery via cesarean section as opposed to vaginal breech delivery, it is important to note that cesarean section is not without its own risks. In developed countries, cesarean section is one of the largest contributing factors to maternal morbidity following childbirth (5). Work by Liu and colleagues (2007) found that planned cesarean section compared to planned vaginal birth was associated with increased risk of postpartum cardiac arrest, wound hematoma, hysterectomy, infection, anesthetic complications, venous thromboembolism, hemorrhage, and longer hospital stay (5).

Furthermore, cesarean deliveries pose the risk of more complications in subsequent pregnancies, including uterine rupture, hemorrhage, placental implantation problems, and

frequently result in longer hospital stays (6,7). A further issue related to cesarean section is that the procedure requires the expertise of an obstetrician or other physician with surgical training, and limits the opportunity to use a low-risk obstetrical care provider such as a midwife or family practitioner (8).

Given the potential for maternal and fetal complications with vaginal breech delivery and cesarean delivery, it is ideal to achieve cephalic version prior to labour and delivery so that a cephalic vaginal delivery may be attempted. External cephalic version (ECV) is an intervention that has been shown to lower the likelihood of breech presentation at birth.

1.2 Intervention for Breech Presentation: External Cephalic Version

1.2.1. ECV Procedure

ECV is an obstetric maneuver that is undertaken to attempt to manually turn a fetus from breech to cephalic presentation by externally manipulating the fetus through the maternal abdomen (9). A successful ECV can turn a baby into a cephalic presentation, and thus a normal vaginal delivery may be attempted (3). This appealing intervention has the potential to reduce the morbidity associated with delivering a breech baby, as described above. Experts and guidelines now suggest that ECV be offered during pregnancy to all eligible women rather than an automatic cesarean delivery (10).

1.2.2. Risks and Success of ECV

Risks associated with an ECV procedure are low. Collaris & Oei (2004) undertook a systematic review to report on the risks associated with ECV at term (11). Results of this review revealed the most frequently reported complications were transient abnormal cardiotocography (CTG) patterns (5.7%). Persistent pathological CTG readings (0.37%) and vaginal bleeding occurred rarely (0.47%), with the incidence of placental abruption being even lower (0.12%). Emergency cesareans were performed in 0.43% of all versions, and the perinatal mortality rate was 0.16% (11). In summary, these authors concluded that ECV at term seems to be a safe procedure, with a very low rate of risk.

The success rates for ECV performed at term can vary widely, with studies reporting ranges of 20% to 80% (12,13). In a recent systematic review assessing ECV outcomes, the most important predictor variables included nulliparity, anterior placental location, breech engagement, amniotic fluid index and palpation of the fetal head (13). These factors are hypothesized to make the turning of a fetus more difficult through uterine tone and/or space limitations, thus contributing to ECV failure. In a recent study, it was determined that the success rate of ECVs performed by trained midwives in primary health care or hospital settings was comparable with other providers, and the procedure is safe (14).

1.2.4. Timing of External Cephalic Version

1.2.4.1. ECV Performed at Term

Generally, an ECV is attempted when a women has reached a full term pregnancy (i.e., 37 weeks gestation), in order to allow the opportunity for the fetus to turn spontaneously before that time. Further rationale for performing the ECV at term is that if the ECV procedure has complications and requires an emergency delivery, this will result in a full term delivery.

A recent Cochrane review by Hofmeyr and colleagues (2015) examined the success of ECV at term compared to no ECV attempt for women with a fetus in breech presentation (15). The results of this review found that compared to no ECV, the ECV at term group had a significant reduction in non-cephalic presentation at birth (RR: 0.42, 95% CI: 0.29 – 0.61), cephalic vaginal birth not achieved (RR: 0.46, 95% CI: 0.44 – 0.62), and a reduction in cesarean section (RR: 0.57, 95% CI: 0.40 – 0.82). There were no significant differences reported in adverse neonatal outcomes, such as Apgar scores at one or five minutes, umbilical vein pH levels, neonatal admission, perinatal death, or time from enrollment to delivery (15). In summary, Hofmeyr and colleagues concluded that ECV at term is a useful procedure to reduce the complications associated with delivering a baby in breech presentation (15).

1.2.4.2. ECV Performed Before Term

While the results of the recent review by Hofmeyr and colleagues (2015) show that ECV at term is more effective for breech presentation than not performing an ECV at all,

it has been hypothesized that beginning the ECV procedure before term might be more effective. Earlier in the pregnancy there might be maximal levels of amniotic fluid present, and the breech fetus might not be engaged in the pelvis. These factors are associated with a successful version and therefore could further decrease the rate of non-cephalic presentation at birth following an ECV (16).

A recent Cochrane review by Hutton and colleagues (2015) examined the outcomes and complications of women randomized to receive ECV before term (i.e., before 37 weeks gestation; "early ECV") compared to women randomized to receive ECV completed at term (i.e., 37 weeks onwards; "late ECV"). Results of this review found the rate of non-cephalic presentation at birth was significantly lower for women randomized to receive an early ECV compared to the women randomized to receive a late ECV (RR: 0.81, 95% CI: 0.74-0.90) (8). Further, women in the early ECV group were at less risk of failing to achieve a cephalic vaginal birth (RR: 0.90, CI: 0.83 – 0.97). The rate of cesarean section was reduced for the women in the early ECV group, though this did not quite reach statistical significance (RR: 0.92, CI: 0.85-1.00). The women who were randomized to early ECV were at a considerably reduced risk of having a vaginal breech birth compared to the group randomized to ECV after term (RR: 0.44, 95% CI 0.25 – 0.78) (8).

There were no differences between the two groups on the rate of five minute Apgar scores less than seven, the rate of still birth or neonatal mortality less than seven days, or neonatal intensive care unit (NICU) stay for four days or longer (8). However, the rate of

preterm birth less than 37 weeks was increased in the women randomized to the early ECV group compared to the late ECV group (RR: 1.51, 95% CI: 1.03-2.21)(8).

In summary, results of the Cochrane review for early versus late ECV suggest that performing the ECV before term decreases the rate of non-cephalic presentation at birth by 19%, decreases the risk of failing to achieve a cephalic vaginal birth by 10%, and decreases the rate of cesarean section by 8%. However, randomization to the early ECV group appeared to be associated with a 51% increased risk for late preterm birth relative to the women randomized to the ECV at term group.

1.3. The Clinical Issue: Preterm Birth

1.3.1. Definition and Rate of Preterm Birth

Preterm birth refers to all deliveries at less than 37 weeks' gestational age (17). Preterm birth rates have been reported as 5-7% in developed countries but substantially higher in developing countries. On a global scale, it has been estimated that 9.6% of all births worldwide are preterm (18).

Preterm births can be subdivided according to gestational age, with about 5% of all preterm births occurring at less than 28 weeks' gestation (extreme prematurity), about 10-15% occurring at 28–31 weeks' gestation (severe prematurity), about 10-15% occurring at $32^{0/7}$ to $33^{6/7}$weeks' gestation (moderate prematurity), and 70-75% occurring at $34^{0/7}$ to $36^{6/7}$ weeks' gestation (late preterm) (17). In total, approximately 7-8% of all births in general are late preterm births (17).

There are two types of preterm birth. The first type is planned preterm birth and includes deliveries for maternal or fetal indications. The most common diagnoses associated with indicated preterm births are hypertensive disorders, hemorrhage, and acute or chronic fetal compromise (19). Preeclampsia affects about 3-5% of women during pregnancy and may manifest as hypertension, renal dysfunction and neurological symptoms. When severe symptoms threaten maternal wellbeing before term, treatment involved in ending the pregnancy can occur which result in preterm delivery. However, planned delivery for issues of fetal wellbeing are more common (19). The second type of preterm births include deliveries that are spontaneous (17). Spontaneous preterm births may follow preterm premature rupture of the membranes (PPROM), or may result from spontaneous preterm labour with intact membranes.

About 30–35% of all preterm births are indicated, 40–45% follow spontaneous preterm labour, and 25–30% follow PPROM (17). The causes of indicated late preterm births are similar to that for all preterm births, including preeclampsia, fetal indications, placental abruption, and other indications (20). However, late preterm births are more likely to be the result of spontaneous idiopathic preterm labor or PPROM than medical or pregnancy indications. For late preterm births, the relative distribution of etiologies changes to 20% indicated, 25% PPROM, and 55% preterm labor (21). As such, a larger proportion of late preterm births are due to spontaneous preterm labor. It is important to note that the line dividing spontaneous and indicated preterm birth is not always clear (17).

1.3.2. Consequences of Late Preterm Birth

The incidence of preterm birth has continued to rise, despite the extensive research and clinical efforts designed towards its reduction (22). During the past few decades preventative and therapeutic interventions have focused primarily on infants born with very low birth weight or at very early gestations.

In obstetric and pediatric practice, late preterm infants are often erroneously considered functionally full term and management decisions are usually made accordingly (24–27). However, this practice pattern is not evidence-based, and this practice may not always be appropriate (24). Despite their apparent maturity, late preterm infants are at increased risk for neonatal medical problems compared with infants born at term. Recent research has raised awareness that late preterm neonates have significantly higher rates of morbidity and mortality both short-term and long-term relative to those born at term (28,29).

Wang and colleagues (2004) found that despite appropriate size and favourable Apgar scores in late preterm infants, the clinical outcomes differed between late preterm and term infants (24). The late preterm infants were more likely to exhibit temperature instability, difficulty with feeding, hypoglycemia, receive intravenous infusions more often, more respiratory distress and were clinically jaundiced more often (24). There was also a trend towards the late preterm group to show more signs of apnea and bradycardia (24).

Similarly, using a sample of over 5000 late preterm infants, Bird and colleagues (2010) found that late preterm infants were at an increased risk for needing mechanical

ventilation and respiratory distress syndrome compared to the term controls. Outpatient and inpatient medical expenditures were also moderately higher in the late preterm infants compared to the term controls (30).

Given that late preterm infants were historically perceived to have similar risks for developmental problems as infants born at term, the long-term follow-up of these infants is not common. Since the last 6 weeks of gestation are a critical period of growth and development of the fetal brain (31), the brain of a late preterm infant has low cortical volumes and cerebellar development is incomplete (31). There has been increasing awareness of this susceptibility in late preterm infants and research pertaining to the long-term neurodevelopmental sequelae is beginning to surface. Late preterm infants are at increased risk for mental and physical developmental delay compared to term infants in early childhood (32,33). By school age, this can result in poorer academic performance and school-related problems (28). Further, these can manifest as behavioural problems such as inattention that persist beyond childhood (28).

1.3.3. Etiology of Spontaneous Preterm Birth

Preterm labour is a syndrome initiated by multiple mechanisms. In many cases, a precise biological mechanism cannot be detected to explain the pathway to preterm birth. However, there are four biological pathways that are commonly used to describe spontaneous preterm birth: maternal and/or fetal stress, inflammation, hemorrhage, and mechanical stretching of the uterus (34).

First, maternal and/or fetal stress during pregnancy can activate the hypothalamic-

pituitary-adrenal (HPA) axis and can result in an increased secretion of cortisol and corticotropin-releasing-hormone (CRH), interacting with other hormones (e.g., prostaglandins and oxytocin), which can mediate uterine contractions (34). Second, an inflammatory response in utero (e.g., chorioamnionitis) can result in preterm labour and rupture of the membranes via myometrical contractions, weakening of the chorioamnion and cervical ripening (34). Third, placental abruption and/or uteroplacental hemorrhage has been shown to be highly associated with preterm birth (34). Finally, mechanical stretch of the uterus has been associated with preterm delivery. For example, overstretching of the uterus and fetal membranes, as in cases of multiple pregnancies is often associated with premature cervical ripening and delivery (34).

1.3.4. Risk Factors for Preterm Birth

There are multiple well-established risk factors for preterm birth. Maternal demographic characteristics associated with risk of preterm birth include maternal age less than 18 and maternal age greater than 35, low education attainment, short stature, African-American race, single marital status, low socioeconomic status, short inter-pregnancy interval (less than 6 months), and social factors such as poor access to health care (34–36). Nutritional status also plays a role in risk of preterm birth, including low and high pre-pregnancy BMI, poor nutrition, long working hours and hard physical labour (17,36–38). The following characteristics of a woman's current pregnancy also play a role in risk of preterm birth: assisted reproductive technologies, multiple gestation, fetal disease, parity, maternal medical complications (e.g., hypertension, diabetes),

psychological disorders (e.g., stress, depression), adverse health behaviours (e.g., smoking, alcohol consumption, drug use), and short cervical length (17,35,36,39–42). Furthermore, exposure to objectively stressful conditions, such as housing instability and severe material hardship, has also been associated with preterm birth (17).

In summary, although there are many established risk factors and several proposed etiologic pathways for preterm birth, the pathogenesis of preterm birth is poorly understood despite significant research efforts. In many cases, a mechanism cannot be identified, with approximately 45-50% of preterm births classified as idiopathic (18).

1.4. The Present Study: Exploring Links between Early ECV and Preterm Birth

In light of the evidence suggesting (a) an increased risk of late preterm births in women randomized to early ECV compared to late ECV, and (b) the poorer prognosis associated with late preterm birth, the objective of the present study is to further explore the association between early ECV exposure and the risk of preterm birth.

The objective was addressed using two different methods (i.e., predictive and descriptive), which comprised a total of three research questions. To see if there were any predictive factors associated with preterm birth we addressed the following questions: (1) Among all women enrolled in the study, what factors (including ECV exposure before term) are associated with the odds of preterm birth?; and (2) Among all women who received at least one ECV before term, what factors are associated with a preterm birth? The third research question, which was descriptive in nature, was: What are the characteristics among women who had a preterm birth and received an ECV before 37 weeks?

Exploring the association between early ECV and preterm birth can provide evidence on subgroups of women who may be at particular risk for preterm birth. This will be useful to clinicians in guiding the counseling and obstetric management of individual women with breech pregnancies. Further, characterizing women who receive an ECV before term and deliver preterm might provide insights into mechanisms associated with preterm birth in this population.

II: METHOD

2.1. Overview of the Early ECV Trials

This thesis performs secondary data analyses on the combined data set of the Early ECV Pilot trial (N= 233) which was published in 2003 (9), as well as the full-scale Early ECV2 trial (N= 1543) published in 2011 (16). Collectively, these two trials will be referred to as the Early ECV (EECV) trials.

The EECV trials used a pragmatic, multicenter, parallel group RCT design. Women were randomized to receive early ECV (at $34^{0/7}$ weeks to $35^{6/7}$) or delayed ECV (not before $37^{0/7}$ weeks gestation). Women were randomized using computer generated random block sizes and 1:1 allocation. The studies received ethical approval and women enrolled in the study provided consent before randomization. Centers were eligible to participate in the trials if they had clinicians who were experienced in performing ECV (9,16). The ECV procedures were undertaken or supervised by experienced clinicians.

2.1.1 Sample

Participants were recruited from a total of 22 countries, with a total of 81 centers. The 22 countries included Egypt, Jordan, South Africa, Canada, United States of America, Denmark, Estonia, Germany, Hungary, Ireland, United Kingdom, Israel, Oman, Portugal, Spain, Netherlands, Poland, Argentina, Brazil, Chile, Australia and New Zealand.

Women were eligible for enrollment if they had a singleton fetus in breech presentation and were between $33^{0/7}$ weeks and $35^{6/7}$ weeks of gestation. Women were ineligible if they were at risk for unstable lie, if they planned to move to a non-trial center, if they had a contraindication to labour or vaginal birth (such as placenta previa, or previous classic cesarean section), a contraindication to ECV (such as fetal heart rate abnormalities, oligohydramnios, rupture of membranes, overdistended uterus), a contraindication to early ECV (such as increased risk of preterm labour, increased risk of abruptio placentae), if they planned to give birth by cesarean section even if the fetus turned into a cephalic position and/or if they planned a vaginal birth even if the breech remained breech (9,16).

2.2. Procedure for Present Study

Although the original EECV trials utilized randomization, it is important to note that the present thesis will not be using the randomization groups. Although women were *randomized* to the early ECV or delayed ECV group, some women in the delayed group received an ECV before term, and not all women randomized to the early ECV group received the exposure of interest for this study. Therefore, to address the thesis objective, groups are explored based on actual *exposure* to an ECV before term, as opposed to using the randomization groups. To address the thesis objective, both a predictive and descriptive approach were undertaken. All research questions are summarized in Figure 1.

2.2.1. Specific Research Questions

2.2.1.1. Predictive Approach

The predictive approach comprised two research questions. The first research question of the predictive approach is: **Among all women enrolled in the study, what factors (including ECV exposure before term) are associated with the odds of preterm birth?** The first research question will look at all women enrolled in the EECV trials. The aim of the first research question is to explore how actual *exposure* to an ECV before term contributes to the risk of preterm birth while controlling for available maternal risk factors for preterm birth.

The second research question of the predictive approach is: **Among all women who received at least one ECV before term, what factors are associated with a preterm birth?** The second research question will look at the subset of women who received at least one ECV before term. Among this group, risk factors will be explored in terms of their contribution to preterm birth. Furthermore, ECV procedural specific variables will be explored to see if there are characteristics related to the ECV procedure itself that might predict risk of preterm birth.

2.2.1.2. Descriptive Approach

The third research question is: **What are the characteristics among women who had a preterm birth and received an ECV before 37 weeks (N=48)?** The third research question will help identify factors among the group of women who received an ECV before term and delivered preterm that may be associated with the preterm birth.

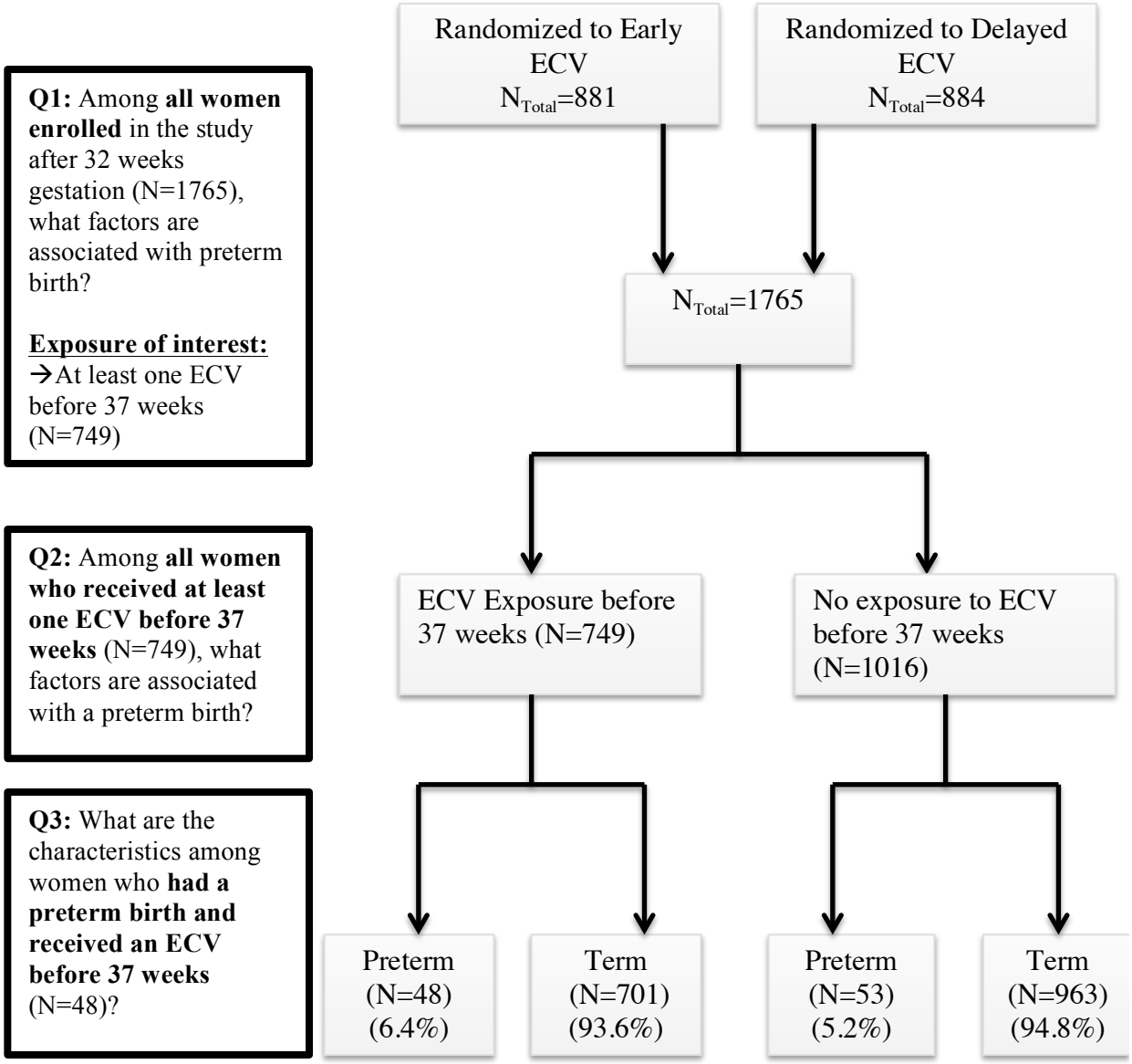


Figure 1. Overview of Research Questions and Distribution of Exposure to Early ECV and Preterm Births

2.3. Measures

2.3.1. Dependent Variable: Preterm Birth

Weeks of gestation at time of birth were calculated using the gestational age at randomization and the date of delivery. Preterm birth was a binary outcome defined as less than 37 weeks gestation at delivery for preterm and 37 weeks or greater for full term (coded: 0 = term birth; 1= preterm birth).

2.3.2. Independent Variables

2.3.2.1. Risk Factors for Preterm Birth

Exposure to ECV Before Term. A variable that captured actual *exposure* to one or more ECVs before term was computed. ECV exposure was a binary predictor (coded: 0= no early ECV exposure; 1 = At least one early ECV exposure).

Maternal Age. Maternal age was computed using mother's date of birth provided at enrollment. Initially, maternal age was categorized using the following categories: age ≤ 17; age 18-34 years, and ≥ 35 years, because both low and high maternal ages have previously been reported to increase the risk of preterm birth (34). However, preliminary descriptive statistics on the distribution of these categories yielded small sample size for the age ≤ 17 category (further discussed in the Results Section; See Table 2). In order to preserve statistical power, it was therefore decided to define maternal age as a dichotomous predictor with the categories being <35 years and ≥ 35 years.

Maternal BMI. Literature reports the risk of preterm birth based on pre-pregnancy BMI. Although these risks are generally observed in women with very low, or very high

BMI (34,37,38), data on pre-pregnancy BMI was not collected in the present study. Therefore, BMI at time of enrollment was included as an exploratory variable. BMI was computed using maternal weight in kilograms divided by height in meters squared at time of enrollment. BMI was categorized using the following categories: BMI < 25 kg/m^2, BMI 25-29.9 kg/m^2, and BMI ≥ 30 kg/m^2.

Maternal Height. Maternal height was reported at time of enrollment in centimeters. Height was dichotomized to classify shorter stature (<167 cm) and taller stature (≥167 cm) (35).

Parity. Parity was self-reported by women at time of enrollment and was defined as the number of pregnancies with delivery of one or more fetuses at ≥ 20 weeks gestation or birth weight ≥ 500 grams. A binary variable was computed to classify women with no previous pregnancies (i.e., nulliparous) and women who had at least one prior pregnancy (i.e., multiparous) (coded: 0 = nulliparous, 1 = multiparous).

Placental Location. This was a binary variable based on ultrasound reported at the time of enrollment (coded: 0 = not anterior location, 1 = anterior location).

Perinatal Mortality Rate (PMR). The national PMR is used as an indicator of the quality of antenatal and perinatal care. Given the international nature of the EECV trials and variations in antenatal and perinatal care between participating countries, a dichotomous variable was created to denote a PMR of ≤10/1000 and a PMR <10/1000 for each country in the study (43).

2.3.2.2. ECV Procedural Specific Characteristics

A total of 749 women received at least one ECV before term. The majority of women received only one ECV before term (N=683). There were 60 women who received two ECVs before term, 5 women who received three ECVs before term, and one woman who received 4 ECVs before term. The following procedural related variables were computed using data from the most recent early ECV.

Station of presenting part prior to ECV. This is an indication of how far the fetal breech has travelled down the birth canal. A binary variable was computed which was defined as floating/dipping = 0; and well engaged into pelvis = 1.

Use of Tocolytics. Tocolytics are medications used to relax the uterus during the ECV procedure. This was a binary variable (coded: no =0; yes=1).

Pain During ECV. Pain during ECV was self-reported by women using a visual analogue scale with continuous scores ranging from 0-100, with the lower end point signifying no pain and the higher end point signifying the most pain imaginable.

2.4. Statistical Analyses

2.4.1. Predictive Approach

2.4.1.1. Sample Characteristics

Sample characteristics for women who received an ECV before term and women who did not receive an ECV before term were examined using independent sample *t*-tests for continuous variables, with means and standard deviations reported. For dichotomous

variables, chi-squared tests tested group differences, and counts and percentages were reported.

2.4.1.2. Descriptive Statistics

The first goal of the analyses was to gain an understanding of the distribution of data for each predictor variable using descriptive statistics. For categorical variables, frequencies were examined. Frequency tables provide information about the number of cases for each response and reveal responses with low frequency. This provides information on whether some categories of the variable should be collapsed or deleted altogether.

2.4.1.3. Univariable Logistic Regression

During univariable analyses, the association between each independent variable (i.e., risk factor) and the dependent variable (i.e., preterm birth) without adjusting for other independent variables was tested. This gives unadjusted estimates for the influence of predictor variables on the outcome. Binary logistic regression is used when the dependent variable is binary in nature (i.e., outcome can take on one of two values). For the present study, the outcome was term birth or preterm birth and therefore binary logistic regression was used.

2.3.1.4. Testing for Multicollinearity

If two explanatory variables are highly correlated with each other, they can cause problems during multivariable analysis because they are explaining almost the same variability in the outcome. This is referred to as multicollinearity. To test for multicollinearity, correlations among independent variables were examined using Spearman's rank correlation. Tabachnick and Fidell (2012) suggest that if correlation coefficients among independent variables are less than 0.90, then multicollinearity is not likely to be an issue (44).

2.3.1.5. Multivariable Logistic Regression

In multivariable logistic regression, one can test associations of independent variables with the outcome after accounting for other variables and confounders. This results in an adjusted model.

Research Question 1. Participants included all women enrolled in the EECV trials and the dichotomous outcome was preterm birth. In the first block of the logistic regression model, the following risk factors for preterm birth were included: maternal age, parity, maternal height, maternal BMI, placenta location, and PMR. In the second block of the model, the exposure of interest (ECV before term) was added to the model. Finally, in the third block interactions between risk factors and ECV exposure were explored.

Statistical interaction means the effect of one independent variable on the outcome variable depends on the value of another independent variable. For the present

study, interactions were computed between ECV exposure and other independent variables. The rationale for this approach is to identify a subgroup of women who might be at risk for preterm birth when they are exposed to an ECV before term. Model fit was examined using the -2ln[likelihood].

Research Question 2. Participants included women enrolled in the EECV trials who received at least one ECV before term and the dichotomous outcome was preterm birth. In the first block of the logistic regression model, risk factors for preterm birth including maternal age, parity, maternal height, maternal BMI, placenta location, and PMR were included. In the second block of the model, the procedural-specific variables of interest were entered. Model fit was examined using the -2ln[likelihood].

2.5.1.6. Accounting for Centre

In RCTs with multiple centers, it can be expected that patient outcomes may differ according to study center. This could be due to differences between patients who present to different centers, or because of differences between the centers themselves. Because of this, many RCTs attempt to minimize the impact of any between-center differences on the trial results, by accounting for center-effects in the analysis model (45).

Therefore, a generalized linear mixed model (GLMM) was used to control for the effect of center (45,46). Specifically, trial center was entered as a random-effect, with the fixed effects including the predictor variables used in binary logistic regression. Since it has been suggested that low-recruiting centers in RCTs contribute small number of participants (47), sensitivity analyses were also performed with exclusion of centers that

recruited less than 5 patients. All statistical analyses were performed using SPSS Version 21.0, with significance levels set at $\propto = 0.05$.

2.4.2. Descriptive Approach

First, all women who delivered preterm (N=101) were compared based on their exposure to ECV before term. This resulted in comparison of 48 women who had an ECV before term and delivered preterm, and 53 women who did not have the exposure of interest but delivered preterm. Group differences on risk factors for preterm birth were examined using chi-squared analysis.

Second, the subset of women who had the exposure and outcome of interest (N=48) were further explored. Time in hours from the early ECV exposure to the time of delivery was examined. A time period of 96 hours was used to signify that the ECV procedure is *potentially* associated with the preterm delivery. Information on available complications (defined as abrupted placenta, non-reassuring fetal heart rate, signs/symptoms of preterm labour) was examined among the women who delivered within 96 hours of ECV exposure. Rationale for this was to explore if there is any specific mechanism by which ECV might be associated with a preterm birth.

Finally, to further examine the role of early ECV on preterm birth, characteristics among the subset of women who delivered within 48 hours of the early ECV exposure were explored. It was felt that a time period of 48 hours would more precisely represent the preterm delivery being attributable to the early ECV procedure, although it is acknowledged that the study design does not allow for certainty of this association.

III: RESULTS

3.1. Sample Characteristics

In total, the EECV trials had 1776 women enrolled. There were 9 participants lost to follow-up and 2 withdrawals. This resulted in a dataset with 1765 women included in the analyses with the outcome variable. A total of 749 women received at least one ECV before term. There were 683 who received only one ECV, 60 who received two ECVs before term, 5 who received three ECVs before term, and one who received four ECVs before term. There were a total of 1016 women who did not receive an ECV before term. Of these 1016 women, there were 505 women who received an ECV after term, and there were 511 who did not receive an ECV at all. Reasons for no ECV being performed included fetus turning spontaneously (N=329), contraindication to ECV developed (N=65), mother delivered before ECV (N=35), mother refused (N=76), clinician refused (N=9), other reason (not specified, N=13).[1]

Table 1 presents sample characteristics for all women who received at least one ECV exposure before term, and women who did not receive an ECV exposure before term. Chi-squared tests revealed that the two groups were not statistically different on gestational age at delivery, maternal age, maternal BMI at time of enrollment, maternal height, parity, placental location, PMR, or continent of origin ($p > .05$).

[1] More than one reason could be recorded.

Table 1: Sample Characteristics Based on Early ECV Exposure Status

	At least 1 ECV Exposure Before 37 weeks (N=749)	**No ECV Exposure Before 37 weeks (N=1016)**
Birth weight, kilograms, mean (SD)	3311.7 (496)	3343.9 (490)
Gestational Age at Delivery		
Term (37 weeks and greater)	701 (93.6%)	963 (94.8%)
Preterm Total (less than 37 weeks)	48 (6.4%)	53 (5.2%)
$34^{0/7}$ weeks to $34^{6/7}$ weeks	3 (0.4%)	4 (0.4%)
$35^{0/7}$ to $35^{6/7}$ weeks	16 (2.1%)	19 (1.9%)
$36^{0/7}$ to $36^{6/7}$ weeks	29 (3.9%)	30 (2.9%)
Baseline Characteristics		
Maternal Age (dichotomous)		
<35 years	598 (79.8%)	802 (78.9%)
≥35 years	151 (20.2%)	214 (21.1%)
Maternal BMI (categorical)[1]		
Less than 25 kg/m^2	210 (28.2%)	321 (31.7%)
25-29.9 kg/m^2	314 (42.2%)	408 (40.3%)
30 kg/m^2 and higher	221 (29.6%)	283 (28.0%)
Continent		
Africa	46 (6.1%)	53 (5.2%)
North America	204 (27.2%)	267 (26.3%)
Europe	215 (28.7%)	275 (27.1%)
South America	126 (16.8%)	221 (21.8%)
Australia	158 (21.1%)	200 (19.7%)
Maternal Height, centimetres, mean (SD)	162.42 (7.89)	164.46 (7.19)
Parity		
Nulliparous	438 (58.5%)	530 (52.2%)
Multiparous	311 (41.5%)	486 (47.8%)
Placenta Location[2]		
Anterior	286 (38.2%)	413 (41.1%)
Not Anterior	462 (61.8%)	592 (58.9%)
Perinatal Mortality Rate (PMR)		
PMR ≤10/1000	660 (88.1%)	884 (87 %)
PMR >10/1000	89 (11.9%)	132 (13 %)

Missing values in the exposure before term, and no exposure before term as follows: [1]4, 4; [2]1, 11
BMI – body mass index, ECV – external cephalic version, PMR – perinatal mortality rate
SD – standard deviation

3.2. Predictive Approach - Research Question 1: Among all women enrolled in the study, what factors (including ECV exposure before term) are associated with the odds of preterm birth?

3.2.1. Descriptive Statistics

Table 2 presents the descriptive statistics used for research question 1. Preliminary descriptive statistics on the distribution of these categories yielded small sample size for the age ≤ 17 category (2%). Therefore, the two lower age categories were collapsed to create a dichotomous variable with < 35 and ≥35 years.

Table 2: Descriptive Statistics for Question 1 Predictor Variables

Independent Variables		**Frequency**
Maternal BMI at Enrollment[1]	Less than 25 kg/m^2	531 (30.2%)
	25-29.9 kg/m^2	722 (41.1%)
	30 kg/m^2 and higher	504 (28.7%)
Placenta Location[2]	Not Anterior	1054 (60.1%)
	Anterior	699 (39.9%)
Maternal Height	Short Stature (<167 cm)	1175 (66.6%)
	Tall Stature (≥167 cm)	590 (33.4%)
Maternal Age	(<35 years)	1400 (79.3%)
	(≥ 35 years)	365 (20.7%)
Perinatal Mortality Rate (PMR)	≤ 10/1000	1544 (87.5%)
	>10/1000	221 (12.5%)
Parity	Nulliparous	968 (54.8%)
	Multiparous	797 (45.2%)
ECV Exposure <37 weeks	No early ECV exposure	1016 (57.6%)
	Early ECV exposure	749 (42.2%)

Missing Values: [1]8; [2]12;
BMI – body mass index, ECV – external cephalic version, PMR – perinatal mortality rate

3.2.2. Univariable Logistic Regression

Significant independent predictors of preterm birth included parity, placenta location, and PMR>10/1000. The odds of preterm birth were 37% lower for multiparous women compared to nulliparous women (OR: 0.63; 95% CI: 0.41-0.96; *p*=.03); the odds of preterm birth were 55% higher in women with anterior placenta location compared to other placenta location (OR: 1.55; 95% CI: 1.03 – 2.32; *p*=.03), and the odds of preterm birth were 2.92 times higher for women with a PMR>10/1000 compared to women with a PMR ≤10/1000 (OR: 2.92; 95% CI: 1.84 – 4.64; *p*<.001). Although it did not reach statistical significance, the odds of preterm birth were 56% higher for short statured women compared to those with a taller stature (OR: 1.56; 95% CI: 0.98 – 2.48; *p*=.06). Non-significant independent predictors of preterm birth included maternal age, maternal BMI and ECV exposure before 37 weeks. Table 3 includes the results for the unadjusted univariable logistic regression analyses.

Table 3: Predictors of Preterm Birth Among All Women Randomized in EECV Trials

	Odds of Preterm Birth			
	Unadjusted[1]		**Adjusted[2]**	
Predictors	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Maternal Age (Ref. age>35)	1.53 (0.87 – 2.68)	.14	1.20 (0.67 – 2.14)	.54
Parity (Ref. multiparous)	**1.59 (1.05 – 2.42)**	**.03****	**1.70 (1.09 – 2.65)**	**.02****
Maternal Height (Ref. >167cm)	1.56 (0.98 – 2.48)	.06*	1.57 (0.98 – 2.54)	.06*
Maternal BMI (Ref. <25 kg/m^2)				
BMI = 25-29.9 kg/m^2	0.74 (0.46 – 1.2)	.23	0.76 (0.46 – 1.25)	.28
BMI > 30 kg/m^2	0.90 (0.54 – 1.48)	.67	0.85 (0.51 – 1.42)	.53
ECV<37 wks (Ref. No ECV < 37 wks)	1.24 (0.83 –1.86)	.28	1.48 (0.81 – 2.70)	.20
Placenta Location (Ref. Not Anterior)	**1.55 (1.03 – 2.32)**	**.03****	1.07 (0.61 – 2.65)	.81
Perinatal Mortality Rate (Ref. <10/1000)	**2.92 (1.84 – 4.64)**	**<.001****	**3.01 (1.86 – 4.89)**	**<.001****
ECV*Placenta Location			**3.08 (1.32 – 7.14)**	**.009****

OR=odds ratio; CI=confidence interval; BMI=body mass index; ECV=external cephalic version; Ref.= reference group
[1]Results of the univariable logistic regression; [2]Results of the multivariable logistic regression model, **p<.05; *p≤.10

3.2.3. Multicollinearity

There was no evidence of multicollinearity for any of the independent variables. Correlation coefficients were all below 0.90. Please refer to Table 4 for the correlation matrix between predictor variables.

Table 4: Correlation Matrix for Predictor Variables in Question 1

	1	2	3	4	5	6	7
1. Maternal Age							
2. Parity	-.06						
3. Placenta Location	.02	.01					
4. PMR	.15	.10	-.02				
5. BMI	.02	.01	-.001	-.03			
6. Maternal Height	-.02	.04	.02	-.01	.16		
7. ECV exposure before term	-.01	.06	-.03	-.02	.04	.13	

BMI – body mass index, ECV – external cephalic version, PMR – perinatal mortality rate

3.2.4. Multivariable Logistic Regression Model

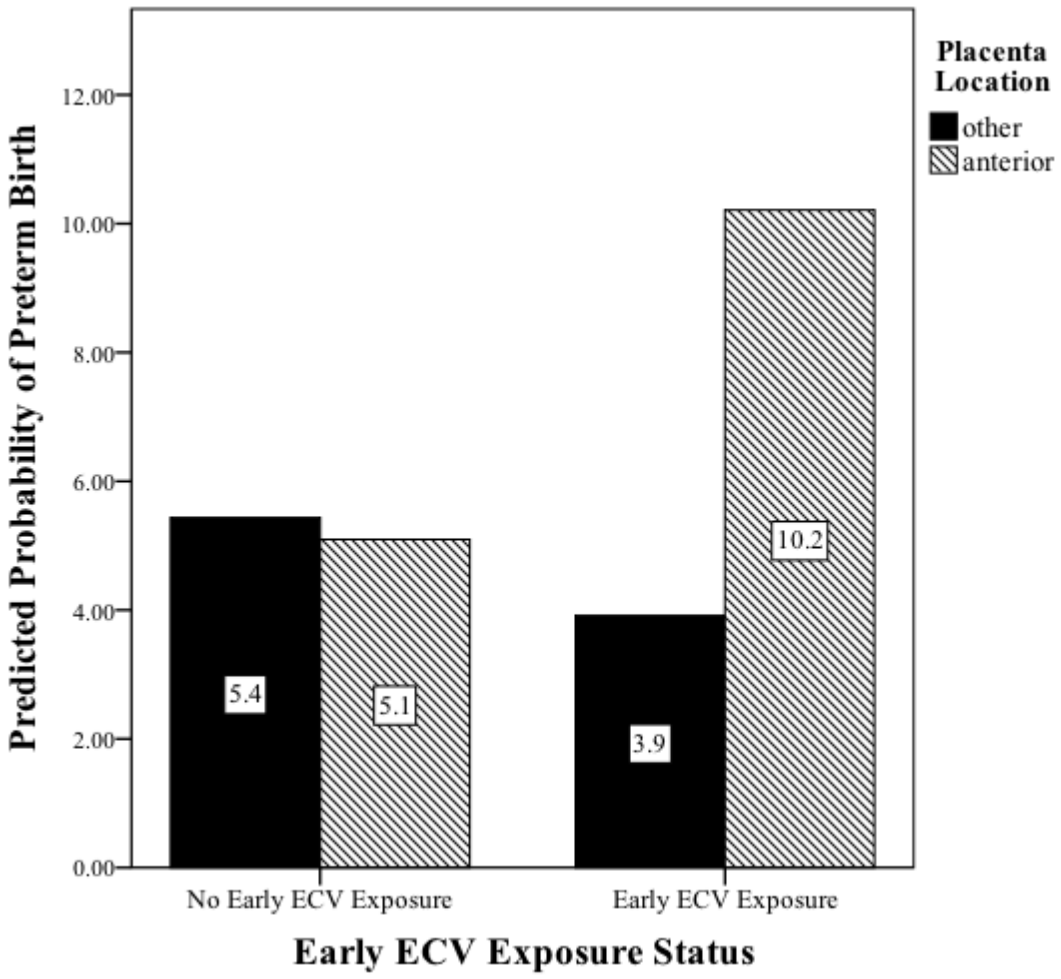
As indicated by the Omnibus Test of Model Coefficients, the overall final multivariable logistic regression model was statistically significant, $\chi^2(9) = 40.77$; $p < .001$. Model fit was examined using the -2ln[likelihood]. With only the baseline risk factors in the model, the -2ln[likelihood] was 732.95. After adding in the variable for exposure to early ECV, this value dropped very slightly to 732.31 indicating that the early ECV exposure variable did not aid in improving the model. After inclusion of an interaction term between early ECV exposure and placenta location, the model had the lowest -2ln[likelihood] at 725.26. The Hosmer and Lemeshow test of Goodness of Fit indicated a $p > .05$, which is an additional indication that the model was a good fit.

Addition of other interaction terms between early ECV exposure and risk factors did not improve the statistical model.

Table 3 includes the results for the final multivariable logistic regression model. Multivariable logistic regression revealed that independent of early ECV exposure, significant risk factors for preterm birth included nulliparity (OR: 1.70; 95% CI: 1.09 – 2.65; p=.02) and living in a country with a PMR ≥10/1000 (OR: 3.01; 95% CI: 1.86 – 4.89; p< .001) after adjusting for all other risk factors. Having a short stature approached statistical significance for its association with preterm birth, after adjusting for all other predictors (OR: 1.57; 95% CI: 0.98 – 2.54; p=.06). Although early ECV exposure was not an independent predictor of preterm birth, the interaction between early ECV and placenta location was a significant predictor after adjusting for all other predictors.

Decomposition of the interaction between ECV exposure and placental location revealed that ECV exposure before term increased the risk of preterm birth in women with an anterior placenta location (OR: 2.05; 95% CI: 1.12 – 3.71; p=.018), but not in women without anterior placenta location (OR: 0.69; 95% CI: 0.38 – 1.26; p=.23). Figure 2 illustrates the nature of this interaction.

Figure 2: Predicted Probability of Preterm Birth Based on Exposure to ECV Before Term and Placenta Location



3.2.5. Centre-Effect: Generalized Linear Mixed Model

After accounting for center in the analyses, results mirrored those obtained in multivariable logistic regression (See Table 5). After adjustment for center and other predictors, living in a country with a PMR ≥10/1000 was significantly associated with odds of preterm birth (OR: 2.37; 95% CI: 1.49 – 3.77; $p< .001$). Although it approached statistical significance, nulliparity did not remain significant in the GLMM (OR: 1.41; 95% CI: 0.95 – 2.10; $p=.089$). Finally, the interaction between ECV exposure and anterior placenta location remained statistically significant. Sensitivity analysis revealed that exclusion of low recruiting centers did not affect the significance of the results.

Table 5: Predictors of Preterm Birth Accounting for Centre

	Odds of Preterm Birth	
	Adjusted	
Predictors	**OR (95% CI)**	**p-value**
Maternal Age (Ref. age>35)	0.87 (0.37 – 2.05)	.67
Parity (Ref. multiparous)	1.41 (0.95 – 2.10)	.09
Maternal Height (Ref. >167cm)	1.32 (0.87 – 2.01)	.20
Maternal BMI (Ref. <25 kg/m^2)		
BMI = 25-29.9 kg/m^2	1.19 (0.76 –1.9)	.44
BMI > 30 kg/m^2	1.12 (0.69 – 1.81)	.65
ECV<37 wks (Ref. No ECV < 37 wks)	1.26 (0.73 – 2.13)	.39
Placenta Location (Ref. Not Anterior)	0.97 (0.58 – 1.64)	.92
Perinatal Mortality Rate (Ref. <10/1000)	**2.37 (1.49 – 3.77)**	**<.001****
ECV*Placenta Location	**2.17 (1.01 – 4.65)**	**.047****

OR=odds ratio; CI=confidence interval; BMI=body mass index; ECV=external cephalic version; Ref. = reference group
**p<.05; *p≤.10

3.3. Predictive Approach - Research Question 2: Among all women who received at least one ECV before term, what factors are associated with a preterm birth?

3.3.1. Descriptive Analysis

In addition to risk factors for preterm birth presented in Table 2, question 2 also utilizes procedural specific variables. Descriptive statistics for the three procedural-related variables can be found in Table 6.

Table 6: Descriptive Statistics for Question 2 Procedural-related Predictor Variables

Procedural-Related Variables		Frequency
Use of Tocolytics	Yes	485 (64.8%)
	No	264 (35.2%)
Station of Presenting Part	Floating/Dipping	574 (76.7%)
	Well Engaged	174 (23.3%)
Pain during ECV	Mean (SD): 40.57 (26.47)	
	Range: 0 - 100	

ECV – external cephalic version, SD – standard deviation

3.3.2. Univariable Logistic Regression

Unadjusted results revealed that among women who received an ECV before term, anterior placenta location was a significant predictor of preterm birth (OR: 2.78; 95% CI: 1.52 – 3.19; p=.001). Furthermore, living in a country with a PMR ≥10/1000 was associated with an increased risk of preterm birth (OR: 2.38; 95% CI: 1.16 – 4.85; p=.017). Having a short stature approached statistical significance for its association with

preterm birth (OR: 1.56; 95% CI: 0.98 – 2.48; *p*=.06). The station of the presenting part prior to the ECV was a significant predictor of preterm birth, with the odds of preterm birth being 2.53 times higher for women with a baby well into the pelvis/engaged relative to women with a floating/dipping fetus (OR: 2.53; 95% CI: 1.39 – 4.62; *p*=.002). Table 7 includes the estimates for all univariable estimates for question 2.

Table 7: Predictors of Preterm Birth Among Women Who Received ECV before Term

	Odds of Preterm Birth			
	Unadjusted[1]		**Adjusted[2]**	
Predictors	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Maternal Age (Ref. age>35)	0.66 (0.37 – 1.15)	.14	0.76 (0.37 – 2.00)	.72
Parity (Ref. multiparous)	0.62 (0.33 – 1.16)	.14	1.60 (0.78 – 3.26)	.20
Maternal Height (Ref. >167cm)	1.56 (0.98 – 2.48)	.06*	1.47 (0.69 – 3.16)	.32
Maternal BMI (Ref. <25 kg/m^2)				
BMI = 25-29.9 kg/m^2	0.74 (0.46 – 1.20)	.23	0.55 (.26 – 1.17)	.12
BMI >over 30 kg/m^2	0.90 (0.54 – 1.80)	.67	0.56 (.25 – 1.26)	.13
Placenta Location (Ref. Not Anterior)	**2.78 (1.52 – 3.19)**	**.001****	**2.64 (1.39 – 5.02)**	**.003****
Perinatal Mortality Rate (Ref. <10/1000)	**2.38 (1.16 – 4.85)**	**.017****	**2.47 (1.06 – 5.74)**	**.035****
Station (Ref. Floating/Dipping)	**2.53 (1.39 – 4.62)**	**.002****	**2.79 (1.42 – 5.49)**	**.003****
Tocolytic Use (Ref. no tocolytics)	0.68 (.38 – 1.23)	.201	0.53 (0.28 – 1.03)	.06*
Pain (continuous)	1.01 (.99 – 1.02)	.13	1.01 (0.99 – 1.02)	.38

OR=odds ratio; CI=confidence interval; BMI=body mass index; ECV=external cephalic version
[1]Results of the univariable logistic regression
[2]Results of the final multivariable logistic regression model
**p<.05; *p≤.10

3.3.3. Multicollinearity

There was no evidence of multicollinearity for any of the predictor variables. Correlation coefficients were all below 0.90. Please refer to Table 8 for the correlation matrix between all predictor variables.

Table 8: Correlation Matrix for Predictor Variables in Question 2

	1	2	3	4	5	6	7	8	9
1. Maternal Age									
2. Parity	-.06								
3. Placenta Location	.02	.01							
4. PMR	.15	.10	-.02						
5. BMI	.02	.01	-.001	-.03					
6. Maternal Height	-.02	.04	.02	-.01	.16				
7. Pain During ECV	-.16	.23	.07	.004	.004	-.05			
8. Tocolytic Use	-.05	-.08	.08	.13	-.12	.13	.05		
9. Station	-.01	-.19	.03	.10	.004	-.03	.17	.08	

BMI – body mass index, ECV – external cephalic version, PMR – perinatal mortality rate

3.3.4. Multivariable Logistic Regression Model

Table 7 includes the results for the final multivariable logistic regression model. After adjusting for all risk factors, anterior placenta location (OR: 2.64; 95% CI: 1.39 – 5.02; p=.003) and living in a country with a PMR ≥10/1000 (OR: 2.47; 95% CI: 1.06 – 5.74; p=.035) remained significant predictors of preterm birth. Adjusted results also indicated that station of presenting part remained a significant procedural-related characteristic. The odds of preterm birth were 2.79 times higher when women had a fetus engaged into the pelvis relative to those with a floating/dipping fetus (OR: 2.79; 95% CI: 1.42 – 5.49; p=.003). While it did not quite reach statistical significance, the odds of preterm birth

were 0.53 times lower for women who received tocolytics for the ECV procedure in the adjusted analyses (OR: 0.53; 95% CI: 0.28-1.03; p=.06).

3.3.5. Centre-Effect: Generalized Linear Mixed Model

After accounting for centre in the analyses, results mirrored those obtained in multivariable logistic regression (See Table 9). However, after adjustment for centre and other predictors, living in a country with a PMR ≥10/1000 was no longer significantly associated with odds of preterm birth, though estimates were in the same direction. Further, although it approached statistical significance, nulliparity did not remain significant in the GLMM. Finally, anterior placenta location remained a significant predictor of preterm birth (OR: 1.94; 95% CI: 1.09 – 3.46; p=.03), as did the station of presenting part (OR: 2.11; 95% CI: 1.12 – 3.96; p=.02). Sensitivity analyses revealed that exclusion of low recruiting centres did not affect the significance of the results.

Table 9: Predictors of Preterm Birth Among Women Who Received ECV before Term Accounting for Centre

Predictors	Odds of Preterm Birth	
	Adjusted	
	OR (95% CI)	p-value
Maternal Age (Ref. age>35)	1.09 (0.51 – 2.32)	.82
Parity (Ref. multiparous)	1.34 (0.71 – 2.54)	.37
Maternal Height (Ref. >167cm)	1.28 (0.65 – 2.53)	.47
Maternal BMI (Ref. <25 kg/m^2)		
BMI = 25-29.9 kg/m^2	1.50 (.76 – 2.96)	.25
BMI >over 30 kg/m^2	1.50 (.71 – 3.16)	.29
Placenta Location (Ref. Not Anterior)	**1.94 (1.09 – 3.46)**	**.03****
Perinatal Mortality Rate (Ref. <10/1000)	1.94 (0.88 – 4.30)	.10
Station (Ref. Floating/Dipping)	**2.11 (1.12 – 3.96)**	**.02****
Tocolytic Use (Ref. no tocolytics)	0.65 (0.36 – 1.19)	.16
Pain (continuous)	1.00 (0.99 – 1.01)	.58

OR=odds ratio; CI=confidence interval; BMI=body mass index; ECV=external cephalic version
**p<.05; *p≤.10

3.3. Descriptive Approach - Research Question 3: What are the characteristics among women who had a preterm birth and received an ECV before 37 weeks?

3.3.1. Description of Women Who Had Early ECV Exposure and Delivered Preterm

3.3.1.1. Group Differences

In total, there were 48 women who received an ECV before term and also delivered preterm. The remaining 53 preterm births were in women who did not receive an ECV before term (Refer to Figure 1). After exploring the women who delivered preterm (N=101), stratified by exposure status (early ECV versus no early ECV), a Chi-

square test for independence (with Yates Continuity Correction) indicated a significant difference in placenta location for these two groups, X^2 (1, n = 100) = 4.01, p = .04. The group of women who received an ECV before term and had a preterm birth were significantly more likely to have an anterior placenta (61.7%), whereas the women who did not receive an ECV before term and had a preterm birth were more likely to have a non-anterior placenta location (60.4%). Chi-square tests indicated that there were no significant differences on any other variables explored (See Table 10).

3.3.1.2. Time from ECV Exposure to Delivery in Subset of 48 Women

Figure 3 illustrates the distribution of time from early ECV exposure to preterm delivery among the subset of women who received an ECV before term and delivered preterm (N=48). There were a total of 20 (41.7%) women who delivered within 96 hours of the early ECV exposure, with the remaining 28 (58.3%) delivering after 96 hours of early ECV exposure**.** Of the 20 who delivered within 96 hours of the procedure, 7 (14.6%) were within 24 hours[2], 6 (12.5%) were between 25 and 48 hours, 4 (8.3%) were between 49 and 72 hours, and 3 (6.3%) were between 73-96 hours.

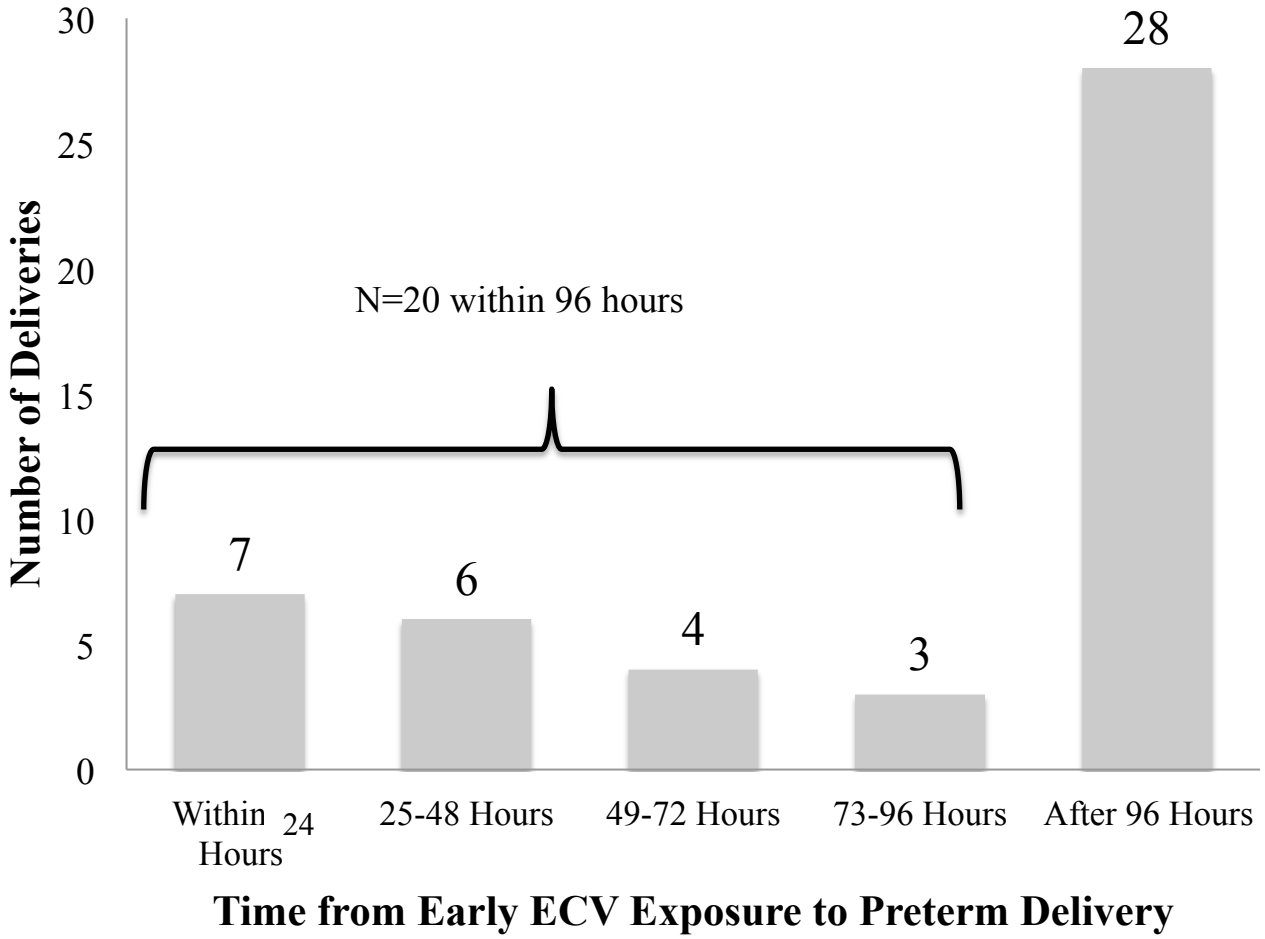
[2] There was one woman who did not have information recorded pertaining to time of entry to hospital, time of early ECV procedure, and time of delivery. However, all three of these events occurred on the same date. This woman was randomized to the delayed ECV group. Therefore, it is possible that the ECV was administered after she arrived to the hospital to deliver, in order to try to turn breech fetus following the onset of spontaneous preterm labour. Therefore this case should be interpreted with caution, as the ECV may not have been on the causal pathway to preterm delivery.

Table 10: Characteristics of Preterm Births, Stratified by Exposure to ECV before term

	At least one ECV Before 37 weeks and Preterm Outcome (N=48)	**No ECV Exposure Before 37 weeks and Preterm Outcome (N=53)**
Gestational Age at Delivery		
Less than 34 weeks	0/48	1/53 (1.9%)
34 weeks to 34.6 weeks	2/48 (4.2%)	4/53 (7.5%)
35 to 35.6 weeks	15/48 (31.3%)	20/53 (37.7%)
36 to 36.6 weeks	31/48 (64.6%)	28/53 (52.8%)
Maternal Characteristics		
Maternal Age		
(<35 years)	40/48 (83.3%)	46/53 (86.8%)
(≥ 35 years)	8/48 (16.7%)	7/53 (13.2%)
Body Mass Index		
Less than 25 kg/m^2	17/48 (35.4%)	18/53 (34.0%)
25-29.9 kg/m^2	18/48 (37.5%)	18/53 (34.0%)
30 kg/m^2 and higher	13/48 (27.1%)	17/53 (32.0%)
Maternal Height (cm)		
Short Stature (<167 cm)	38/48 (79.2%)	38/53 (71.7%)
Tall Stature (≥167 cm)	10/48 (20.8%)	15/53 (28.4%)
Parity		
Nulliparous	33/48 (68.8%)	33/53 (62.3%)
Multiparous	15/48 (31.2%)	20/53 (37.7%)
Placenta Location[1]		
Not Anterior	18/47 (38.3%)	32/53 (60.4%)**
Anterior	29/47 (61.7%)	21/53 (39.6%)**
PMR		
≤ 10/1000	37/48 (77.1%)	36/53 (67.9%)
>10/1000	11/48 (22.9%)	17/53 (32.1%)

ECV, external cephalic version; PMR, perinatal mortality rate
[1]Data missing for one participant.
** *p<.05*

Figure 3: Number of Hours from Early ECV Exposure to Preterm Delivery



Of all women who received an ECV before term (N=749), only 20/749 (2.6%) are reported to have delivered within 96 hours of the procedure and delivered preterm, and therefore it is hypothesized that there *may* have been an association between the ECV and preterm birth.

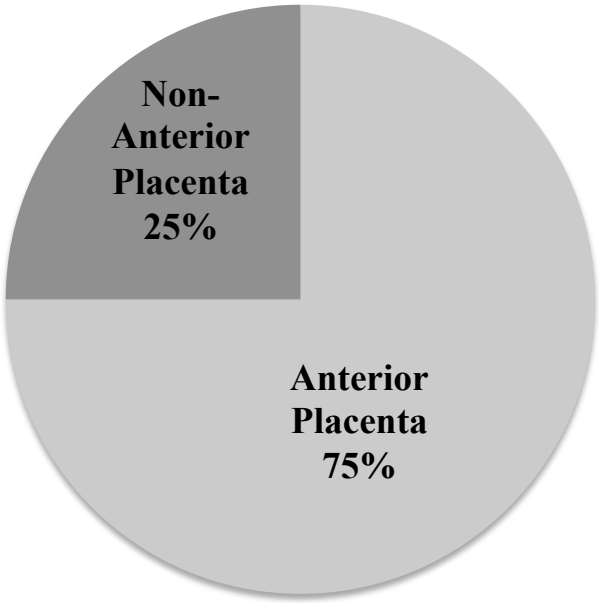
Among the women who delivered within 96 hours of the ECV exposure (N=20), there were a total of four cases non-reassuring fetal heart rate, no cases of reported abrupted placenta, and 9 women who had signs of preterm labour. In total, there were 13 women who had a reported 'complication' following the early ECV procedure.

3.3.1.3. Women Who Delivered Within 48 hours of ECV Procedure

Further exploration was made on the subset of women who delivered within 48 hours (N=13). When placenta location was explored among this subset of women, 75% of the women had an anterior placenta[3], which is approximately double the proportion of anterior placenta relative to the sample of women in the trials. There was no evidence of other disproportions on other preterm risk factors in this group, including maternal height, age, BMI, parity or PMR.

[3] Data on placenta location was missing for one woman; therefore, 8/12 had anterior placenta.

Figure 4. Frequency of Anterior Placenta Location Among Women Who Delivered Within 48 Hours of Early ECV Exposure



Among the women who delivered within 48 hours of the ECV exposure (N=13), there were a total of four cases non-reassuring fetal heart rate, no cases of reported abrupted placenta, and 5 women who had signs of preterm labour. In total, there were 9 women who had a reported 'complication' following the early ECV procedure.

IV: DISCUSSION

4.1. Overview of Findings in Relation to Objective

In light of the recent Cochrane review revealing that preterm birth appears to be associated with early ECV, the present study set out to examine this association in women enrolled in the EECV trials using three different approaches. Although the Cochrane review reported a 51% increase in the likelihood of preterm birth among women randomized to have an early ECV, results of the present study indicated that after adjusting for several risk factors, early ECV exposure is not independently associated with preterm birth. However, further exploration revealed that the association between early ECV exposure and preterm birth was moderated by anterior placental location with approximately a two-fold increased odds when these conditions were met. In addition, women receiving an ECV before term with a fetus well engaged into the pelvis may be at risk for a preterm birth with increased odds of 2.11 (95% CI: 1.12 – 3.96). Finally, living in a country with a PMR >10/1000 was a significant independent predictor of preterm birth among women enrolled in the EECV trials with increased odds of 2.37 (95% CI: 1.49 – 3.77).

4.2. Interaction of Early ECV and Anterior Placenta on Risk of Preterm Birth

Collectively, the results from both the predictive and descriptive approaches provide robust evidence that there is a link between early ECV exposure, anterior placenta location, and increased odds of preterm birth. Women who have an anterior placenta and who receive an early ECV represent a subgroup at particular risk for preterm

birth. The mechanism by which this risk manifests is not clear, however two plausible biological pathways are discussed.

4.2.1. Uteroplacental Hemorrhage

Placental hemorrhage is an established biological pathway associated with preterm birth, and preterm labour occur frequently in the context of intrauterine bleeding (17). During the 1980s, authors conducting ECV trials at term deemed anterior placental location as a contraindication for ECV because of a possibility for higher risk of placental abruption and fetal-maternal hemorrhage (48). However, there has not been a clear causal relationship elucidated between placenta location and the occurrence of these complications at term (49). Most studies in modern day, including the EECV trials, did not classify anterior placenta location as a contraindication to ECV given the lack of studies finding this association.

While previous studies have not looked at the influence of anterior placenta location on outcomes in women receiving an ECV before term, in line with previous authors' hypotheses (48), it is possible that performing an ECV in women with an anterior placenta might disrupt the maternal-fetal interface and result in damaged arteries or arterioles and placenta hemorrhage (34). In the preterm time frame, this might be particularly significant as it may result in a fetus that is delivered prematurely.

Although there were no reported cases of placental abruption recognized by frank vaginal bleeding among the women who received an ECV before term and delivered preterm in the present study, it is possible that covert bleeding occurred internally following the early ECV procedure that did not manifest clinically as vaginal bleeding

and was therefore not captured on case report forms. A high proportion of women who received an ECV before term and delivered preterm birth (62%) had an anterior placenta. An even higher proportion (75%) of the women who received an ECV before term and delivered within 48 hours of the procedure had an anterior placenta. This proportion of anterior placenta is approximately double of what was observed among all women enrolled in the trial, and more than double the rate reported among breech pregnancies in other studies (14). Previous research has shown more histological evidence of bleeding in placentas that were from preterm births than among placentas of term born infants, which may be the case for women in the present study who delivered shortly after the ECV procedure (50); however, future research would be required to confirm this.

4.2.1. Fetal Stress Response

In addition to the possibility of ECV-induced internal hemorrhage, it is possible that fetal distress played a role in preterm birth for women with an anterior placenta. It has been established that an anterior placenta is associated with increased likelihood of an unsuccessful version of a breech fetus (13,51,52). It has been speculated that an anterior placenta affects the ability of the health care provider to grasp and turn the fetus. With the difficulty turning the fetus, a clinician may use increased pressure and force while performing the ECV, leading to a potentially more dangerous maneuver (51). Although the pressure associated with an ECV is less than the pressure generated by uterine contractions, it should be noted that this is unphysiological in nature (53). Particularly for an immature (i.e., preterm) fetus, the more forceful external manipulation accompanying

the ECV in women with an anterior placenta may induce a fetal distress response.

As an endocrine organ, the placenta produces a wide array of hormones that affect both the mother and fetus (54). Fetal distress has been shown to stimulate the placental synthesis of the corticotropin-releasing hormone (CRH) (55). Increased placental CRH is able to stimulate fetal pituitary adrenocorticotropic hormone (ACTH) production and subsequently fetal cortisol synthesis. Increases of these stress hormones are a major risk factor for preterm labor and preterm rupture of the membranes (54). Together, increased external manipulation before term in women with an anterior placenta may result in fetal stress and potentially a stress response that alters placental hormone production and a feedback loop initiating preterm birth (56).

4.3. Additional Risk Factors for Preterm Birth

Similar to an anterior placental location, performing an ECV procedure on women who have a fetus well engaged into the pelvis may require more manipulation to disengage the breech from the pelvis prior to attempting to version. Indeed, we found that among women who received an ECV before term, those with a fetus well engaged into the pelvis were at increased risk of preterm birth. This could be a result of uterine stimulation or a fetal distress response as described above. However, it is also possible that an engaged fetus is simply closer to spontaneous onset of labour and delivery and therefore this finding should be interpreted with caution.

Among all women enrolled in the EECV trials, results revealed that living in a country with a PMR >10/1000 was a significant independent predictor of preterm birth.

The national PMR is used as an indicator of the quality of antenatal and perinatal care. Although it might be hypothesized that women enrolled in the EECV trials were receiving close prenatal monitoring given recruitment in a research study, it is likely that a higher PMR is also indicative of decreased healthcare resources and/or less favourable socioeconomic status relative to women from a country with a low PMR. Previous research has shown that these factors are linked to preterm birth (41,42) and that developing countries have a higher rate of preterm birth in general (18).

4.4. Implications

Findings from this study suggest that performing an ECV before term is not independently associated with preterm birth in low-risk women with breech pregnancies; however, women who receive an ECV before term and have an anterior placenta constitute a subgroup at more than double the risk for preterm birth.

Although the rate of preterm birth was relatively low in the present study (5-6%) relative to general population rates of late preterm birth (7-8%) (18), the possible association of ECV before term and preterm birth in women with an anterior placenta needs to be considered when balancing the positive outcomes associated with early ECV. Through counseling from a health care professional, women offered an ECV before term should receive information pertaining to her risk of preterm birth. This could allow the woman to make an informed decision on the management and delivery of her breech baby and aid in balancing the benefits and risks of receiving an ECV before term.

4.5. Limitations

It is important to interpret the findings of the present study with acknowledgment of the following limitations. Given the nature of the project (i.e., secondary data analysis), variables were limited to the data collected in the original EECV trials. Since the original RCTs were designed to assess the effectiveness of ECV based on timing, there were a number of known risk factors for preterm birth that were not considered during data collection. For example, information pertaining to smoking/drug use, nutritional status, and psychopathology were not collected and these are known to be associated with preterm birth (34). Given the limited number of available risk factors to explore, it is recognized that the predictors included in the statistical models are not exhaustive. Therefore, the results presented are a limited model of clinical predictors of preterm delivery among women with breech presentation and there may be additional subgroups aside from those with an anterior placenta that are at heightened odds for preterm birth when undergoing an ECV before term.

It should also be noted that the sample of women enrolled in the EECV trials were relatively homogenous in terms of pregnancy risk (i.e., low risk) which affects the generalizability of the results. Enrollment criteria excluded participants who were at risk for preterm delivery and this may reflect the overall low rate of preterm birth that was observed relative to other population estimates (18). Therefore, these findings should be interpreted with caution when considered for women with high-risk breech pregnancies including women at a higher risk of preterm birth.

Finally, although the number of women enrolled in the RCTs was relatively large, the outcome explored in the present thesis was infrequent. Given the nature of the research question and subgroup analyses, some analyses were underpowered and this may have affected the ability to detect statistically significant findings.

V. CONCLUSION

A secondary data analysis of the EECV trials was undertaken to explore the association between early ECV and odds of preterm birth. Results revealed that although early ECV exposure was not independently related to odds of preterm birth among women with low-risk breech pregnancies, and specifically at low risk for preterm birth, those who receive an ECV before term and have an anterior placenta appear to be at two times the risk for preterm birth.

Although the rate of preterm birth in the present study was below estimates of worldwide rates, these results significantly contribute to knowledge on the risk factors associated with preterm birth in women with low-risk breech pregnancies. Medical professionals should carefully assess the risk of preterm birth in women with breech pregnancies undergoing an ECV before term, and these risks should include having an anterior placenta, as this appears to put women at a particularly high risk. It is speculated that this risk may manifest through biological pathways involved in preterm birth. Additional research is needed to fully elucidate the mechanisms by which an anterior placenta might interact with an ECV before term and result in a preterm birth.

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