Analyzing the Clinical and Economic Impact of Cesarean Delivery on Maternal and Infant Outcomes

by

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Abstract

Background: Current cesarean delivery (CD) rates in many industrialized countries are well above the recommended rates. **Objective:** The overall goal of this thesis was to identify sources for unnecessary CD. Specific objectives were to: 1) analyze the leading indications for CD and their associations with neonatal outcomes; 2) compare adverse birth outcomes between elective primary cesarean delivery (EPCD) and trial of labor after vaginal birth (TOLAV), and between elective repeat cesarean delivery (ERCD) and trial of labor after cesarean birth (TOLAC); and 3) assess the cost-effectiveness of ERCD and TOLAC. **Methods:** A retrospective cohort study was conducted. Leading indications for CD were analyzed and risks of neonatal outcomes between "soft" indications and "hard" indications were compared first, using 2006 to 2013 Better Outcomes and Registry Network Ontario data. A pair of analyses: comparing risks of adverse birth outcomes between EPCD and TOLAV and between ERCD and TOLAC, were then conducted using United States 2005 to 2010 birth registration data. Analysis were performed using logistic regression and propensity score matching models. Finally, a cost-effectiveness analysis between ERCD and TOLAC was performed. **Results:** The single largest contributor for overall CD was ERCD (34.3%) and for primary CD was dystocia (31.9%) in Ontario. Compared with infants of mothers with CD for "hard" indications, the risks of Apgar score <7 at 5 minutes for infants of mothers with CD for non-reassuring-fetal-status was increased, while the risks of Apgar score <7 at 5 minutes and neonatal death for infants of mothers with ERCD and dystocia were decreased. Compared with infants of mothers who underwent TOLAV, infants of mothers who underwent EPCD were more likely to require antibiotics and ventilation support, but less likely to have birth injury. On the other hand, compared with infants of mothers who underwent TOLAC, infants of mothers who underwent ERCD were less likely to require antibiotics and

ventilation support. ERCD was similar to the TOLAC birth option in terms of cost effectiveness.

Conclusions: Tight up criteria for "soft" indications such as labor dystocia could result in substantial reduction in CD without harming the infants.

Acknowledgement and Dedication

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Dedication

I dedicate this thesis to my late friend, Gloria Kwarteng who died during childbirth; a tragedy which inspired me to conduct research on maternal and child health issues with the view to help improve the health of mothers and their babies.

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List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
BMI	Body mass index
BORN	Better Outcomes Registry & Network
CD	Cesarean delivery
CI	Confidence interval
EFM	Electronic fetal monitoring
EPCD	Elective primary cesarean delivery
ERCD	Elective repeat cesarean delivery
HIE	Hypoxic ischemic encephalopathy
IUGR	Intrauterine growth restriction
LGA	Large for gestational age
LHIN	Local Health Integration Networks
NICU	Neonatal intensive care unit
NRFS	Non-reassuring fetal status
OECD	Organization for Economic Co-operation and Development
OR	Odds ratio
QALYs	Quality adjusted life years
RDS	Respiratory distress syndrome
SGA	Small for gestational age baby
TOLAC	Trial of labor after cesarean birth
TOLAV	Trial of labor after vaginal birth

TTN	Transient tachypnea of the newborn
VBAC	Vaginal birth after cesarean
VD	Vaginal delivery

Outline of thesis research

This thesis dissertation is organized into seven chapters: Chapter one comprises introduction, background and a general overview of the topic. Chapter two presents a literature review of maternal and neonatal outcomes and economic evaluation of cesarean delivery (CD), rationale, significance and objectives of study. Chapter three assessed the indications for CD and compared neonatal outcomes of "soft" versus "hard" indications for CD and is based on objective one. Chapter four examines adverse birth outcomes among low risk women with one previous vaginal delivery (VD) who underwent elective primary cesarean delivery (EPCD) versus trial of labor after vaginal birth (TOLAV), and those with one previous CD who underwent elective repeat cesarean delivery (ERCD) versus trial of labor after cesarean birth (TOLAC) based on objective two. Chapter five assesses the cost effectiveness of having a TOLAC and ERCD among women with low risk deliveries (objective three). Separate introduction, methods, results and discussion of results are presented for Chapters three, four and five. Chapter six provides a general discussion of the overall findings from the three research objectives with a focus on implications for clinical practice and then a final conclusion is provided in Chapter seven.

Chapter 1: Introduction

1.1 Background

Cesarean delivery (CD) is a major surgical procedure used to deliver a baby through an incision in the mother's abdomen and uterus.[1] It is one of the most common surgical procedures performed in the United States (US) and Canada. [2-3] In recent years, CD rates have risen considerably in many parts of the world.[4-6] In 2011, more than one in four deliveries (28.0%) in Canada were by CD compared with one in twenty deliveries (5%) in 1969.[6-7] In US, almost one in three deliveries (32.7%) occurred via CD in 2013.[5] Similar scenarios have been observed in other developed and developing countries.[4] The main factors attributed to the rise in CD rates are increase in primary and repeat CDs as well as decline in vaginal birth after cesarean birth (VBAC) or trial of labor after cesarean (TOLAC)[8] About 90% of women with primary CD will have repeat CD in their next pregnancy.[9] The Public Health Agency of Canada reported that the rate of repeat CD increased from 74.2 in 2002 to 81.8 per 100 hospital deliveries in 2011[6] The Canadian Institute for Health Information reported that VBAC rate among women with prior cesarean birth declined from 35% in 1998 to 27% in 2002.[10] A similar pattern was observed in the US where the rate of repeat CD increased, whereas the rate of VBAC decreased. Menacker et al[11] reported repeat CD rate was 71.7% in 1996 whereas Curtin et al[12] reported repeat CD rate of 89.4% in 2013. VBAC rate was 28.3% in 1996, whereas the rate was 8.3% in 2007.

TOLAC has been considered a safe alternative delivery option for majority of low risk women with a previous low segment CD.[13-15] However, elective repeat cesarean delivery (ERCD) is the most common choice for many women.[9] Other factors contributing to the rising rates of CD are increasing trends in higher maternal age at delivery (35 years or older)[16-17] and growing rates of

body mass index (BMI) greater than 30 kg/m^2, among women of reproductive age.[18] Considerable changes in physician practices overtime, partly in response to legal issues and aversion for litigation, may also be contributing factors to rising CD rates.[19]

There is no doubt that CD can save the lives of the mother and baby in situations where a vaginal delivery (VD) may put them at risk.[20-22] Medical situations for which cesarean birth may be indicated include prolapse of the umbilical cord which can lead to fetal asphyxia or failed induction of labor, placenta abruption and placenta previa.[23-24] It may also be necessary in conditions such as non-progressive labor or difficult labor related to abnormalities in the position of the fetus which can pose risk to the mother and fetus through VD.[23-24] Thus, CD has potential benefits to both mothers and their babies in high risk pregnancies or difficult labor siutations.[20] However, as a major surgical procedure, CD is reported to carry increased risk of maternal and neonatal complications in the immediate and future pregnancies compared with VD.[22,25-26] CD performed routinely with no clear medical indication adversely affects maternal and fetal health and well-being.[21-22] CD is also associated with higher hospital cost and extra cost burden on the health care system in general.[27-29]

The current high rates of CD have received much attention in Canada and internationally. [30-31] It has also generated discussions on the effective and safe use of the procedure, particularly among low risk women who opt or request for CD when there is no clear medical indication for the procedure.[20-21] There are limited data on the true rates on maternal requested CD, since it not a well-recognized clinical and different studies provide various definitions for this non-medical indication. Some investigators have called for data that distinguishes between CD based solely

on maternal request from other indications for direct comparison across studies.[32-35] Previous studies evaluating complications of CD have focused mainly on the immediate and future maternal outcomes such as postpartum infection, hemorrhage, uterine rupture, placental abruption, placenta previa and placenta accretae.[13,36] In a systematic review that examined maternal and neonatal outcomes related to ERCD compared with TOLAC deliveries, one of the issues the authors specified was the lack of data on cost-effectiveness particularly from the health-care payer perspective between the delivery groups.[13]

Only a few studies[37-40] have incorporated economic evaluation of mode of delivery in their studies despite the increasing rate and cost of childbirth-related hospitalizations.[3, 29] There is a dearth of information on the economic implications of maternal and infant outcomes related to mode of delivery following previous cesarean among low risk women in Canada. Besides, ample information regarding single and co-occurring CD indications and the impact of prior route of delivery on subsequent neonatal outcomes in low risk women with term cephalic fetal presentation are limited. To provide further perspective on these issues, a cohort study was conducted using existing nationwide data, as well as states and provincial data sources to evaluate the clinical and economic impact of CD on maternal and infant outcomes. This information will provide important knowledge that may be used to further improve obstetric and perinatal care.

1.2 Definition of terms regarding mode of delivery

Methods of delivering a baby are broadly described as VD or CD. However, various subcategories could be defined for VD and CD based on several factors including research

question, study population and available covariates in an investigator's database. The following are definition of method of delivery terminology used in this research.

Overall cesarean delivery

Overall CD was defined as the total CD performed for a singleton pregnancy including primary CD among women who have not had a previous CD before and repeat cesarean delivery among women who have had a previous CD before.

Primary cesarean delivery

Primary CD was defined as the first or primary CD performed for a singleton pregnancy among women who have not had a previous CD before.

*Cesarean delivery on maternal request (*CDMR)

CDMR request refers to a planned CD for a singleton pregnancy following a mother's decline of the vaginal birth after cesarean option and her request for CD, in the absence of maternal or obstetric indication for the CD.

Elective repeat cesarean delivery (ERCD)

ERCD was defined as a planned CD with no attempt of a trial of labor among woman with only one previous CD who had a singleton term birth in the second pregnancy with cephalic presentation (baby's head enters the pelvis first).

Elective primary cesarean delivery (EPCD)

EPCD was defined as a planned CD with no attempt of a trial of labor among woman with only one previous VD who had a singleton term birth in the second pregnancy with cephalic presentation (baby's head enters the pelvis first).

Emergency repeat cesarean delivery

Emergency repeat cesarean was defined as unplanned repeat cesarean delivery after a failed or unsuccessfully trial of labor.

Trial of labor after vaginal birth (TOLAV)

TOLAV was defined as a planned VD with attempt of a trial of labor among woman with only one previous VD who had a singleton term birth in the second pregnancy with cephalic presentation (baby's head enters the pelvis first).

Trial of labor after cesarean birth (TOLAC)

TOLAC was defined as a planned VD with attempt of a trial of labor among woman with only one previous CD who had a singleton term birth in the second pregnancy with cephalic presentation (baby's head enters the pelvis first).

Single indication for cesarean delivery

Single indication comprised only one indication recorded for having CD and none of the other maternal or fetal medical or obstetric indications for CD. Examples of single indication includes breech presentation only or labor dystocia only.

Co-occurring indications for cesarean delivery

Co-occurring indications comprised only two indications recorded for having CD and none of the other maternal or fetal medical or obstetric indications for CD. Examples of co-occurring indications include paired dystocia and NRFS only or paired ERCD and breech presentation only.

Three indications for cesarean delivery

Three indications indicate there were only three indications recorded for having CD and none of the other maternal or fetal medical or obstetric indications for CD. Examples of three indications include dystocia and NRFS and failed forceps only or ERCD and NRFS and OMHP only.

"Soft" indications

"Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, non-reassuring-fetal-status and suspected large-for-gestational-age (LGA) baby. These indications are reported to be adjustable and have lower thresholds for performing CD. They can also be can be desirable target for efforts to reduced unnecessary CD.

"Hard" indications

"Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation which is abnormal fetal presentation where the fetus enters the pelvis with buttocks or feet first rather than the normal head first fetal presentation. Additional "hard" indications include maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

Nulliparous woman

Nulliparous woman was defined as a first birth for a woman who has never given birth to a child.

Multiparous woman

Multiparous woman was defined as a woman who has given birth to one or more children.

Chapter 2: Review of literature, significance and objectives of research

The purpose of this chapter is to review the literature and identify studies that provide information on the following topics regarding cesarean delivery (CD): 1) the trend and variation in rates of CD; 2) indications for having CD; 3) maternal and neonatal complications related to elective repeat cesarean delivery (ERCD) and trial of labor after cesarean (TOLAC) and 4) cost and economic evaluation of TOLAC and ERCD. The chapter has been divided into six sections. The first four sections provide an overview of the trend and variation in rate of CD, the indications for having CD, maternal and neonatal complications, and the cost and economic implications among women who underwent TOLAC and ERCD. Sections five and six focused on the significance and objectives of the research, respectively.

Ovid Medline and Embase databases were searched for literature from the period of 1986 to May 2016 using key words such as 'cesarean section', 'caesarean section', 'c-section', 'repeat cesarean delivery', 'trial of labor', 'vaginal birth after cesarean' in combination with maternal and neonatal complications as well as other terms (Appendix A-1). Studies included in the review were those that reported on trends and variation of CD rates, indications for CD, maternal and neonatal complications associated with TOLAC and ERCD as well as studies that discussed cost effectiveness or cost utility analysis of TOLAC and ERCD. Studies excluded were case series, animal studies, letters, personal communications, and non-English language publications or studies that only reported costs or outcomes. The search yielded 5,490 citations. References of included studies were searched for further inclusion of relevant studies. After removing duplicates, 98 papers met the inclusion criteria and were included in the review. The characteristics of the studies including the author, publication year, study description, study

period, total population and outcomes are presented in (Appendix B-2). Information and data included in this literature review were drawn from a variety of sources including systematic reviews, observational studies, primary research studies, studies from governmental bodies and relevant research institutions that provide evidence and pertinent information on CD. The review of literature is followed by significance and objectives of the research in sections five and six respectively.

2.1 Trends and variation in rate of CD

Variation in rate of CD among various countries

CD rates have risen remarkably in many parts of the world in recent years (Figures 1 and 2). A recent report by Organization for Economic Co-operation and Development (OECD)[4] showed a general rapid increase in cesarean rates among member countries over the past decades, although some countries reported reversal in CD rates.[4] The average rate across countries increased from 20% in 2000 to 28% in 2013 (Figure 1).

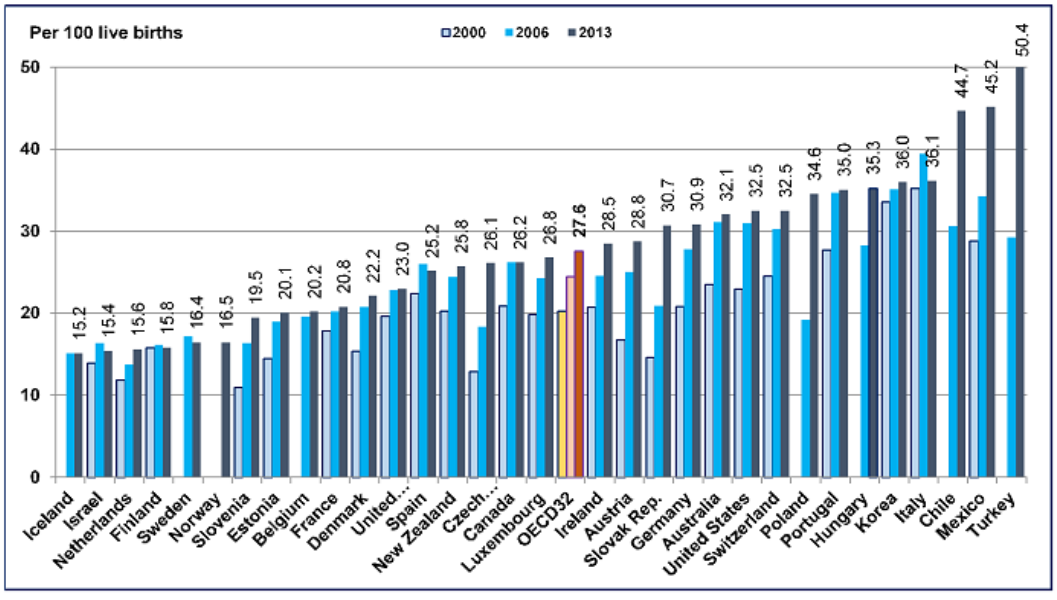

Figure 1: Changes in cesarean section rates, 2000 to 2013 (or nearest years).
Source: OECD Health Data 2015

Among the countries where a rise in CD rates were observed, Turkey and Mexico had the highest rates of over 45%, followed by Chile, Italy and Korea with rates ranging between 36.0% and 44.7%. Conversely, the Nordic countries (Iceland, Finland, Sweden and Norway), Israel and the Netherlands had the lowest rates of increase in CD with a range of 15% to 16.5% CS for all live births in 2013[4] (Figure 2). In Canada, the CD rate increased from 20.9% to 26.3% from 2000 to 2013, while in the United States (US), rates increased from 23.0% in 2000 to 32.5% in 2013. However, in contrast to the general rising trends, many countries have reported a slowdown in rates of CD since 2006, with countries such as Israel, Finland, Sweden, Spain and Italy showing reversed rates since the mid-2000s[4] (Figure 1).

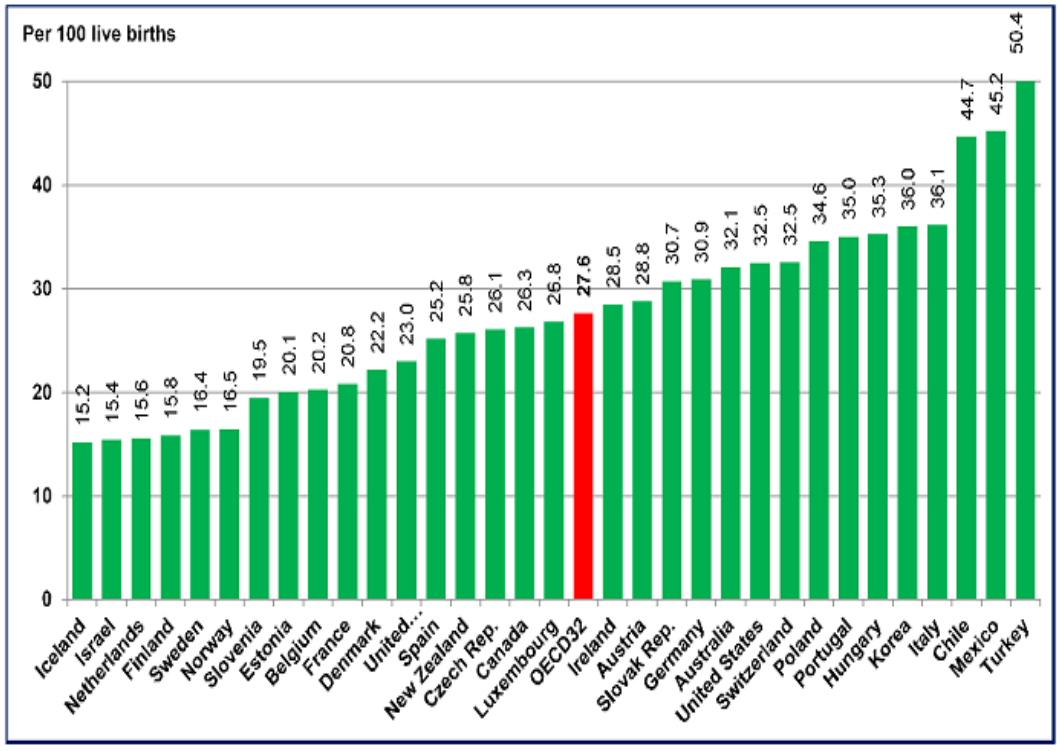

Figure 2: Cesarean section rates, 2013 (or nearest year)

Source: OECD Health Statistics 2015

Variation in rate of cesarean delivery among regions in the same countries

There are variations in the rate of increase in cesarean birth that manifest across geographical regions and between hospitals within the same country. In Canada, CD rates in the Territories are lower than in the provinces. Nunavut has the lowest overall CD rate of 8.4%, followed by Yukon at 19.9%, and the Northwest Territories at 20.1%. Provincial CD rates range from 21.5% to 31.8%. Manitoba has the lowest provincial rate while British Columbia[6] has the highest (Figure 3). Repeat CD rates also vary across geographical regions. For instance, in 2010/2011 Manitoba and Saskatchewan had repeat CD rates of 72.1% and 76.0%, respectively, whereas Newfoundland and Labrador and New Brunswick had CD rates of 91.5% and 87.2% respectively.[41]

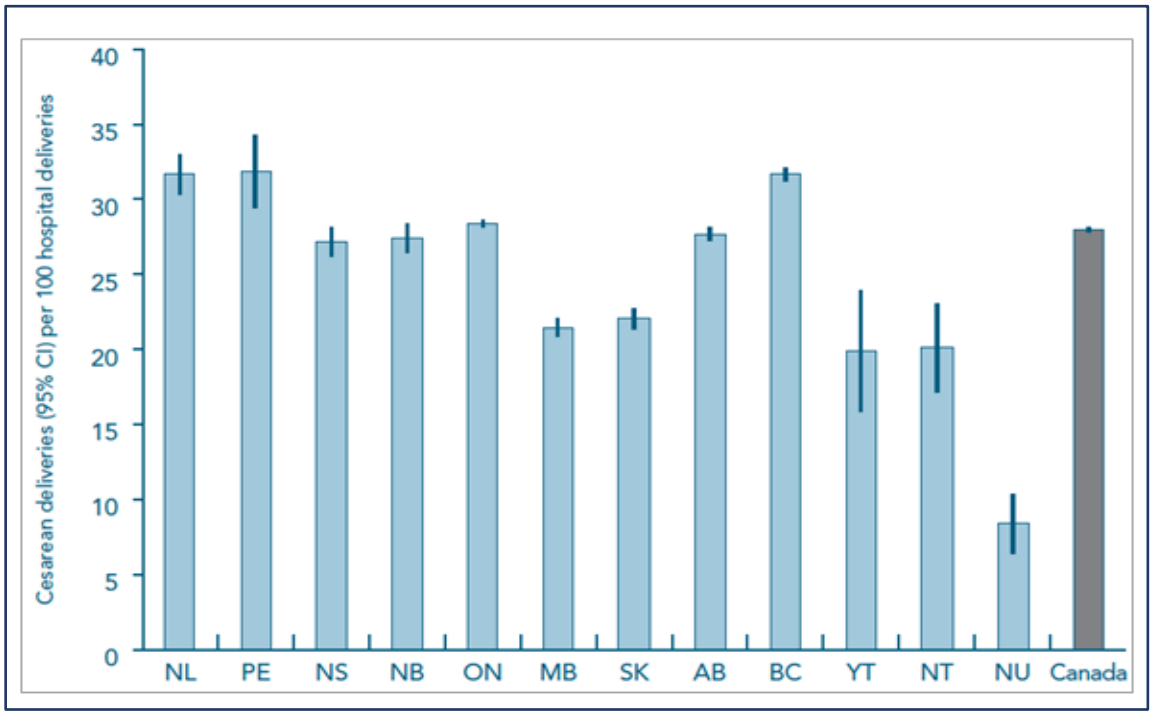

Figure 3. Rates of cesarean deliveries by province/territory of residence, Canada (excluding Quebec) 2010-2011 fiscal year.

Canadian Institute of Health Information (CIHI), Discharge Abstract Database.

For 2011-2012 period, the Local Health Integration Networks (LHINs) in Ontario reported varying rates of CD. The LHINs are community-based, non-profit organizations that manage the planning, integration, performance, and funding of the health care system in the Province of Ontario.[42]As shown in Figure 4, the overall CD rate ranged from 23.4% to 32.3% during the reporting period, with the South West LHIN having the lowest rate while the Central West LHIN had the highest. [42]

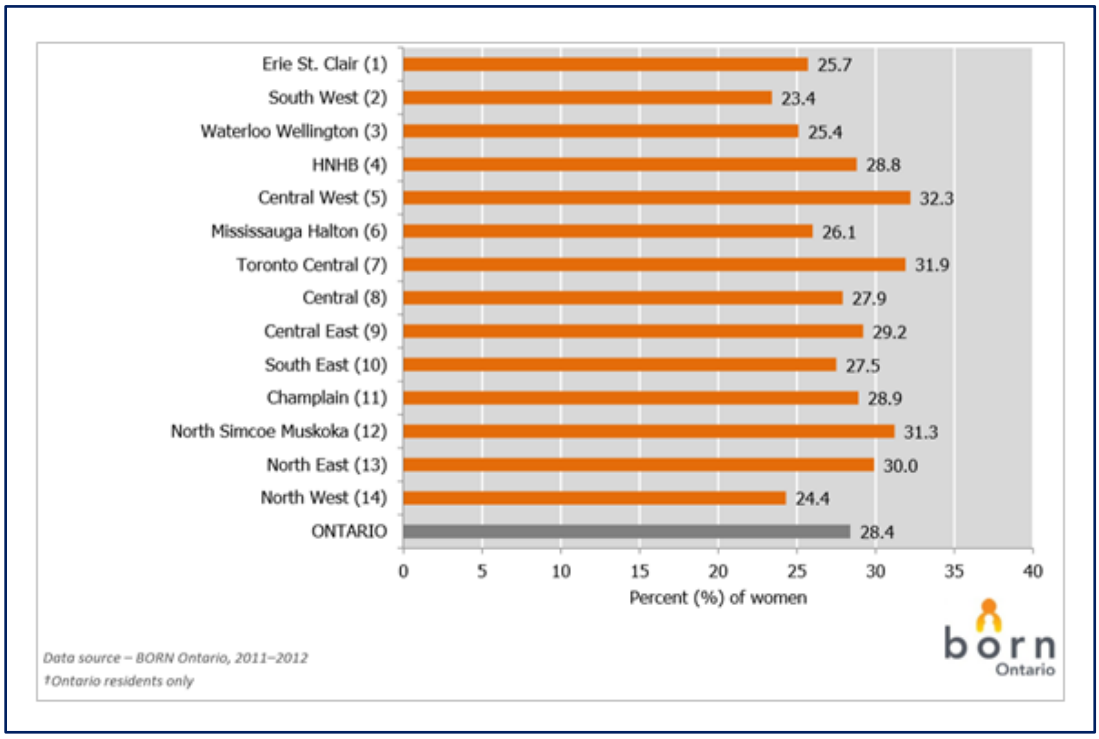

Figure 4 Rate of CD, by LHIN of birth Ontario[+], 2011-2012.

Source: https://www.bornontario.ca/assets/documents/regionalreports/Provincial

In British Columbia, Hanley and investigators[43] examined regional variations in rates of CD and assisted VD in all deliveries in sixteen Health Services Delivery Areas between 2004 and 2007. The authors found nearly two-fold regional variation in the lower and upper limits of CD rates, with rates ranging from 14.7 to 27.6 per 100 deliveries among the areas under study.[43] The authors also reported that the regions that had upper limits of CD rates had lower rates of assisted vaginal delivery (VD). They also suggested the main variation in CD rates stems from differences in practitioners' responses to the diagnosis of labor dystocia or prolonged labor. The decision to perform CD also depends on the availability of resources. This is because smaller institutions often lack the resources required to respond to medical emergencies in the same manner as a tertiary care institution. The investigators stated health practitioners in smaller institutions are therefore more likely to recommend a CD with a lower medical indication than in a larger institution.[43]

Stavrou and colleagues[44] also found that CD rate ranges from 28% in Tasmania to 33.1% in Queensland regions in New South Wales, Australia. There seems to be little variation in CD rates in Australia relative to CD rates in regions in other countries. Specific CD rates were 29.0% in New South Wales, 30.8% in Victoria, 32.7% in Western Australia, 32.3% in South Australia, 28.9% in Australian Capital Territory and 29.6%. in Northern Territory. The authors reported the variation of CD rates among regions cannot be explained by known and collected maternal or pregnancy characteristics, but rather it may be related to differences in clinical decision making or maternal request. [44]

Other variation in CD rates across hospitals was demonstrated in a study of 620,640 births across 146 different National Health Service (NHS) trusts or maternity units in England.[45] The authors reported the CD rate varied from 14.9% to 32.1% among the NHS trust units.[45] In Germany, 30% of births occurred by CS in West Germany whereas 22% of births occurred by CD in East Germany.[46] In Italy, Stivanello and associates[47] examined inter-hospital comparison of 24 hospitals in The Emilia Romagna Region. They reported substantial inter-hospital variations of overall CD rate at a range of 19.2% to 53.9% from 2007-2009 across the 24 hospitals. In Ireland, Turner and colleagues[48] reported the cesarean rate varied from 18.7% to 35.6% in 2009 in 19 Irish maternity hospitals.

In another study by Kozhimannil et al,[28] the authors compared the rates of overall CD rate among 593 hospitals from 44 states in the US and found a substantially ten-fold variation with a range of 7.1% to 69.9% in CD rates across hospitals. The authors reported variations in CD rates were not explained by clinical risk factor, hospital size, nor geographic location of hospitals. Rather, the differences in practice patterns are a likely reason of variations in CD rates across hospitals. One benefit of this study is the large number of hospitals included in their analysis. However, this study included only hospitals with 100 deliveries thereby limiting generalizability to other hospitals with smaller-volume obstetrical units. [28]

Besides the variation in CD rates reported by studies in different locations, there is also variation of CS rates in private and public hospitals.[49-52] In a study that examined the role of public and private hospitals in the rising CD rate in Western Australia, the authors found the rate of CD in private hospitals increased from 13% in 1996 to 26% in 2008. Dahlen and investigators also[51]

reported CD rate from 1996-1997 to 2000-2008 was higher in private hospitals than public hospitals with rates of 11% relative to 6.7% respectively.[51]

In Switzerland, there was higher cesarean rates of 41% in private clinics than 30.5% in public hospitals.[4] However, another study found comparable rates in the rise of CS from 1994 to 2009 between women giving birth at private or public hospitals.[52] The authors reported the large increase in CD rates that were similar in private and public hospitals may be due to a civil suit alleging negligence in a VD in Australia which resulted to general changes in attitudes of obstetricians to obstetric risk factors and delivery management.[52] Generally, the variations in the rate of CS rate across geographical regions and between hospitals are of great concern. These observations have raised the question of whether there is a standard of appropriateness in the application of CD interventions which may account for the variation in Cd rates between countries, region, and hospitals.

In 1985, the World Health Organization (WHO) stated there was no reason for any region to have a CD rate higher than 10 to15%" [53-55] They also specified that CD beyond the 10 to15% rate have not shown any further improvement in maternal and perinatal outcomes. In 2009, the WHO suggested CD rates between 5% and 15%.[53-54] Despite the recommendations, the CD rates have generally increased in both developed and some developing countries, generating concerns about the use of CD and its consequences on maternal and infant health. However, the rise in CD rates is not uniformly distributed. While there is growing concern about excessive and unnecessary CS (>15%) in developed countries, there is also concern about lack or underuse of CD (<5%) in some developing and low income countries such as those in sub-Saharan Africa where mothers may not have access to CD even when it is medically indicated. In response to this disparity, the

WHO recommended in 2013 that every effort should be made to provide CD to women with established medical indication for the procedure, while considering the CD rate of 15% as a limiting threshold. [53-54]

CD has been effective in saving lives in situations where there is clinical indication,[56] although adverse outcomes have also been reported. Therefore, it is important to evaluate CD rates at population level among countries since it serves as a measure of the level of access and use of CD. It is also useful to assess varying CD rates within regions in the same country, since this will enable governments, policy-makers and health professionals to address disparities in service distribution to promote maternal and infant health while taking steps to curb overuse of the procedure. [56] Thus availability of reliable data and information about CD rates is essential for effective monitoring of the distribution and use of emergency obstetric care resource and associated economic impact on the general healthcare system.

Areas of debate regarding CD rates include ways to safely reduce the increased CD rate without compromising maternal and fetal health [20] and support for vaginal birth after cesarean birth (VBAC) or TOLAC among women with no contra-indication to TOLAC.[14-15] A policy statement of the Society of Obstetricians and Gynaecologists of Canada (SOGC) has provided recommendations to support and promote normal birth in Canadian hospitals as a way of reducing cesareans.[14] The American College of Obstetricians and Gynecologists (ACOG)[15] issued clinical guidelines for VBAC[15]and guidelines to reduce the occurrence of CD that are not medically indicated.[57] and national goals to reduce CD rate, the upward trend generally continues in many countries. In the US, a program (Healthy People 2010 initiative) developed by the

Department of Health and Human Services with a 10-year public health objective was unable to achieve its national goal of reducing CD to 15% of all births by the year 2010[58] among women who had not had a prior CD. In a revised program, a new goal has been set to reduce CD to 23.9% among low-risk women in a first pregnancy with a full-term singleton pregnancy in vertex presentation by 2020.[59]

2.2 Indications for having CD

A universally accepted set of indications for CD is not currently defined. Zhang et al[60] assessed indications for CD among 228,668 nulliparous women from 19 hospitals in the US. The investigators described the following three groups of indications for intrapartum CD (1) clinically indicated, which constitutes 74.9% of cesarean indication and comprises conditions such as non-reassuring fetal status (NRFS) or fetal distress, failure to progress, and cephalopelvic disproportion; (2) 'mixed categories' which includes previous uterine scar, breech or malpresentation, fetal anomalies, and fetal macrosomia, among others, and forms 23.0% of cesarean indication; and (3) 'truly elective' representing indications other than the first two and which accounts for 2.1% of cesarean indication[60]

Mylonas et al[24] also categorized indications for CD as absolute indications (including absolute disproportion, chorioamnionitis and placenta previa) and relative indications (including pathological cardiotocography, failure to progress in labor and previous CD). However, the Zhang[60] and Mylonas[24] categorization/classifications are not universally accepted. For example, the position of some researchers[61] is that conditions such as NRFS or fetal distress and labor dystocia are subjective and not clearly defined, although they are accepted by others to be

medical indications for CD.[60] These inconsistencies in the definition of indications for CD makes it difficult to compare rates across studies.[34, 61] It has been speculated that the variations in definitions and the subjectivity of CD indications may account for a significant part of the increasing trend in CDs.[62-63.]

Other investigators[64-65] also used hierarchical method to assign indications for CD. The authors created a hierarchy of CD indications (where history of previous CD was the first indication in the hierarchy, followed by breech presentation, labor dystocia, NRFS or fetal distress and other indications). Based on this hierarchy, all deliveries for which one of the indication was a previous CD were assigned to the indication class "previous CD". Women with indication of breech presentation, labor dystocia or fetal distress were assigned to the indication class "breech". Women with indication of labor dystocia and fetal distress were assigned to the indication class " labor dystocia".[64] The problem with this hierarchical classification of combining indications into one category is that the main clinical indication can be obscured by other coexisting indications included in the same category. It becomes difficult to know which specific indication contributed to the increasing rate of CD. Some authors[60-61,63] have called for consensus criteria to improve diagnosis of clinically accepted indications for cesarean such as failure to progress, cephalopelvic disproportion, NRFS or fetal distress. Some of the commonly described indications for CD are having a history of previous CD, labor dystocia or failure to progress, NRFS or fetal distress and fetal mal-presentation.

History of previous CD

History of previous CD is one of the main indications and contributors to the rise in repeat CDrate[31, 65-70] In a Canadian study[31] that examined CD rates in five provinces (British Columbia, Alberta, Ontario, Nova Scotia, and Newfoundland and Labrador) over a four-year period from 2007-2008 to 2010-2011, Kelly and colleagues[31] reported women with previous CD was the largest group that contributed to the overall CD rate. The CD rate for these women ranged from 76.1% in Alberta to 89.9%% in Newfoundland and Labrador in 2010 to 2011. In another Canadian study conducted by Rossignol et al[66] the authors reported 40% of CD being performed in Quebec, were among women with a previous CD. Liu and colleagues [65] have also reported elective repeat CD was the largest contributor to increase in repeat CD ranging from 37.7% to 40.3% during 1994/1995 to 2000/2001 in Canada.

Choudhury et al[67] examined changes in indication for cesarean over a seven-year period in Wales from 2001-2007. They found that previous CD was the commonest indication increasing from 20.1% in 2001 to 26.1% in 2006. In Australia, Stravou[44] and associates also found that previous CD accounted for 32.5% of all total CD rate between 1998 and 2008. In 2011, Kalogiannidis et al[68] also indicated 63.1% of the indications for elective CD were due to previous CD in Greece. Other studies[69-75] have also reported prior CD as one of the largest contributor to the rise in CS rate. However, most of these studies provided rates of CD indication without accounting for confounding factors such as maternal age and gestational age.[67, 69-70]

Labor dystocia

Labor dystocia is defined as abnormal progression in labor or failure of labor to progress or descend[76] The SOGC[76] guidelines regarding dystocia is that women should not be diagnosed as having labor dystocia until they have reached 3 to 4 cm dilation and are 80 to 90% effaced. Labor dystocia is one of the largest contributing indications for primary CD. In a Canadian study by Hanley et al,[43] the authors found labor dystocia to be the most common indication for primary CD, accounting for 30.0% of all CDs in their study that investigated all deliveries from 2004-2007 in British Columbia. Groen and colleagues[70] also found 30.3% of recorded indications for CD were for failure to progress or cephalopelvic disproportion. Others studies[60-61,63,77-81] reported similar findings of failure to progress or labor dystocia being the most common indication for CD. Boyle and associates[63] reported that 35.4% of indications for primary CD were for failure to progress or labor dystocia. This was supported by a study by Zhang et al[60] which reported that failure to progress accounted for 47.1% of CD indications in the US.

Non-reassuring fetal status (NRFS)

Another common indication for CD is NRFS or fetal distress. Electronic fetal monitoring (EFM) have been reported to be related to the increase likelihood of having a CD due to misinterpretation of fetal heart rate monitoring results.[82] Some researchers have also reported that CD performed for NFHS and labor dystocia are highly subjective and strongly influenced by obstetric practice.[33,61] A large multi-center study[60] found that 27.3% of indications for CD among women in the US were due to NRFS or fetal distress, whereas a recent study[70] that examined indications for CDs across 17 countries reported NRFS accounted for 14.5% of the total CD. Others studies[83-85] found fetal distress as the most common indication for having a CD.

In British Columbia, Hanley et al[43] reported NRFS was the second leading indication for cesarean birth accounting for 19.1% all CDs from 2004 to 2007. Barber and colleagues[62] also reported NRFS or fetal distress as one of the contributors to the rise in CD rate increasing from 40 to 66 per 1,000 live births from 2003 to 2006, respectively, but their study was limited to a single academic center.

Malpresentation

Unlike cesarean indications like labor dystocia and NRFS that are considered as subjective indications, fetal mal-presentation is one of the indication for having a CD that has objective definition or diagnosis.[61] Fetal malpresentation including breech, transverse, oblique, brow and face presentation are common indication for having a CD. Zhang and colleagues[60] indicated 17% of prelabor CD were for malpresentation relative to 7.5% of intrapartum CS. Penn et al[82] and Gao et al[86] each reported breech presentation or malpresentation accounted for 11.0% of all CD respectively. Breech presentation has also been reported by other studies[61,87] as one of the leading indication for having a CD.

Other reported indications for CD include maternal-fetal indications, hypertension, fetal macrosomia, and preeclampsia. Although preeclampsia has been reported as an indication for CS, some researchers including Tita and colleagues[61] contend that preeclampsia alone is not an appropriate indication for CD; given that 1 in 3 women with preeclampsia who deliver before 28 weeks usually deliver successfully by VD. However, the authors argue that preeclampsia associated with progressive acute renal failure is an appropriate indication for having a cesarean birth, although the situation is uncommon[61]

Maternal requested CD

Maternal requested CD or CD performed in the absence of maternal or fetal indication has been identified as the common non-medical indication for having a CD.[32, 88] Some investigators have reported reasons driving maternal requested CD as fear of pain at childbirth or vaginal birth, fear of subsequent pelvic floor collapse, as well as urinary and anal incontinence associated with VD[88-89] Other reasons for maternal requested CD are previous birth experience, need for choice, control and cultural practices. [88-89] A Cochrane review by Lavendar et al[88] reported that the rate of CD on maternal request could be as high as 48% in public system hospitals and 60% in private hospitals. However, there are concerns regarding the inconsistencies on the actual number of maternal requested CD due lack of consistency in terminology by different investigators for this indication.[32,88] Liu and colleagues[89] reported the most common indication for CD was maternal request accounting for 28.43% of total CD A population based study[90] in China that used data from 21 cities and counties in two provinces in southeast China, reported rates of CD on maternal request per 100 deliveries for three various years were 0.8%, 22%, and 20% for 1994, 2003 and 2006 respectively. Another Chinese study by Gao and colleagues[86] found maternal request was 9.07% of all total CD, but their analysis was based on data from a university teaching hospital in China.

Other studies have reported lower occurrences of maternal requested CD. Kottmel et al[91] found the rate of CD on maternal request in a tertiary care clinic in Switzerland more than doubled from 2002 to 2008. Even so, the rates were low at 2.1% to 5.1% respectively. In a multi-country study comprising 24 countries (and 373 health facilities, the authors reported 1.0 % of all deliveries were by CD without medical indications, either due to maternal request or in the

absence of other recorded indications.[21] A recent Canadian study[92] found lower rates of patient-initiated elective cesarean at 1.09% of all nulliparous cesarean births. A survey[93] study conducted in Canada on Maternal Experiences related to childbirth reported 8.1 percent of participants in the survey requested a CD from their health care practitioner before their labor or birth. Hanley et al[43] reported that less than 2% of primary CDs in British Columbia were performed based on maternal request. It should be noted that the survey study[93] was based on self-reported data whereas the British Columbia[43] study was based on hospital medical records. A Swedish study[94] that examined CD without medical indication using medical records from 1997 to 2006 reported 29.9% CD without recorded medical indication/maternal request during a 10-year period. Barber and associates[62] found that maternal request contributed to 8% of the increase in the overall CD rate. However, their study was confined to a major academic medical center likely to have a significantly different maternal population than the general population.

Other variations in rates of CD indications

There is also variation of cesarean indication over time and along with demographic factors such as age, race and obesity. Stjernholm and associates[95] compared the indications for CD in the early 1990s with indications during the mid-2000s. The authors defined elective or planned CD as a procedure performed due to an antepartum indication and at a time to suit the patient and their maternity team. They found that the main indications for an elective CD in 1992 were NRFS or fetal distress or uterine factors, accounting for 28.8% and 22.8% respectively. However, the leading indication for an elective cesarean in 2005 was psychosocial - related to maternal fear of childbirth or maternal request without any co-existing medical indication accounting for 38.5% of all deliveries.[95] Age-related differences in rates of CD have been

reported. A study[96] in the US found that previous uterine scar or repeat cesarean was the leading indication (36.9%) for CD in women aged 25.0 years or older, whereas failure to progress or cephalopelvic disproportion were common (37.0%) in women aged 20.0 years and (31.1%) for those aged 20.0 to 24.9 years. Another study[97] found that higher rates of CS indications of failure to progress and fetal distress among women older than age 40 years.

A multi-country study[70] reported that while previous uterine scar was a more common indication in women aged at least 20 years, uterine rupture was more common in women aged 30 years or older; and failure to progress or cephalopelvic disproportion were more prevalent in women younger than 25 years. A wide variability in the rate of indications for primary CD has been reported along with racial and ethnic differences in the US.[80,98] Specifically, Washington and colleagues[98] found African-American women, Latina women and Asian women were more likely to have failure to progress as indication for CD than White women, whereas white women were more likely to have mal-presentation as indication for CD than African-American, Latina, and Asian women.[98]

Furthermore, the relationship between body mass index (BMI) and cesarean indication of labor dystocia or failure to progress and suspected fetal distress has been reported. Bergholt and associates evaluated the effect of BMI on the incidence of CD and found suspected fetal distress and failure to progress increased significantly among women with BMI ≥35 than those with BMI <35.[99] Sheiner and colleagues[100] also examined the relationship between pregnancy outcome among obese women and incidence of CD and found a three-fold higher rate of failure to progress and one-fold higher rate of malpresentation in obese women than non-obese women.

Another study also reported obese women were 6 times more likely to have CD due to cesarean indication of cephalopelvic disproportion or failure to progress than non-obese women.[101]

One of the limitations of studies reporting on indications for CD is that there are no clear uniform definitions for common indications such as labor dystocia, fetal distress and failure to progress. The reasons for CD indications vary according to author and study population making it difficult to compare rates across studies.

2.3. Maternal and neonatal complications related to ERCD and TOLAC

Maternal outcomes

Many investigators[13,102-105] have reported on adverse maternal outcomes including maternal mortality and morbidity such as uterine rupture, hysterectomy, endometritis, thromboembolism and the need for blood transfusion following TOLAC or ERCD. A systematic review and meta-analysis published by Guise et al[13] and commissioned by the Agency for Healthcare Research and Quality in the US, provides an insight into maternal and neonatal outcomes related to TOLAC and ERCD. The authors reviewed 963 papers from 1996 to 2009 of which 203 were used for their analysis. They compared maternal mortality and morbidity in women with previous CD undergoing TOLAC compared with ERCD. The authors found that maternal mortality among women with a prior CD is rare, occurring in about 10.1 per 100,000 women who underwent CD. Combined estimates of 12 studies showed 67% reduction in maternal mortality (RR=0.33; 95% CI: 0.13-0.88) in the TOLAC group compared with the ERCD group. Rates of maternal mortality in the ERCD group was higher at 13.4 per 100,000 compared with 3.8 per 100,000 in the TOLAC group (p=0.027).[13]

A large Canadian study conducted by Wen et al[106] in 2004 was a major contributor to the findings of a systematic review and meta-analysis conducted by Guise et al[13] on maternal and neonatal outcomes related to TOLAC and ERCD. Wen and colleagues[106] compared maternal complications and death between women who had TOLAC and ERCD. Wen's study was the largest in the systematic review conducted by Guise and colleagues [13] comprising 308,755 Canadian women with a previous CD who underwent TOLAC compared with ERCD. In addition, it was the only study that evaluated the effect of hospital settings on outcomes of TOLAC and ERCD. Wen and investigators[106] stratified their analysis by type of institution and volume as follows: large volume obstetric unit (defined as hospitals with greater than 500 deliveries per year) and low volume obstetric unit (defined as hospitals with less than 500 deliveries per year). Maternal death is rare and many studies do not have enough sample size to assess such outcome. Due to adequate sample size of Wen et al study[106], they were able to provide information on in-hospital maternal deaths. After controlling for year of birth, hospital volume, and maternal age, it was reported that maternal death was lower in the TOLAC group than in the ERCD group (1.6 per 100,000 compared with 5.6 per 100,000, respectively). The investigators found that although large volume obstetric units had higher overall TOLAC rate than low volume obstetric units per year (43.3% versus 27.8%) maternal death per year did not increase in the large volume obstetric units. This may be due to the fact that the hospitals with greater than 500 births per year were better equipped to offer safe TOLAC to their patients. An important benefit of the study by Wen et al[106] is that the large sample size enabled the investigators to assess uncommon outcomes such as maternal death and evaluate their possible association with delivery settings.

Guise et al[13] examined uterine rupture related to TOLAC and ERCD in four studies with a total of 47,202 patients. Uterine rupture refers to a complete separation through the entire thickness of the uterine wall including the serosa. They reported a total of 154 uterine ruptures, of which 148 occurred in the TOLAC group and 6 in the ERCD. Based on four combined studies, the authors reported that the overall rate of uterine rupture for all women with prior cesarean was low (0.30%). However, women who experienced a TOLAC had a higher risk of uterine rupture (0.47%) compared with women who had ERCD (0.026%). The TOLAC group had a significantly 20-fold higher risk of uterine rupture (RR 20.74, 95% CI 9.77–44.02) in relation to the ERCD group[13] Kok and associates[103] found that the rate of uterine rupture was lower in the ERCD group relative to the TOLAC group (OR=0.1, 95%: 0.003–0.8) with occurrence of uterine rupture at 0.02% for one woman who had ERCD compared with 0.20% among 9 women who underwent TOLAC (p=0.02).

Another study found uterine rupture occurred in 124 women who had a TOLAC whereas no woman in the ERCD group had uterine rupture.[107]

Studsgaard[108] also found more than two-fold increased rate of uterine rupture in women who had a TOLAC birth compared with women who had ERCS in their study (OR=2.9, 95%: 1.1 –7.6) with occurrence of uterine rupture at 1.3% vs 0.0% for the TOLAC and ERCS respectively.[108] In a systematic review and meta-analysis study by Rossi et al,[104] the investigators compared the maternal morbidity in 24,349 women who had TOLAC with 18,621 women who had ERCD. They reported that the rate of composite maternal morbidity in the TOLAC group (6.7%) was not significantly different from the rate in the ERCD group (4.0%) with p-value of p=0.12. Specifically, the combine rate of uterine rupture and dehiscence was significantly higher in

women who had a TOLAC than ERCD at 1.3% versus 0.4% p=0.01) respectively. The authors further stratified their analysis by successful TOLAC and failed TOLAC. They found the rate of uterine rupture was lower in women with successful TOLAC compared with those who had failed TOLAC (0.2% vs. 4.4%, p<0.0001) respectively. [104] A limitation of this meta-analysis was the combination of uterine dehiscence and uterine rupture data. This is an important issue since there are clinical differences between these conditions. While uterine rupture represents a true symptomatic rupture with a complete separation of the entire thickness of the uterine wall including the serosa, uterine dehiscence represents an asymptomatic and incomplete separation of the uterine wall in which the uterine serosa is intact. [107] Further, uterine rupture is an uncommon condition which has serious fetal and maternal complications, whereas uterine dehiscence is a more common event, which does not usually represent serious risk for fetal or maternal outcomes.[107]

Uterine rupture has been reported to be related to induction of labor in women undergoing TOLAC. Harper et al[109] found that among women undergoing TOLAC, the risk of uterine rupture in women who had induced labor was comparable to the risk of uterine rupture in those who had spontaneous-onset labor (hazard ratio, 1.52; 95% CI, 0.97-2.36). However, Lydon-Rochelle and associates[110] reported increased risk of uterine rupture with induction of labor. The authors stated the rate of uterine rupture with induction of labor without prostaglandins was 7.7 per 1000, and induction with prostaglandins was 24.5 per 1000 compared with spontaneous onset of labor of 5.2 per 1000 women. This study has been criticized for not specifying the type of prostaglandin agent used in their study (whether prostaglandin was used alone or in combination with other agents)[111-112]

In a multicenter study by Grobman et al[113] the authors reported the risk of uterine rupture among women with no prior VD who had induction of labor with oxytocin and without prostaglandin was two-fold higher compared with women who had spontaneous onset of labor. However, the risk of uterine rupture in women with induction of labor with oxytocin and prostaglandin was not different from women who had spontaneous onset of labor. In another study by Landon et al[111] the authors did not find increased risk of uterine rupture when prostaglandin alone was used for induction of labor, but found more than three-fold increased risk when prostaglandin with or without oxytocin was used compared with deliveries by spontaneous onset of labor. The use of prostaglandin to induce labor in women who underwent TOLAC is still conflicting and still debatable [107,111-112,114]

Other maternal outcomes associated with TOLAC and ERCD include hysterectomy, endometritis, transfusion, and thromboembolism. Reported differences in rates of hysterectomy between the two delivery methods have not been consistent. Rossi et al[104] found no difference between the TOLAC and ERCS with regards to hysterectomy (0.2% vs 0.3%, p=0.32). However, the authors reported the occurrence of hysterectomy were more common in women who had a failed TOLAC requiring emergency CD at 0.5% than those who had a successful TOLAC at 0.1% (p=<0.0001) based on three studies. Furthermore, Guise and associates[13] found no apparent difference between women who underwent TOLAC and those who had ERCD with respect to hysterectomy after analyzing data from eight studies. However, Gilbert et al[102] reported a four-fold higher rate of hysterectomy in the ERCD group relative to the TOLAC group(p=0.02). This study was based on nineteen clinical centers in US, [102] whereas the Rossi[104] and Guise et al studies were based on systematic review across three and eight studies respectively[13]

With regards to endometritis, one study[102] reported lower incidence of endometritis 2.1% among women who had ERCD compared with 3.6 for those who had TOLAC ($p<0.001$). Related to blood transfusion, Guise and associates[13] synthesized nine studies and found that the need for transfusion was not significantly different in women who underwent TOLAC compared with those who had ERCD, with the incidence of transfusion reported as 0.9% and 1.2% ($p=0.25$) respectively. Rossi et al[104] also found no difference in women who underwent TOLAC and those who had ERCD group with regards to receipt of blood transfusion with rates of 1.7 and 1.2, ($p=0.86$) respectively based on five studies. Landon et al[111] reported the rates of thromboembolic disease were not significantly different from the ERCD versus the TOLAC groups, (OR 0.62, 95% CI: 0.24-1.62). The main benefit of this study,[111] was its standardized definitions for assessing outcomes. However, this study was limited to women giving birth in academic medical centers thereby reducing the results of its generalizability to other non-academic clinical centers.

Neonatal outcomes

Adverse neonatal outcomes associated with both ERCD and TOLAC includes neonatal intensive care unit admissions, transient tachypnea of the newborn, respiratory distress syndrome, neonatal infection, ventilation support and neonatal death. A population based study conducted in the Netherlands by Kok and colleagues[103] reported more than one-fold higher rate (OR=1.7, 95% CI: 1.0-2.8) of transient tachypnea of the new born in the ERCD group than in the TOLAC group. In contrast, Gilbert and co-authors[102] found a lower occurrence of respiratory distress syndrome, (1.0% versus 1.7%, OR=0.69, 95% CI: 0.41-0.89), and neonatal infection (3.1% versus 5.3%, OR=0.58, 95% CI: 0.46-0.72) in the ERCD group than in the TOLAC group. The authors found no statistically difference between the two groups with regards to transient tachypnea of the new

born (3.0% versus 2.7%, *p*=0.41, OR=1.12, 95% CI: 0.86-1.46).[102] In analysis of pooled estimates of three studies that evaluated transient tachypnea of the new born and the need for bag-and-mask ventilation, Guise and co-authors[13] found no significant difference in the incidence of transient tachypnea of the new born in the TOLAC and the ERCD groups but reported a higher proportion of neonates delivered by mothers who underwent TOLAC received bag-and-mask ventilation compared with neonates delivered by mothers in the ERCD group. Kamath et al[115] reported the neonates born by mothers who had intended CD were more likely to have oxygen supplementation for delivery room resuscitation than neonates born by mothers who had intended VBAC with rates of (41.5% compared with 23.2%, p<0.001).

With regards to neonatal intensive care unit admission, Kamath et al[115] found babies born by mothers who had intended CD or ERCD had higher neonatal intensive care unit admission rates compared with those born by mothers who had intended VBAC or TOLAC (9.3% vs 4.9%, p=0.025). However, Loebel[116] et al found no significant difference with regards to neonatal intensive care unit admission between the babies born by mothers who underwent TOLAC and those who had ERCD (4.2% vs 5.6%, p=0.240). Likewise, Hook et al[117] found no significant difference with regards to neonatal intensive care unit admission between neonates of mothers who had TOLAC and ERCD (3% vs 2%, p=>.05). However, the authors found neonates born by mothers with a failed VBAC requiring CS were significantly more likely to be admitted to neonatal intensive care unit compared with those born by mothers with successful VBAC (7% vs 2%, p=<0.007). Comparison of neonatal intensive care unit admission across studies is challenging, since not all studies define the criteria and hospital level of care for admission to the neonatal intensive care unit.

In a recent multi-center prospective study by Crowther et al,[118] the investigators compared neonatal complications including perinatal death among women undergoing a planned VBAC to women undergoing planned ERCD in 14 Australian maternity hospitals. The authors reported that the planned ERCD group had a 61% lower risk of perinatal mortality compared with planned VBAC group. Smith et al[119] reported higher rate of perinatal death among infants born to mothers who underwent TOLAC compared to those who underwent ERCD (12.9 versus 1.1 per 10,000 deliveries, p=0.001) respectively. This was consistent with results of a pooled data analysis of five studies reported by Guise and colleagues[13] showing that the risk of neonatal mortality was 2 times higher among infants born to mothers who underwent TOLAC compared to those who underwent ERCD (RR=2.06; 95% CI: 1.35-3.13) [13]

In a meta-analysis of 9 studies including more than 33,000 women, Mozurkewich and investigators[120] reported an increase in fetal or neonatal deaths among infants who underwent a TOLAC, compared to those who underwent ERCD (OR=1.71; 95% CI: 1.28-2.28). A U.S. population-based study of neonatal and infant mortality by mode of delivery among women with "no indicated risk," showed neonatal mortality was increased more than two-fold after birth by CD. In contrast, Gilbert and associates[102] found no statistically difference between the ERCD and TOLAC groups with regards to neonatal death (0.3% versus 0.5%, (OR=0.50, 95% CI: 0.05-5.51). In these studies[120] and others, [13, 102, 118-119] the reported rates of neonatal death after ERCD are low. One main drawback of these studies is the variation with regards to definitions of maternal and neonatal outcomes which hinders comparison of data across the studies.

2.4 Economic evaluation of TOLAC and ERCD

Economic evaluation is a comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes, effects). Economic evaluation can be used to address the pertinent effectiveness and costs between a TOLAC and ERCD delivery strategy. [121] However, only a few economic evaluation studies have compared the cost effectiveness of TOLAC and ERCD.

Gilbert et al[40] performed a cost effectiveness analysis using a decision analytical model to determine whether TOLAC or ERCD is the most cost effective strategy in a hypothetical cohort of 100,000 women with no contraindication to a TOLAC. The primary outcome of this study was cost effectiveness, measured as the marginal cost per quality adjusted life years (QALYs) gained. The authors concluded that the TOLAC strategy dominated the ERCD strategy at baseline with US$ 138.6 million saved and 1703 QALYs gained per 100,000 women.[40]

Another study[122] that evaluated cost of maternal hospitalization associated with TOLAC and ERCD pointed out that TOLAC was associated with modest reductions of cost for maternal hospitalization than ERCD. The cost of maternal hospitalization for ERCD was US$5,512.00, TOLAC was U$5,166.00, Successful TOLAC was $4,175.00 and failed TOLAC was $5,759.00. The authors reported TOLAC was associated with modest reductions of cost for maternal hospitalizations. However, the authors did not perform probabilistic analysis which could have taken into account uncertainty regarding the hospital costs related to TOLAC and ERCD delivery strategies. [122]

Wymer et al.[37] conducted a cost effectiveness analyses with the aim to estimate costs and outcomes of subsequent TOLAC compared with ERCD from the second the sixth pregnancy. The investigators found TOLAC to be less costly and more effective with subsequent deliveries. Specifically, there was a decreasing incremental cost of $US4700.00 and increasing incremental effectiveness of 0.073 QALYs. The cost perspective of this study was limited to the health care payer system, which considers only direct medical cost estimates. In another study that assessed the future health and economic consequences of TOLAC and ERCD,

Gilbert and associates[123] indicated the TOLAC delivery option saved $US164.2 million and 500 QALYs gained per 100,000 women. The cost of maternal and neonatal outcomes of this study was based on societal perspective, where all health outcomes and economic costs irrespective of who paid the costs were included in the analysis. Fawsitt et al.[39] conducted a cost effectiveness analysis to examine the costs and short-term maternal outcomes associated with a TOLAC and an ERCD for a hypothetical cohort of low-risk women in Ireland, using Irish health care system estimates. The outcome measure was QALYs with a six-week time horizon. The investigators found TOLAC to be the dominant strategy with cost of an ERCD at €4,038.40 with 0.70 QALYs whereas the cost of a TOLAC was €1,833.56 with 0.84 QALYs. However, no neonatal outcomes were included in their analysis.

Grobman and colleagues[124] used a decision tree to analyze the cost effectiveness of a hypothetical cohort of 100,000 women with one prior low transverse CD. The outcome measure of this study was the overall cost of maternal and neonatal morbidity and mortality. They

concluded that TOLAC was more cost effective than ERCD. However, the authors did not include QALYs in their decision analysis.

Chung et al[38] conducted a cost effectiveness analysis with the aim of determining which mode of delivery (ERCD or TOLAC) is cost effective. Their outcome measure was the overall cost of maternal and neonatal morbidity and mortality based on a societal perspective. The authors reported US$112,023 per QALY for the ERCD which was above the threshold of $50,000 per quality adjusted life-years used to define cost-effectiveness in their analysis. They stated that TOLAC was cost effective if the success rate was between 0.74 and 0.76. However, the overall total QALYs was not stated.

Summary of literature review

Trends and variation in rate of CD

In summary, the afore-mentioned studies have shown CD rates are high and increasing with major variations across countries[4] among regions in the same country as well as hospitals.[6, 28,43,47-48] rates ranged from as low as 15.2% to as high as 50.4% from 2000 to 2013 across OECD countries. [4] It was observed that the Netherlands and the Nordic countries (Iceland, Finland, Sweden and Norway) had the lowest CD rates relative to the other OECD countries. In Canada, there were variation of CD rates in the provincial level[6] In Ontario, CD rates ranged from 23.4% in South West LHIN to 32.3% in Central West LHIN in 2011-2012[42] and in British Columbia, rates ranged from 14.7% to 27.6% across sixteen Health Services Delivery Areas.[43] In US, there was also vast difference of CD ranging from 7.1% to 69.9% in CD rates across hospitals.[28]

The main reason for variation in CD rates across regions and hospitals is due to differences in practice patterns across hospitals including individual clinician approaches to labor and delivery management. Other reasons include lack of resources required to respond to medical emergencies associated with complications of labor in smaller institutions in the same way as a tertiary care institution would respond. Therefore, smaller institutions have the likelihood of recommending a CD with a lower medical indication than in a larger institution. Even though there is no consensus about the expected CD rate for each country.[53-54] There is an agreement that national CD values <5% are extremely low and underuse, particularly in sub-Saharan Africa and poor countries where there is lack of access to the surgical procedure even when it is needed. There is also an agreement that national CD values >15% are excessive and overuse, particularly in developed countries. Increasing CD rate does not imply improvement in maternal and perinatal outcome.[53-54] There are deliberations regarding ways to safely reduce the increased rate of CS births. Professional associations of obstetrics such as SOGC and ACOG all support normal birth in as a way of reducing CD. Therefore, evaluation the level of variation of CD rates, reasons for such variation will provide opportunities for identifying ways to reduce the overall rising CD rates.

Indications for having cesarean delivery

This review revealed that the four main indications for CD were having history of previous CD, labor dystocia, NRFS or fetal distress and malpresentation. The common indications for CD in countries like Canada, US and Belgium were having a history of previous CD, labor dystocia, breech presentation and fetal distress. Some previous studies that examined indications for CD did not separate single indications from multiple indications. Combining all indications into one

category can obscure distinctions between which indications are contributing to increasing CD rate. Also, most studies reporting on indications for CD only provided a snapshot of rate of indication without any controlling for confounding variables like maternal age, gestational age or BMI. There were also inconsistencies in the definition of various indications for CS which makes it difficult to compare rates across studies. Some investigators have called for analysis that distinguishes between CD based solely on maternal request or as a separate entity from other indications for direct comparison across studies.

Maternal and neonatal complications related to elective repeat cesarean delivery (ERCD) and trial of labor after cesarean birth (TOLAC)

The review also showed maternal and neonatal complications associated with delivery by ERCD and TOLAC. In general, while ERCD was associated with a higher risk of maternal mortality than TOLAC, it was associated with a lower risk of uterine rupture compared with TOLAC. However, uterine rupture was more common among women with a failed or unsuccessful TOLAC requiring an emergency CD than those with successful TOLAC. The rates of blood transfusion and thromboembolic disease were not different between ERCD and TOLAC. Generally, the combined risks of maternal and perinatal morbidity and mortality were small and similar in magnitude for both ERCD and TOLAC across studies. Yet, there were reported differences in rates of hysterectomy, newborn respiratory support and transient tachypnea of the new born between the two delivery methods and the clinical significance of the differences in incidence is still not clear. There were considerable differences among the studies which hampered comparison of data across the studies and patients stemming from lack of standardized definitions of maternal and neonatal outcomes. Moreover, we found that newborn outcomes such as the need for antibiotic due to suspected neonatal sepsis and birth injury following delivery

associated with delivery have not been explored among women with a previous CD who underwent ERCD and TOLAC groups.

Economic evaluation of TOLAC and ERCD

There were only a few economic evaluation studies. The review shows that the TOLAC strategy dominated the ERCD strategy at baseline because it was less costly and more effective. The TOLAC delivery option was associated with modest reductions of cost for maternal hospitalizations than the ERCD option in some of the studies. Most of these studies considered cost from a health care perspective, which is the common perspective of interest to decision makers. However, most of the studies were limited by the inability to perform probabilistic analysis which could have taken into account uncertainty regarding the hospital costs related to TOLAC and ERCD strategies. There was no economic evaluation of TOLAC and ERCD from a Canadian perspective.

2.5 Rationale and significance of the study

The overarching aim of this study was to identify ways to reduce unnecessary CD. In 2012/2013, CD rate among women with history of previous CD ranged from 72.1% in Manitoba to 91.5%% in Newfoundland and Labrador. For the same period, the Canadian Institute of Health Information[3] reported that childbirth was the most common with an average length of stay of 2.4 days. In addition, the most common reason for inpatient surgical hospitalization was CD accounting for 100,686 (7.2%) of all inpatient surgeries with average length of stay of 3.3 day. CD performed routinely without medical indication have major economic implications on the health care system. There is no study in Canada that has examined single and two co-occurring indications for CD among mothers with and without medical cesarean indications and its impact

on perinatal outcomes. Using a novel way of identifying single and co-occurring indications contributing to the increasing CD rate is an important step towards the goal of identifying potential areas for reduction of unnecessary cesarean birth. Adverse birth outcomes such as respiratory morbidity, low birth weight, newborn transient tachypnea, neonatal infection, neonatal intensive care unit admission, stillbirth and neonatal death related to mode of delivery have been examined by previous studies. However, newborn use of antibiotic after delivery due to neonatal sepsis and birth injury after birth associated with mode of delivery are seldom examined in non-anomalous neonates. This study sought to address these issues using statistical techniques such as propensity score matching on baseline characteristics which will allow for a valid estimation of adverse birth outcomes in low risk woman with one previous VD who underwent elective primary cesarean delivery (EPCD) versus trial of labor after vaginal birth (TOLAV) and those with one previous CD who underwent ERCD versus TOLAC.

Furthermore, while increasing CD rates have an impact on the health care system, majority of the previous studies did not perform cost effectiveness analysis comparing a TOLAC and ERCD delivery option, and the few that did were conducted in the US or Ireland raising a question of generalizability of their findings to the Canadian context. This study addresses the paucity of information on the cost effectiveness of TOLAC and ERCD among women in Canada with low risk deliveries, and provides a Canadian perspective on the cost implications of the increasing number of CD being performed.

2.6. Research study objectives

Three specific objectives have been defined for this research as follows:

Objective 1:

To assess indications for CD and their associations with neonatal outcomes;

Objective 2:

a. To compare adverse birth outcomes among low risk women who underwent EPCD and TOLAV at term in cephalic presentation in the second pregnancy;

b. To compare adverse birth outcomes among low risk women who underwent ERCD and TOLAC at term in cephalic presentation in the second pregnancy; and

Objective 3:

To assess the short term cost effectiveness of having a TOLAC and ERCD among women with low risk deliveries.

The respective main research questions for each of the defined objectives are:

Objective 1

Research Question One:

What are the leading single and co-occurring indications for having CD?

Research Question Two:

What are the neonatal outcomes associated with CD due to "soft" indications such as ERCD, labor dystocia, NRFS, suspected LGA baby, CDMR and paired ERCD and CDMR compared with CD due to "hard" indications "(combination of breech presentation, placental previa, placenta and cord prolapse, etc.)?

Objective 2

a. Research Question Three:

What are the adverse birth outcomes associated with EPCD compared with TOLAV in low risk women with term cephalic presentation in the second pregnancy?

a. Research Question Four:

What are the adverse birth outcomes associated with a subgroup of low risk women who had a failed TOLAV compared with those who had a successful TOLAV?

b. Research Question Five:

What are the adverse birth outcomes associated with ERCD compared with TOLAC in low risk women with term cephalic presentation in the second pregnancy?

b. Research Question Six:

What are the adverse birth outcomes associated with a subgroup of low risk women who had a failed TOLAC compared with those who had a successful TOLAC?

Objective 3

Question Seven:

What is cost effectiveness of having a TOLAC in relation to ERCD among women with low risk deliveries?

Chapter 3:

Assessment of indications for cesarean delivery and their associations with neonatal outcomes (Objective 1)

3.1 Introduction

At present, a woman with a previous cesarean delivery (CD) has the likelihood of delivering by CD in the subsequent pregnancy without any clear medical indication for the procedure.[125] There is growing concern regarding CD with no clear obstetric indication, since it has impact on the health of mothers and their babies and has implication on the health care system.[21,28] Studies that assessed CD indication revealed the main indications responsible for CD were having a previous cesarean, labor dystocia (referred to as failure to progress), breech presentation and fetal distress.[61-63] Some investigators have also reported that provider-discretion indications emanating from considerations such as non-reassuring fetal heart tracings, labor arrest disorders and suspected macrosomia, account for most of the variations in the increases in primary CD rates among hospitals and providers.[33,62-63]

A recent Cochrane review by Lavender et al[88] examined planned CD for non-medical reasons, the authors found no randomized controlled trials to guide practice recommendations relating to elective CD and neonatal and maternal outcomes. Previous observational studies that assessed neonatal outcomes such as birthweight and respiratory morbidity associated with indications for CD focused mainly on comparison between cesarean delivery on maternal request (CDMR) or elective repeat cesarean delivery (ERCD) or planned CD versus planned vaginal delivery (VD).[32,126-127] Comparing neonatal outcomes between mothers who had CD for elective indications such as ERCD and CDMR or subjective indications such as labor dystocia and non-reassurring-feta-status (NRFS) and objective indications such as breech presentation, placental

previa or cord prolapse will help to appreciate the impact of indications for CD on neonatal outcomes. This will in turn provide information for counseling mothers regarding their delivery option for CD, particularly in the absence of a clear medical or obstetric indication.

Further, studies regarding single and two co-occurring indications for CD among mothers with and without medical or obstetric cesarean indications in Canada are limited. Understanding the contribution of single and co-occurring indications for CD to the increasing CD rate and its impact on neonatal outcomes is an important step towards the goal of identifying potential areas for reduction of unnecessary cesarean birth. The aim of this chapter was to (1) assess the leading single and co-occurring indications for having CD and; (2) compare rates of neonatal outcomes of newborn Apgar score <4 at 5 minutes, newborn Apgar score <7 at 5 minutes and neonatal death among women who had CD due to "soft" indications (ERCD, labor dystocia, NRFS, suspected large-for-gestational-age (LGA) baby, CDMR and co-occurring indication of paired ERCD and CDMR) versus CD due to "hard" indications (combination of breech presentation, placental previa, placenta and cord prolapse, etc).

3.2 Methods

3.2.1 Design and data source

The design applied for objective one was a retrospective study. Data for the study were from 2006 to 2013, obtained from the Better Outcomes Registry & Network Ontario's (BORN). This population-based birth prescribed registry in Ontario, Canada (www.bornontario.ca) includes more than 99% of all births in the province of Ontario. The database is administered under the auspices of the Children's Hospital of Eastern Ontario (CHEO) and includes 100% of all hospital

births in the province. The BORN data are abstracted from medical records, clinical forms, and through patient interviews from women admitted to hospital for delivery. Data are then entered into the database after birth either through a secured website by hospital staff, or uploaded directly from hospitals that have electronic record capability. Accuracy and validity of the data is ensured through ongoing quality checks. Staff who collect and enter data into the system undergo formal training sessions to ensure that a high level of data quality is maintained. The BORN database contains information on maternal demographic characteristics, type of delivery, indications for having CD and birth outcomes.

3.2.2 Study population

The study population included women who underwent overall CD for singleton term births with gestational age at 37-41 weeks with infant birth weight ≥500 grams in the province of Ontario hospitals in the period 2006 to 2013. CDs with no documented indication were excluded. Births with missing mode of delivery and birthweight were also excluded. The study women consisted of two groups (1) those with a recorded medical or obstetric indication for CD; and (2) those with a recorded non-medical or obstetric indication for CD (i.e. underwent CD solely on maternal request). A subgroup of women who underwent primary CD was also analyzed. Overall CD was defined as the total CD performed for a singleton pregnancy including primary CD among women who have not had a previous CD before and repeat CD among women who have had a previous cesarean delivery before. Primary CD was defined as the first or primary CD performed for a singleton pregnancy among women who have not had a previous CD before.

3.2.3 Outcome and exposure variables

Outcome variables

The outcome or dependent variables were Apgar score <4 at 5 minutes, Apgar score <7 at 5 minutes after birth and neonatal death. The Apgar scores were measured 5 minutes after birth on a 0-10 scale to assess the clinical status of the newborn. A 0–3 Apgar score (also called <4 score) at 5 minutes indicates that immediate life-saving measures are required for the neonate. A 0–6 Apgar score (also called <7 score) at 5 minutes is assigned to neonates who requires immediate life saving measures and those who require immediate intervention. A 7–10 Apgar score (also called >7) at 5 minutes is the normal and indicates that the newborn is in good health. Neonatal death was defined as death between 20 weeks of gestation and 28 days of life. Apgar score <4 at 5 minutes was dichotomized as 'Yes' for score of 0–3 versus 'No' for scores of 4–10. For Agar score <7 at 5 minutes, 'Yes' was for a score of 0–7 (yes) and 'No' was for a score 7–10. Neonatal death was dichotomized as 'Yes' for death versus ''No' for alive.

Exposure variables and groups

The exposure variables are indications for having CD. In order to ascertain which indication contributed substantially to the total rate of CD, the indications were reported as documented in the hospital medical records. These indications include those with a recorded medical or obstetric indication for CD such as labor dystocia or non-progressive labor, history of previous CD which leading to ERCD. Additional indications include breech presentation, non-reassuring fetal status (NRFS) or fetal distress, large for gestational age (LGA) baby, failed forceps or vacuum, cord prolapse, intrauterine growth restriction (IUGR), other maternal health problem (OMHP),

placenta previa, placental abruption, preeclampsia, fetal anomaly. Other indications include non-medical indication for CD such as CDMR. (Table 1).

The exposure group were women who had CD due to "soft" indications such as ERCD, labor dystocia, NRFS, CDMR and co-occurring indication of paired ERCD and CDMR. The unexposed group were women who had CD due to "hard" indications. (Table 3). "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby. These indications are reported to be adjustable and have lower thresholds for performing CD. They can also be can be desirable target for efforts to reduced unnecessary CDs. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation which is abnormal fetal presentation where the fetus enters the pelvis with buttocks or feet first rather than the normal head first fetal presentation. Additional "hard" indications include maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group. All other indications that did meet the criteria for "soft" or "hard" indications were classified as other indications, Table 3.

Covariates

Covariates included in this study are maternal age at delivery (grouped as <20 years, 20 – 34 years, and ≥35 years);

infant gender (male, female); parity (nulliparous, multiparous) for the overall and primary CD study cohort. Other characteristics include neighborhood education in quartiles with 1 as the lowest quartiles and 4 the highest. Data on neighborhood-level education were obtained by linking the perinatal database with Statistics Canada's Postal Code Conversion File Plus (PCCF+), which contains information from the 2006 Canadian census.

Power

All available data was used for analysis for objective 1. For power calculation, for objective 1, with an alpha of 0.05, two-sided test, with given sample size, there was sufficient power (> 85%) to detect a difference of 20% between the two comparison groups ("soft" versus "hard" indications) for most of the outcomes assessed.

3.2.4 Statistical methods

Analyses began by first selecting all reported medical and non-medical indications for overall CD. Considering the possibility of more than one indication in a patient, the indications were grouped into single indication, two or more indications. Women with only one indication for having overall CD and none of maternal or fetal medical or obstetric indications were classified as having a single indication (e.g. breech presentation, labor dystocia, etc.). Women with only two indications for overall CD and none of the maternal or fetal medical or obstetric indications were classified as having two co-occurring overall CD indications (e.g. labor dystocia and NRFS

pair; labor dystocia and breech pair, etc.). Women with only three indications for overall CD and no other maternal or fetal medical or obstetric indications were classified as having three overall CD indications (e.g. labor dystocia, breech, and failed forceps triad or breech, NRFS and previa triad). Women with more than three indications were classified as other multiple indications. (Appendix B).

The next step was to assess the proportion and frequency of each CD indication and its contribution to the overall CD rate. The baseline characteristics and the occurrences of neonatal outcomes were examined between each of the exposure group of mothers who had "soft" indications for overall CD such as ERCD, labor dystocia, NRFS, suspected LGA baby, CDMR, paired ERCD and CDMR and those with other indications compared with mothers who had overall CD due to "hard" indications (breech presentationy, LGA, failed forceps, cord prolapse, IUGR/SGA, OMPH, placenta previa, placental abruption, preeclampsia and fetal anomaly). All categorical variables were examined using chi squared test and Fisher exact test where necessary.

Since the dependent outcome variables of newborn Apgar score <4 at 5 minutes, newborn Apgar score <7 at 5 minutes and neonatal death were each categorized as dichotomous variables, unconditional logistic regression models were developed to compare rates of newborn Apgar score <4, <7 at 5 minutes and neonatal death among the exposure group of women who had "soft" indications for overall CD versus those who had "hard" indications for overall CD (reference group). Subgroup analyses were performed by restricting the analysis to primary CD to assess any difference on the effect of Apgar scores <4 and <7 at 5 minutes as well as neonatal death among the mothers who underwent primary CD relative to overall CD performed.

Separate regression models were fitted for analysis that compared Apgar scores <4, <7 at 5 minutes and neonatal death among each of the group of women while adjusting for confounding variables. Before developing the regression models, we initially assessed potentially confounding covariates. We defined confounders as covariates that were statistically associated with the exposure variable and at least one of the outcome variable at significance level of $p<0.05$. Chi square test was used to evaluate the association between each potential confounder covariate and each of our exposure variables (ERCD, labor dystocia, NRFS, suspected LGA baby, CDMR, paired ERCD and CDMR and those with other indications versus those who had overall CD due to "hard" indications group (reference).). Covariates with significance level of <0.05 were considered as confounders. We also conducted bivariate analysis to assess the association between potential confounding variables and our outcome variables by regressing each of the outcome variables separately on each potential confounder. Covariates with significance level of <0.05 identified from the wald test p-values in the bivariate analysis were considered as confounders. Maternal age and gestational age at delivery, based on their clinical importance were included in the model as confounders irrespective of their significance level. All other variables that met the inclusion criteria for confounding at a significance level of <0.05 were included in the unconditional logistic regression models. The variables adjusted in the logistic regression models were maternal age at delivery, education, parity, infant gender and gestational age at delivery.

We then examined effect modifiers in the model. We included interaction terms (the multiplicative effect of two variables) in the logistic regression model to assess its contribution to the model. Interactions of parity, maternal age and gestational age at delivery were assessed by

each of the exposure group. All the interaction terms with a significance level of <0.05 were included in the final unconditional logistic regression models. The fit of the regression models with and without interaction terms were evaluated until a parsimonious model was selected. Crude, adjusted (OR) and 95% confidence interval (CI) were reported for each exposure group and each outcome. All tests were reported based on statistical significance, which was concluded if $p<0.05$. Analyses were carried out using Statistical Analysis System (SAS) software version 9.4 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Ottawa Hospital Research Institute and Children's Hospital of Eastern Ontario Research Ethics Boards.

3.3 Results (objective 1)

A total of 199,294 singleton term births with single, two and three co-occurring and more than three indications for having overall CD were included in this analysis. Of this sample, 160,108 women had single CD indications and 39,186 had two co-occurring, three or more CD indications. Among the women with single CD indication, 155,397 had medical or obstetric indication for CD and 4,711 had non-medical indication for CD. Among the women with two or more indications, 24,221 had two co-occurring and 14,965 had three or more cesarean indications. (Figure 5). The overall CD rate was 28.8% of overall singleton births.

3.3.1 Assessment of single, two and more indications contributing to overall and primary CD

Table 1 shows the rate of single indications for overall CD. The most common indication for overall CD was ERCD, which accounted for 34.3% of all CDs: followed by labor dystocia (18.1%), breech (10.6%), and NRFS (9.4%). The other indications generally accounted for small proportions of overall CDs, with the most notable being OMHP (2.6%), CDMR (2.4%) and

placenta previa (1.0%). Each of the remaining indications accounted for less than 1% of the overall CDs performed, (Table 1).

Table 2 shows the rate of single indications for primary CD. The most common indication for primary CD was labor dystocia, which represented 31.9% of all primary CDs: followed by breech (18.5%), and NRFS (16.6%). The other indications generally accounted for small proportions of all primary CDs. This include OMHP (4.4%), CDMR (3.0%) and placenta previa (1.8%). Each of the remaining indications accounted for less than 1.2% of all primary CDs performed, (Table 2).

The rates of co-occurring indications for overall CD are also shown in Table 1. Analysis showed that labor dystocia and NRFS were the most common pair indications for overall CD accounting for 5.6% of overall CDs (Table 1). CD for NRFS were included in most of the co-occurring indications compared with all other co-occurring indications, (Appendix C). Each of the other pair indications are in Appendix C. Labor dystocia and NRFS and OMHP were the most commonly three indications for overall CD. Even so, it accounted for 0.2% of overall CDs performed. All other three and more indications are in Appendix C.

Table 2 also shows the rates of co-occurring indications for primary CD. The most common co-occurring indication was the paired labor dystocia and NRFS accounting for 10.1% of all primary CD. Each of the other pair indications are in Appendix D.

3.3.2 Maternal characteristics by CD indications

Details of maternal characteristics are presented in Tables 4 and 5. Mothers who had overall CD due to "soft" indications of ERCD, labor dystocia, NRFS, suspected LGA baby, CDMR and co-occurring indication of ERCD and CDMR pair as well as those with other indications were each compared with mothers who had CD due to "hard" indications in terms of their characteristics. Generally, the mothers who had ERCD were more likely to be older, multiparous and more likely to have a male infant than mothers who had overall CD for "hard" indications. The ERCD group were also more likely to deliver at 37-38 weeks' gestation, but less likely to have a low birth weight infant compared with the overall CD for "hard" indications group (p=<0.0001), Table 4, Column B. The CD performed due to labor dystocia and NRFS groups were each more likely to be younger, nulliparous and delivered at 39-41 weeks' gestation compared with the CD performed due to "hard" indication group, (p=<0.0001). Table 4, Column C and D respectively. Mothers who had CD because of suspected LGA baby had similar rates of maternal age and education like the mothers who had CD because of "hard" indications (p=0.1515) and (p=0.3501) respectively. The CD for suspected LGA baby group were more likely to be nulliparous and less likely to deliver at 37-38 weeks' gestation and none of their babies had low birth weight compared with the CD for "hard" indication group (p=<0.0001), Table 4, Column E. The suspected LGA baby group had no baby with low birth weight because the reason for having CD for this indication was due to expected big babies with high birth weight.

Also, the CDMR group tended to be older, multiparous and highly educated than mothers who had CD for "hard" indication group (p=<0.0001). The CDMR group were also more likely to deliver at 37-38 weeks' gestation (p=0.0038), but less likely to have a low birth weight baby

(p=<0.0001), Table 4, Column F. Mothers with co-occurring indication of the paired ERCD and CDMR were more likely to deliver at 37-38 weeks' gestation (p=<0.0006) than the mothers who had CD due to "hard" indications. The paired ERCD and CDMR group tended to be multiparous and had lower education than the CD due to "hard" indications group (p=<0.0001), Table 4, Column G. Mothers who had CD performed due to other indications and the mothers who had CD performed due to "hard" indications had comparable rates with regards to maternal age (p=0.0785) and education (p=0.1346). The CD for other indications group were more likely to be multiparous and had delivery at 37-38 weeks' gestation than the CD for "hard" indications group, (p=<0.0001), Table 4, Column H.

Table 5 presents details of maternal characteristics for the mothers who underwent primary CD. The mothers who had CD for labor dystocia and those who had CD for NRFS were more likely to be younger, nulliparous and delivered at 39-41 weeks' gestation compared with the mothers who had CD due to "hard" indication group (p=<0.0001), Table 5, Column B and C respectively. The CDMR group were older, multiparous and highly educated but were less likely to have a low birth weight infant compared with the CD due to "hard" indications group (p=<0.0001), Table 5, Column D. For the suspected LGA group, they tended to be older, but less likely to deliver at 37-38 weeks' gestation than the CD due to "hard" indications group (p=<0.005) Table 5, Column E. The suspected LGA group and the CD due to "hard" indications group had comparable rates with regards education (p=0.5147), but the suspected LGA group were more likely to be older (p=<0.0031) and delivered at 39-41 weeks' gestation (p=<0.0001) compared with the CD for "hard" indications group. Maternal education was comparable between mothers who had CD performed due to other indications and those who had CD performed due to "hard"

indications (p=0.3550). The CD for other indications group were more likely to be nulliparous and had delivery at 39-41 weeks' gestation than the CD for "hard" indication group, (p=<0.05), Table 4, Column F.

3.3.3 Analysis of CD indications by year of birth

Figure 6 shows the trend of overall CD indications by year of birth among mothers with CD for "soft" indications and mothers with CD for "hard" indications. ERCD increased from 31.8% in 2006 to 35.7% in 2013. Additionally, CD for NRFS increased overtime from 8.9% in 2006 to 11.0% in 2013. CD performed for other indications increased slightly overtime from 13.6% in 2006 to 14.5% in 2013. CD performed because of labor dystocia decreased overtime during the study period from 19.5% in 2006 to 16.7% in 2013. CD for "hard" indications decreased from 21.9% in 2006 to 19.4% in 2013. The trend of CDMR was inconsistent over the years. The rate decreased from 2.2% to 1.9% from 2006 to 2007, then increased to 2.7% in 2010 and finally decreased to 1.8% in 2013. For CD due to suspected LGA baby, the rate increased slightly from 0.5% in 2006 to 0.7% in 2013. The trend of CD for co-occurring indication of ERCD and CDMR pair was 1.7 in 2006, but decreased to 0.0% since there was only one woman with this indication in 2010 and no woman with this indication in 2011. In 2012, the rate of the paired ERCD and CDMR was 0.6% but dropped to 0.5% in 2013. The lower rate of the paired ERCD and CDMR indication overtime may be as a result of the low occurrence of this indication in general. Figure 6.

Figure 7 shows distribution of the indications by year of birth for the women who underwent primary CD. There was an increase overtime for CD for NRFS from 15.0% in 2006 to 19.6% in 2013 whereas CD for other indications increased from 14.9% in 2006 to 16.6% in 2013. CD

performed because suspected LGA baby increased overtime from 0.8% in 2006 to 1.2% in 2013. On the other hand, there was a decrease of CD for "hard" indications overtime from 33.3% in 2006 to 30.6% in 2013 whereas CD for labor dystocia decreased overtime from 33.0% to 29.4 in 2013. CDMR also decreased overtime from 3.1% in 2006 to 2.6% in 2013. Figure 7.

3.3.4 Comparison of rates of newborn Apgar score <4 at 5 minutes among women who had CD due to "soft" indications versus CD due to "hard "indications (reference group).

Tables 6 and 7 present infant outcome of Apgar score <4 at 5 minutes among the study groups who underwent overall CD and primary CD due to "soft" indications versus "hard" indications. The results show that babies born to mothers who had CD due to "soft" indications such as NRFS were significantly more likely to have higher rates of Apgar score <4 at 5 minutes compared with those born to mothers who had CD due to "hard" indications, (OR=2.46, 95% CI: 1.87-3.25). On the other hand, the babies of mothers who had other "soft" indications such as ERCD, labor dystocia and CDMR had lower rates of Apgar score <4 at 5 minutes. In detail, the rates for ERCD was (OR=0.16, 95% CI: 0.11-0.24), labor dystocia (OR=0.42, 95% CI: 0.29-0.63) and CDMR (OR=0.15, 95% CI: 0.04-0.59). There was no baby delivered by the mothers who had suspected LGA baby as indication for CD. Newborn Apgar score <4 at 5 minutes were statistically similar in the mothers who had CD due to other indications (OR=1.20, 95% CI: 0.90-1.59) or CD due to paired ERCD and CDMR (OR=0.29, 95% CI: 0.04-2.11) and mothers who had CD due to "hard" indications, Table 6.

Among the primary CD cohort in Table 7, the babies of mothers who had CD performed due to "soft" indications of labor dystocia and CDMR were less likely to have Apgar score <4 at 5 minutes compared with babies of mothers who had CD due to "hard" indications. There was also

no baby of the suspected LGA baby group who had Apgar score <4 at 5 minutes. However, the mothers who had CD due to NRFS and other indications were significantly more likely to have Apgar score <4 at 5 minutes (OR=2.18, 95% CI: 1.63-2.91) and (OR=1.90, 95% CI: 1.39-2.63) respectively, Table 7.

3.3.5 Comparison of rates of newborn Apgar score <7 at 5 minutes among women who had CD due to "soft" indications versus CD due to "hard "indications (reference group).

Tables 8 and 9 present infant outcome of Apgar score <7 at 5 minutes among the study groups who underwent overall CD and primary CD due to "soft" indications versus "hard" indications. The results show that compared with babies born to mothers who had overall CD performed because of "hard" indications, those born to mothers who had CD performed because of NRFS were more likely to have two-fold increased rate of Apgar score <7 at 5 minutes (OR=2.36, 95% CI: 2.08-2.66), Table 8. However, in comparison with the babies of mothers who had CD for "hard" indications, the babies of mothers who had ERCD were 79% less likely to have Apgar score <7 at 5 minutes, (OR=0.21, 95% CI: 0.18-0.25), 28% less likely for labor dystocia (OR=0.72, 95% CI: 0.62-0.83), 64% less likely for suspected LGA baby (OR=0.36, 95% CI: 0.17-0.76), 86% less likely for CDMR (OR=0.14, 95% CI: 0.07-0.26), and 88% less likely for ERCD and CDMR pair (OR=0.12, 95% CI: 0.03-0.47). There were statistically comparable rates of newborn Apgar score <7 at 5 minutes between the mothers who had CD performed due to other indications and those performed due to "hard" indications (OR=1.12, 95% CI: 0.99-1.27), Table 8.

Among the primary CD cohort, the mothers who had CD performed due to "soft" indication of NRFS and those performed due to other indications were more likely to have babies with Apgar

score <7 at 5 minutes compared with mothers who had CD performed due to "hard" indications. On the other hand, compared with mother who had CD due to "hard" indications, those who had CD due to labor dystocia, suspected LGA baby and CDMR were less likely to have babies with Apgar score <7 at 5 minutes, Table 9.

3.3.6 Comparison of rates of neonatal death among women who had CD due to "soft" indications versus CD due to "hard "indications (reference group).

Tables 10 and 11 present infant outcome of neonatal death among the study groups who underwent overall CD and primary CD due to "soft" indications versus "hard" indications. Neonatal death ranged from 0.0% to 0.1% across all the study groups for overall CD and primary CD performed. In the overall CD cohort, there was a decreased rate of neonatal death among babies of mothers who had "soft" indication of ERCD (OR=0.22, 95% CI: 0.11-0.43) and labor dystocia (OR=0.17, 95% CI: 0.06-0.50) compared with babies of mothers with CD due to "hard" indications. The rate of neonatal death was not statistically different from the babies of mothers who had NRFS (OR=1.26, 95% CI: 0.68-2.34), or CDMR (OR=0.73 95% CI: 0.22-2.38) or the paired ERCD and CDMR (OR=0.91, 95% CI: 0.12-6.83) or CD due to other indications (OR=0.76, 95% CI: 0.41-1.39) and the babies of mothers who had CD due to "hard" indications, Table 10.

For the primary CD cohort in Table 11, similar situation as demonstrated in the overall cohort was seen in the primary cohort too. Except for ERCD and the paired ERCD and CDMR which were not part of the primary CD cohort, there was a decreased rate of neonatal death among neonates of mothers who had CD due to "soft" indication of labor dystocia compared with

neonates of mothers who had CD due to "hard" indications. Neonatal death was not statistically different between neonates of mothers who had CD due to NRFS, CDMR, those with other indications and neonates of mothers who had CD due to "hard" indications, Table 11. In both the overall and primary CD cohort, regression analysis for neonatal death were not performed for the babies of mothers who had CD because of suspected LGA baby, since there was no baby who died during the neonatal period, (Tables 10 and 11).

3.4 Discussion

The contribution of single and co-occurring indications to the overall CD rate and the effect of "soft" indications versus "hard" indications on neonatal outcomes were examined. The following are summary of the findings and are discussed according to the study objectives and associated research questions.

Objective 1: Indications for cesarean delivery (CD) and its effect of neonatal outcomes.

Research Question One: What are the leading single, co-occurring and three indications for having a CD?

The most common single indication for CD was a previous CD leading to ERCD, representing more than a third (34.3%) of all overall CDs. The next three common indications were labor dystocia (18.1%), breech presentation (10.6%) and NRFS (9.4%). The most common single indication for primary CD was labor dystocia, also accounting for more than a third (31.9%) of all primary CD. The other common indications were breech presentation (18.5%) and NRFS (16.6%).

These findings are buttressed by other studies[60, 62, 65-66] which found previous CD, labor dystocia, breech presentation and NRFS to be the most common indications for overall CD and labor

dystocia, breech presentation and NRFS to be the common indications for primary CD. A recent study by Rossignol et al[66] found comparable trends with approximately 40% of overall CD among women with a previous CD, 25% for labor dystocia, 15% for breech presentation, 10% for fetal distress or NRFS, and 10% for other reasons in Quebec in Canada.

It was found that over the eight-year period that data were available, in general CD due to "soft" indications such as ERCD, NRFS and other indications increased overtime whereas CD due to labor dystocia and CD due to "hard" indications decreased over the same period (Figures 6 and 7). Barber and colleagues[62] also found CD for NRFS or fetal distress increased over the seven-year time period of their study than to CD for mal-presentation, maternal-fetal and obstetric conditions.

The contributions of co-occurring and three indications to overall CD were also examined in this study. While many previous studies collectively examined multiple indications and a few in exclusive cases, our study is the first that examined the contribution of co-occurring indication pairs and three indications to the increasing rates of CD. The leading co-occurring indication pair for overall and primary CD were the paired labor dystocia and NRFS at 5.6% for overall CD and 10.1% for primary CD. The most common three indications for CD were labor dystocia and NRFS and OMHP accounting for 0.2% of all overall CDs (Appendix B).

The common single non-medical indication for CD was cesarean delivery on maternal request (CDMR). It was found that the rate of CDMR was low and did not contribute significantly to the overall CD rate as CD due to ERCD, labor dystocia, breech presentation and NRFS. Only 2.4% of women with CDMR accounted for the overall CD rate relative to a range of 9.4% to 34.3%

across CD performed due to ERCD, labor dystocia, breech presentation and NRFS, (Table 1). For primary CD, CDMR represented only 3% relative to 16.6% to 31.9% across CD performed due to labor dystocia, breech presentation and NRFS, (Table 2). Similar lower rates of CDMR have been reported by other studies [43,62,91,94] Hanley et al[43] reported that less than 2% of primary CDs in British Columbia were due to maternal request and Barber et al[62] found that maternal request represented 8% of the overall CD rate in an academic medical hospital in the United States (US). However, other studies including Karlstrom and associates[94] have reported higher rate of maternal requested CD at 29.9% in Sweden whereas Liu and associates[89] reported 28.4% of CD in China.

Some researchers have suggested that the true rates of CDMR could be higher than reported, with the actual rates distorted by factors such as inadequate documentation of maternal request as a separate indication for CD. [32-34] To test the latter assertion, we examined CDMR both exclusively and in combination with one or two other indications. It was observed that the contribution of CDMR to the overall CD rate was low in both the exclusive scenario at 2.4% for overall CD and 3.0% for primary CD, Table 1 and Table 2 respectively and when it was in combination with other indications at a range of 0.0 to 0.5% for overall CD and 0.0 to 0.1% for primary CD, (Tables 1-2 and Appendix B and C).

Research Question Two: What are the neonatal outcomes associated with CD performed due to "soft" indications of ERCD, labor dystocia, NRFS, suspected LGA baby, CDMR and paired ERCD and CDMR compared with CD due to "hard" indications?

It was found that babies of mothers with "soft" indications for CD such as NRFS were more likely to have Apgar score <4 at 5 minutes in comparison with babies of mothers who had CD

due to “hard” indications in both the overall CD and primary CD cohort. Newborn Apgar score <4 at 5 minutes were less likely to be associated with babies of mothers with other “soft” indications such as CD for labor dystocia and CDMR in comparison with babies of mothers who had CD due to “hard” indications in both the overall and primary CD cohort. The babies of mothers with ERCD had less likelihood of Apgar score <4 at 5 minutes compared with babies of mothers with CD due to “hard” indications in the overall CD cohort. While there were comparable rates with regards to newborn Apgar score <4 at 5 minutes between the mothers who had CD for other indications and those who had CD for “hard” indications in the overall CD cohort, the mothers who had CD for other indications were more likely to have newborns with Apgar score <4 at 5 minutes in comparison with the mothers who had CD due to “hard” indications in primary CD cohort. Babies of the mothers who had CD because of paired ERCD and CDMR and those who had CD due to “hard” indications had comparable rates of Apgar score <4 at 5 minutes in the overall CD cohort. There was no baby with Apgar score <4 delivered by mothers who had CD because of suspected LGA baby in the overall and primary CD cohort.

With respect to newborn Apgar score <7 at 5 minutes, it was more likely to be associated with neonates born to mothers who had “soft” indications for CD such as for NRFS compared with neonates born to mothers who had CD due to “hard” indications in both the overall and primary CD cohort. However, newborn Apgar score <7 at 5 minutes was less likely to be associated with CD performed for labor dystocia, ERCD, CDMR, suspected LGA baby as well as the paired ERCD and CDMR compared with CD performed for “hard” indications in the overall cohort. Newborn Apgar score <7 at 5 minutes were also less likely to be associated with CD due to labor

dystocia, CDMR, and suspected LGA baby compared with CD due to "hard" indications in the primary CD cohort. Even though babies of mothers with other indications for CD and those of mothers with "hard" indications for CD had similar rates of Apgar score <7 at 5 minutes in the overall cohort, the babies of the CD for other indication group were more likely to have Apgar score <7 at 5 minutes compared with the babies of mothers with CD for "hard" indications in the primary CD cohort.

Sheiner and associates[128] found that newborns delivered by mothers who had CD for labor dystocia or failure of labor to progress were more likely to have Apgar score <7 at 5 minutes after birth in comparison with mothers who had CD without failure of labor to progress which was in contrast to this study. Consistent with findings of this study, McPherson and colleagues[129] reported association between NRFS and Apgar <7 at 5 minutes compared with CD due to other indications. It has to be pointed out that the comparator group of the authors[129] comprised women with all other indications whereas the comparator group of our study comprised women who had CD performed due to "hard" indications.

Regarding neonatal death, it was found that babies of mothers who had CD performed due to "soft" indication such as ERCD and labor dystocia had lower rates of neonatal death in comparison with babies of mothers who had CD performed due to "hard" indications. Although babies of mothers who had CD for NRFS had higher rates of neonatal death and those who had CDMR or CD for other indications or the paired ERCD and CDMR group had lower rates of neonatal death, they were all not statistically different from babies of mothers who had CD for "hard" indications.

There are studies[13] that also found ERCD was not associated with neonatal death which was consistent with this study. Other studies[125] have reported association between ERCD and neonatal death which is in contrast to findings of this study. However, most of these studies used different comparator group of previous VD or trial of labor than comparator in our study which was CD performed due to "hard" indications. Sheiner and associates[128] found no significant difference with regards to perinatal mortality between the babies born to mothers with cesarean indication of labor dystocia or failure of labor to progress relative to those born by mothers without these indications. It has to be noted that the authors[128] included in their labor dystocia group women with placenta previa, fetal distress or NRFS and cord prolapse whereas these indications were excluded in the labor dystocia group of this study.

3.4.1 Strengths and limitations

Strength

One strength was the ability to assess single indications for CD, as well as two (pair) and three (triad) co-occurring multiple indications for CD which are not often examined in previous studies. Also, the comprehensive method of stratified analysis allowed for evaluation of which CD indications contributed more considerably to overall CD rates. Data on indications for CD were from hospital medical records rather than birth certificate data which usually do not have the specific indications for having CD. This allowed us to assess each recorded indication for CD separately and concurrently over an eight-year period.

In addition, the BORN Ontario data capture about 99% of hospital births in Ontario; and for the period covered in this study, data had been acquired from 100 hospitals and 84 midwifery

practice groups. Moreover, perinatal reports and studies from other provinces have shown similar pattern of the common indications for CD examined in this study. Also, the likelihood of recall bias is low, since data used for analysis in this study were obtained from hospital medical records rather than from interviews with mothers who may be not be able to correctly recall the indication for which they had CD.

Limitation

This study has limitations. Since this study is retrospective, there is always the possibility of residual confounding where unknown confounders and characteristics could not be controlled for in this study due to inability in the dataset. For example, there was no information on important variables such as the duration of the first and second stage of labor, inter-delivery interval, maternal race and women's narrative about their motivations for CDMR.

Also, even though the indications for having CD were obtained from hospital medical record, institution type was not available in the dataset. As a result, we could not ascertain which of the women in our study were born in a tertiary or community hospital. There is the possibility of demographic differences in CD rates between community and university or tertiary hospitals. Additionally, even though the BORN Ontario data are subjected to ongoing quality checks and the data are continuously updated, since it is an administrative database, there is the likelihood of miscoding and data entry errors which can lead to misclassification of outcomes.

Moreover, there were low occurrences in neonatal death rate in this study which may be due to the fact that the BORN data does not include all neonatal intensive care unit level of care

hospitals which could have led to under-reporting of this outcome. Lastly, the data used for this study may not be representative of the entire Canada, because it is mainly from Ontario. However, other reports from other provinces have shown similar pattern of the common indications for CD evaluated in our study. In spite of these drawbacks, the data provides knowledge regarding which CD indications are exclusively and in combination contributes to the increase rate of CD in Ontario.

3.5 Lessons learned from the findings of objective 1

The research question for objective one assessed the leading single and co-occurring indications for having CD and neonatal outcomes associated with CD performed due to "soft indication" versus "hard" indications. It was found that ERCD was the single largest indication representing one third of all overall CD in Ontario. The next three leading indications for overall CD were labor dystocia, breech presentation and NRFS. It was also found that labor dystocia was the single largest indication representing one third of all first or primary CD in Ontario. The other three leading indications for primary CD were NRFS, OMHP and CDMR. The leading co-occurring indications for both overall and primary cesarean delivery were the paired labor dystocia and NRFS. Also, there is the notion that CDMR is a major factor to the increasing rate of CD. The findings of this study suggested otherwise. CDMR was not a significant contributor to the rise in rates of CD in Ontario. The single indication of CDMR in Ontario was low at 2.4% for overall CD and 3.0% for primary CD.

Generally, compared with infants of mothers who had CD due to "hard" indications, infants of mothers who had CD due to "soft" indications such as NRFS were at increased risk of lower Apgar score <7 at 5 minutes and had statistically comparable rates of neonatal death as the

"hard" indication group, but infants of mothers who had CD due to other "soft" indications such as ERCD and labor dystocia had decreased risk of lower Apgar score <7 at 5 minutes and neonatal death. Infants of mothers with other indications for CD had increased risk of lower Apgar score <7 at 5 minutes in relation to infants of mothers who had CD due to "hard" indications only in the primary CD cohort.

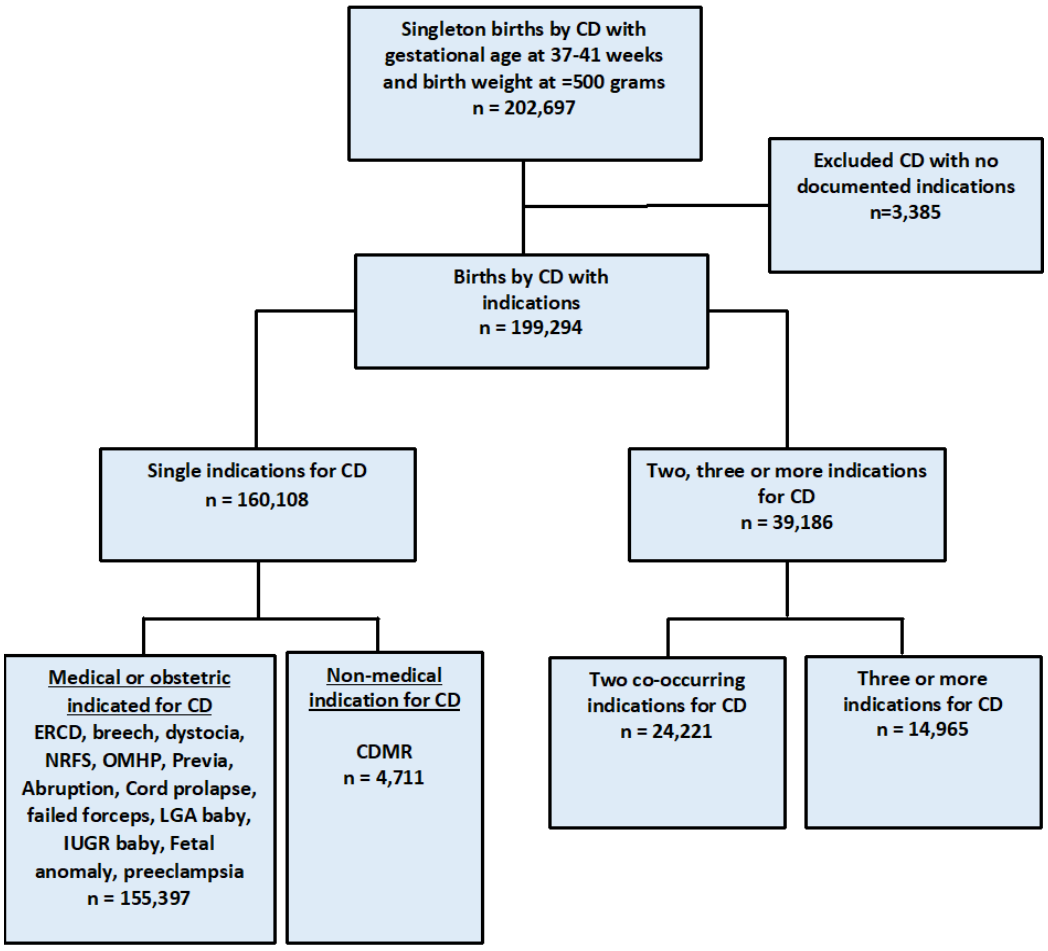

Figure 5. Flow diagram of study population of women with CD indications for Objective 1.

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.
Abbreviations: CD, cesarean delivery; CDMR, cesarean delivery on maternal request; ERCD, elective repeat cesarean delivery; LGA, large for gestational age baby; IUGR, intrauterine growth restriction baby; NRFS, non-reassuring-fetal-status; OMHP, other maternal health problem,

Table 1: Single and co-occurring indications for having overall cesarean delivery in term singleton births		
Number of women	**199,294**	
	n	**%**
Single indications [a]		
ERCD	68,388	34.3
Dystocia	36,165	18.1
Breech	21,128	10.6
NRFS	18,819	9.4
OMHP	5,161	2.6
CDMR	4,711	2.4
Previa	1,963	1.0
LGA baby	1,275	0.6
Failed forceps	827	0.4
Preeclampsia	507	0.2
Cord prolapse	457	0.2
Abruption	411	0.2
IUGR baby	224	0.1
Fetal anomaly	72	0.0
Co-occurring indications [b]		
Dystocia and NRFS	11,225	5.6
ERCD and breech	1,556	0.8
ERCD and CDMR	937	0.5
ERCD and dystocia	766	0.4
ERCD and OMHP	739	0.4
Dystocia and failed forceps	671	0.3
Dystocia and OMHP	666	0.3
OMHP and NRFS	481	0.2
ERCD and NRFS	415	0.2
NRFS and abruption	402	0.2
ERCD and LGA baby	364	0.2
ERCD and breech	282	0.1
NRFS and failed forceps	274	0.1

NRFS and IUGR baby	273	0.1
ERCD and previa	224	0.1
Dystocia and preeclampsia	224	0.1
Breech and OMHP	216	0.1
Breech and IUGR baby	198	0.1
ERCD and IUGR baby	193	0.1
ERCD and NRFS	177	0.1
ERCD and preeclampsia	167	0.1
Dystocia and CDMR	160	0.1
ERCD and OMHP	156	0.1
ERCD and CDMR	120	0.1
LGA and OMHP	120	0.1
Breech and NRFS	98	0.0
NRFS and preeclampsia	98	0.0
OMHP and CDMR	95	0.0
NRFS and cord prolapse	94	0.0
NRFS and IUGR baby	88	0.0
NRFS and LGA baby	86	0.0
Breech and LGA baby	79	0.0
Breech and CDMR	75	0.0
Breech and preeclampsia	71	0.0
Dystocia and IUGR baby	68	0.0
CDMR and NRFS	65	0.0
Preeclampsia and OMHP	64	0.0
ERCD and abruption	61	0.0

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: n, number; CDMR, cesarean delivery on maternal request; ERCD, elective repeat cesarean delivery; IUGR, intrauterine growth restriction; LGA, large for gestational age baby; NRFS, non-reassuring fetal status; OMHP, other maternal health problem.

a. Each woman had single indication for cesarean delivery and none of the other indications.

b. Each woman had two co-occurring indications for cesarean delivery and none of the other indications.

Table 2: **Single and co-occurring indications for having primary cesarean delivery in term singleton births**		
Number of women	**108,343**	
Indications	**n**	**%**
Single indications [a]		
Dystocia	34,564	31.9
Breech	20,053	18.5
NRFS	17,998	16.6
OMHP	4,808	4.4
CDMR	3,199	3.0
Previa	1,933	1.8
Suspected LGA baby	1,227	1.1
Failed forceps	823	0.8
Abruption	533	0.5
Cord prolapse	494	0.5
Preeclampsia	412	0.4
IUGR baby	230	0.2
Fetal anomaly	96	0.1
Co-occurring indications [b]		
Dystocia and NRFS	10,942	10.1
Dystocia and OMHP	674	0.6
Dystocia and failed forceps	665	0.6
Dystocia and LGA baby	613	0.6
OMHP and NRFS	500	0.5
NRFS and abruption	375	0.4
NRFS and IUGR baby	343	0.3
NRFS and failed forceps	274	0.3
Breech and NRFS	264	0.2
Breech and OMHP	247	0.2
Dystocia and preeclampsia	227	0.2
Breech and IUGR baby	212	0.2
Dystocia and CDMR	154	0.1

Dystocia and breech	146	0.1
Suspected LGA baby and OMHP	116	0.1
NRFS and preeclampsia	114	0.1
OMHP and CDMR	107	0.1
Breech and previa	103	0.1
NRFS and suspected LGA baby	92	0.1
NRFS and cord prolapse	90	0.1
Breech and CDMR	88	0.1
Breech and suspected LGA baby	75	0.1
Breech and preeclampsia	69	0.1
Dystocia and IUGR baby	66	0.1
CDMR and NRFS	62	0.1
Preeclampsia and OMHP	60	0.1
Dystocia and abruption	53	0.0
Suspected LGA baby and CDMR	51	0.0
Breech and cord prolapse	35	0.0
NRFS and fetal anomaly	25	0.0
Previa and OMHP	25	0.0
IUGR and OMHP	21	0.0
IUGR and OMHP	21	0.02
LGA and preeclampsia	20	0.02
Suspected LGA baby and preeclampsia	20	0.0
Breech and fetal anomaly	19	0.0
IUGR and previa	18	0.0
Previa and abruption	16	0.01

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: n, number; CDMR, cesarean delivery on maternal request; LGA, large for gestational age baby; NRFS, non-reassuring fetal status; OMHP, other maternal health problem; IUGR, intrauterine growth restriction.

a. Each woman had single indication for cesarean delivery and none of the other indications.

b. Each woman had two co-occurring indications for cesarean delivery and none of the other indications.

Table 3: **Exposure and comparison groups of overall and primary cesarean delivery indications for term singleton births**

	Overall CD (N=199,294)		**Primary CD (N=108,343)**	
Indications	**n**	**%**	**n**	**%**
Exposed groups				
CD due to "soft" indications [a]				
ERCD	68,388	34.3	n/a	n/a
Dystocia	36,165	18.2	34,564	31.9
NRFS	18,819	9.4	17,998	16.6
Suspected LGA baby	1,275	0.6	1,227	1.1
CDMR	4,711	2.4	3,199	3.0
ERCD and CDMR pair	937	0.47	n/a	n/a
Other	26,937	13.5	15,469	14.3
Comparison group (reference)				
CD due to "hard" indications (overall)[b]	42,062	21.1	35,886	33.1
Breech	21,128	10.6	20,053	18.5
OMHP	5,161	2.4	4,808	4.4
Previa	1,963	1.0	1,802	1.7
Failed forceps	827	0.4	801	0.7
Abruption	603	0.3	533	0.5
Cord prolapse	457	0.2	443	0.4
Preeclampsia	507	0.3	412	0.4
IUGR baby	224	0.1	142	0.1
Fetal anomaly	72	0.0	60	0.1
Other	11,120	5.6	6,832	6.3

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; ERCD, elective repeat cesarean delivery; CDMR, cesarean delivery on maternal request; LGA, large for gestational age baby; NRFS, non-reassuring fetal status; other maternal health problem, OMHP; CD, cesarean delivery; IUGR, intrauterine growth restriction.

a. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

b. “Hard” indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other “hard” indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the “hard” indication group

Table 4: **Characteristics of women who had overall cesarean delivery due to “soft” indications compared with “hard” indications**[a]

Characteristics	**CD due to “hard” indications** [b] **(reference) N=42,062 Column A**		**CD due to “soft” indications** [c] **ERCD N=68,388 Column B**			**Dystocia N=36,165 Column C**		
	n	%	n	%	p-value [d]	n	%	p-value [d]
Maternal age (years)								
<20	1,025	2.4	330	0.5	<0.0001	1,259	3.5	<0.0001
≥20-34	29,977	71.3	44,357	64.9		27,803	76.9	
≥35	1,1060	26.3	23,701	34.7		7,103	19.6	
Parity								
Nulliparous	25,467	60.5	216	0.3	<0.0001	31,248	86.4	<0.0001
Multiparous	16,595	39.5	68,172	99.7		4,917	13.6	
Gestational age (weeks)								
37-38	21,708	51.6	40,719	59.5	<0.0001	5,825	16.1	<0.0001
39-41	20,354	48.4	27,669	40.5		30,340	83.9	
Education (quartiles)								
1 (lowest)	9,356	22.2	15,283	22.3	0.0402	8,307	23	0.0024
2	11,046	26.3	17,905	26.2		9,640	26.7	
3	10,941	26.0	18,213	26.6		9,385	26	
4 (highest)	10,719	25.5	16,987	24.8		8,833	24.4	
Birth weight (grams)								
500-2500	1,900	4.5	789	1.2	<0.0001	208	0.6	<0.0001

Table 4: **Characteristics of women who had overall cesarean delivery due to "soft" indications compared with "hard" indications[a]**								
2500-4,499	39,469	93.8	66,489	97.2		34,256	94.7	
4,500 or more	693	1.6	1,110	1.6		1,701	4.7	
Infant gender								
Male	20,586	48.90	34,887	51.0	<0.0001	20,127	55.6	<0.0001
Female	21,476	51.10	33,501	49.0		16,038	44.3	

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; CD, cesarean delivery; CDMR, cesarean delivery on maternal request; ERCD, elective repeat cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Characteristics of women who had overall CD due to "soft" indications such as ERCD (column B) and dystocia (column C) were each compared with women who had overall CD due to "hard" indications (column A);

b. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

c. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

d. The p-value was derived from Chi squared test analysis.

Table 4: Characteristics of women who had overall cesarean delivery due to "soft" indications compared with "hard" indications continued [a]									
	CD due to soft indications [b]								
Characteristics	**NRFS N=18,819 Column D**			**Suspected LGA baby N= 1,275 Column E**			**CDMR N=4,711 Column F**		
	n	%	p-value [c]	n	%	p-value [c]	n	%	p-value [c]
Maternal age (years)									
<20	708	3.8	<0.0001	23	1.8	0.1515	64	1.4	<0.0001

≥20-34	13,926	74.0		894	70.1		3,020	64.1	
≥35	4,185	22.2		358	28.1		1,627	34.5	
Parity									
Nulliparous	14,562	77.4	<0.0001	900	70.6	<0.0001	1,981	42.1	<0.0001
Multiparous	4,257	22.6		375	29.4		2,730	57.9	
Gestational age (weeks)									
37-38	3,418	18.2	<0.0001	341	26.7	<0.0001	2,536	53.8	0.0038
39-41	15,401	81.8		934	73.3		2,175	46.2	
Education (quartiles)									
1 (lowest)	4,311	22.9	<0.0001	290	22.7	0.3501	995	21.1	<0.0001
2	4,931	26.2		331	26.0		1,166	24.8	
3	5,085	27		345	27.1		1,179	25	
4 (highest)	4,492	23.9		309	24.2		1,371	29.1	
Birth weight (grams)									
500-2500	808	4.3	<0.0001	402	31.5	<0.0001	50	1.1	<0.0001
2500-4,499	17,792	94.5		0	0		4,587	97.4	
4,500 or more	219	1.2		873	68.5		74	1.6	
Infant gender									
Male	10,932	58.1	<0.0001	769	60.3	<0.0001	2,175	46.2	<0.0001
Female	7,887	41.9		506	39.7		2,536	53.8	

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; CD, cesarean delivery; CDMR, cesarean delivery on maternal request; ERCD, elective repeat cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Characteristics of women who had overall CD due to "soft" indications such as NRFS (column D), suspected LGA baby, (column E) and CDMR (column F) were each compared with women who had overall CD due to "hard" indications (column A);

b. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby.

c. The p-value was derived from Chi squared test analysis.

Table 4: Characteristics of women who had overall cesarean delivery due to "soft" indications compared with "hard" indications continued [a]

	CD due to soft indications[b]					
Characteristics	**ERCD and CDMR pair N=937 Column G**			**Other [c] N=26,937 Column H**		
	n	%	p-value [d]	n	%	p-value [d]
Maternal age (years)						
<20	3	0.3	0.0001	587	2.18	0.0785
≥20-34	677	72.3		19,197	71.3	
≥35	257	27.4		7,153	26.6	
Parity						
Nulliparous	2	0.2	<0.0001	13,143	48.8	<0.0001
Multiparous	935	99.8		13,794	51.2	
Gestational age (weeks)						
37-38	537	57.3	0.0006	9,410	34.9	<0.0001
39-41	400	42.7		17,527	65.1	
Education (quartiles)						
1 (lowest)	274	29.2	<0.0001	6,069	22.5	0.1346
2	306	32.7		7,151	26.5	
3	226	24.1		7,067	26.2	
4 (highest)	131	14.0		6,650	24.7	
Birth weight (grams)						
500-2500	13	1.4	<0.0001	561	2.1	<0.0001
2500-4,499	906	96.7		25,190	93.5	
4,500 or more	18	1.9		1,186	4.4	
Infant gender						
Male	474	50.6	0.3191	15,003	55.7	<0.0001
Female	463	49.4		11,934	44.3	

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; CD, cesarean delivery; CDMR, cesarean delivery on maternal request; ERCD, elective repeat cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Characteristics of women who had overall CD due to "soft" indications such as the paired ERCD and CDMR (column G) and other indications (column H) were each compared with women who had overall CD due to "hard" indications (column A).

b. “Soft” indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;
c. All other “soft” indications.
d. The p-value was derived from Chi squared test analysis.

Table 5: Characteristics of women who had primary cesarean delivery due to “soft” indications compared with “hard” indications[a]

Characteristics	**CD due to hard indications [b] (reference) N= 35,886 Column A**		**CD due to soft indications[c]**					
			Dystocia N=34,564 Column B			**NRFS N=17,998 Column C**		
	n	**%**	**n**	**%**	**p-value [d]**	**n**	**%**	**p-value [d]**
Maternal age (years)								
<20	988	2.8	1,246	3.6	<0.0001	707	3.9	<0.0001
≥20-34	26156	72.9	26,673	77.2		13,366	74.3	
≥35	8742	24.4	6,645	19.2		3,925	21.8	
Parity								
Nulliparous	25,443	70.9	31,246	90.4	<0.0001	14,561	80.9	<0.0001
Multiparous	10,443	29.1	3,318	9.6		3,437	19.1	
Gestational age in weeks								
37-38	17,668	49.2	5,527	16	<0.0001	17,423	96.8	<0.0001
39-41	18,218	50.8	29,037	84		3,256	18.1	
Education (quartiles)								
1 (lowest)	7,927	22.1	7,917	22.9	0.0012	4,114	22.9	<0.0001
2	9,400	26.2	9,201	26.6		4,705	26.1	
3	9,328	26.0	8,954	25.9		4,879	27.1	
4 (highest)	9,231	25.7	8,492	24.6		4,300	23.9	
Birth weight (grams)								
500-2500	1,539	4.3	199	0.6	<0.0001	779	4.3	0.0004

2500-4,499	33,783	94.1	32,728	94.7		17,013	94.5	
4,500 or more	564	1.6	1,637	4.7		206	1.1	
Infant gender								
Male	17,524	48.8	19,273	55.8	<0.0001	10,471	58.2	<0.0001
Female	18,362	51.2	15,291	44.2		7,527	41.8	

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; CD, cesarean delivery; CDMR, cesarean delivery on maternal request; ERCD, elective repeat cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Characteristics of women who had primary CD due to "soft" indications such as dystocia (column B) and NRFS (column C) were each compared with women who had overall CD due to "hard" indications (column A).

b. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

c. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group

d. The p-value was derived from Chi squared test analysis.

Table 5: Characteristics of women who had primary cesarean delivery due to "soft" indications compared with "hard" indications continued[a]

	CD due to soft indications [b]								
Characteristics	**CDMR N=3,199 Column D**			**Suspected LGA baby N=1,227 Column E**			**Other[c] N=15,469 Column F**		
	n	**%**	**p-value [d]**	**n**	**%**	**p-value [d]**	**n**	**%**	**p-value [d]**
Maternal age (years)									
<20	51	1.6	<0.0001	23	1.9	0.0031	517	3.34	<0.0001
≥20-34	1,984	62.0		859	70.0		11,546	74.6	
≥35	1,164	36.4		345	28.1		3,406	22.0	
Parity									
Nulliparous	1,981	61.9	<0.0001	900	73.3	0.0630	13,096	84.7	<0.0001

Multiparous	1,218	38.1		327	26.7		2,373	15.3	
Gestational age									
37-38	1,707	53.4	<0.0001	317	25.8	<0.0001	2,731	17.7	<0.0001
39-41	1,492	46.6		910	74.2		12,738	82.3	
Education (quartiles)									
1 (lowest)	556	17.4	<0.0001	272	22.2	0.5147	3,391	21.9	0.3550
2	735	23		302	24.6		4,156	26.9	
3	818	25.6		318	25.9		4,027	26	
4 (highest)	1,090	34.1		335	27.3		3,895	25.2	
Birth weight (grams)									
500-2500	48	1.5	<0.0001	0	0	<0.0001	307	2	<0.0001
2500-4,499	3,199	100		842	68.6		14,372	92.9	
4,500 or more	34	1.1		385	31.4		790	5.1	
Infant gender									
Male	1,673	52.3	0.0002	743	60.6	<0.0001	8,907	57.6	<0.0001
Female	1,526	47.7		484	39.4		6,562	42.4	

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; CD, cesarean delivery; CDMR, cesarean delivery on maternal request; ERCD, elective repeat cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Characteristics of women who had primary CD due to "soft" indications such as CDMR (column D), suspected LGA baby, (column E) and other (column F) were each compared with women who had overall CD due to "hard" indications (column A). a. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby; c. All other "soft" indications.

d. The p-value was derived from Chi squared test analysis.

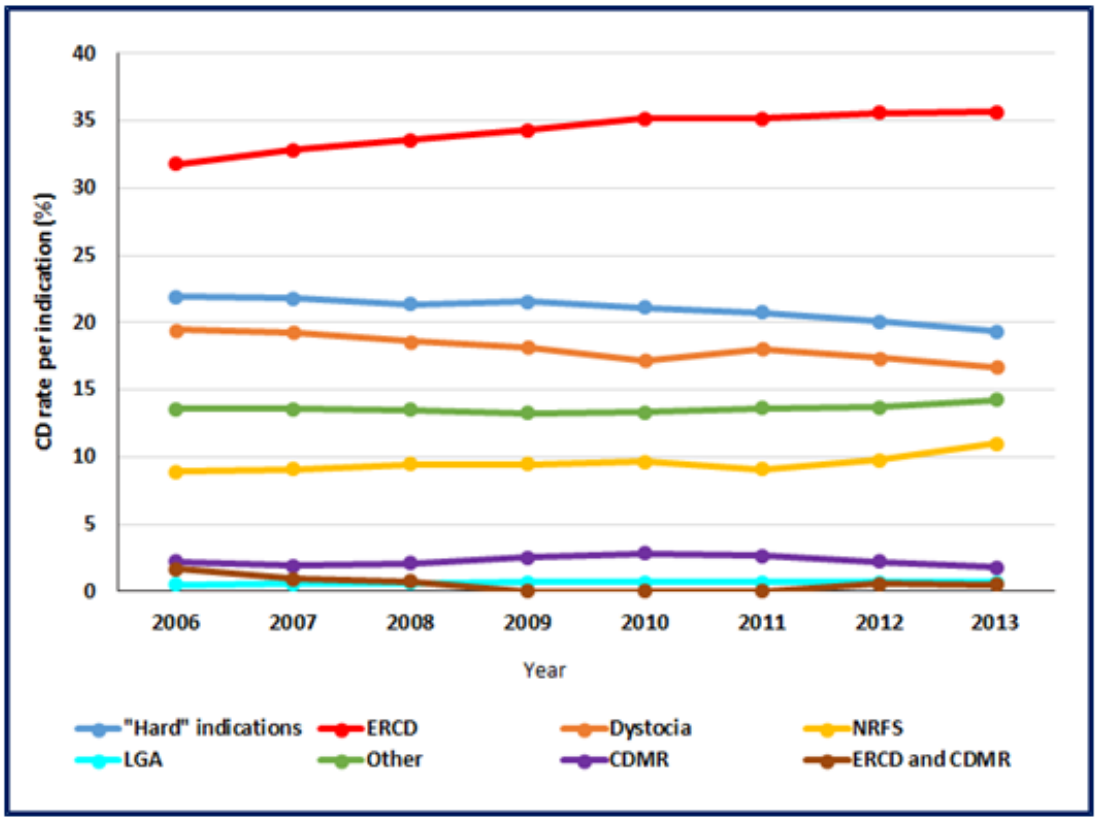

Figure 6. Percentage of indications for overall cesarean delivery stratified by year of birth

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.
Abbreviations: CD, cesarean delivery; ERCD, elective repeat cesarean delivery; CDMR, cesarean delivery on maternal request; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.
Other includes all other "soft" indications.
"Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;
"Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group

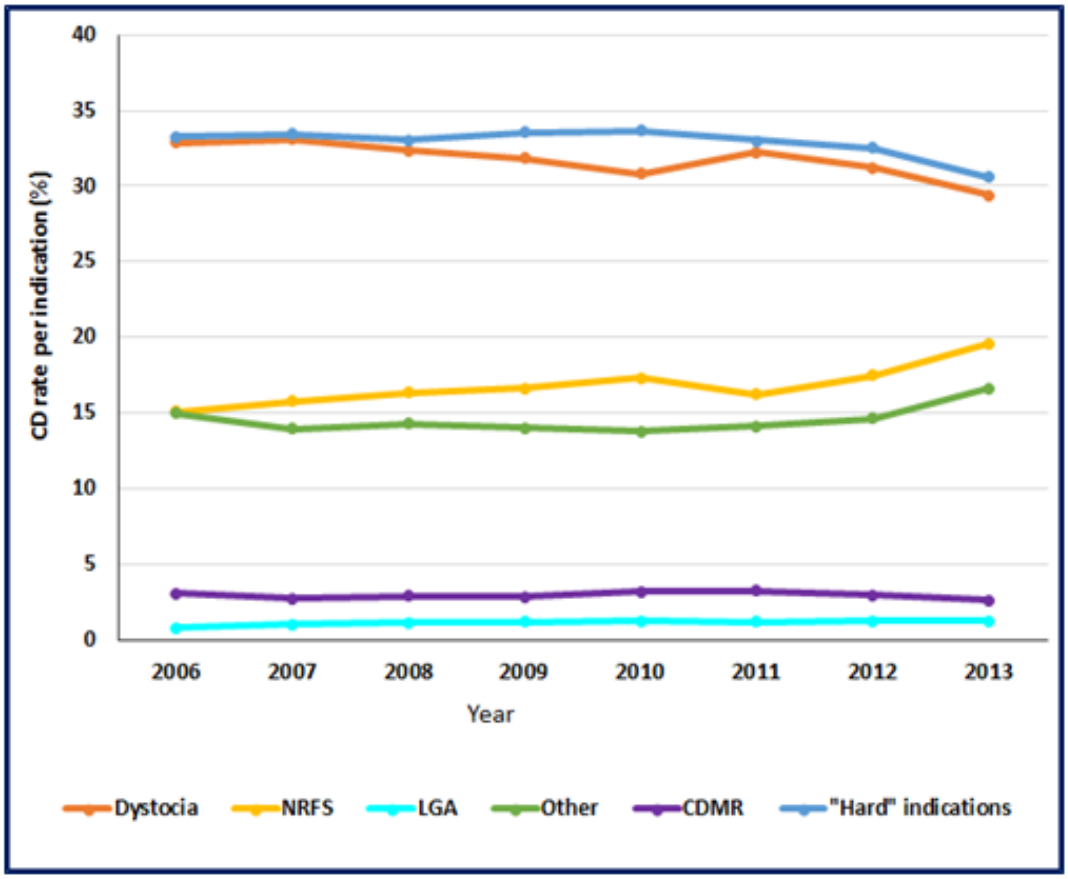

Figure 7. Percentage of indications for primary cesarean delivery stratified by year of birth

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.
Abbreviations: CD, cesarean delivery; CDMR, cesarean delivery on maternal request; LGA, large-for-gestational-age baby; NRFS, non-reassuring-fetal-status.
Other includes all other "soft" indications.
"Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;
"Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group

Table 6: Comparison of rates of newborn Apgar score <4 at 5 minutes associated with overall cesarean delivery due to "soft" indications versus "hard" indications

Indications	Total N	Apgar score <4 at 5 minutes				
		n	(%)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)	p-value [b]
Overall CD						
CD due to "soft" indications [c]						
ERCD	68,388	37	0.05	0.20 (0.14-0.28)	0.16 (0.11-0.24)	<0.0001
Dystocia	36,165	39	0.11	0.39 (0.27-0.56)	0.42 (0.29-0.63)	<0.0001
NRFS	18,819	121	0.64	2.34 (1.81-3.02)	2.46 (1.87-3.25)	<0.0001
Suspected LGA baby	1,275	0	0.0	-	-	-
CDMR	4,711	2	0.04	0.15 (0.04-0.62)	0.15 (0.04-0.59)	0.0070
ERCD and CDMR pair	937	1	0.11	0.39 (0.05-2.77)	0.29 (0.04-2.11)	0.2232
Other [d]	26,937	91	0.34	1.23 (0.93-1.61)	1.20 (0.90-1.59)	0.2126
CD due to hard indications [e]	42,062	116	0.28	reference	reference	-

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; OR, odds ratio; CI, confidence interval; CD, cesarean delivery; ERCD, elective repeat cesarean delivery; NRFS, non-reassuring-fetal-status; LGA, large-for-gestational-age; CDMR, cesarean delivery on maternal request.

a. Adjusted for maternal age, parity, education, infant gender and gestational age at delivery.

b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

c. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

d. All other "soft" indications.

e. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

Table 7: Comparison of rates of newborn Apgar score <4 at 5 minutes associated with primary cesarean delivery due to "soft" indications versus "hard" indications

Indications	Total N	Apgar score <4 at 5 minutes				
		n	(%)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)	p-value [b]
Primary CD						
CD due to soft indications [c]						
Dystocia	34,564	38	0.11	0.38 (0.26-0.55)	0.44 (0.29-0.65)	<0.0001
NRFS	17,998	108	0.60	2.10 (1.60- 2.75)	2.18 (1.63-2.91)	<0.0001
Suspected LGA baby	1,227	0	0.00	-	-	-
CDMR	3,199	1	0.03	0.109 (0.02-.78)	0.11 (0.02-0.78)	0.0270
Other [d]	15,469	76	0.49	1.71 (1.27-2.31)	1.90 (1.39-2.63)	<0.0001
CD due to hard indications e	35,886	103	0.29	reference	reference	-

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; OR, odds ratio; CI, confidence interval; CD, cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Adjusted for maternal age, parity, education, infant gender and gestational age at delivery.

b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

c. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

d. All other "soft" indications.

e. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

Table 8: **Comparison of rates of newborn Apgar score <7 at 5 minutes associated with overall cesarean delivery due to "soft" indications versus "hard" indications**						
Indications	**Total N**	**Apgar score <7 at 5 minutes**				
		n	**(%)**	**Crude OR (95% CI)**	**Adjusted OR [a] (95% CI)**	**p-value [b]**
Overall CD						
CD due to soft indications [c]						
ERCD	68,388	247	0.4	0.25 (0.21-0.29)	0.21 (0.18-0.25)	<0.0001
Dystocia	36,165	364	1.0	0.69 (0.61-0.79)	0.72 (0.62-0.83)	<0.0001
NRFS	18,819	621	3.3	2.32 (2.07-2.60)	2.36 (2.08-2.66)	<0.0001
Suspected LGA baby	1,275	7	0.6	0.38 (0.18-0.79)	0.36(0.17-0.76)	0.0074
CDMR	4,711	10	0.2	0.14 (0.08-0.27)	0.14 (0.07-0.26)	<0.0001
ERCD and CDMR pair	937	2	0.2	0.15 (0.04-0.58)	0.12 (0.03-0.47)	0.0024
Other [d]	26,937	450	1.7	1.15 (1.02-1.31)	1.12 (0.99-1.27)	0.0820
CD due to hard indications [e]	42,062	610	1.45	reference	reference	-

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; OR, odds ratio; CI, confidence interval; CD, cesarean delivery; ERCD, elective repeat cesarean delivery; NRFS, non-reassuring-fetal-status; LGA, large-for-gestational-age; CDMR, cesarean delivery on maternal request.

a. Adjusted for maternal age, parity, education, infant gender and gestational age at delivery.

b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

c. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

d. All other "soft" indications.

e. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

Table 9: Comparison of rates of newborn Apgar score <7 at 5 minutes associated with primary cesarean delivery due to "soft" indications versus "hard" indications

Indications	Total N	Apgar score <7 at 5 minutes				
		n	(%)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)	p-value [b]
Primary CD						
CD due to soft indications[c]						
Dystocia	34,564	350	1.0	0.70 (0.61-0.80)	0.73 (0.63-0.85)	<0.0001
NRFS	17,998	571	3.2	2.23 (1.98-2.52)	2.23 (1.96-2.53)	<0.0001
Suspected LGA baby	1,227	6	0.5	0.33 (0.15-0.75)	0.32 (0.14- 0.71)	0.0051
CDMR	3,199	4	0.1	0.09 (0.03-0.23)	0.09 (0.03-0.23)	<0.0001
Other [d]	15,469	347	2.24	1.56 (1.36-1.79)	1.62 (1.40-1.88)	<0.0001
CD due to hard indications [e]	35,886	519	1.45	reference	reference	-

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; OR, odds ratio; CI, confidence interval; CD, cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Adjusted for maternal age, parity, education, infant gender and gestational age at delivery.

b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

c. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

d. All other "soft" indications.

e. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

Table 10: Comparison of rates of neonatal death associated with overall cesarean delivery due to "soft" indications versus "hard" indications

Indications	Total N	Neonatal death				
		n	(%)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)	p-value [b]
Overall CD						
CD due to soft indications [c]						
ERCD	68,388	16	0.02	0.31 (0.17-0.56)	0.22 (0.11-0.43)	<0.0001
Dystocia	36,165	4	0.01	0.15 (0.05-0.41)	0.17 (0.06-0.50)	0.0013
NRFS	18,819	18	0.1	1.26 (0.71-2.24)	1.26 (0.68-2.34)	0.4632
Suspected LGA baby	1275	0	0.0	-	-	-
CDMR	4,711	3	0.06	0.84 (0.26-2.73)	0.73 (0.22-2.38)	0.5961
ERCD and CDMR pair	937	1	0.1	1.40 (0.19-10.28)	0.91 (0.12-6.83)	0.9271
Other [d]	26,937	16	0.06	0.78 (0.43-1.42)	0.76 (0.41-1.39)	0.3688
CD due to hard indications [e]	42,062	32	0.08	reference	reference	-

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; OR, odds ratio; CI, confidence interval; CD, cesarean delivery; ERCD, elective repeat cesarean delivery; NRFS, non-reassuring-fetal-status; LGA, large-for-gestational-age; CDMR, cesarean delivery on maternal request.

a. Adjusted for maternal age, parity, education, infant gender and gestational age at delivery.

b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

c. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

d. All other "soft" indications.

e. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

Table 11: Comparison of rates of neonatal death associated with primary cesarean delivery due to "soft" indications versus "hard" indications

Indications	Total N	Neonatal death				
		count	(%)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)	p-value [b]
Primary CD						
CD due to soft indications [c]						
Dystocia	34,564	4	0.01	0.16 (0.06-0.46)	0.18 (0.06-0.55)	0.0024
NRFS	17,998	18	0.1	1.38 (0.76-2.52)	1.37 (0.73-2.59)	0.3314
Suspected LGA baby	1,227	0	0.0	-	-	-
CDMR	3,199	2	0.06	0.86 (0.20-3.64)	0.86 (0.20-3.63)	0.8342
Other[d]	15469	13	0.08	1.16 (0.60-2.26)	1.43 (0.70-2.90)	0.3284
CD due to hard indications [e]	35886	26	0.07	reference	reference	-

Data used for analyses is from Better Outcomes Registry Network (BORN) Ontario.

Abbreviations: N, total number; n, number; OR, odds ratio; CI, confidence interval; CD, cesarean delivery; LGA, large-for-gestational-age; NRFS, non-reassuring-fetal-status.

a. Adjusted for maternal age, parity, education, infant gender and gestational age at delivery.

b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

c. "Soft" indications were defined as indications for CD that are elective such as ERCD or non-medical indication such as CDMR or indications that are highly subjective to clinician discretion such as labor dystocia, NRFS and suspected LGA baby;

d. All other "soft" indications.

e. "Hard" indications were defined as conditions that affect the placenta such as placental previa, placenta abruption and cord prolapse. Other "hard" indications include breech presentation, maternal severe medical problems such as preeclampsia that can prevent the placenta from receiving enough blood which can affect the fetus, failed forceps, other maternal health problem and fetal indications such as intrauterine growth restriction and fetal anomalies. Since all these indications have similarities in terms of impact on neonatal outcomes and have a higher medical threshold for performing CD, they were all combined as the "hard" indication group.

Chapter 4

Adverse birth outcomes among low risk women with one previous vaginal delivery who underwent elective primary cesarean delivery versus trial of labor after vaginal birth and those with one previous cesarean delivery who underwent elective repeat cesarean delivery versus trial of labor after cesarean birth (Objective 2)

4.1 Introduction

Recent epidemiological studies have revealed an increase of cesarean birth among multiparous women with at least one previous cesarean (CD), a group that is becoming more common in obstetric practice[31,44] An important clinical decision for health care providers and their patients for a woman with a previous CD is to plan an appropriate mode of delivery by either choosing a trail of labor after cesarean birth (TOLAC) or elective repeat cesarean delivery (ERCD) and for a woman with previous vaginal delivery (VD) by either choosing an elective primary cesarean delivery (EPCD) or trial of labor after vaginal birth (TOLAV) based on the patient's clinical presentation and characteristics. Maternal complications following cesarean birth including uterine rupture, placenta previa, placental abruption, infection, hysterectomy and neonatal complications including respiratory morbidity, preterm birth and stillbirth have been reported in previous studies[13, 35, 106,115]

Comparison of these outcomes are usually among women with a history of previous CD delivering their subsequent birth by trial of labor or repeat CD. There is limited information regarding whether adverse birth outcomes including newborn birth injury, usage of antibiotic after birth is associated with an EPCD or TOLAV mode of delivery, particularly among study groups with similar baseline characteristics such as maternal age and gestational age. Propensity score matching technique can help reduce or eliminate the imbalance or differences of patient characteristics between study comparison groups. Yet, a few studies[102-103] examining birth

outcomes related to mode of delivery have incorporated propensity score matching techniques in their study. Even so, these studies differ by study population and patient selection. The aim of this chapter was to examine adverse birth outcomes in low risk woman with (2a) one previous VD who underwent EPCD versus TOLAV and (2b) those with one previous CD who underwent ERCD versus TOLAC at term gestation (37-41weeks gestation), with a cephalic fetal presentation in the second pregnancy using statistical techniques such as propensity score matching on baseline characteristics.

4.2 Methods

4.2.1 Design and data source

The design applied for objective 2 is a retrospective cohort study. Data used for the study was obtained from the linked birth/infant death datasets of the United States (US), as complied for the 2005 to 2010 birth cohort by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The linked birth-death database contains data from US on all infant deaths up to their first year that are linked to their corresponding birth record through a unique identifier in the fifty states and the District of Columbia. The NCHS extracts final edited data from the linked record and code them according to uniform coding specifications into a single national linked file representing births in the US. This database contains maternal characteristics, pre-existing health problems, complications associated with pregnancy, neonatal mortality and morbidity as well as mode of delivery.

4.2.2 Study population

The study population included second singleton live births by low risk women who had one previous CD or one previous VD. Low risk women were defined as women with no medical

problems such as pre-existing or pregnancy-related diabetes or hypertension who delivered their second infant in a cephalic presentation at term. In order to reduce confounding by preterm births (<37 weeks' gestation) and post-term births (>41 weeks' gestation), the study population was restricted to term births defined as 37-41 weeks' gestational period. Births with unknown gestational age and unknown delivery methods were excluded. Also, births with congenital anomalies and multiple gestations were excluded from the analysis.

4.2.3 Outcome and exposure variables

Outcome variables

Neonatal outcomes such as respiratory distress syndrome, transient tachypnea of the new born, hypoxic ischemic encephalopathy, neonatal intensive care unit, admission, neonatal death have all been studied among ERCD and TOLAC delivery groups[13, 102, 115, 117] Therefore, our outcome variables of interest considered were those that have not been evaluated between birth by EPCD versus TOLAV and ERCD versus TOLAC mode of delivery. These outcomes include newborn antibiotic use and birth injury. Other outcomes include, assisted ventilation immediately after delivery, assisted ventilation >6 hours following delivery, neonatal intensive care unit admission and infant death. The outcomes were dichotomized as 'yes' or 'no' where yes indicates the newborn had the outcome and no indicates the newborn did not have the outcome. Newborn antibiotic use includes antibiotic received by the newborn for suspected neonatal sepsis including any antibacterial drug (e.g. penicillin, ampicillin, gentamicin, cefotoxine etc.) given systemically (intravenous or intramuscular). Assisted ventilation immediately after delivery consist of infant given manual breaths for any duration with bag and mask or bag and endotracheal tube within the first several minutes from birth. Assisted ventilation >6 hours following delivery includes

infant given mechanical ventilation by any method for >6 hours (conventional, high frequency and/or continuous positive pressure). Birth injury includes skeletal fracture(s), peripheral nerve injury, and/or soft tissue/solid organ hemorrhage at present immediately following delivery or manifesting soon after delivery. Neonatal intensive care unit admission includes admission into a facility or unit staffed and equipped to provide continuous mechanical ventilator support for a newborn and infant death is defined as death of an infant within the first year of life.

Exposure variables

The exposure variable was mode of delivery in the second pregnancy. In objective 2a, women with one previous VD were categorized based on their mode of delivery; (1) those who had EPCD in the second pregnancy and (2) those who had a TOLAV (Figure 8). The EPCD group includes women with one previous VD who had primary CD with no attempt of trial of labor in the second pregnancy. The TOLAV group includes women with one previous VD who had a trial of labor in the second pregnancy. This includes women with successful TOLAV and failed TOLAV, Figure 8.

In objective 2b, women with one previous CD were categorized based on their mode of delivery; 1) those who had ERCD in the second pregnancy and (2) those who had a TOLAC (Figure 9). The ERCD group includes women with one previous CD who had repeat CD with no attempt of trial of labor in the second pregnancy. The TOLAC group includes women with one previous CD who had a trial of labor in the second pregnancy. This includes women with successful TOLAC and failed TOLAC, Figure 9.

Covariates

Co-variables include maternal age at delivery (grouped as <20 years, 20–29 years, 30-34 years, and ≥35 years); infant gender (male, female); smoking during pregnancy (yes, no); gestational age at delivery (37 – 38, 39 – 40, 41 weeks); education (some high school or less, graduated high school, college/university), maternal race (White, Black, Hispanic), marital status (yes, no) and first trimester prenatal care (yes, no).

Power

All available data was used for analysis for objective 3. For power calculation, for objective 3, with an alpha of 0.05, two-sided test, with given sample size, there was sufficient power (> 85%) to detect a difference of 20% between the comparison groups ("EPCD" versus "TOLAV") and ("ERCD" versus "TOLAC") for most of the outcomes assessed.

4.2.4 Statistical methods

The statistical analysis consisted of regression analysis in the original (unmatched) cohort of women and propensity score matching modelling in a matched cohort of women.

Regression analysis approach

Since the outcome variables of interest namely newborn antibiotic use, assisted ventilation immediately after delivery, assisted ventilation >6 hours following delivery, birth injury, neonatal intensive care unit admission and infant death were binary, dichotomized as yes or no, unconditional logistic regression models were developed in our first analysis to compare adverse birth outcomes between low risk women who underwent EPCD and TOLAV in the second pregnancy. Before developing the regression models, we initially assessed potentially

confounding covariates. We defined confounders as covariates that were statistically associated with the exposure variable and at least one of the outcome variable at significance level of $p<0.05$. Chi square test was used to evaluate the association between each potential confounder covariate and our exposure variable. We also conducted bivariate analysis to assess the association between potential confounding variables and our outcome variables by regressing each of the outcome variables separately on each potential confounder. Covariates with significance level of <0.05 identified from the wald test p-values in the bivariate analysis were considered as confounders. Maternal age and gestational age at delivery, based on their clinical importance were included in the model as confounders irrespective of their significance level. All other variables that met the inclusion criteria for confounding at a significance level of <0.05 were included in the unconditional logistic regression models. The variables adjusted in the logistic regression models were maternal age, race, marital status, infant gender, education, gestational age at delivery, smoking during pregnancy and prenatal visit in first trimester.

We then examined effect modifiers in the model. We included interaction terms (the multiplicative effect of two variables) in the logistic regression model to assess its contribution to the model. Interactions of maternal age, gestational age and race were assessed by each of the exposure group. All the interaction terms with a significance level of <0.05 were included in the final unconditional logistic regression models. The fit of the regression models with and without interaction terms were evaluated until a parsimonious model was selected. Crude, adjusted (OR) and 95% confidence interval (CI) were reported for each exposure group and each outcome. All tests were reported based on statistical significance, which was concluded if $p<0.05$.

To ascertain the influence of labor on neonatal outcomes, the analyses were repeated for a subgroup of women who underwent TOLAV and had unsuccessful outcome or failed TOLAV (requiring emergency primary CS) compared with those who had a successful TOLAV. The occurrences of birth outcomes in the unmatched cohort was evaluated using chi squared test and Fisher exact test where necessary for all the categorical variables. Crude, adjusted (OR) and 95% confidence interval (CI) were reported for each outcome. All tests were reported based on statistical significance of *p*-value of ≤0.05. Analyses were carried out using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Ottawa Hospital Research Institute Ethics Boards.

Propensity score matching modeling approach

In our second analysis, adverse birth outcomes were compared between EPCD and TOLAV groups using propensity score matching techniques. The propensity score matching technique was introduced by Rosenbaum and Rubin[130] to reduce bias in unbalanced groups usually seen in observational studies. One important property of propensity score is to create a balanced study population based on their characteristics or baseline covariates. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. In this study, the propensity score represents the baseline characteristics and is defined as the probability of undergoing EPCD relative TOLAV. The aim of using this statistical technique was to generate a matched cohort of women who are balanced in terms of their baseline characteristics. The first step in the propensity score analysis was to select baseline covariates of the study groups. The covariates included maternal age, race, marital status, infant gender, education, gestational age at delivery, smoking during pregnancy and prenatal visit in first

trimester. These variables were used to generate propensity scores in logistic regression model. Each variable was analyzed separately without using a stepwise procedure in the logistic regression model. Additionally, multiplicative interactions of maternal age, gestational age and race were assessed with all the covariates to get optimal balance between the delivery groups and infant outcomes.

In the next step, one-to-one nearest neighbor matching within a caliper distance or width of 0.25 standard deviation of the logit of the propensity score was employed. In nearest neighbor matching, the first randomly selected exposed women is matched to unexposed women with the closest propensity score of 0.25 caliper width.[131] After the matching procedure, the baseline characteristics of the matched cohort was compared with the unmatched group to assess balance of the covariates between the study groups before and after matching. The standardized difference of the covariates was used to assess the balance of the covariates between the two groups. This statistic was used because it is not influenced by sample size and compares the difference in means or proportion in units of the pooled standard deviation or proportions of balance of variables. [131] A standardized difference greater than the absolute value of 10% was used to indicate that the characteristics of the comparison group were imbalance or different. [131] Equation 1 shows details of computation of standard difference.

$$d = \frac{(\hat{P}_1 - \hat{P}_2)}{\sqrt{\frac{[\hat{P}_1(1-\hat{P}_1) + \hat{P}_2(1-\hat{P}_2)]}{2}}}$$

d is the standard difference and p^ and p^ denote the proportion of the baseline covariates in the EPCD versus TOLAV and ERCD versus TOLAC groups respectively.

Equation 1: Standard difference equation used to assess balance of covariates between EPCD versus TOLAV and ERCD versus TOLAC

Since the study cohort were matched, conditional logistic regression analysis was used to estimate odds ratio (OR) and 95% confidence interval (CI) for all adverse birth outcomes. The analyses were repeated for a subgroup of women who underwent TOLAV and had a failed TOLAV (requiring emergency primary CS) compared with those who had a successful TOLAV. All tests were reported based on statistical significance, which was concluded if *p*-value was ≤0.05. Analyses were carried out using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) for regression analysis. For the matched analysis, the R statistical software and the R MatchIt library was used (http://www.r-project.org/). The data source and statistical analysis described for objective two was described for objective three. Subgroup analyses were conducted for women who underwent TOLAC and had failed TOLAC (requiring emergency repeat CS) compared with those who had Successful TOLAC.

4.3 Results (objective 2)

4.3.1 Results objective 2a

The study cohort comprised low risk women with one previous VD with a singleton live birth without congenital anomalies, born in cephalic presentation at term by women with no medical problems such as pre-existing or pregnancy-related diabetes or hypertension in the second pregnancy. The un-matched cohort consisted of 1,416,537 women of whom 104,499 (0.74%) had EPCD and 1,312,038 (92.6%) had a TOLAV. The matched cohort consisted of 208,998 women of whom 104,499 had EPCD and 104,499 had a TOLAV (Figure 8).

4.3.1.1. Baseline characteristics of EPCD versus TOLAV before and after propensity score matching

Table 12 summarizes maternal baseline characteristics and the standardized difference between the TOLAV and EPCD groups before matching was performed. The baseline characteristics were unequally distributed between the two study groups with an absolute standardized difference of 10% in more than one third of the baseline covariates indicating imbalance between the two groups. Variables that had the most notable standardized differences between the two groups were maternal age at 20-29 years (60.9% vs 52.4%), ≥35 years (9.6% vs 16.0%) and early term period of delivery (31.5% vs 40.7%) with absolute standardized difference of -17.28, 19.43 and 19.27 for the TOLAV and EPCD groups respectively. Generally, the EPCD group were more likely to be older with higher educational level. They were also more likely to deliver at early term period of gestation whereas the TOLAV group were more likely to deliver at full and late term period of gestation.

Table 13 presents maternal baseline characteristics between the EPCD and TOLAV groups after propensity score matching was performed. Apart from maternal age at 30-34 years which had the highest absolute standardized difference of 12.98, all baseline characteristics were attenuated as indicated by small standardized differences between the TOLAV and ERCD groups after the matching procedure. Maternal age at 20-29 years, ≥35 years and early term period of delivery that showed a significant difference between the two groups in the unmatched cohort (Table 12) reduced in the matched cohort with rates at 56.8% vs 52.4% for aged 20-29 years, 15.8 vs 16.0 for aged ≥35 years and 39.6 vs 40.7 for early term period of delivery for the TOLAV and EPCD groups respectively. The absolute standardized rate for these variables decreased leading to small standard difference between the two groups with regards to maternal age at 20-29 years, ≥35 years and early term period. This resulted in a more balanced distribution of the variables.

4.3.1.2 Regression analysis estimates of adverse birth outcomes associated with EPCD versus TOLAV (reference group) in unmatched cohort of low risk women

Analyses results of adverse birth outcomes of EPCD versus TOLAV have been summarized in Table 14. Compared with neonates born by mothers who underwent TOLAV, those born by mothers who had EPCD were 1.3 times more likely to receive antibiotic after birth (OR=1.31, 95% CI: 1.22-1.40), 1.2 and 2.1 times more likely to receive assisted ventilation immediately after birth and ventilation > 6 hours after birth, (OR=1.29, 95% CI: 1.24-1.34) and (OR=2.10, 95% CI: 1.90-2.32) respectively. The babies of the mothers with EPCD were also 2.2 times more likely to be admitted to a neonatal intensive care unit (OR=2.21, 95% CI: 2.14-2.29) and 1.6 times more likely to die in the first year of life (OR=1.66, 95% CI: 1.47-1.87) than the babies of mothers who underwent TOLAV. However, the babies of mothers who had EPCD were 54%

less likely to have birth injury after delivery (OR=0.46, 95% CI: 0.32-0.66) relative to the babies of mothers who underwent TOLAV.

4.3.1.3 Subgroup regression analysis estimates of adverse birth outcomes associated with failed TOLAV versus successful TOLAV (reference group) in unmatched cohort of women

Results of the sub-group regression analysis is presented in Table 15. Compared with neonates delivered by mothers who had successful TOLAV, those delivered by mothers with failed TOLAV (requiring emergency primary CD) were 3.0 times more likely to require antibiotic. Neonates of mothers with failed TOLAV were also 2.3, 1.2 and 1.6 times more likely to receive assisted ventilation immediately after birth, ventilation > 6 hours after birth or die during the first year of life respectively. In addition, neonates of mothers with failed TOLAV were 3.2 times more likely to be admitted to a neonatal intensive care unit than neonates of mothers with successful TOLAV. However, there was no statistically difference between the two groups with respect to birth injury (OR=0.83, 95% CI: 0.55-1.25).

4.3.1.4 Propensity score matching estimates of adverse birth outcomes associated with EPCD versus TOLAV (reference group) in a matched cohort of low risk women

The results of adverse birth outcomes of EPCD versus TOLAV after propensity score matching modelling have been summarized in Table 16. The effect estimates for infant death were higher after the propensity score matching modelling. On the other hand, the effect estimate was lower for newborn birth injury, assisted ventilation immediately after delivery, ventilation >6 hours after delivery and neonatal intensive care unit admissions. However, the direction of the results was still the same as the regression estimates. Compared with neonates delivered by mothers who underwent TOLAV, those delivered by mothers who underwent who had EPCD were 1.3 times more likely to receive antibiotic after birth (OR=1.31, 95% CI: 1.19-1.45). The EPCD

group were also 1.3 and 2.0 times more likely to have neonates who required assisted ventilation immediately after birth and ventilation >6 hours after birth (OR=1.26, 95% CI: 1.20-1.33) and (OR=2.00, 95% CI: 1.71-2.35) respectively. Furthermore, the babies of the EPCD group were 2.1 times more likely to be admitted to a neonatal intensive care unit than the babies of the TOLAV group (OR=2.14, 95% CI: 2.03-2.27). Also, the babies of the EPCD group were 1.7 times more likely to suffer infant death (OR=1.73, 95% CI: 1.44-2.08) compared with the babies of the TOLAV group. However, newborn birth injury after delivery was 61% less likely to be associated with the EPCD group in relation to the TOLAV group (OR=0.39, 95% CI: 0.26-0.59).

4.3.1.5 Subgroup propensity score matching estimates of adverse birth outcomes associated with failed TOLAV versus successful TOLAV (reference group) in a matched cohort of women

Results of the sub-group propensity score analysis is presented in Table 17. Even though, the effect estimates for assisted ventilation immediately after birth at >6 hours were higher after the propensity score matching modelling and lower for newborn antibiotic use, birth injury, neonatal intensive care unit admissions, assisted ventilation immediately after birth and infant death, the direction of the results was similar to the regression estimates. There was no statistical difference with respect to newborn birth injury between the failed TOLAV (requiring emergency primary CD) and successful TOLAV groups. The results also showed rates were generally higher for newborn requirement for assisted ventilation immediately after birth and ventilation >6 hours, as well as antibiotic usage, neonatal intensive care unit admissions and infant death in the failed TOLAV group than successful TOLAV group.

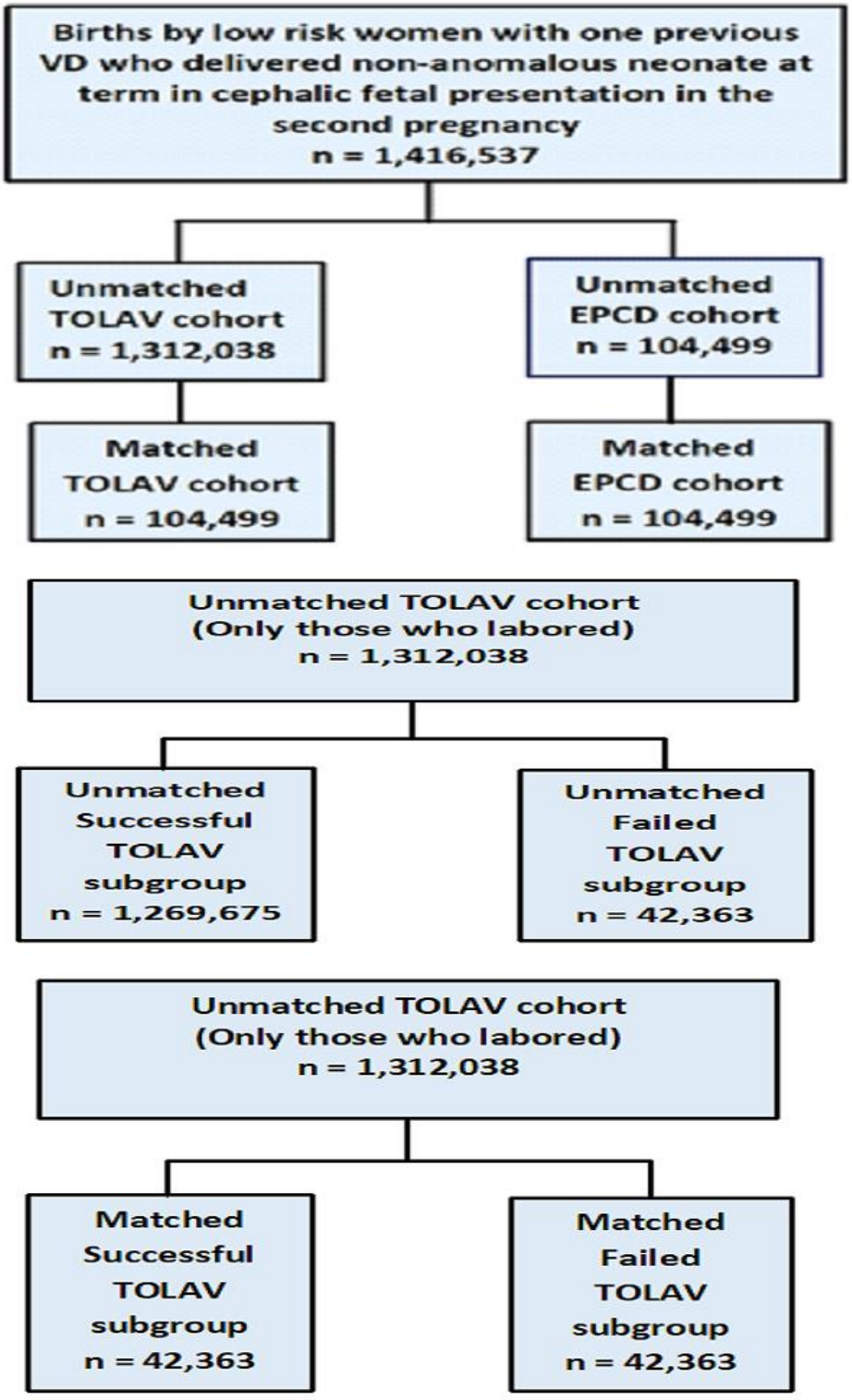

Figure 8. Flow diagram of study population of EPCD and TOLAV cohort of women for objective 2a.

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: EPCD, elective primary cesarean delivery; TOLAV, trial of labor after vaginal birth

Table 12: **Baseline characteristics of unmatched cohort of women with EPCD and TOLAV**			
Characteristics	**TOLAV** **n= 1,312,038 (%)**	**EPCD** **n= 104,499 (%)**	**Standardized** **difference (%)[a]**
Maternal age (years)			
<20	85,818 (6.54)	4,363 (4.18)	-10.49
20-29	799,176 (60.91)	54,737 (52.38)	-17.28
30-34	301,678 (22.99)	28,655 (27.42)	10.22
≥35	125,366 (9.56)	16,744 (16.02)	19.43
Maternal education (years)			
Some high school or less	249,734 (19.03)	17,243 (16.50)	-6.62
Graduated high school	336,979 (25.68)	25,699 (24.59)	-2.51
College/university	725,325 (55.28)	61,557 (58.91)	7.34
Maternal race			
White race	737,499 (56.21)	59,764 (57.19)	1.98
Black race	107,253 (8.17)	9,658 (9.24)	3.80
Hispanic race	369,022 (28.13)	28,158 (26.95)	-2.64
Gestational age (weeks)			
Early term	412,952 (31.47)	42,513 (40.68)	19.27
Full term	769,860 (58.68)	55,409 (53.02)	-11.42
Late term	129,226 (9.85)	6,577 (6.29)	-13.10
Male infant gender	667,987 (50.91)	55,250 (52.87)	3.92
Married	880,140 (67.08)	72,691 (69.56)	5.33
Smoked during pregnancy	115,980 (8.84)	9,067 (8.68)	-0.57
Had first trimester prenatal care	968,281 (73.80)	78,935 (75.54)	4.00

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: n, number; TOLAV, trial of labor after vaginal birth; EPCD, elective primary cesarean delivery.

a. Absolute standardized differences (%) for measuring baseline characteristics between women who underwent EPCD and TOLAV before propensity-score matching. A standardized difference of the absolute value of 10% indicates balance in the characteristics of the study groups[131] Equation 1 shows details of computation of standard difference.

Table 13: **Baseline characteristics of a matched cohort of women with EPCD and TOLAV**			
Characteristics	**TOLAV (n= 104,499) (%)**	**EPCD (n=104,499) (%)**	**Standardized difference (%)[a]**
Maternal age (years)			
<20	5810 (5.56)	4,363 (4.18)	-6.41
20-29	59389 (56.83)	54,737 (52.38)	-8.95
30-34	22825 (21.84)	28,655 (27.42)	12.98
>35	16475 (15.77)	16,744 (16.02)	0.68
Maternal education (years)			
Some high school or less	17243 (16.50)	17,243 (16.50)	-0.00
Graduated high school	24693 (23.63)	25,699 (24.59)	2.24
College/university	62563 (59.87)	61,557 (58.91)	-1.95
Maternal race			
White race	61082 (58.45)	59,764 (57.19)	-2.55
Black race	9194 (8.80)	9,658 (9.24)	1.54
Hispanic race	27,583 (26.40)	28,158 (26.95)	1.24
Gestational age (weeks)			
Early term	41373 (39.59)	42,513 (40.68)	2.22
Full term	56941 (54.49)	55,409 (53.02)	-2.95
Late term	6185 (5.92)	6,577 (6.29)	1.55
Male infant gender	55124 (52.75)	55,250 (52.87)	0.24
Married	72905 (69.77)	72,691 (69.56)	-0.46
Smoked during pregnancy	9199 (8.80)	9,067 (8.68)	-0.42
Had first trimester prenatal care	79146 (75.74)	78,935 (75.54	-0.47

Abbreviations: n, number; TOLAV, trial of labor after vaginal birth; EPCD, Elective primary cesarean delivery. Data used for analyses is from National Center for Health Statistics in the United States.

a. Absolute standardized differences (%) for measuring baseline characteristics between women who underwent EPCD and TOLAV after propensity-score matching. A standardized difference of the absolute value of 10% indicates balance in the characteristics of the study groups[131]. Equation 1 shows details of computation of standard difference.

Table 14: **Regression analysis estimates of adverse birth outcomes of EPCD versus TOLAV (reference group) in unmatched cohort of women**

Outcome	TOLAV N=1,312,038	EPCD N=104,499	Adjusted odds ratio [a] (95% CI)	p-value[b]
	n (%)	n (%)		
Newborn antibiotic use	8,687 (0.66)	927 (0.89)	1.31 (1.22-1.40)	<.0001
Newborn birth injury	866 (0.07)	31 (0.03)	0.46 (0.32-0.66)	<.0001
Assisted ventilation immediately after birth	30,341 (2.31)	3,161 (3.02)	1.29 (1.24-1.34)	<.0001
Assisted ventilation >6 hours	2,575 (0.20)	459 (0.44)	2.10 (1.90-2.32)	<.0001
Admission to neonatal intensive care unit	22,895 (1.74)	4,146 (3.97)	2.21 (2.14-2.29)	<.0001
Infant death	2,385 (0.18)	313 (0.30)	1.66 (1.47-1.87)	<.0001

Data used for analyses is from National Center for Health Statistics in the United States.
Abbreviations: n, number; TOLAV, trial of labor after vaginal birth; EPCD, Elective primary cesarean delivery; CI, confidence interval.
a. Adjusted for maternal age, race, education, prenatal care in first trimester, marital status, infant sex, smoking during pregnancy and gestational age at delivery.
b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

Table 15: Regression analysis estimates of adverse birth outcomes by subgroups - failed TOLAV versus successful TOLAV (reference group) in unmatched cohort of women

Outcome	Successful TOLAV N=1,269,675	Failed TOLAV N=42,363	Adjusted odds ratio [a] (95% CI)	p-value[b]
	n (%)	n (%)		
Newborn antibiotic use	7,870 (0.62)	817 (1.93)	3.04 (2.82-3.27)	<0.0001
Newborn birth injury	842 (0.07)	24 (0.06)	0.83 (0.55-1.25)	0.3677
Assisted ventilation immediately after birth	28,133 (2.22)	2,208 (5.21)	2.35 (2.24-2.45)	<0.0001
Assisted ventilation >6 hours	2,295 (0.18)	280 (0.66)	1.24 (1.12-1.37)	<0.0001
Admission to neonatal intensive care unit	20,695 (1.63)	2,200 (5.19)	3.18 (3.04-3.33)	<0.0001
Infant death	2,246 (0.18)	139 (0.33)	1.65 (1.39-1.97)	<0.0001

Data used for analyses is from National Center for Health Statistics in the United States.
Abbreviations: n, number; TOLAV, trial of labor after vaginal birth; EPCD, Elective primary cesarean delivery; CI, confidence interval.
a. Adjusted for maternal age, race, education, prenatal care in first trimester, marital status, infant sex, smoking during pregnancy and gestational age at delivery.
b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

Table 16: **Propensity score matched estimates of adverse birth outcomes of EPCD versus TOLAV (reference group) in a matched cohort of women**

Outcome	TOLAV N=104,499	EPCD N=104,499	Conditional odds ratio (95% CI)	p-value[a]
	n (%)	n (%)		
Newborn antibiotic use	708 (0.68)	927 (0.89)	1.31 (1.19-1.45)	<.0001
Newborn birth injury	79 (0.08)	31 (0.03)	0.39 (0.26-0.59)	<.0001
Assisted ventilation immediately after birth	2520 (2.41)	3,161 (3.02)	1.26 (1.20-1.33)	<.0001
Assisted ventilation >6 hours	229 (0.22)	459 (0.44)	2.00 (1.71-2.35)	<.0001
Admission to neonatal intensive care unit	1975 (1.89)	4,146 (3.97)	2.14 (2.03-2.27)	<.0001
Infant death	181 (0.17)	313 (0.30)	1.73 (1.44-2.08)	<.0001

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: n, number; TOLAV, trial of labor after vaginal birth; EPCD, Elective primary cesarean delivery CI, confidence interval. The TOLAV and EPCD study groups were matched according to the propensity score of maternal characteristics including maternal age, race, marital status, infant gender, education, gestational age at delivery, smoking during pregnancy and prenatal visit in first trimester.

a. The p-value was the Wald chi square p-value derived from logistic regression analysis.

Table 17: **Propensity score matched estimates of adverse birth outcomes by subgroups - failed TOLAV versus successful TOLAV (reference group) in a matched cohort of women**

Outcome	Successful TOLAV N= 42,363	Failed TOLAV N=42,363	Conditional odds ratio (95% CI)	p-value[a]
	n (%)	n (%)		
Newborn antibiotic use	286 (0.68)	817 (1.93)	2.91 (2.54- 3.34)	<.0001
Newborn birth injury	40 (0.09)	24 (0.06)	0.60 (0.36-1.00)	0.0479
Assisted ventilation immediately after birth	1027 (2.42	2,208 (5.21)	2.20 (2.04-2.38)	<.0001
Assisted ventilation >6 hours	85 (0.20)	280 (0.66)	3.29 (2.58-4.20)	<.0001
Admission to neonatal intensive care unit	753 (1.78)	2,200 (5.19)	3.02 (2.78-3.29)	<.0001
Infant death	96 (0.23)	139 (0.33)	1.45 (1.12-1.88)	0.0053

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: n, number; TOLAV, trial of labor after vaginal birth; CI, confidence interval.

The successful TOLAV and failed TOLAV study groups were matched according to the propensity score of maternal characteristics including maternal age, race, marital status, infant gender, education, gestational age at delivery, smoking during pregnancy and prenatal visit in first trimester.

a. The p-value was the Wald chi square p-value derived from logistic regression analysis

4.3.2 Results objective 2b

The study cohort comprised low risk women with one previous CD and a singleton live birth without congenital anomalies, born in cephalic presentation at term by women with no medical problems such as pre-existing or pregnancy-related diabetes or hypertension in the second pregnancy. The un-matched cohort consisted of 368,754 women of whom 321,811 had ERCD and 46,943 had a TOLAC. The matched cohort consisted of 93,886 women of whom 46,943 had ERCD and 46,943 had TOLAC (Figure 9).

4.3.2.1 Baseline characteristics of ERCD versus TOLAC before and after propensity score matching

Table 18 summarizes maternal baseline characteristics and the standardized difference between the ERCD and TOLAC groups before matching was performed. Most of the baseline characteristics were not evenly distributed between the two groups. Variables that had the most notable standardized differences between the groups were early term (33.1% vs 41.2%), late term delivery (10.3% vs 4.9%) and first prenatal care visit (71.2% vs 77.0%) with absolute standardized difference of 16.72, -20.27 and 13.40 respectively. Generally, the ERCD group were more likely to have first trimester prenatal care visit. They were also more likely to deliver at the early term period of gestation weeks whereas the TOLAC group were more likely to deliver at the full and late term period of gestation.

Table 19 presents maternal baseline characteristics between the ERCD and TOLAC groups after propensity score matching was performed. Generally, there was improvement with regards to balance of most of the baseline characteristics between the groups. Even though the standardized difference of maternal age at 30-34 years, women with college/university education and married

women did not reduce after propensity matching, the variables were less than 10% absolute standardized difference, the criterion used to indicate balance between the groups. Early term, late term gestational periods of delivery and the first prenatal care visit that showed a significant difference between the two groups in the unmatched cohort in Table 18 decreased resulting in a more balanced distribution of these variables, Table 19. The absolute standardized rates for these variables were 2.10, 0.92, and -0.07 for early term, late term gestational period and first prenatal care visit respectively. The standardized differences for all the other baseline characteristics between the ERCD and TOLAC group reduced as demonstrated by small standardized differences between the groups after the property score matching.

4.3.2.2 Regression analysis estimates of adverse birth outcomes associated with ERCD versus TOLAC (reference group) in unmatched cohort of women

The adverse birth outcomes of ERCD versus TOLAC have been summarized in Table 20. Compared with neonates born by mothers who underwent TOLAC, those born by mothers who had ERCD were 13% less likely to require assisted ventilation immediately after birth (OR=0.87, 95% CI: 0.82-0.91) and 24% less likely to be admitted to a neonatal intensive care unit (OR=0.76, 95% CI: 0.72-0.80). The babies delivered by the ERCD group were also 54% less likely to require antibiotic after birth (OR=0.46, 95% CI: 0.43-0.50) and 68% less likely to have birth injury after delivery (OR=0.32, 95% CI: 0.20-0.49) than the babies delivered by the TOLAC group. However, while the rates of newborn assisted ventilation >6 hours and infant death were lower in the ERCD group than the TOLAC group, it was not statistically different between the two delivery groups (OR=0.86, 95% CI: 0.74-1.00) and (OR=0.96, 95% CI: 0.76-1.20) respectively.

4.3.2.3 Subgroup regression analysis estimates of adverse birth outcomes associated with failed TOLAC versus successful TOLAC (reference group) in unmatched cohort of women

Results of the sub-group regression analysis are presented in Table 21. Compared with neonates delivered by mothers who had successful TOLAC, those delivered by mothers who had failed TOLAC (requiring emergency repeat CD) had 1.2 likelihood of requiring antibiotic after birth (OR=1.18, 95% CI: 1.02-1.35) and 1.5 times for admission to a neonatal intensive care unit (OR=1.48, 95% CI: 1.35-1.63). The neonates of mothers in the failed TOLAC group were also 1.4 times more likely to require assisted ventilation immediately after birth (OR=1.42, 95% CI: 1.29–1.56) and 1.6 times for requiring ventilation >6 hours after birth (OR=1.64, 95% CI: 1.24–2.17) than the neonates of mothers in the successful TOLAC group. Even though the rate of newborn birth injury was lower, and infant death was higher in the failed TOLAC group relative to the successful TOLAC, they were not statistically different between the two groups (OR=0.60, 95% CI: 0.26-1.35) for birth injury and (OR=1.23, 95% CI: 0.81-1.89) for infant death.

4.3.2.4 Propensity score matching estimates of adverse birth outcomes associated with ERCD versus TOLAC (reference group) in a matched cohort of women

The adverse birth outcomes of ERCD versus TOLAC have been summarized in Table 22. The effect estimates for newborn antibiotic usage after birth, admission to a neonatal intensive care unit and infant death were slightly higher after the propensity score matching. On the other hand, the effect estimate was slightly lower for newborn birth injury, requirement for assisted ventilation immediately after delivery and at >6 hours. However, the direction of the results was still the same as the regression estimates. Compared with the babies of mothers who had TOLAC, the babies of mothers who had ERCD were 18% less likely to require assisted ventilation immediately after delivery, (OR=0.82, 95% CI: 0.77-0.88) and 20% less likely to be

admitted to a neonatal intensive care unit (OR=0.80, 95% CI: 0.74-0.85). They were also 52% less likely to receive antibiotic after birth (OR=0.48, 95% CI: 0.43-0.55) and 73% less likelihood for birth injury (OR=0.27, 95% CI: 0.11-0.60) in the ERCD group compared with the TOLAC group respectively. Like the regression estimates, there was no statistically difference with regards to newborn assisted ventilation >6 hours and infant death between the two groups.

4.3.2.5 Subgroup propensity score matching estimates of adverse birth outcomes associated with failed TOLAC versus successful TOLAC (reference group) in a matched cohort of women.

Results of the sub-group propensity score analysis is presented in Table 23. The analysis showed that the magnitude of the effect estimates of birth injury and infant death were higher whereas newborn ventilation support immediately after birth, ventilation at >6 hours after birth, antibiotic use and neonatal intensive care unit admissions were lower after the propensity score matching. The direction of the results changed for newborn antibiotic use and requirement for ventilation at >6 hours after birth. In detail, the one-fold modest rate (OR=1.18, 95% CI: 1.02-1.35) of newborn requirement for antibiotic after birth in the regression analysis (Table 21) resulted in no statistically difference between the failed TOLAC and successful TOLAC groups after the propensity score matching (OR=1.03, 95% CI: 0.87-1.21), Table 23. Likewise, the more than one-fold likelihood (OR=1.64, 95% CI: 1.24–2.17) of newborn requirement for ventilation >6 hours after birth resulted in no statistically difference between the failed TOLAC compared with the successful TOLAC group after the propensity score matching (OR=1.30, 95% CI: 0.98-1.73). Even though the magnitude of the effect estimate changed for newborn ventilation support immediately after birth, neonatal intensive care unit admissions, birth injury and infant death after the propensity score matching, the direction of the results was like the regression estimates. Neonates of mothers with a failed TOLAC had a modest likelihood of requiring ventilation

support immediately after birth (OR=1.10, 95% CI: 1.00-1.23) and being admitted to a neonatal intensive care unit (OR=1.14, 95% CI: 1.00-1.29) compared with the neonates of mothers with successful TOLAC. Even though the rate of newborn birth injury and infant death were higher in the failed TOLAC group relative to the successful TOLAC group, they were not statistically different between the two groups with rates of (OR=1.35, 95% CI: 0.76-2.41) for birth injury and (OR=1.70, 95% CI: 0.98-2.95) for infant death.

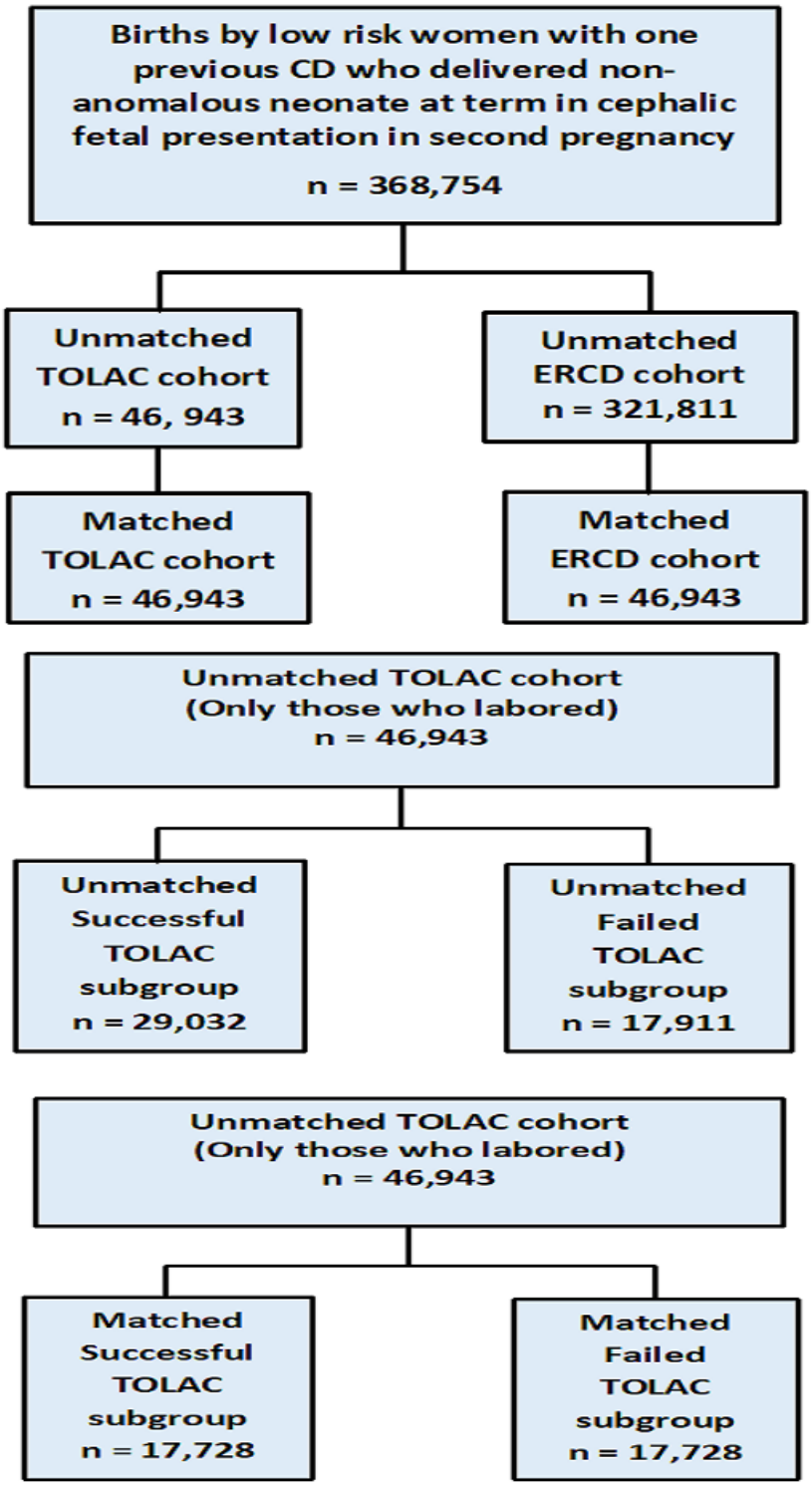

Figure 9. Flow diagram of study population of ERCD and TOLAC cohort of women for objective 2b.

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: ERCD, elective primary cesarean delivery; TOLAC, trial of labor after cesarean birth

Table 18: **Baseline characteristics of unmatched cohort of women with ERCD and TOLAC**			
Characteristics	**TOLAC N=46,943 (%)**	**ERCD N=321,811 (%)**	**Standardized difference (%)[a]**
Maternal age (years)			
<20	2,269 (4.8)	13,476 (4.2)	-3.08
20-29	25,689 (54.7)	167,281 (52.0)	-5.49
30-34	12,699 (27.1)	89,726 (27.9)	1.86
>35	6,286 (13.4)	51,328 (16.0)	7.24
Maternal education (years)			
Some high school or less	8, 837 (18.8)	52,235 (16.2)	-6.85
Graduated high school	10,344 (22.0)	77,905 (24.2)	5.22
College/university	27,762 (59.1)	191,671 (59.6)	0.86
Maternal race			
White race	24,194 (51.5)	180,057 (56.0)	8.85
Black race	4,760 (10.1)	26,809 (8.3)	-6.25
Hispanic race	14,161 (30.2)	89,183 (27.7)	-5.43
Gestational age (weeks)			
Early term	15,553 (33.1)	132,516 (41.2)	16.72
Full term	26,572 (56.6)	173,457 (53.9)	-5.43
Late term	4,818 (10.2)	15,838 (4.9)	-20.27
Male infant gender	23,996 (51.1)	165,057 (51.3)	0.34
Married	33,702 (71.8)	228,493 (71.0)	-1.75
Smoked during pregnancy	2,833 (6.0)	27,277 (8.5)	9.46
First trimester prenatal care	33,404 (71.2)	247,861 (77.0)	13.40

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: n, number; TOLAC, trial of labor after cesarean birth; ERCD, elective repeat cesarean delivery.

a. Absolute standardized differences (%) for measuring baseline characteristics between women who underwent ERCD and TOLAC after propensity-score matching. A standardized difference of the absolute value of 10% indicates balance in the characteristics of the study groups.[131] Equation 1 shows details of computation of standard difference.

Table 19: **Baseline characteristics of a matched cohort of women with ERCD and TOLAC**			
Characteristics	**TOLAC N=46,943 (%)**	**ERCD N=46,943 (%)**	**Standardized difference (%)[a]**
Maternal age (years)			
<20	2,269 (4.8)	2,187 (4.7)	-0.80
20-29	25,689 (54.7)	25,291 (53.9)	-1.69
30-34	12,699 (27.1)	13,557 (28.9)	4.08
>35	6,286 (13.4)	5,908 (12.6)	-2.38
Maternal education (years)			
Some high school or less	8,837 (18.8)	8,480 (18.1)	-1.96
Graduated high school	10,344 (22.0)	11,279 (24.0)	4.73
College/university	27,762 (59.1)	27,184 (57.9)	-2.50
Maternal race			
White race	24,194 (51.5)	23,789 (50.7)	-1.72
Black race	4,760 (10.1)	4,773 (10.2)	0.10
Hispanic race	14,161 (30.2)	14,630 (31.2)	2.17
Gestational age (weeks)			
Early term	15,553 (33.1)	16,017 (34.1)	2.10
Full term	26,572 (56.6)	25,976 (55.3)	-2.54
Late term	4,818(10.3)	4,950 (10.5)	0.92
Male infant gender	23,996 51.1)	23,979 (51.1)	-0.08
Married	33,702 (71.8)	33,146 (70.6)	-2.61
Smoked during pregnancy	2,833 (6.0)	2,928 (6.2)	0.88
First trimester prenatal care	33,404 (71.2)	33,391 (71.1)	-0.07

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: n, number; TOLAC, trial of labor after cesarean birth; ERCD, elective repeat cesarean delivery.

a. Absolute standardized differences (%) for measuring baseline characteristics between women who underwent ERCD and TOLAC after propensity-score matching. A standardized difference of the absolute value of 10% indicates balance in the characteristics of the study groups.[131] Equation 1 shows details of computation of standard difference.

Table 20: **Regression analysis estimates of adverse birth outcomes of ERCD versus TOLAC (reference group) in unmatched cohort of women**

Outcome	TOLAC N=46,943	ERCD N=321,811	Adjusted odds ratio [a]	p value[b]
	n (%)	n (%)	95% CI	
Newborn antibiotic use	810 (1.7)	2,650 (0.8)	0.46 (0.43-0.50)	<.0001
Newborn birth injury	30 (0.06)	65 (0.02)	0.32 (0.20-0.49)	<.0001
Assisted ventilation immediately after birth	1,848 (3.9)	11,083 (3.4)	0.87 (0.82-0.91)	<.0001
Assisted ventilation >6 hours	204 (0.4)	1,258 (0.4)	0.86 (0.74-1.00)	0.0554
Admission to neonatal intensive care unit	1,783 (3.8)	9,643 (3.0)	0.76 (0.72-0.80)	<.0001
Infant death	87 (0.2)	586 (0.2)	0.96 (0.76-1.20)	0.6994

Data used for analyses is from National Center for Health Statistics in the United States.
Abbreviations: n, number; TOLAC, trial of labor after cesarean birth; ERCD, elective repeat cesarean delivery; CI, confidence interval.
a. Adjusted for maternal age, race, education, prenatal care in first trimester, marital status, infant sex, smoking during pregnancy and gestational age at delivery.
b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

Table 21: **Regression analysis estimates of adverse birth outcomes by subgroups - failed TOLAC versus successful TOLAC (reference group) in unmatched cohort of women**

Outcome	Successful TOLAC N=29,032	Failed TOLAC N= 17,911	Adjusted odds ratio [a]	p-value[b]
	n (%)	n (%)	95% CI	
Newborn antibiotic use	471 (1.62)	339 (1.89)	1.18 (1.02-1.35)	0.0260
Newborn birth injury	22 (0.08)	8 (0.04)	0.60 (0.26-1.35)	0.2136
Assisted ventilation immediately after birth	991 (3.41)	857 (4.78)	1.42 (1.29-1.56)	<.0001
Assisted ventilation >6 hours	102 (0.35)	102 (0.57)	1.64 (1.24-2.17)	0.0005
Admission to neonatal intensive care unit	929 (3.20)	854 (4.77)	1.48 (1.35-1.63)	<.0001
Infant death	48 (0.17)	39 (0.22)	1.23 (0.81-1.89)	0.3336

Data used for analyses is from National Center for Health Statistics in the United States.
Abbreviations: n, number; TOLAC, trial of labor after cesarean birth; CI, confidence interval.
a. Adjusted for maternal age, race, education, prenatal care in first trimester, marital status, infant sex, smoking during pregnancy and gestational age at delivery.
b. The p-value was the Wald chi square p-value derived from logistic regression analysis.

Table 22: **Propensity score matched estimates of adverse birth outcomes of EPCD versus TOLAC (reference group) in a matched cohort of women**

Outcome	TOLAC N=46,943	ERCD N=46,943	Conditional odds ratio (95% CI)	p-value[a]
	n (%)	n (%)		
Newborn antibiotic use	810 (1.7)	397 (0.9)	0.48 (0.43-0.55)	<.0001
Newborn birth injury	30 (0.06)	8 (0.02)	0.27 (0.11-0.60)	0.0009
Assisted ventilation immediately after birth	1,848 (3.9)	1,529 (3.3)	0.82 (0.77-0.88)	<.0001
Assisted ventilation >6 hours	204 (0.4)	172 (0.4)	0.84 (0.69-1.03)	0.0993
Admission to neonatal intensive care unit	1,783 (3.8)	1,427 (3.0)	0.80 (0.74-0.85)	<.0001
Infant death	87 (0.2)	96 (0.2)	1.10 (0.83-1.48)	0.5060

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: n, number; TOLAC, trial of labor after cesarean birth; ERCD, elective repeat cesarean delivery CI, confidence interval. The TOLAC and ERCD study groups were matched according to the propensity score of maternal characteristics of maternal age, race, marital status, infant gender, education, gestational age at delivery, smoking during pregnancy and prenatal visit in first trimester.

a. The p-value was the Wald chi square p-value derived from logistic regression analysis.

Table 23: **Propensity score matched estimates of adverse birth outcomes by subgroups - failed TOLAC versus successful TOLAC (reference group) in a matched cohort of women**

Outcome	Successful TOLAC N=17,728	Failed TOLAC N=17,728	Conditional odds ratio (95% CI)	p-value[a]
	n (%)	n (%)		
Newborn antibiotic use	291 (1.6)	299 (1.7)	1.03 (0.87-1.21)	0.7353
Newborn birth injury	20 (0.1)	27 (0.2)	1.35 (0.76-2.41)	0.3090
Assisted ventilation immediately after birth	723 (4.1)	798 (4.5)	1.10 (1.00-1.23)	0.0483
Assisted ventilation >6 hours	86 (0.5)	112 (0.6)	1.30 (0.98-1.73)	0.0654
Admission to neonatal intensive care unit	483 (2.7)	544 (3.1)	1.14 (1.00-1.29)	0.0495
Infant death	25 (0.1)	39 (0.2)	1.70 (0.98-2.95)	0.0597

Data used for analyses is from National Center for Health Statistics in the United States.

Abbreviations: n, number; TOLAC, trial of labor after cesarean birth CI, confidence interval.

The successful TOLAC and failed TOLAC study groups were matched according to the propensity score of maternal characteristics of maternal age, race, marital status, infant gender, education, gestational age at delivery, smoking during pregnancy and prenatal visit in first trimester.

a. The p-value was the Wald chi square p-value derived from logistic regression analysis.

4.5 Discussion

This study assessed the adverse birth outcomes in second pregnancy between low risk women with one previous VD who underwent EPCD versus TOLAV, and those with one previous CD who underwent ERCD versus TOLAC using regression estimates and propensity score matching approach. The following are summary of the findings and are discussed according to study objectives two and three and associated research questions.

Objective 2a: To compare adverse birth outcomes among low risk women who underwent EPCD and TOLAV at term in cephalic presentation in the second pregnancy.

Research Question Three: What are the adverse birth outcomes associated with EPCD compared TOLAV in low risk women with term cephalic presentation in the second pregnancy?

It was found in the regression analysis results of the low risk women that babies born by mothers with one previous VD who underwent an EPCD in second pregnancy were more likely than babies born to mothers who underwent TOLAV to require antibiotic after birth. The babies of the EPCD group had increased likelihood of requiring ventilation support immediately after delivery, be admitted to neonatal intensive care unit, or die in the first year of life compared with the babies of the TOLAV group. However, the babies of the EPCD group had decreased likelihood of having birth injury after delivery relative to the babies of the TOLAV group. Analysis using propensity score matched cohort of women showed a similar trend of results. Though the magnitude of the effect estimates increased for outcomes such as infant death and decreased for others (requirement for ventilation support, birth injury and neonatal intensive care unit admissions) when compared to what was reported for the regression analysis, the general direction of association of these outcomes between EPCD and TOLAV remained the same as in the regression analysis.

There are few data in literature that have specifically compared adverse birth outcomes in second pregnancy in low risk women with one previous VD who underwent EPCD versus TOLAV at term in cephalic presentation using propensity score matching approach. Geller et al[132] used regression analysis to examine neonatal outcomes related to planned VD versus planned CD. The authors found lower rates of neonatal intensive care unit admissions among babies born by women who had planned VD in relation to planned CD, but their study was based on outcomes in the first pregnancy whereas this present study focused on outcomes in the second pregnancy. Bickford and colleagues[133] found that the rate of neonatal intensive care unit admissions was lower among babies born to mothers who had planned VD than babies born by mothers who had planned CD, and there was no difference between the two groups with regards to neonatal requirement for ventilation after birth. However, their study population included women with one or more prior VDs whereas this present study population included women with one previous VD.

The findings suggest that even though the EPCD group was associated with adverse infant outcomes in relation to the TOLAV group, the babies of the EPCD group had protective effect with regards to birth injury than the babies of the TOLAV group. Not all adverse birth outcomes were assessed in the study. It has to be noted that our analyses were based on select infant outcomes such as newborn requirement for antibiotic and birth injury that have not been examined sufficiently among EPCD versus TOLAV groups. One explanation for the more likelihood of adverse birth outcomes in the EPCD group than TOLAV group may be due to confounding by indication. Unlike hospital data that have the indication for CD and previous birth history, birth certificate data do not have these variables. This study focused on low risk

births by excluding women with no medical problems such as pre-existing or pregnancy-related diabetes or hypertension and non-cephalic presentation births such as breech presentation. In the regression analysis, women who had EPCD tended to be older, and the likelihood of older age contributing to the higher birth outcomes could not be ruled out. However, in a secondary analysis where maternal characteristics including maternal age were matched between the EPCD and TOLAV group using propensity score technique, it was found that except for birth injury, adverse birth outcomes were still apparent in the EPCD group than TOLAV group suggesting unmeasured factors of other underlying clinical factors including indications for the CD, maternal obesity, previous birth experience may have necessitated the requirement for an EPCD and may have played a role in the adverse outcomes seen among the EPCD group than the TOLAV group. However, these variables were not available in our dataset and therefore not possible for us to account for in this study.

Objective 2b: To compare adverse birth outcomes among low risk women who underwent ERCD and TOLAC at term in cephalic presentation in the second pregnancy

Question Five: What are the adverse birth outcomes associated with ERCD compared TOLAC in low risk women with term cephalic presentation in the second pregnancy?

The regression analyses results demonstrate that among women with one previous CD, newborn adverse birth outcomes at second birth were generally less frequent among babies born by mothers who had ERCD compared with babies born to mothers who underwent TOLAC. The results in the propensity score matched analysis showed similar trend as the regression analysis although the effect estimates in the former were slightly higher for rates of neonatal intensive care unit admissions and antibiotic use after delivery, and slightly lower for newborn birth injury and requirement for assisted ventilation immediately after delivery. Specifically, in both

regression and propensity score analyses, babies of mothers who had ERCD had less likelihood of requiring assisted ventilation immediately after delivery, antibiotic usage, birth injury after delivery and admitted to a neonatal intensive care unit. However, there were comparable rates found between the ERCD and TOLAC groups with regards to newborn requirement for assisted ventilation >6 hours and infant death. These observations are in agreement with other studies [102-103] even though not all of our neonatal outcomes were examined in previous studies. Also, few studies have used propensity score matching, and even so these studies and this present study differed by study population.

Kok and associates[103] performed a similar study in a matched cohort based on propensity score matching, but the authors included women with maternal health conditions such as pre-existing and pregnancy induced hypertension whereas our study focused on low risk deliveries and excluded women with these conditions. They found no difference with regards perinatal death between the women who had TOLAC and ERCD. Gilbert and colleagues[102] also found no difference existed with respect to neonatal death among the TOLAC and ERCD groups, but also included in their study women with health conditions such as pre-existing and gestational diabetes and hypertension. However, three studies[9, 13, 118] that used regression analysis to examine neonatal outcomes in relation to ERCD and TOLAC reported between higher perinatal and infant death associated with the TOLAC group than ERCD group.

Regarding neonatal intensive care unit admission, Patel et al[9] Kamath et al[115] and Go et al[134] all found that neonates delivered by ERCD were more likely to be admitted to neonatal intensive care unit than those delivered by TOLAC. With regards to birth injury, Alexander et al[135] found

fetal injury after birth was lowest among babies born to mothers with ERCD, which was consistent with findings in our study. However, Alfirevic et al[136] found no difference in birth injury among babies of mothers with planned immediate CDs and planned VDs, but their study was based on preterm births whereas our study was based on babies delivered at term by low risk mothers.

Even though we found the babies of the ERCD group had lower adverse outcome than the babies of TOLAC group, just like neonatal outcomes in objective 2a, analyses for this section were also based on select infant outcomes such as newborn requirement for antibiotic and birth injury that have not been explored among ERCD versus TOLAC groups. Results of other outcomes in our study such as neonatal intensive care unit admission and infant outcomes were consistent with results of previous studies that have explored these outcomes. Evidence from future studies may provide more insight regarding the effect of mode of delivery and the likelihood of newborn antibiotic usage and birth injury.

4.5.1 Strengths and limitations

Strength

The National Center for Health Statistics (NCHS) data analyzed for this study was large and provided the ability to conduct propensity score matching analysis as well as sub-group analyses, examining differences in rates of uncommon outcomes such as newborn antibiotics and birth injury while controlling for a variety of potential confounding variables. Also, even though propensity score matching approach has been used in a wide variety of pharmaco-epidemiology studies[137], there is growing interest in the application of this approach in the field of reproductive and perinatal epidemiologic studies. The application of propensity score methods used in this

study allowed for the distribution of covariates to be balanced between the exposure groups. Comparing the results of propensity score matching analysis and traditional multivariable regression analysis also provided additional level of evidence for the robustness of the study findings.

Limitation

This study has several limitations. First, confounding by indication is a common issue in observational studies. To reduce the potential for this confounding in objectives 2a and 2b, the analyses were performed among low risk women by excluding data for women with pre-existing and chronic medical problems, and those who delivered by non-cephalic fetal presentation which have been shown to be a common reason for cesarean birth. However, these exclusions may be inadequate, and residual confounding may still have occurred.

Although propensity score method was applied in this research to generate balanced covariate among the exposure group, it has limitations. Propensity scores can be estimated from measured covariates, therefore, residual confounding is a problem where unknown confounders and desired characteristics were not available to be accounted for this study. The data used for this research contained information on maternal medical conditions, obstetric factors, types of delivery as well as demographic information, but the dataset did not contain information on variables such as duration of neonatal intensive care unit admissions and maternal pre-pregnancy obesity, an important confounder for having a CD.

In addition, administrative databases are generally subject to underreporting of medical risk factors and obstetric complications, and there may be concerns about inconsistency in coding, recording and misclassification of certain factors such as smoking status in pregnancy. Another limitation is the wide confidence intervals for some of the results. However, this may be explained by the limited data associated with rare outcomes such as infant death, newborn birth injury and antibiotic use among healthy term deliveries. Despite these limitations, our data offers health care providers and women information useful for counselling about adverse birth outcomes separately for women with one previous VD who underwent EPCD versus TOLAV and those with one previous CD who underwent ERCD versus TOLAC.

4.6 Lessons learned from the findings of objective 2

The aim for objective 2a and 2b was to assess adverse birth outcomes between low risk women with one previous VD who had EPCD compared with TOLAV birth in second pregnancy (objective 2a) and those with one previous CD who had ERCD versus TOLAC birth in second pregnancy (objective 2b). For objective 2a, the findings provide new evidence that in second pregnancies following one previous VD, the rates of specific adverse birth outcomes such as newborn requirement for antibiotic after birth, ventilation support immediately after delivery and >6 hours, neonatal intensive care unit admission and infant death were higher in women who underwent EPCD than TOLAV. On the other hand, newborn birth injury was lower in the EPCD group than the TOLAV group. This area of research has received little attention.

For objective 2b, it was found that in second pregnancies following one previous CD, some neonatal outcome rates were lower for mothers who underwent ERCD compared with TOLAC,

whereas some were similar for both the ERCD and TOLAC groups. Specifically, the rates of newborn requirement for antibiotic after birth, ventilation support immediately after delivery and neonatal intensive care unit admissions were lower in women who underwent ERCD compared with TOLAC in second pregnancies. On the other hand, the occurrence of newborn requirement for assisted ventilation >6 hours after birth and infant death were comparable between the ERCD and TOLAC group.

Chapter 5:

Assessing the cost effectiveness of having a trial of labor after cesarean birth (TOLAC) and elective repeat cesarean delivery (ERCD) among women with low risk deliveries (objective 3)

5.1 Introduction

In 2012/2013, the Canadian Institute of Health Information reported child birth was the common reason for inpatient hospitalization, accounting for 369,454 hospital stays in Canada[3,138] Additionally, there were more cesarean delivery (CD) than any other inpatient surgery in Canada.[3, 138] There has been increase in rates of repeat CD and a decline in trial of labor after cesarean (TOLAC) for the past two decades due to concerns about uterine rupture[9] Despite the reported rarity of uterine rupture (absolute risk of less than 1%), some obstetricians are reluctant to recommend TOLAC[13,15] Women with a previous CD has the option to either undergo a TOLAC or elective repeat cesarean delivery (ERCD). Many of these women usually choose a repeat CD[9] even though TOLAC have been demonstrated to be a viable and safe alternative delivery option for majority of women with a prior low segment CD who are eligible for a TOLAC[13-15] Previous studies have shown women who undergo a TOLAC have between 60%–80% probability of having a successful vaginal delivery (VD)[15,111] There is growing concern regarding CD performed with no clinical indication, since it affects the health outcomes of women and their off springs and has economic implication for the health care system due to a longer recovery period and hospital stay.[29]

Despite the increasing rate of CD and its significant cost to the health care delivery system, a few studies comparing TOLAC and ERCD have incorporated economic analyses and most of these

studies took place in the United States (US) and Ireland.[37-40] There is still dearth of information on the cost effectiveness of TOLAC and ERCD, particularly as it relates to cost and variations in health-related quality of life associated with maternal and neonatal outcomes in Canada.

The aim of this chapter was to assess the cost effectiveness of having a TOLAC and ERCD among women with low risk deliveries. Results generated from this study will add to the body of knowledge regarding health service use related to child birth and will also be useful in the planning of perinatal care.

5.2 Methods

5.2.1 Design and study population

Design

The design was a short-term cost effectiveness analysis which was conducted to evaluate the potential cost and complications of TOLAC compared with ERCD. Cost effectiveness was measured in terms of incremental cost per quality adjusted life years (QALYs) gained.

Target population

The target population consisted of a hypothetical cohort of 100,000 low risk women with a previous low transverse CD who opt to have an ERCD and those who had no contraindication to TOLAC with results presented on a per woman basis. Deliveries of these women were at term with singleton pregnancies. The intervention for the study is TOLAC whereas the comparator is ERCD which is a routine mode of delivery after a previous CD.

5.2.2 Perspective and time horizon of economic evaluation

Perspective

The perspective of an economic analysis reveals the range of costs that need to be considered in the analysis. Cost was analyzed from the perspective of the health care payer system. As a result, the range of costs that were utilized in the model included direct medical cost incurred by the health care system.

Time horizon

A time horizon of six weeks was utilized in the study to capture the events taking place during the beginning of admission for delivery and child birth till the mother and child are discharged from the hospital. This time horizon takes into consideration the average maternal postpartum recovery period which rarely exceeds six weeks. Discounting was not necessary since this was a short-term analysis where both costs and QALYs were captured within the six weeks' time horizon used in the model.

5.2.3 Decision analytic model structure

Decision analytic model

In order to assess the cost effectiveness of the two modes of delivery, a decision tree model depicted in Figure 10 was developed to capture the possible pathways and most likely scenarios that could occur in each delivery stream including type of delivery, maternal and neonatal complications and death. At the start of the model is the decision of a mother to either have a TOLAC or ERCD. Some women in the TOLAC arm will experience a successful TOLAC while others will experience a failed TOLAC. After a successful TOLAC, the mother may be alive

with or without maternal complications, or may die during or following the delivery. Women with a failed TOLAC will receive an emergency CD. Maternal complications of a failed TOLAC may result with the mother alive after delivery with or without maternal complications, or may die during or after the delivery. Likewise, women in the ERCD arm will have maternal outcomes resulting with the mother alive following delivery with or without maternal complications, or may die during or following the delivery. The same analyses for neonatal complications were incorporated in the model.

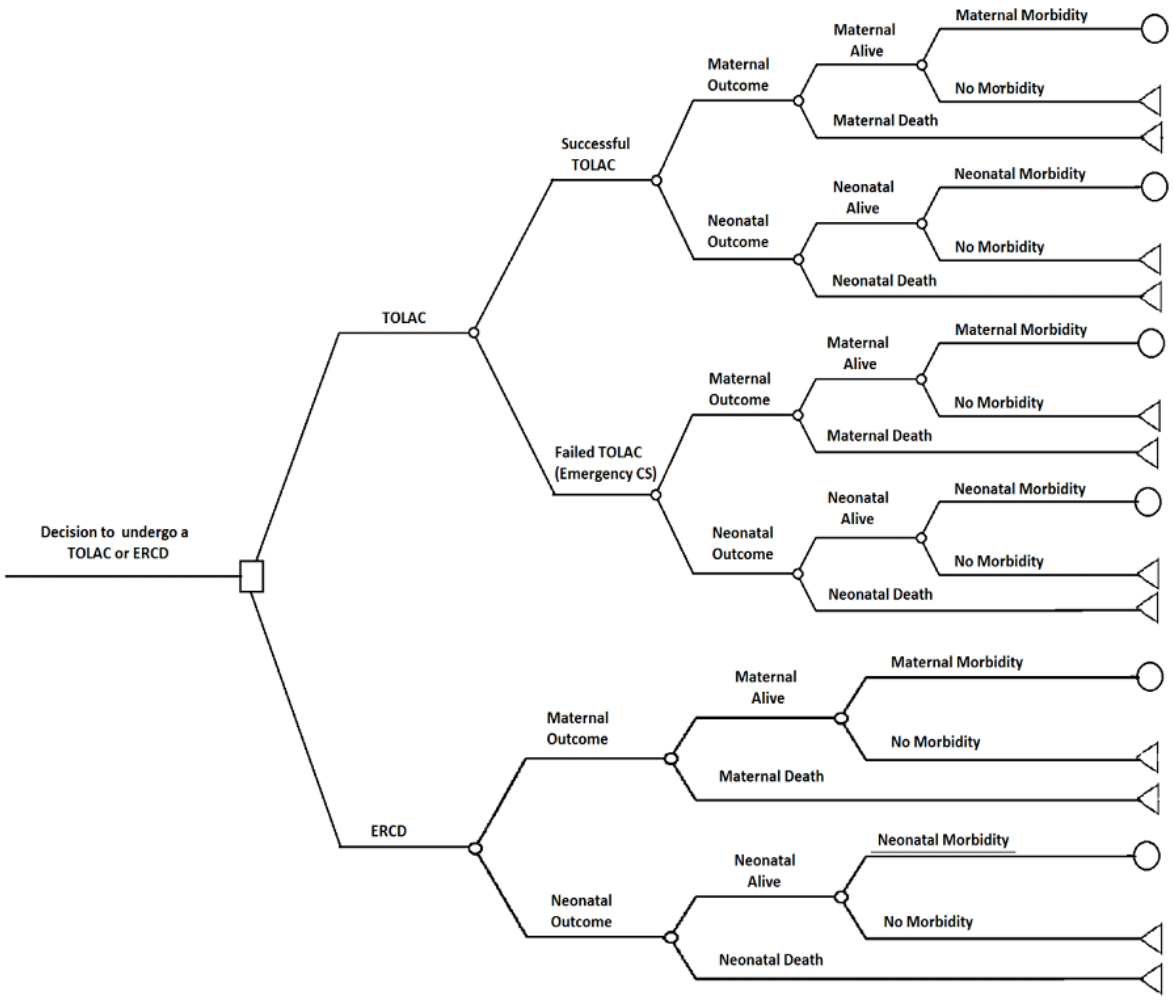

Figure 10. Decision tree model for TOLAC versus ERCD

Abbreviations: CS = cesarean section; ERCD = elective repeat cesarean delivery; TOLAC = trial of labor after cesarean birth. Maternal outcomes include maternal death, hysterectomy, endometritis, thromboembolic events, uterine rupture during a trial of labor and the need for transfusion; Neonatal outcomes comprised neonatal death, respiratory distress syndrome, transient tachypnea of the new born, hypoxic ischemic encephalopathy, neonatal intensive care utilization.

□ - The decision to undergo a TOLAC or ERCD

O - Chance nodes which lead to an event for specified probabilities

Δ - Final outcomes

5.2.4 Data inputs required for model

In objective 2, our analyses were based on select outcomes identified from birth certificate data including newborn antibiotic use and birth injury that have not been sufficiently assessed using propensity scored techniques. Given the rare events of outcomes such as maternal death, uterine rupture, neonatal death and hypoxic ischemic encephalopathy, it required larger numbers of outcomes necessary for comprehensive analysis of economic evaluation of TOLAC and ERCD mode of delivery. In this section (Chapter 5), maternal and neonatal outcomes of interest are those that have been reported to be associated with TOLAC and ERCD and were based on published studies including information from systematic reviews.

Probabilities

The probability of maternal and neonatal outcome estimates required for the decision tree model was obtained from literature. Included studies were those that evaluated all three patient populations of interest in this study namely successful TOLAC (vaginal birth after CD), failed trial of labor requiring emergency CD and ERCD. Studies that provided relevant information so the rates of maternal and neonatal conditions related to a TOLAC and ERCD can be calculated were included in the analysis (Table 24). The mean probability of maternal and neonatal outcomes weighted by the number of subjects in the individual studies was calculated as well as the lower and upper values, 2.5% and 97.5% of the distribution. This method allowed for studies to be weighed according to number of subjects in the selected studies. Details of probability estimates for maternal and neonatal complications related to TOLAC and ERCD and their plausible ranges for testing in sensitivity analyses are shown in Table 24.

Maternal outcomes included events occurring during the peripartum period such as hysterectomy (surgical removal of the uterus); endometritis (inflammatory condition of the lining of the uterus due to infection); thromboembolic events including deep vein thrombosis or pulmonary embolism; uterine rupture during a trial of labor (full thickness disruption of the uterine wall and accompanying clinical evidence of uterine rupture); the need for transfusion due to severe bleeding; and maternal death deaths due to complications from pregnancy or childbirth.

Neonatal outcomes comprised respiratory distress syndrome (respiratory distress syndrome) (Breathing disorder that affects newborns, usually developed in the first few hours of life), transient tachypnea of the new born, hypoxic ischemic encephalopathy (hypoxic ischemic encephalopathy, neurological changes caused by lack of sufficiently oxygenated blood perfusing brain tissue resulting in compromised neurological function manifesting during the first few days after birth. hypoxic ischemic encephalopathy may be associated with multiple organs damaged by similar perfusion injuries) of the newborn, neonatal intensive care unit and neonatal death. These outcomes were chosen because they are common associated with TOLAC and ERCD and adversely affect the quality of life of women and their babies.

Cost elements

Resource utilization and costs associated with TOLAC and ERCD were incorporated in the model. These includes mode of delivery, hospitalization, obstetrician, pediatrician and anesthesiologist professional service fees as well as costs related to maternal and neonatal complications. Hospital costs were obtained from the Ontario Case Costing Initiative (OCCI).139 The OCCI is a database under the auspices of the Ontario Ministry of Health and

Long-Term Care and has bundled cost including average inpatient costs and services, drugs, laboratory tests, nursing time for specific diagnosis and procedures. Obstetricians, pediatrician and anesthesiologist cost were obtained from the Ontario Schedule of Benefits and Fees[140] and the medical procedure list of the Alberta Health Care Insurance Plan[141] since physician fees are not included in the OCCI database.

With respect to maternal complications such as hysterectomy, the inpatient hospital cost included cost derived from the OCCI plus obstetricians and anesthesiologists' professional service fees. The cost of uterine rupture occurring during a trial of labor was obtained from the OCCI[139] and endometritis cost was determined based on the mean hospital cost of inflammatory disease of the uterus. We derived the cost of thromboembolism based on hospitalization cost for patients with the primary diagnosis of deep vein thrombosis or pulmonary embolus during or following delivery.[139] Transfusion costs were obtained from literature and included three units of packed red blood cells.[142-143]

Concerning neonatal outcomes, the cost of respiratory distress syndrome, transient tachypnea of the new born, hypoxic ischemic encephalopathy were based on the average cost of hospitalization for newborns with these conditions obtained from the OCCI records.[139] neonatal intensive care unit admission cost was based on information on newborns on admission with and without any oxygen support. [140] Additional cost for neonatal outcomes included the cost of pediatrician professional services[139] provided as a result of neonatal complications. Both maternal and neonatal death were assumed to incur no cost. It is assumed that both maternal and neonatal death at the time of delivery or immediately after delivery till discharge from the

hospital would not incur any cost. This assumption was based on the fact that maternal or neonatal death later after discharge may not be directly attributable to mode of delivery.

Costs that are were incurred at different time frames were adjusted to ensure that all costs are based on a common year. The consumer price index for health and personal care from Statistics Canada, which reflects the change in cost to the medical consumer, was used to standardize these cost estimates to 2014 price index. All costs are presented in 2014 Canadian dollars. Costs not available in 2014 Canadian dollars (C$) were converted from other years to 2014. The cost of each mode of delivery and associated complications were itemized separately and the total costs were derived by summation. Variation in each of the cost parameters with lower and upper bounds of the 95% CI were accounted for in sensitivity analysis. This was performed by including the lower and upper bound of each cost parameter in the model to assess its impact on the base case results. Details of cost components are listed in (Table 25).

Utilities

The measure of effectiveness was quality-adjusted life-years (QALY). QALYs offer a standard and comparable unit of health to compare cost-effectiveness estimates in different populations.[144] A QALY comprises both a length of life element (e.g. 1 year) and health-related quality of life component (e.g. utility). Utility decrement and the duration of the disutility related to the complications experienced were incorporated in the model. Utility values were obtained from literature. A literature search was conducted to obtain studies that reported the health-related quality of life or utility values related to TOLAC and ERCD and associated maternal and neonatal complications among women with a prior CD. Utility values were obtained from two studies[37,145] that used standard gamble or time trade off methods techniques to elicit utility values

regarding women's preferences for VD versus CD. Standard gamble or time trade off techniques are preference based measures used to determine how much an individual would be willing to sacrifice to avoid a particular state of health, or how one type of outcome compares to another.[146] In this case, how much women value the processes and outcomes of TOLAC versus ERCD delivery methods in terms of their health quality of life. The utility values were modification to reflect the duration of each delivery method, maternal and neonatal health outcomes as well as the study's time frame.

Utilities specify the preference for health states on a linear scale from 0.00 (death) to 1.00 (perfect health). The QALYS were determined based on quality of life component (utility), the duration of the quality of life in that health states and the total length of time framed captured in the model. For instance, a woman's health related quality of life or utility for successful TOLAC, failed TOLAC and ERCD were based on a duration of six weeks with values of 0.9873 for successful TOLAC, 0.9478 for failed TOLAC and 0.9577 for ERCD over the study's six weeks' time frame. The duration of a mother's health state for uterine rupture after delivery was two weeks and three weeks for thromboembolic event. Utility values were 0.7283 for uterine rupture and 0.5240 for thromboembolic event. QALYs were computed by multiplying the utility value of each condition by the assigned duration of the utility and time period in that condition. Details of utility values for all maternal and neonatal outcomes are presented in Table 25 and were all examined in both one-way deterministic and probabilistic sensitivity analyses. Additional sensitivity analysis was conducted to assess different time horizon as well as the life time QALYs of some outcomes.

5.2.5 Model analytical analyses

Analyses of the base case estimate were performed by calculating the mean costs and QALYs for TOLAC and ERCD. Cost effectiveness was measured as incremental cost utility ratio (ICUR) and was estimated by dividing the incremental cost by the incremental effectiveness, and expressed as incremental cost per QALYs gained as follows:

$$ICUR = \frac{(Cost, Intevention) - (Cost, Comparator)}{(Effectiveness, Intervention) - (Effectiveness, Comparator)}$$

Equation 2: Incremental cost utility ratio (ICUR)

ICURs generally describe the additional cost per additional QALYs gained. The numerator in the ICUR represents incremental costs (the net cost) and were calculated as the difference in the mean cost of the two delivery strategy options. The denominator in the ICUR represents incremental effectiveness (the net effectiveness) and were calculated as the difference in the mean effectiveness (QALYs) of the two delivery strategy options. To determine the comparative cost-effectiveness of TOLAC to ERCD, the findings were compared to a decision maker's willingness to pay λ thresholds of C$50,000 per QALYs gained.

5.2.6 Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of the base case analysis in the model. One-way deterministic sensitivity analyses were performed on all probabilities, costs and

QALY by varying one variable at a time using the lower and upper bounds of the 95% CI of the parameters. Additionally, a Monte Carlo simulation of 5,000 iterations was performed and used in a probabilistic sensitivity analysis to assess the joint effects of variability and uncertainty around all input parameters simultaneously. The simulation was conducted by specifying a beta distribution for probabilities based on number of events and non-events and gamma distributions for costs and with normal distribution for utility values characterized by standard errors of the mean. Results generated from the simulation were represented by means and the 95% credible intervals. It was also depicted by cost effectiveness acceptability curve to determine which mode of delivery strategy is cost-effective for different values of thresholds of a decision-maker's willingness to pay.

5.3 Results (objective 3)

5.3.1 Base case deterministic results

The base-case deterministic result of the decision analytic model shows that the TOLAC option dominated the ERCD option. This means that the TOLAC option was more cost effective than an ERCD option. Specifically, the TOLAC strategy resulted in an incremental cost savings of C$607 and incremental benefit of 0.0103 per patient (Table 26).

5.3.2 One-way deterministic sensitivity analyses

The various ranges of all parameters were tested in one-way deterministic sensitivity analyses to assess any impact on the stability of the base case results. For each parameter, the lower and upper limit of the associated 95% CI were employed in sensitivity analysis. The results were robust to changes in the base case findings in most of the parameters observed in the model,

particularly the probability of maternal and neonatal outcomes. Other variables that were robust to changes in the baseline estimates were the rates of costs, utilities and probability of successful, failed and ERCD as well as twelve and twenty-four weeks' time horizon. (Table 27). Even though there was a slight change in value of all these variables in the model, they did not change the direction of the base case results of the TOLAC strategy being the dominant option of less costly and more effective compared with the ERCD strategy (Table 27).

5.3.3 Base case probabilistic results

The base case probabilistic results of the Monte Carlo simulations analysis which simultaneously assessed the uncertainty around the model parameter estimates are shown in Table 28. The average incremental cost of TOLAC compared with ERCD resulted in a cost savings of C$602 (95% CI: C$855−C$344) whereas incremental QALYs was slightly effective at 0.0102 (95% CI: -0.0498−0.0926) per woman. This suggests that although the TOLAC delivery option was less costly than the ERCD delivery option, the effectiveness in terms of health quality of life between the delivery modes did not reach statistical significance indicating no difference in terms of cost effectiveness between the two delivery options. This result did not support the base case deterministic results that showed TOLAC as the dominant delivery option relative to the ERCD option. The results of the Monte Carlo simulations analysis were also depicted by a cost effectiveness acceptability curve in Figure 11. This figure shows the probability of an intervention being cost effective at different thresholds of cost per QALYs. With a willingness to pay at C$25,000, C$50,000 and C$100,000 per QALY, TOLAC was the preferred strategy at 92.0%, 84.0% and 76.0% respectively of the time. This analysis is in accordance with the base

case deterministic results that revealed that the TOLAC option was dominant than the ERCD option, but not the base case probabilistic results.

5.3.4 Probabilistic sensitivity analyses

When additional probabilistic analyses were conducted to assess the stability of the study findings to the uncertainty of the overall parameter of the probabilities, utilities and cost associated with ERCD and TOLAC, the model remained mostly insensitive to changes in the base case results demonstrating the robustness of the model.

5.4 Discussion

This study assessed the comparative cost effectiveness of having a TOLAC and ERCD from the health care payer perspective using deterministic and probabilistic analyses. The following are summary of the findings and are discussed according to the study objective and associated research question.

Objective 4: To assess the cost effectiveness of having a TOLAC and ERCD among women with low risk deliveries.

Question Six: What is the cost effectiveness of having a trial of labor after cesarean birth (TOLAC) compared with elective repeat cesarean delivery (ERCD) among women with low risk deliveries?

In a short-term decision analysis, this study demonstrated that the TOLAC delivery strategy was cost effective compared with the ERCD delivery strategy for a woman at term in the second pregnancy only in the base case deterministic analysis, but not in probabilistic analysis. The TOLAC option dominated the ERCD option, meaning it was less costly and more effective with cost savings of C$607 and improved benefit of 0.0103 QALYs per woman only in the base case analysis.

The base case findings of TOLAC as the dominant delivery option were not confirmed in the probabilistic analysis that took into consideration the uncertainty around the model parameter estimates. In detail, although the incremental cost of TOLAC compared with ERCD resulted in a cost savings of C$602 whereas incremental QALYs was slightly effective in terms of health quality of life at 0.0102 per woman, the confidence interval did not reach statistical significance (-0.0498–0.0926) in the probabilistic analyses. This indicates that there was no difference in terms of cost effectiveness between the two delivery options suggesting that both delivery options are equally effective.

The base case results are consistent with other studies. Gilbert et al[40] reported that the TOLAC strategy dominated the ERCD strategy at baseline, with US dollar (US$) 138.6 million saved and 1703 QALYs gained per 100, 000 women. Chung et al[38] found TOL was cost effective compared with ERCD and would cost $US112, 023 per QALY compared with TOL. In another paper that examined the future health and economic consequences of TOLAC and ERCD, Gilbert and colleagues[123] stated that the TOLAC strategy was dominant, saving $US164.2 million and 500 QALYs gained per 100,000 women. Grobman and associates[124] found that TOLAC was more

cost effective than ERCD. However, their decision analysis did not include QALYs. Fawsitt et al[39] indicated that TOLAC was the dominating strategy compared to ERCD in both deterministic and probabilistic analysis which their probabilistic findings were inconsistent with the probabilistic findings of this study that showed TOLAC and ERCD were equally effective delivery strategy. Consistent with the probabilistic analysis of this study, Wymer et al[37] reported that the TOLAC delivery option and the ERCD delivery option were nearly equally effective for a woman's second delivery. However, they found that TOLAC was less costly and more effective in successive subsequent deliveries than ERCD.

5.4.1 Strengths and limitations

Strength

One strength of this study is the consideration of costs and outcomes for the mothers and babies which provides a more comprehensive view of the cost-effectiveness of ERCD versus TOLAC. Finally, the probabilistic techniques used in the cost-effectiveness analysis in this study allowed variation of the outcomes and analysis of uncertainty around the model parameters rather than using deterministic approach which yields a single point estimate. Cost-effectiveness was presented with 95% CI, and a cost-effectiveness acceptability curve was used to determine which delivery mode had the optimal probability under various cost thresholds.

Limitation

There are several limitations in this study. The analyses of the economic evaluation were based on healthcare payer perspective rather than societal perspective which has a broader perspective and considers indirect costs to patients, families and caregivers. Moreover, this study focused on

short-term maternal and neonatal complications associated with a TOLAC and an ERCD and did not include all possible outcomes such as the potential long-term maternal outcomes of fecal and urinary incontinence, placenta accreta and previa in subsequent pregnancies. Another drawback was the six weeks' time horizon used in the study. We assessed short-term outcomes which takes into accounts the events that occurred at the time of admission for delivery and child birth till discharged from the hospital including the average maternal postpartum recovery period which usually do not exceed six weeks. As a result, longer-term health effects regarding costs of future deliveries associated with TOLAC and ERCD were not included in the model.

Furthermore, like most economic evaluations, data used in the model were obtained from various sources and studies, which employed methodologies not directly transposable to address the focus of this study design and therefore required modifications. Even though the cost data were obtained mainly from Canadian sources and database, data for probabilities and utilities were derived from literature. To address this issue, extensive deterministic sensitivity analyses were performed to assess the robustness of the base findings which included variation of probabilities, utilities values and cost estimates. Probabilistic sensitivity analysis was also carried out, allowing the variability of uncertainty of all the model parameters to be assessed simultaneously.

5.5 Lessons learned from the findings of objective 3

The aim for objective three was to assess the comparative cost effectiveness of having a TOLAC and ERCD among women with low risk deliveries. In a short-term decision analysis, the findings showed in base case deterministic analyses that the TOLAC delivery option was less costly and more effective than the ERCD delivery option. On the other hand, this finding was not confirmed

in the probabilistic analysis that took into account uncertainty around the model parameters including cost and QALYs. Even though the TOLAC delivery option was less costly with a slight benefit in terms of quality of life relative to the ERCD delivery option, it did reach statistical significance. Thus, both delivery options were equally effective for women with a previous CD who are eligible for a TOLAC or ERCD delivery.

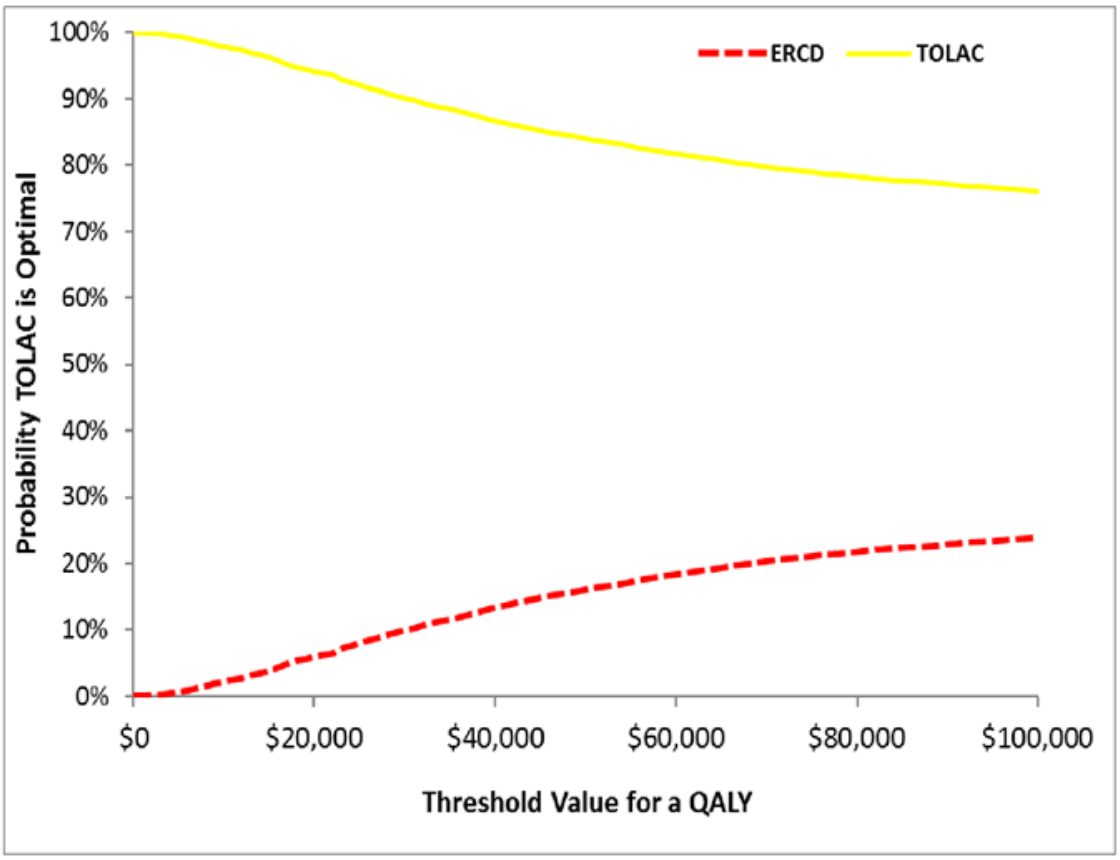

Figure 11. Cost Effectiveness Acceptability Curve for base case analysis - TOLAC versus ERCD

Abbreviations: ERCD = elective repeat cesarean delivery; TOLAC = trial of labor after cesarean birth

Table 24: Model parameters of probability values				
Probabilities Parameters	**Baseline**	**95% CI**	**Distribution**	**Reference**
Mode of Delivery				
Successful TOLAC	71.71%	71.49%–71.94%	Beta	106, 107,115-116,150-152
Failed TOLAC	28.29%	28.06%–28.51%	Beta	106, 107,115-116,150-152
ERCD	100.0%		Beta	106, 107,115-116,150-152
Maternal outcomes				
Successful TOLAC				
Blood transfusion	0.32%	0.29%–0.36%	Beta	106-107,116,150-152
Uterine rupture	0.10%	0.06%–0.16%	Beta	107,116,150-152
Hysterectomy	0.04%	0.03%–0.05%	Beta	40,106-107, 116,150-151
Thromboembolism	0.02%	0.00%–0.05%	Beta	40,107
Endometritis	1.34%	1.18%–1.52%	Beta	40,107,151-152
Maternal death	0.002%	0.000%–0.005%	Beta	40, 106-107
Failed TOLAC				
Blood transfusion	0.60%	0.53%–0.67%	Beta	106-107, 116, 150-151,153
Uterine rupture	2.08%	1.76%–2.44%	Beta	107, 116, 150-152
Hysterectomy	0.21%	0.17%–0.26%	Beta	40, 106-107,150-152
Thromboembolism	0.07%	0.02%–0.15%	Beta	40,107,153
Endometritis	7. 94%	7.18%–8.40%	Beta	40,107,151-153
Maternal death	0.007%	0.001%–0.017%	Beta	40,106-107
ERCD				
Blood transfusion	0.29%	0.27%–0.32%	Beta	106-107,116,151-152,154
Hysterectomy	0.10%	0.09%–0.11%	Beta	40,106-107,150-152
Thromboembolism	0.05%	0.03%–0.09%	Beta	40,107,153
Endometritis	2.01%	1.83%–2.20%	Beta	40,107,151-153
Maternal death	0.009%	0.005%–0.014%	Beta	11,106-107

Table 24: Model parameters of probability values				
Probabilities Parameters	**Baseline**	**95% CI**	**Distribution**	**Reference**
Neonatal outcomes				
Successful TOLAC				
TTN	0.43%	0.36%–0.51%	Beta	[40,155]
RDS	0.15%	0.11%–0.19%	Beta	[40,155]
HIE	0.00%	0.00%–0.12%	Beta	[40]
NICU	3.24%	2.35%–4.25%	Beta	[115-117]
Neonatal death	0.03%	0.01%–0.12%	Beta	[40]
Failed TOLAC				
TTN	1.30%	0.96%–1.69%	Beta	[40, 117, 155]
RDS	0.61%	0.38%–0.89%	Beta	[40,155]
HIE	0.08%	0.00%–0.30%	Beta	[40]
NICU	6.92%	4.70%–9.54%	Beta	[115-117]
Neonatal death	0.08%	0.00%–0.29%	Beta	[40]
ERCD				
TTN	1.97%	1.67%–2.29%	Beta	[40, 117,155-156]
RDS	0.52%	0.44%–0.61%	Beta	[40,106,154-155]
HIE	0.00%	0.00%–0.08%	Beta	[40]
NICU	6.31%	5.30%–7.40%	Beta	[115-117,156]
Neonatal death	0.04%	0.02%–0.06%	Beta	[40]

Data for probability values were from published literature.

Abbreviations: TOLAC, trial of labor after CD; ERCD, elective repeat cesarean delivery; NICU, neonatal intensive care unit; TTN, transient tachypnea of the newborn; HIE, hypoxic ischemic encephalopathy; RDS, respiratory distress syndrome.

Table 25: Model parameters of cost estimates and utility values				
Cost Estimates	**Baseline**	**95% CI**	**Distribution**	**Reference**
Cost of Delivery [a]				
Successful TOLAC	C$3,766	C$3,583– C$3,950	Gamma	139-141
Failed TOLAC	C$4,971	C$4,635– C$5,308	Gamma	139-141
ERCD	C$4,519	C$4,350– C$4,687	Gamma	139-141
Cost of maternal complications				
Successful TOLAC				
Hysterectomy	C$11,936	C$10,640–C$13,232	Gamma	139-141
Thromboembolism	C$5,449	C$2,113–C$8,785	Gamma	139
Uterine rupture	C$7,778	C$4,185–C$11,371	Gamma	139
Endometritis	C$3,690	C$1,091–C$6,290	Gamma	139
Transfusion	C$841	C$740–C$941	Gamma	142-143
Failed TOLAC				
Hysterectomy	C$11,620	C$10,401–C$12,838	Gamma	139-141
Thromboembolism	C$5,449	C$2,113–C$8,785	Gamma	139
Uterine rupture	C$6,703	C$2,842–C$10,564	Gamma	139
Endometritis	C$3,690	C$1,091–C$6,290	Gamma	139
Transfusion	C$841	C$676–C$1,005	Gamma	142-143
ERCD				
Hysterectomy	C$11,620	C$10,401–C$12,838	Gamma	139-141
Thromboembolism	C$5,449	C$2,113–C$8,785	Gamma	139
Endometritis	C$3,690	C$1,091–C$6,290	Gamma	139
Transfusion	C$841	C$603–C$1,078	Gamma	142-143
Cost of neonatal complications [b]				
TTN	C$4,683	C$4,258–C$5,108	Gamma	139-140
RDS	C$13,065	C$9,772–C$16,359	Gamma	139-140

Table 25: Model parameters of cost estimates and utility values				
Cost Estimates	**Baseline**	**95% CI**	**Distribution**	**Reference**
HIE	C$23,932	C$12,732–C$35,131	Gamma	[139-140]
NICU	C$10,936	C$7,363–C$14,508	Gamma	[143]
Newborn with no complication				
Successful TOLAC	C$1,036	C$1,028–C$1,045	Gamma	[139-140]
Failed TOLAC	C$1,451	C$1433–C$1,469	Gamma	[139-140]
ERCD	C$1,451	C$1,433–C$1,469	Gamma	[139-140]
Utility of maternal outcomes				
Successful TOLAC	0.9873	0.8691–0.9999	Normal	[37,145]
Failed TOLAC	0.9478	0.8147–0.9987	Normal	[37,145]
ERCD	0.9577	0.8514–0.9988	Normal	[37,145]
Uterine rupture [c]	0.7283	0.6252–0.8204	Normal	[37]
Hysterectomy	0.5925	0.4929–0.6884	Normal	[37]
Blood transfusion [d]	0.9924	0.9124–0.9999	Normal	[37]
Thromboembolism	0.5240	0.3865–0.6597	Normal	[37]
Endometritis	0.9924	0.9124–0.9999	Normal	[37]
Utility of neonatal outcomes				
TTN	0.9924	0.9124–0.9999	Normal	[37]
RDS	0.9783	0.8584–0.9999	Normal	[37]
HIE	0.9733	0.8569–0.9999	Normal	[37]
NICU	0.9867	0.8672–0.9999	Normal	[37]
Well neonatal health	1.0000	n/a	n/a	n/a

Data for cost values were obtained from Ontario Case Costing Initiative and utility values were from published literature. Abbreviations: TOLAC, trial of labor after CD; ERCD, elective repeat cesarean delivery;

a. Includes hospital, obstetrician, and anesthesiologist costs; Cost of outcomes represent the cost of mode of delivery plus the cost of complication. For example, the cost of ERCD was C$4,519 and the cost of thromboembolism was C$5,449 resulting in an ERCD with thromboembolism cost of C$9,968.

b. Includes hospital and pediatrician costs;

c. Utility value for hysterectomy was used as estimates for uterine rupture with duration of two weeks.

d. Utility value for endometritis was used as estimates for transfusion with duration of four days.
Neonatal intensive care unit(NICU) utility value was used as estimate for transient tachypnea of the newborn (TTN) and hypoxic ischemic encephalopathy (HIE) with the duration of four days and two weeks respectively based on length of hospital stay for these events derived from the Ontario Case Costing Initiative database; respiratory distress syndrome (RDS); n/a, not applicable.

Table 26: Base case deterministic results

Delivery Strategy	Cost (C$)	Incremental Cost (C$)	Effectiveness	Incremental Effectiveness	ICER a
ERCD	5,112	–	0.9677	–	–
TOLAC	4,505	-607	0.9780	0.0103	Dominant [b]

Data used for analysis of base case deterministic results were based on cost information from Ontario Case Costing Initiative, utility and probability information from published literature.
TOLAC, trial of labor after CD; ERCD, elective repeat CD; C$, Canadian dollars.
a. ICER, incremental cost effectiveness ratio=incremental cost (C$) / incremental effectiveness.
b. Dominant represents TOLAC is both more effective and less costly compared with ERCD

Table 27: Parameters of one-way deterministic sensitivity analysis		
Parameter	**Incremental Cost (C$)**	**Incremental Effectiveness**
Baseline value	-607	0.0103
Probability of Successful TOLAC		
60.00%	-603	0.0102
80.00%	-610	0.0104
Cost of Successful TOLAC		
$3,583	-738	0.0103
$3,950	-475	0.0103
Cost of Failed TOLAC		
$4,635	-702	0.0103
$5,308	-512	0.0103
Cost of ERCD		
$4,350	-438	0.0103
$4,687	-775	0.0103
Utility of Successful TOLAC		
Decrease of utility from to 0.9873 to 0.8691	-607	-0.0601
Increase of utility from to 0.9873 to 0.9999	-607	0.0173
Utility of Failed TOLAC		
Decrease of utility from 0.9478 to 0.8147	-607	-0.0182
Increase of utility from 0.9478 to 0.9987	-607	0.0212
Utility of ERCD		
Decrease of utility from 0.9577 to 0.8514	-607	0.0887
Increase of utility from 0.9577 to 0.9988	-607	-0.0200
Time horizon		
12 weeks	-607	0.0048
24 weeks	-607	0.0051

TOLAC, trial of labor after CD; ERCD, elective repeat CD; C$, Canadian dollars.

Data used for analysis of one-way deterministic sensitivity results were based on cost information from Ontario Case Costing Initiative, utility and probability information from published literature.

Table 28: Results of probabilistic sensitivity analysis					
Delivery Strategy	**Mean Cost (C$) 95% CI**	**Mean Incremental Cost (C$) 95% CI**	**Mean Effectiveness 95% CI**	**Mean Incremental Effectiveness 95% CI**	**ICER a**
ERCD	5109 (4930−5295)	–	0.9674 (0.8890−0.9943)	–	–
TOLAC	4507 (4335−4683)	-602 (-855−-344)	0.9776 (0.9257−0.9939)	0.0102 (-0.0498−0.0926)	Both TOLAC and ERCD are equally effective option [b]

Data used for analysis of probabilistic sensitivity results were based on cost information from Ontario Case Costing Initiative, utility and probability information from published literature.

TOLAC, trial of labor after CD; ERCD, elective repeat CD; C$, Canadian dollars; CI-confidence interval.

a ICER, incremental cost effectiveness ratio=Mean incremental cost (C$) / mean incremental effectiveness.

b. Both TOLAC and ERCD are equally effective because even though TOLAC was less costly and slightly effective compared with ERCD, the confidence interval of incremental effectiveness did not reach statistical significance; The 95% CI was estimated from the Monte Carlo Simulation analysis.

Chapter 6

General discussion and clinical implication of overall findings of study

This chapter discusses the overall research findings and implications. I first reviewed the literature on trends and variation of cesarean delivery (CD) rates in industrialized countries. I then assessed the contribution of indications for CD and compared the effects between "soft" and "hard" indications on neonatal outcomes. Third, I compared adverse birth outcomes in second pregnancy between low risk women with one previous vaginal delivery (VD) who underwent elective primary cesarean delivery (EPCD) versus trial of labor after vaginal birth (TOLAV), and compared adverse birth outcomes in second pregnancy between low risk women with one previous cesarean delivery (CD) who underwent elective repeat cesarean delivery (ERCD) versus trial of labor after cesarean birth (TOLAC). Finally, I assessed the cost effectiveness of TOLAC and ERCD among women with low risk deliveries. The following are general discussion of the findings based on the objectives of the study:

6.1 Overview

A review of the literature revealed major increases and high rates of CD among industrialized countries including Canada, with variations across countries and in regions within the same country. The World Health Organization recommended that CD rate in a country that exceeds 15% will not bring any benefit to the mothers and their offspring. [53-55] However, a report in 2013 showed that half of industrialized countries had CD rates above 25%, many exceeded 30%, and a few had more than 50%.[4] CD rates also varied within regions in the same country. In Canada, CD rates in 2011-2012 at the provincial level ranged from 23.4% in South West LHIN to 32.3% in Central West LHIN in Ontario[42] whereas rates in British Columbia ranged from 14.7% to

27.6% across sixteen Health Services Delivery Areas.[43] A recent study with data from 31 high-income industrialized countries found that CD rates were positively correlated with infant mortality rates, after adjustment for maternal age, infant sex, per capita GDP, and the Gini index ($p < 0.03$).[147] This finding suggests that over-use of CD is not only a wasteful of the precious health care resources but may actually harm the infants among these high-income industrialized countries. There is general consensus among clinician-scientists and obstetric professional organizations alike that the current level of CD rate in many industrialized countries is too high and there is an urgent need to reduce it. [56,148-149]

The overall goal of this thesis was to identify the sources and reasons for unnecessary CD, so that policies/guidelines/implementation measures can be better developed to reduce the unnecessary CD. More specifically, there were three objectives: 1) to analyze the leading indications for CD and their associations with adverse birth outcomes; 2) to compare adverse birth outcomes between EPCD and TOLAV after a previous vaginal birth, and to compare adverse birth outcomes between ERCD and TOLAC after a previous cesarean birth; and 3) to assess the cost-effectiveness of ERCD and TOLAC.

The analyses revealed that ERCD and labor dystocia accounted for one third of all overall and primary CD, respectively. Compared with "hard" indications, infants born with CD because of non-reassuring-fetal-status (NRFS) were at increased risk of lower Apgar score <7 at 5 minutes, but infants born with other "soft" indications such as ERCD and labor dystocia had lower risks of lower Apgar score <7 at 5 minutes and neonatal death. Compared with infants born with TOLAV, infants born with EPCD had increased risks of requiring antibiotic after birth,

ventilation support immediately after birth and at >6 hours after birth, be admitted to a neonatal intensive care unit, or die in the first year of life. On the other hand, compared with infants born with TOLAC, infants born with ERCD had reduced risks of requiring antibiotic, ventilation support immediately after birth, and be admitted to neonatal intensive care unit. ERCD and TOLAC were equal in terms of cost effectiveness.

Objective one

The first objective of this research assessed the contribution of indications to the overall and primary CD and its effect on neonatal outcomes using hospital data from Better Outcomes Registry Network (BORN) in Ontario (2006 to 2013). The findings showed the leading indication for overall CD was ERCD. This indication accounted for more than a third (34.3%) of overall CDs in Ontario. It was followed by labor dystocia (18.1%), breech presentation (10.6%) and non-reassuring-fetal-status (NRFS), (9.4%). It was also found that more than a third (31.9%) of all first or primary CD was performed due to the single indication of labor dystocia. All indications for CD were categorized into "soft" versus "hard" indications with details in Table 3. In assessment of newborn Apgar score <4 at 5 minutes and Apgar score <7 at 5 minutes among mothers who had "soft" indications versus "hard" indications for overall CD, it was found that babies of mothers who had CD performed due to "soft" indications of ERCD, labor dystocia and CDMR were less likely to have lower Apgar score <4 and <7 at 5 minutes than babies of mothers who had CD performed due to "hard" indications of CD. On the other hand, compared with babies born to mothers with "hard" indications for CD, babies born to mothers with "soft" indication such as NRFS were more likely to have lower Apgar score <4 and <7 at 5 minutes.

Babies of mothers with other indications for CD and those of mothers with "hard" indication for CD had comparable rates of Apgar score <4 and <7 at 5 minutes in the overall CD cohort. There was no baby with Apgar score <4 born to the mothers who had overall CD due to suspected LGA baby and only one baby with Apgar score <4 was born by the paired ERCD and CDMR group. The CD performed due to suspected LGA baby group and the paired ERCD and CDMR group were less likely to have babies with Apgar score <7 at five minutes compared with the CD due to "hard" indications group.

Assessment of neonatal death showed it was less likely to be associated with mothers who had CD due to "soft" indications of ERCD and labor dystocia in comparison with CD due to "hard" indications. However, the rate of neonatal death was not statistically different between mothers who had CD due to "soft" indications of CDMR or NRFS or those with other indications and the mothers who had CD due to "hard" indications. When the analyses were restricted to mothers who underwent primary CD, similar findings with regards to Apgar score at 5 minutes and neonatal death as demonstrated in the overall CD cohort was seen. However, newborn Apgar score <7 at 5 minutes was more likely to be associated with the babies of the mothers who had other indication for CD than the babies of mothers with CD for "hard" indication.

The findings of more likelihood of Apgar score <7 associated with babies of mothers who had CD due to "soft" indication of NRFS was consistent with a study[129] that found an association between NRFS and Apgar <7 at 5 minutes compared with CD due to other indications. It has to be noted that the comparator group of this study[129] was based on women with all other indications whereas the comparator group of our present study was based on women who had

CD performed for "hard" indications. Another study[128] found CD due to "soft" indication of labor dystocia was associated with newborn Apgar score <7 which was in contrast to findings of this present study. This study[128] included in their labor dystocia group women with placenta previa, non-reassuring fetal monitoring and cord prolapse whereas these indications were excluded in the labor dystocia group of this present study.

Objective two

The second objective (2a) compared adverse birth outcomes among low risk women who underwent EPCD and TOLAV in the second pregnancy using birth certificate data from the National Center for Health Statistics in the United States (US), (NCHS). It has to be pointed out that not all adverse neonatal outcomes were examined. The adverse birth outcomes that were assessed in this study were specific ones including newborn usage of antibiotic after delivery and birth injury after delivery which have not been evaluated extensively by previous studies among women with only one previous VD and non-anomalous neonate with cephalic presentation. The findings demonstrated in both regression analysis and propensity score matched analysis that babies of low risk mothers with one previous VD who had EPCD in second pregnancy had increased likelihood of requiring antibiotic after birth than babies delivered by mothers who had TOLAV. The babies of the EPCD group were also more likely to require ventilation support immediately after delivery, be admitted to neonatal intensive care unit, or die in the first year of life than the babies of the TOLAV group. On the other hand, babies delivered by EPCD had decreased likelihood of having a birth injury.

There are few data in literature have specifically compared adverse birth outcomes in women with only one previous VD who underwent EPCD versus TOLAV in the second pregnancy making it difficult to reconcile our results directly with different studies. However, the findings of higher rate of neonatal intensive care unit admissions associated with the EPCD group in comparison with the TOLAV group was consistent with previous studies[132-133] that compared neonatal outcomes of planned VD versus a planned CD in women with a history of one or more previous cesarean and vaginal birth. On the hand, the more likelihood of newborn requirement for ventilation after birth which was associated with the EPCD than TOLAV was in contrast with one of these previous studies[132] that reported no difference with respect to newborn ventilation support after birth between planned VD compared with planned CD. The increased rate of adverse birth outcomes related to the EPCD group compared with the TOLAV group may be due to confounding by indication of possible unmeasured factors such as previous birth experience, maternal obesity or underlying clinical factors that were not available in the dataset to be controlled for. These factors may be part of the possible reason for an EPCD in the second pregnancy after a previous VD.

I conducted a parallel analysis (objective 2b) on adverse birth outcomes among low risk women who underwent ERCD and TOLAC in the second pregnancy using birth certificate data from the NCHS in the US. Just like objective 2a, adverse birth outcomes that were assessed in this study were specific ones. These outcomes include newborn usage of antibiotic after delivery and birth injury after delivery which have not been assessed extensively by previous studies among women with only one previous CD and non-anomalous neonate with cephalic presentation. The findings demonstrated in both regression analysis and propensity score matched analysis that

babies delivered by low risk mothers with one previous CD who underwent an ERCD in second pregnancy had decreased likelihood of birth injury. The ERCD group were also less likely to require assisted ventilation immediately after birth, antibiotic use, and neonatal intensive care unit admission than the TOLAC group. However, there was no statistically significant difference between ERCD and TOLAC with respect to newborn requirement for assisted ventilation >6 hours after birth and infant death. The findings of more likelihood of neonatal intensive care unit admission associated with the TOLAC group was inconsistent with other studies[9,115.134] who found more likelihood of neonatal intensive care unit admissions in the ERCD than TOLAC groups. For birth injury, one study[135] reported that fetal injury after birth was lower in the ERCD group which was in agreement with findings from this study. Two other studies[102-103] reported no difference with respect to perinatal or neonatal death between ERCD and TOLAC groups which was consistent with findings of this study. There was difference in the study population of ERCD and TOLAC of previous studies which could account for differences in outcomes. For instance, the study population of previous studies were mainly women with one or more previous CD and those with medical problems (pre-existing or pregnancy-related diabetes or hypertension), whereas in this present study, the focus was on women with only one previous CD without these medical problems.

Objective three

The third objective assessed the cost effectiveness of having a TOLAC and ERCD among women with low risk deliveries. It is noteworthy to point out that information on outcomes and quality adjusted life years (QALYs) for the cost effectiveness analysis of ERCD and TOLAC was based on published data whereas cost data was obtained from Ontario Case Costing Initiative. Maternal and neonatal outcomes used for the economic analyses were outcomes that

have been evaluated by previous studies. Apart from rare outcomes such as uterine rupture which is associated with TOLAC and maternal death which is associated with ERCD, several studies have reported lower incidence rates of maternal and perinatal outcomes for both TOLAC and ERCD and these were the outcomes used in the economic analysis.

In a short-term decision analysis, it was found that in the base case deterministic analysis, the TOLAC delivery strategy was the dominant strategy compared with the ERCD delivery strategy. Thus, the TOLAC option was less costly and slightly more effective with cost savings of C$607 and improved benefit of 0.0103 QALYs per woman. However, the base case deterministic findings were not confirmed in the probabilistic analysis where we performed 5,000 Monte Carlo simulations that took into consideration the uncertainty around the model parameter estimates including cost and QALYs. Although, the incremental cost of TOLAC compared with ERCD resulted in a cost savings of C$602 whereas incremental QALYs was slightly effective in terms of health quality of life at 0.0102 per woman, the confidence interval did not reach statistical significance (-0.0498–0.0926) indicating no difference in terms of cost effectiveness between the two delivery options. Thus, the comparative cost effectiveness in terms of quality of life of both TOLAC and ERCD birth options are equally effective.

The base case deterministic findings of this present study were consistent with previous studies[38-40] that reported TOLAC was the dominant delivery option than ERCD. Some of the previous studies[38] did not perform probabilistic analysis. Other studies[39-40] that performed probabilistic analysis found TOLAC was the dominant delivery strategy, meaning it was less costly and more effective than ERCD. This was not consistent with the probabilistic findings of this present study. On the other hand, a study by Wymer[37] et al found TOLAC and ERCD were nearly

equally effective for a woman's second delivery, which was consistent with findings of this present study, but the authors found TOLAC to be more cost effective with successive subsequent deliveries than ERCD.

6.2 Implications of the study findings on obstetric practice

Based on these analysis results, this thesis concludes: 1) there are plenty rooms to cut CD rates in Canada without harming the infants; 2) tight up criteria for "soft" indications such as labor dystocia and CDMR could result in substantial reduction in CD rate without harming the infants; 3) although ERCD and TOLAC are equal in terms of cost effectiveness and ERCD tends to have less adverse birth outcomes, there may still be rooms to reduce ERCDs. The fact that compared with infants born with TOLAV, infants born with EPCD had increased risk but compared with infants born with TOLAC, infants born with ERCD had reduced risk suggests that for women who had a vaginal birth, if they went in second childbirth with CD they may be really in need. On the other hand, for women who had a cesarean birth, if they went in second child birth with CD, they may not necessarily in need but because of the perceived risks by physicians and women alike.

6.3 Strengths

Using BORN Ontario data for this research provided detailed medical chart information from 100 hospitals in Ontario, which allowed for evaluation of the contribution of single and co-occurring indications not only for overall CD, but also for primary CD. In addition, indications for CD from the hospital medical records helped to overcome the limitation of using data from

birth certificates due to their lack of specific details about indications for having CD. Also, the distinction of single and co-occurring indications addresses the issues raised by many researchers suggesting for distinction between CD performed solely on maternal request as a separate entity from other indications for direct comparison across studies.

Moreover, the large data from the NCHS in the US enabled the assessment of the differences in rates of uncommon outcomes such as birth injury and antibiotics use in newborn, while controlling for a variety of potential confounding variables. The application of the propensity score methods in this study allowed for the distribution of covariates to be balanced between the exposure groups. Comparing the results of propensity score matching analysis and traditional multivariable regression analysis also provided additional level of evidence for the robustness of the study findings.

With regards to the economic evaluation of TOLAC and ERCD, the application of the probabilistic technique in the cost-effectiveness analysis enabled assessment of analysis of uncertainty around the model parameters including cost and QALYs than using only the deterministic approach which yields a single point estimate without taking into consideration uncertainty. Cost-effectiveness was presented with 95% CI which is usually not found in the few economic evaluation studies on mode of delivery and neonatal outcomes.

6.4 Limitations

This study has several limitations that are worth mentioning. One drawback is the retrospective nature of this study, which is prone to potential residual confounding. There were unmeasured

confounders and desired characteristics that were not available in the data set to be adjusted for in this study. For instance, in the BORN Ontario dataset, there was no data about important variables such as the duration of the first and second stage of labor, inter-delivery interval, and maternal race, and information was lacking about the reasons and motivation of women who selected the CDMR option of delivery.

A major limitation of using birth certificate data is confounding by indication. For instance, the indications for having an EPCD or ERCD were not available in the NCHS dataset. This is important because it could have been helpful in understanding the clinical or medical reasons for having a CD. Also, the NCHS dataset did not contain information on variables such as previous birth history, duration of intensive care unit admissions and maternal pre-pregnancy obesity, which is an important confounder for having a CD. Previous studies have reported the risk of CD was 50% higher in overweight women, and more than twice as high for obese women compared with women of normal body mass index. There was also no information in the NCHS dataset on whether the women who underwent TOLAC had a previous classical incision, previous hysterectomy or placenta previa which are all contra-indication to having a TOLAC and can have impact on birth outcomes. Also, administrative dataset is subject to underreporting of medical risk factors. There have also been concerns about inconsistency in coding, recording and misclassification of certain factors such as smoking status among women during pregnancy.

The analyses of the economic evaluation focused on short-term (six weeks) maternal and neonatal complications associated with TOLAC and ERCD. This period covered admission for delivery and child birth till discharged from the hospital, and included the average maternal

postpartum recovery period which usually do not exceed six weeks. Therefore, the model did not consider long-term health outcomes, and the cost implications of potential long-term impact of delivery method on mothers such as fecal and urinary incontinence, placenta accreta and placenta previa in subsequent pregnancies. Furthermore, like most economic evaluations, data used in the model were obtained from various sources and studies, which employed methodologies not directly transposable to address the focus of this study design and therefore required modifications. Even though the cost data was obtained mainly from Canadian sources and database, data for probabilities and utilities were derived from literature.

In spite of the drawbacks, in the absence of relevant randomized controlled trials with enough power to evaluate indications for CD and its effect on neonatal outcomes or rare adverse birth outcomes, large observational studies like this one provided information to guide clinical decision-making regarding which indications are contributing significantly to CD and which can be targeted for reduction of CD. Also, knowing the risk and benefit of adverse birth outcomes associated with the various delivery modes may help mothers and clinicians to take steps to minimize such risk, or to respond to them appropriately, in case they occur.

Chapter 7 Conclusion

7.1 Summary of findings

This study showed the four leading single indications for overall cesarean delivery (CD) were a previous CD leading to elective repeat cesarean delivery (ERCD), labor dystocia, breech presentation and non-reassuring-fetal-status (NRFS). The four leading single indications for primary CD were labor dystocia, breech presentation, NRFS and placenta previa. The paired labor dystocia and NRFS were the leading co-occurring indications for having both overall and primary CD.

Also, in comparison with babies born to mothers who underwent overall and primary CD due to "hard" indications, those born to mothers who underwent CD due "soft" indication of NRFS were more likely to have Apgar score <4 and <7 at 5 minutes after birth. On the other hand, babies born to mothers who underwent CD due to "soft" indications of ERCD, labor dystocia and cesarean delivery on maternal request (CDMR) were less likely to have Apgar score <4 and <7 at 5 minutes after birth than babies delivered by mothers who had CD due to "hard" indications. There was no baby born to the mothers with "soft" indication of suspected large-for-gestational-age (LGA) baby who had Apgar score <4 at 5 minutes, whereas newborn Apgar score <7 were less likely to be associated with suspected LGA baby group. Also, only one baby of the paired ERCD and CDMR group had Apgar score <4. Newborn Apgar score <7 at 5 minutes was less likely to be associated with the paired ERCD and CDMR group compared with the "hard" indication group. Regarding neonatal death, babies delivered by mothers with "soft" indication of ERCD and labor dystocia were less likely to die during the neonatal period than babies delivered by mothers with "hard" indication. The CD performed due to CDMR group,

NRFS group and the other indication group all had comparable rates with regards to neonatal deaths as the CD performed due to “hard” indication group.

Moreover, in comparison with infants of mothers with one previous VD who had a TOLAV in the second birth, infants of mothers who underwent EPCD had increased risk of antibiotic usage, ventilation support after birth, admission to neonatal intensive care unit and infant death. However, birth injuries after delivery were less likely in babies delivered by EPCD than babies delivered by TOLAV. Furthermore, compared with infants of mothers with one previous CD who had a TOLAC in the second birth, infants of mothers who underwent ERCD had decreased risk of antibiotic, assisted ventilation immediately after delivery, birth injury, and admission to neonatal intensive care unit. However, there was no significant difference with regards to newborn ventilation support >6 hours after birth and infant death between the TOLAC and ERCD groups. Finally, the TOLAC and ERCD delivery options were equally effective for women with a previous CD.

This thesis research has provided detailed information on potential areas for reduction of overall CD. The information generated from study will add to the body of knowledge on indications for CD and adverse outcomes associated with the various mode of delivery. In addition, the findings will be useful to obstetricians, health care providers in the planning and optimization of maternal and perinatal outcomes regarding CD. Given that ERCD was the number one single driver of increased rate overall CD and labor dystocia was the number single driver of primary CD, and the fact that TOLAC was not safe for every woman with regards to some specific adverse outcomes such as newborn requirement for antibiotic, assisted ventilation immediately after

delivery and admission to neonatal intensive care unit, the focus to reduce unnecessary CD rate should be to tighten up criteria for “soft” indications such as labor dystocia and CDMR. Since, the chance of repeat CD is very high, once the criteria for diagnosis of labor dystocia and CDMR are tightened, it will reduce majority of unnecessary primary CD for these indications and will ultimately decrease the high rate of ERCD in the subsequent pregnancies.

Future research would be to examine the maternal and neonatal complications associated with two and three co-occurring indications for a cesarean birth. Another area of interest includes investigating the impact of indication for labor induction on neonatal outcomes among mothers who had CD for NRFS. Finally, the cost effectiveness of long-term outcomes of maternal and neonatal complications including placenta accreta, placenta previa, urinary incontinence, permanent injury related to brachial plexus injury and increased risk of cerebral palsy associated multiple and successive cesarean delivery will be explored too.

Appendices

Appendix A-1. Manuscripts submitted for publication and scientific conferences attended.

The following are details of manuscripts submitted for publication and abstracts presented at conferences. They were all based on my thesis research.

Titles of manuscripts and journals to which they were submitted

1. "Assessment of single and co-occurring indications contributing to overall and primary cesarean delivery" was submitted to the *European Journal of Obstetrics & Gynecology and Reproductive Biology* on July 14, 2017.
2. "Comparison of neonatal outcomes of "soft" indications versus "hard" indications with cesarean delivery" was submitted to the *Journal of Perinatology* on July 10, 2017.
3. "Adverse birth outcomes in pregnancy after a previous vaginal and cesarean delivery" was submitted to the *British Journal of Obstetrics and Gynecology* on July 10, 2017.

Conferences and poster abstract presentation

Oral presentation

1. "The association between previous cesarean delivery and maternal and perinatal complications" presented at the 2015 National Conference on Health Statistics organized by the Centers for Disease Control and Prevention and held on August 26th, 2015 in Bethesda, Maryland, USA.

Note: I received Exceptional Student Research Award at the 2015 National Conference on Health Statistics on August 26th, 2015 in Bethesda, Maryland, USA.

Abstract poster presentation

1. "Analysis of the effect of cesarean delivery indications on outcomes of newborn Apgar score at 5 minutes and perinatal death" at the Better Outcomes Registry Network (BORN) Ontario Annual Conference, Toronto, Canada on April 24, 2017.

2. "Assessment of early term elective repeated cesarean delivery and associated neonatal morbidity and mortality in breech and cephalic births." at the Canadian National Perinatal Research Conference at Montebello, Quebec, Canada on February 15, 2017.

3. "Examining pre-labor and after labor repeat cesarean delivery indications associated with advanced maternal age" at the Canadian National Perinatal Research Conference at Montebello, Quebec, Canada on February 16, 2017.

4. "Assessing the effect of first cesarean delivery on obstetric complications in second pregnancy" at the Canadian Society for Epidemiology and Biostatistics Conference-University of Ottawa Chapter at Ottawa, Ontario, Canada April 11th, 2015.

Note: I received first prize for research poster and abstract exhibition, Canadian Society for Epidemiology and Biostatistics Conference, on April 11th, 2015.

5. “Analysis of maternal medical conditions, pregnancy complications and adverse perinatal outcomes by previous mode of delivery” at the Canadian National Perinatal Research Conference at Montebello, Quebec, Canada on February 25, 2015.

Appendix B-1. Search Strategy

Search Strategy
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
1 Cesarean Section/ (38522)
2 (cesarean or c-section or c-sect or caesarean).tw. (48912)
3 1 or 2 (61008)
4 (indication or indications).tw. (232688)
5 dystocia.tw. (3286)
6 (failure to progress or failure of labor to progress).tw. (565)
7 (fetal distress or non-reassuring fetal status).tw. (4040)
8 (breech or malpresentation).tw. (4555)
9 maternal request.tw. (258)
10 CDMR.tw. (38)
11 4 or 5 or 6 or 7 or 8 or 9 or 10 (243608)
12 3 and 11 (8244)
13 limit 12 to (english language and humans and yr="1986 - 2016") (4906)
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
1 Cesarean Section/ (38522)
2 (c-section or cesarean or caesarean).tw. (48911)
3 or/1-2 (61007)
4 "trial of labor"/ (982)
5 (trial adj2 (labor or labour)).tw. (1010)
6 or/4-5 (1440)
7 3 and 6 (1266)
8 Vaginal Birth after Cesarean/ (1340)
9 vbac.tw. (522)

Search Strategy	
10	("Vaginal Birth after Cesarean" or "Vaginal Birth after Caesarean").tw. (742)
11	or/7-10 (2206)
12	Cesarean Section, Repeat/ (791)
13	((c-section or cesarean or caesarean) and repeat$).tw. (2184)
14	or/12-13 (2597)
15	11 and 14 (720)
16	exp Uterine Rupture/ (4398)
17	uter$ rupture.tw. (2549)
18	uter$ scar$.tw. (612)
19	exp Obstetric Labor Complications/ (59376)
20	maternal mortality/ or perinatal mortality/ (10440)
21	Endometritis/ (3635)
22	Endometritis.tw. (3211)
23	exp "embolism and thrombosis"/ (196811)
24	(embolism or thromboembolism).tw. (70154)
25	exp Blood Transfusion/ (88284)
26	blood transfusion.tw. (27587)
27	exp Intraoperative Complications/ (45419)
28	mortality.tw. (568235)
29	(neonatal death or neonatal mortality).tw. (8649)
30	(infant death or infant mortality).tw. (15396)
31	exp Respiration, Artificial/ (66596)
32	respiratory distress syndrome, newborn/ or "transient tachypnea of the newborn"/ (12119)
33	Meconium Aspiration Syndrome/ (981)
34	Hypoxic Ischemic Encephalopathy.tw. (1986)
35	Hypoxia-Ischemia, Brain/ (4562)
36	Asphyxia/ (5727)

Search Strategy
37 exp Sepsis/ (105586)
38 exp Birth Injuries/ (5425)
39 birth trauma.tw. (994)
40 (sepsis or septic shock).tw. (86209)
41 (artificial ventilation or artificial respiration).tw. (4385)
42 transient tachypnea.tw. (307)
43 Meconium Aspiration.tw. (1335)
44 risk.mp. or cohort.tw. (2120013)
45 (ae or co).fs. (3091968)
46 or/16-45 (5200741)
47 15 and 46 (563)
48 limit 47 to (english language and humans and yr="1986 - 2016") (470)
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 Vaginal Birth after Cesarean/ (1313)
2 TOLAC.tw. (70)
3 VBAC.tw. (510)
4 trial of labo?r.tw. (959)
5 TOL.tw. (1681)
6 vaginal birth after c?esarean.tw. (717)
7 1 or 2 or 3 or 4 or 5 or 6 (3638)
8 cesarean section, repeat/ (773)
9 ERCD.tw. (26)
10 RCD.tw. (383)
11 repeat c?sarean.tw. (698)
12 8 or 9 or 10 or 11 (1650)
13 ec.fs. (364078)

Search Strategy
14 cost.tw. (292962)
15 Health Care Costs/ (30815)
16 costs.tw. (151072)
17 13 or 14 or 15 or 16 (627922)
18 7 and 12 (521)
19 17 and 18 (44)
Database: Embase Classic+Embase <1947 to 2016 May 27>
Search Strategy:
1 TOLAC.tw. (177)
2 VBAC.tw. (790)
3 trial of labo?r.tw. (1422)
4 TOL.tw. (2038)
5 vaginal birth after c?esarean.tw. (933)
6 1 or 2 or 3 or 4 or 5 (4156)
7 ERCD.tw. (47)
8 RCD.tw. (602)
9 repeat c?esarean.tw. (1304)
10 7 or 8 or 9 (1909)
11 "cost effectiveness analysis"/ (114364)
12 randomized.tw. (516505)
13 economic.tw. (190781)
14 cost?.tw. (517516)
15 11 or 12 or 13 or 14 (1180252)
16 6 and 10 (482)
17 15 and 16 (70)

Appendix B-2 Characteristics of studies for literature review of CD

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
Trends and variation of CD				
WHO – Health at a Glance, 2013	Key health indicators report	33 OECD countries/2013	Not reported	Comparable data on key indicators of health including CD rates across OECD countries
Kozhimanni et al, 2013	Retrospective study using data from 593 hospitals from 44 states in the USA	USA/2009	817,318	CD rates across hospitals
Canadian Institute for Health Information, 2013	Report on birthing process indicators	Canada/2011-2012	373,000	Primary and repeat CS rates, preterm birth rate and small for gestational age rate
Hanley et al, 2010	Retrospective study using data from sixteen Health Services Delivery Areas in British Columbia	Canada/2004-2007	116,839	Primary CD with indications and assisted vaginal delivery. CD indications include breech, labor dystocia, CPD, nonreassuring, fetal heart rate, abruptio/previa, VBAC declined/maternal request, malposition
Stavrou et al, 2011	Retrospective study using data from Midwives Data Collection, a state-wide surveillance system	Australia/1998-2008	965,702	Overall CS rates, age-standardized CS rates and annual percentage change
Milolajczyk et al, 2013	Retrospective study using data from German Pharmaco-epidemiological Research Database (GePaRD)	Germany/2004-2006	294,841	Regional variation in CD rates

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
Einarsdóttiret et al, 2013	Retrospective study using data from Midwives Notification System data linked with data from the Hospital Morbidity Data Collection	Austr alia/1996–2008	155,646	Publicly or privately funded CS rates
Braggs et al, 2010	Retrospective study using data from 146 different National Health Service (NHS) trusts or maternity units in England	The United Kingdom/2008	620,604	CD rates across NHS maternity units
Dahlen et al, 2012	Retrospective study using data from New South Wales Midwives database	Australia/2000-2008.	691,738	Risk profile of women giving birth in public and private hospitals, intervention rates and changes in these rates over the past decade.
Stivanello et al, 2011	Retrospective study using data from 24 hospitals of Emilia-Romagna region in Italy	Italy/2007-2009	98,913	Inter-hospital comparison of CD rates
Turner et al, 2012	Retrospective study using data from 19 public hospitals in Ireland	Ireland/2009	19,326	The mean CD rates per hospital births
Schemann et al, 2015	Retrospective study using data from New South Wales population databases, the Perinatal Data Collection and the Admitted Patient Data	Australia/ 2007-2011	61,894	Variation in hospital rates of CD and rates of maternal and neonatal morbidity including postpartum hemorrhage and Apgar score <7 at five minutes.

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	Collection in Australia			
Roberts et al, 2012	Retrospective study using data from record linkage cohort of New South Wales Centre for Health Record Linkage	Australia/ 1994–1997 2001–2004	82,988 (1994–1997) 85,859 (2001–2004)	CS rates, by parity and onset of labor
WHO report, 2015	Report on WHO Statement on CS rates	Not reported	Not reported	CS delivery rates
Cavallaro et al, 2013	Retrospective study	26 countries in Asia and Africa/1985-2011	686,789	CS delivery rates
Caughey et al, 2014	ACOG report on safe prevention of primary CD	Not reported	Not reported	CD rates, indications, maternal and neonatal outcomes
SOGC, 2005	Clinical practice Guideline	Canada, 2005	Not reported	Fetal and maternal morbidity and mortality associated with VBAC, repeat CS, and guidelines for the provision of a TOL after CS
ACOG, 2013	Clinical practice Guideline	USA, 2013	Not reported	Non-medically indicated early-term deliveries
USDHHS, 2010	Governmental body policy report on Health	USA/2000-2010	Not reported	Description of 10-year public health objective including CD rates for 2010
USDHHS, 2020	Governmental body policy report on Health	USA/2010-2020	Not reported	Description of 10-year public health objective including CD rates for 2020
Indications for having CD				
Zhang et al, 2010	Retrospective study using data from 19 academic hospitals of National Institute of	USA/ 2002-2008	228,668	Overall CD rates, Classification of CD indications a. Clinically indicated CD

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	Child Health and Human Development Maternal–Fetal Medicine Units Network			(includes non-reassuring fetal status, failure to progress, and cephalopelvic disproportion; b. 'Mixed categories' (includes previous uterine scar, breech or malpresentation, fetal anomalies, and fetal macrosomia, among others c. 'Truly elective' (includes indications other than the first two
Mylonas et al, 2015	Review using data from PubMed, Scopus, and DIMDI databases, as well as on media communications, analyses by the German Federal Statistical Office, and guidelines of the Association of Scientific Medical Societies in Germany	Germany/1991-2012	Not reported	Classification of CD indications as: a. Absolute indications (including absolute disproportion, chorioamnionitis and placenta previa) and relative indications (including pathological cardiotocography, failure to progress in labor and previous CD section). b. Pathological cardiotocography (CTG) (includes acute hypoxia or fetal asphyxia); failure to progress in labor (includes prolonged labor, secondary arrest); previous CD section
Tita et al, 2012	Review using data from PubMed, supplemented by a review of relevant	USA/ Not reported	Not reported	Maternal and obstetrical indications for primary CD delivery including labor dystocia, mal-presentation,

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	American College of Obstetricians and Gynecologists (ACOG) bulletins and major obstetrical textbooks			hypertensive disorders, macrosomia, multiple pregnancy, placenta previa, placenta accrete, abruption and preeclampsia
Gregory et al, 1998	Retrospective study using data of National Hospital Discharge Surveys including medical records of non-federal hospital records	USA/1985 and 1994.	41,450 deliveries	CD indications including breech, labor dystocia, fetal distress, elective repeat CD
Getahun et al, 2009	Retrospective study using data from Kaiser Permanente Southern California hospital	USA/1991-1992 and 2007-2008	540,953	CD by racial and ethnic disparities, CD indications includes labor dystocia, breech, fetal distress, other indication
National Institutes of Health State-of-the-Science Statement CD on maternal request, 2006	Report on CD on maternal request	Not reported	Not reported	Maternal and neonatal outcomes for CD on maternal request including urinary incontinence, hysterectomy, uterine rupture, stillbirth, birth injury and fetal mortality
Torloni, et al, 2011	Systematic Review	Country not reported/databases published 1968–2008	Not reported	The main classification systems for CS, and the advantages and deficiencies of each system
Boyle et al, 2012 Boyle et al, 2013	Retrospective study using data from 19 academic hospitals of National Institute of Child Health and Human Development	USA 2002-2008	38,484 deliveries	Primary CD rate, CD indications including failure to progress of labor, non-reassuring fetal heart rate tracing or fetal distress, fetal malpresentation, preeclampsia,

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	Maternal–Fetal Medicine Units Network			eclampsia, multiple gestation, suspected fetal macrosomia, elective, fetal anomaly, previous uterine scar. Review on cesarean delivery rates
Kelly et al, 2013	Retrospective study using data of hospital deliveries from five Canadian provinces (British Columbia, Alberta, Ontario, Nova Scotia, Newfoundland and Labrador)	Canada/2007-2011	965,499	Overall CS rate based on 10 Robson's categories in Alberta, British Columbia, Ontario, Nova Scotia, Newfoundland and Labrador
Rossignol et al, 2013	Review of CS rates across regions, and within, professional practices from MED-ÉCHO, the Quebec hospitalization database	Quebec, Canada 1969-2009.	Not reported	Potential strategies for lowering CS rates, proposal for an analytic framework for CS and report on CD indications including previous CS, labor dystocia, breech presentation and fetal distress
Liu et al, 2004	Retrospective study using data from Canadian Institute for Health Information's Discharge Abstract Database all hospital deliveries in Canada except for those occurring in Manitoba and Quebec	Canada/ 1994/95 to 2000/01	I, 807,388	Overall CD rate, and indication for CD including elective repeat CS, breech presentation, fetal distress and other indications
Choudhary et al, 2009	Retrospective study using data from a district general hospital	The United Kingdom/2001-2007	12,960 d	Overall CS rate and indication for CD

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
Kalogiannidis et al, 2011	Retrospective study using data from University Department of Obstetrics and Gynaecology of Aristotle University of Thessaloniki hospital in Greece	Greece/ 2004-2008	5,362	Overall CS rate, indications of CS including previous CS, breech presentation, advanced maternal age, preeclampsia, IUGR, placenta praevia, congenital abnormalities
Maso et al, 2013	Prospective study using data from 11 single-institutional obstetric cohorts of Friuli Venezia Giulia in Italy	Italy/Not reported	15,726	Inter-institutional variation of overall CD rates
Chong et al, 2012	Retrospective study using data from the National University Hospital in Singapore	Singapore/2000-2010	26,817	Changing trends and main contributors to the rising CS birth rates
Groen et al, 2015	Retrospective study using data from Medecins Sans Frontieres (MSF) personnel from the Operational Center	Brussels/2008-2012	14,151	CD indications including failure to progress, previous uterine scar, non-reassuring fetal status, fetal mal-presentation, placenta or vasa previa, uterine rupture, hypertensive disorders, placental abruption
Lurie et al, 2016	Retrospective study using data from Edith Wolfson Medical Center, Holon	Israel/1997-2012	55,390	CD indications including previous CD, non-reassuring fetal heart rate, mal-presentation, labor dystocia, suspected macrosomia
Dinas et al, 2008	Retrospective study using medical records of Hoppokration	Greece/2002-2006	4,964	CD indications including previous CD. non-reassuring or pathological fetal heart rate

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	hospital			trace by cardiotocography, labor dystocia
Penn et al, 2001	Review	United Kingdom/2001	Not reported	CD rates and indications include repeat CD, labor dystocia, breech presentation and fetal distress
Kolas et al. 2003	Retrospective study using data from 24 maternity units in Norway	Norway/1998-1999	2,778	CD indications including fetal stress, failure to progress, previous CD, breech presentation, maternal request.
MacKenzie et al, 2003	Prospective study using data from maternity unit of a large district teaching hospital	United Kingdom/ 12-month periods for 1976, 1986 and 1996	4,829	CD indications including fetal stress, failure to progress, previous CD, breech presentation, maternal request, preeclampsia, failed induction
Tan et al, 2003	Retrospective study using data from Singapore General Hospital	First 6 months of 1998 and the last 6 months of 2001/Singapore	170	CD indications including failed labor induction, failed progressive labor, failed assisted delivery
Florica et al, 2005	Retrospective study using medical records from Soder Hospital in Stockholm	Sweden/1994-1999	8,183	CD indications including fetal distress, maternal request, labor dystocia, abnormal presentation
Tampakoudis et al, 2004	Retrospective study using data from Greek teaching hospital	Greece/1977-1983 to 1994-2000 and 1977-2000	34,575	CD indications including previous CS, labor dystocia (includes dysfunctional labor, cephalopelvic disproportion and malpresentations), fetal distress, breech presentation, and hypertensive disorders of pregnancy.
Lagrew et al, 2006	Retrospective study using data from Saddleback Memorial	USA/1998-2004	126	CD indications including non-reassuring fetal heart rate, failure to progress, non-

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	Center in California			reassuring antepartum fetal heart rate, breech, transverse lie, placenta previa andabruptio placenta
Lydon-Rochelle et al, 2006	Retrospective study using data from 19 nonfederal short-stay hospitals in Washington state	USA/2000	4,541	CD indications including elective repeat CD, maternal request, failure to progress, breech presentation, cephalopelvic disproportion, maternal request during labor
Chu et al, 2010 .	Prospective study of four hospitals in Taipei	Taiwan/2006-2007	151	CD indications including malpresentation, prior CD, dysfunctional labor and fetal distress
Main et al, 2011	California Maternal Quality Care Collaborative report	USA (California)/ 1990-2009	Not reported	CD rates and their associated health and financial cost
Barber et al, 2011	Prospective study using data from a major urban academic medical center in Connecticut	USA/2003- 2009	32,443	CD delivery rate/ documented indications (non-reassuring fetal status, labor arrest disorders multiple gestation, suspected macrosomia) and the relative contributions of each indication to the total increase in primary CD rate
Gao et al, 2013	Retrospective study using data from Yulin teaching hospital	China/2009 - 2012.	5,267	CD indications including nuchal cord, previous CD, fetal distress, malpresentation, maternal request, preeclampsia, prolonged labor
Lavender et al, 2012	Review	Studies from MEDLINE (1974 to April 2005),	Not reported	Perinatal and maternal morbidity and mortality related to planned

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
		EMBASE (1974 to April 2005), CINAHL (1982 to April 2005) and PsycINFO (1887 to April 2005 including unpublished papers and abstracts submitted to international conferences		cesarean delivery versus planned vaginal birth in women
ZhangZhang et al, 2008	Prospective study using data from 21 cities and counties in two provinces in southeast China	China/1994 -2006	247,831	Overall CD rates and CD on maternal request
Liu et al, 2014	Retrospective study using data from 39 hospitals in 14 provinces in China	China/ 2011	111, 315	CD indications including maternal request, cephalo-pelvic disproportion, fetal distress, previous CS, malpresentation and breech presentation
Kottmel et al, 2012	Retrospective study using data from a tertiary care clinic in Switzerland	Switzerland/ 2002 and 2008	3460	CS rates and CS on maternal request rates
Souza et al, 2010	Retrospective multi-country, facility-population based study	A total of 24 countries including Africa, America and Asia and 373	286,565	The overall CD section rate and CD without medical indication

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
		health facilities,). Data collection took place during 2004 and 2008		
Hutton et al, 2012	Retrospective study using data from 7 British Columbia hospitals	Canada/2002-2004	10,546	Overall rate of CS in all nulliparous births, and contribution of CS on maternal request to all nulliparous CD births.
Gallagher et al, 2012	Survey study	Canada/2008-2009	140	Attitude towards CD on maternal request
Karlström et al, 2013	Retrospective study using data from the Swedish Medical Birth Register	Sweden/ 1997-2006	19,651	Maternal complications (e.g. bleeding, infections, and breastfeeding complications) Adverse infant outcomes (e.g. incidence of respiratory distress and the risk of hypoglycemia) and CD without medical indication
Ecker et al, 2001.	Retrospective study of hospital medical records of Brigham and Women's Hospital in Boston, Massachusetts	USA/January 1, 1998 and December 31, 1998	3715	CD indications including failure to progress and fetal distress by maternal age
Stjernholm et al, 2010.	Retrospective study using data from Karolinska University Hospital in Sweden	Sweden/1992 and 2005	8,996	Total CD rate, CD indications including breech/transverse lie, uterine factor narrow pelvis, psychosocial, maternal disease
Timofeev et al, 2013	Retrospective study of electronic medical	USA/2002-2008	203,517	Adverse obstetric and neonatal outcomes, and timing and

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	records from 12 centers in the US			indications for CD by maternal age
Washington et al, 2012	Retrospective study using data from University of California, San Francisco Medical Center	USA/1990-2008	11,034	Overall rate of CD
Bergholt et al, 2007	Prospective study using data from Wycombe General Hospital in Buckinghamshire	The United Kingdom/1995-2000	4,341	Incidence CD with increase by BMI.
Sheiner et al, 2004	Retrospective study using data from Soroka University Medical Center of Negev	Israel/1988-2002	126,080	Pregnancy outcome of obese patients, and the correlation between maternal obesity and incidence of CS
Young et al, 2002	Retrospective study using the obstetric records of one large private practice	USA/1993-2001	7,453	Overall CD rate, and the incidence CD with increase in BMI
Maternal and neonatal complications associated with ERCD and TOLAC				
Guise et al, 2010	Systematic review and meta-analysis comprising 203 studies	Relevant studies from multiple searches of MEDLINE, DARE, and the Cochrane databases (1980 to September 2009) and from recent systematic reviews, reference lists, reviews,	Not reported	Maternal outcomes related to TOLAC and ERCD including maternal hysterectomy, hemorrhage, and transfusions, uterine rupture, surgical injury and infection and neonatal outcomes including perinatal death, neonatal death, respiratory conditions, transient tachypnea of the newborn, hypoxic–ischemic,

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
		editorials, Web sites, and experts		encephalopathy, sepsis, trauma, neonatal intensive care unit admissions
de Lau et al, 2011	Systematic Review	The Netherlands/NR	56,892	Overall risk and trend of uterine rupture
Wen et al, 2004	Retrospective study using data from Canadian Institute of Health Information	Canada/ 1988-2000	308,755	Maternal outcomes related to TOLAC and ERCD including in-hospital maternal death, uterine rupture, and other severe maternal morbidity
Landon et al, 2004	Prospective study using data from 19 academic hospitals of National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network	USA/1999-2002	33,699	Maternal outcomes related to TOLAC and ERCD including maternal death, uterine rupture, hysterectomy, and transfusion and perinatal outcomes including neonatal death, hypoxic–ischemic encephalopathy, admission to neonatal intensive care unit, and 5-minute Apgar score ≤5.
Kok et al, 2015	Prospective study using the Netherlands Perinatal Registry	The Netherlands /2000-2007	19,567	Maternal outcomes related to TOLAC and ERCD including maternal death, hemorrhage, blood transfusion, and uterine rupture and neonatal outcomes including low Apgar score, birth trauma, meconium aspiration, transient tachypnea of the new born and perinatal death within 28 days after birth
Studsgaard et al, 2013	Prospective study using data from Aarhus University Hospital Birth Cohort	Denmark/ 2003 and 2010	1,783	Adverse neonatal outcomes, risk factors for emergency CD, and uterine rupture in case of TOLAC

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
	database			
Gilbert et al, 2012	Retrospective study using data from 19 academic hospitals of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network	USA/1999-2002	45,988	Maternal outcomes related to TOLAC and ERCD including endometritis, operative injury, hysterectomy and wound complication and infant outcomes including respiratory distress syndrome, and newborn infant infection
Rossi et al, 2008	Systematic review and meta-analysis	Italy/2000-2007	42,312	Maternal outcomes related to TOLAC and ERCD including maternal morbidity including uterine rupture, blood transfusion, and hysterectomy
Harper et al, 2012	Retrospective study using data from 17 centers in the US	USA/1996-2000	718	Induction of labor and uterine rupture risk
Hoffman et al, 2015	Review of literature	Not reported	Not reported	Methods of induction of labor following prior CD including Pitocin, prostaglandins and foley bulb
Grobman et al, 2007	Prospective study using data from19 academic medical centers of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network.	USA/1999-2002	11,778	The effect of labor induction on VBAC success and maternal and perinatal health outcomes
Scott et al, 2011	Review of literature	USA/1980-2011	Not reported	Factors to consider when deciding on TOLAC

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
Hook et al, 1997	Prospective study of 3 U.S. hospitals in Ohio	USA/1992-1993	989	Neonatal outcomes related to TOLAC and ERCD including neonatal intensive care unit admission, transient tachypnea of the new born, respiratory distress syndrome and sepsis
Crowther et al, 2012	Multi-center randomized control trial using data from 14 Australian hospitals	Australia/2002-2007	2,345	Risk of fetal death or death of live born related to planned ERCD and planned VBAC births
Smith et al, 2002	Retrospective study using administrative database in Scotland	Scotland/1992-1997	313,238	Perinatal death related to TOL vs Planned Repeat CD
Mozurkewich et al, 2000	Meta-analysis using data from MEDLINE and EMBASE databases from 15 studies	Canada/1989-1999	47,682	Maternal outcomes related to TOLAC and ERCD including uterine rupture, hysterectomy, maternal febrile morbidity, maternal mortality, 5-minute Apgar score <7, and fetal or neonatal mortality
Kamath et al, 2009	Retrospective study using data from the Perinatal Database of the Department of Obstetrics and Gynecology in Colorado	USA/2005-2008	672	Neonatal outcomes by ERCD and VBAC including oxygen use during delivery room resuscitation, highest level of delivery room resuscitation required, endotracheal intubation outside the delivery room, hypoglycemia and/or respiratory distress requiring neonatal intensive care unit stay, and type of ventilatory support needed in neonatal intensive care unit

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
Landon et al, 2016	Review of studies using data from 19 academic hospitals of National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network	USA/1999-2002	45,988	Risk factors of TOLAC, including uterine rupture and success rate of TOLAC
Loebel et al, 2004	Retrospective study using data from a large community hospital perinatal database	USA/1995-1998	1,408	Maternal outcomes related to TOLAC and ERCD including transfusion, rupture, infection and neonatal outcomes including neonatal intensive care unit admissions, neonatal death and respiratory complications
Lydon-Rochelle et al, 2001	Retrospective study using data from Washington State Birth Events Record Database.	USA/1987-1996	20,095	Risk of uterine rupture associated with spontaneous onset of labor, induction of labor with and without prostaglandins among women with prior CS

Characteristics of studies for literature review of CD				
Economic evaluation of TOLAC and ERCD				
Study/Publication Year	**Study description**	**Population/Intervention vs. Comparator/Outcomes**	**Outcome measure**	**Outcome of TOLAC vs ERCD**
Wymer et al, 2014	Cost effectiveness analysis/USA/ Health care payer system	A hypothetic cohort of women with 1 previous full-term, low-transverse CD/TOLAC vs	Quality-adjusted life-years (QALYs)	TOLAC strategy dominated the ERCD strategy (i.e. TOLAC was less costly and more effective)

Characteristics of studies for literature review of CD				
Study/Publication Year	**Study description**	**Country/ study period**	**Total population**	**Outcomes**
		ERCD		
Gilbert et al, 2013	Cost effectiveness analysis /USA/ Societal perspective	A hypothetical cohort of 100,000 women/TOLAC vs ERCD	Quality-adjusted life-years (QALYs)	TOLAC strategy dominated the ERCD strategy (i.e. TOLAC was less costly and more effective)
Gilbert et al, 2013	Cost effectiveness analysis /USA/ Societal perspective	A hypothetical cohort of 100,000 women / TOLAC vs ERCD	Quality-adjusted life-years (QALYs)	TOLAC strategy dominated the ERCD strategy (i.e. TOLAC was less costly and more effective)
Fawsitt et al, 2013	Cost-effectiveness analysis/Ireland/ Health care system	A hypothetical cohort of 10,000 low risk women /TOLAC vs ERCD	Quality-adjusted life years (QALYs)	TOLAC strategy dominated the ERCD strategy (i.e. TOLAC was less costly and more effective)
Chung et al, 2001	Cost-effectiveness analysis/USA/ Societal perspective	A hypothetical 30-year old woman /VBAC vs ERCD	Quality-adjusted life-years (QALYs)	TOLAC strategy dominated the ERCD strategy (i.e. TOLAC was less costly and more effective)
Grobman et al, 2000	Cost-effectiveness analysis/USA/Health care system	A hypothetical cohort of 100,000 women/ VBAC vs ERCD	Major maternal complications and neonatal complications avoided including death and permanent neurologic sequelae	Averted neonatal neurologic injury and deaths
Friedman et al, 2016	Cost analysis/ USA/Hospital payer system	TOLAC vs ERCD	Maternal hospitalization for TOLAC and ERCD	TOLAC is associated with modest reductions of maternal hospitalizations costs

Abbreviations: CD, cesarean delivery; CS, cesarean section; WHO, World Health organization; OECD, Organization for Economic Co-operation and Development; USA, United States of America; US, United States of America; SOGC, Society of Obstetricians and Gynaecologists of Canada ACOG, American College of Obstetricians and Gynecologists, USDHHS; United States Department of Health and Human Services; VBAC, Vaginal birth after cesarean; transient tachypnea of the new born, transient tachypnoea of the newborn; respiratory distress syndrome, respiratory distress syndrome; ERCD = elective repeat cesarean delivery; TOLAC = trial of labor after cesarean birth

Appendix C-1 Co-occurring, three or more indications for having overall CD in term singleton births

Table C-1: Co-occurring, three or more indications for having overall CD in term singleton births		
Number of patients	**199,294**	
Category	**n**	**%**
Two co-occurring indications for having CD [a]		
ERCD and dystocia	60	0.0
ERCD and LGA	59	0.0
Dystocia and abruption	56	0.0
LGA and CDMR	54	0.0
OMHP and NRFS	50	0.0
Breech and OMHP	39	0.0
ERCD and fetal anomaly	34	0.0
Dystocia and OMHP	31	0.0
NRFS and fetal anomaly	28	0.0
IUGR and OMHP	28	0.0
Previa and OMHP	27	0.0
ERCD and IUGR	25	0.0
Breech and CDMR	24	0.0
Breech and IUGR	23	0.0
LGA and preeclampsia	22	0.0
Breech and fetal anomaly	21	0.0
OMHP and CDMR	21	0.0
NRFS and preeclampsia	20	0.0
ERCD and preeclampsia	19	0.0
IUGR and previa	18	0.0
Failed forceps and OMHP	15	0.0
ERCD and failed forceps	14	0.0
IUGR and preeclampsia	13	0.0
Dystocia and failed forceps	12	0.0
Dystocia and cord prolapse	12	0.0
NRFS and LGA	11	0.0
ERCD and previa	10	0.0
Abruption and OMHP	10	0.0
Previa and CDMR	9	0.0
NRFS and failed forceps	8	0.0

Table C-1: Co-occurring, three or more indications for having overall CD in term singleton births		
Number of patients	**199,294**	
Category	**n**	**%**
IUGR and CDMR	7	0.0
Dystocia and preeclampsia	6	0.0
IUGR and abruption	6	0.0
OMHP and fetal anomaly	6	0.0
Preeclampsia and CDMR	5	0.0
Cord prolapse and OMHP	5	0.0
LGA and fetal anomaly	4	0.0
Previa and preeclampsia	4	0.0
LGA and previa	3	0.0
Abruption and preeclampsia	3	0.0
IUGR and fetal anomaly	2	0.0
LGA and abruption	1	0.0
Previa and fetal anomaly	1	0.0
Fetal anomaly and CDMR	1	0.0
Other co-occurring indications	1,346	0.7
Three indications[b]		
Dystocia and NRFS and OMHP	365	0.2
Dystocia and NRFS and failed forceps	243	0.1
ERCD and dystocia and NRFS	189	0.0
Dystocia and NRFS and CDMR	159	0.1
Dystocia and NRFS and preeclampsia	72	0.0
Dystocia and breech and NRFS	69	0.0
ERCD and NRFS and OMHP	45	0.0
ERCD and breech and CDMR	38	0.0
Dystocia and NRFS and abruption	37	0.0
NRFS and IUGR and preeclampsia	20	0.0
NRFS and LGA and OMHP	18	0.0
NRFS and preeclampsia and OMHP	18	0.0
Breech and NRFS and IUGR	14	0.0
NRFS and IUGR and OMHP	10	0.0
ERCD and NRFS and CDMR	10	0.0
Dystocia and OMHP and CDMR	9	0.0

Table C-1: Co-occurring, three or more indications for having overall CD in term singleton births		
Number of patients	**199,294**	
Category	**n**	**%**
ERCD and dystocia and NRFS	8	0.0
ERCD and NRFS and LGA	8	0.0
ERCD and NRFS and abruption	8	0.0
ERCD and IUGR and preeclampsia	8	0.0
Dystocia and breech and LGA	8	0.0
Dystocia and NRFS and cord	8	0.0
LGA and OMHP and CDMR	8	0.0
ERCD and previa and OMHP	7	0.0
Dystocia and failed forceps and CDMR	7	0.0
Breech and preeclampsia and OMHP	7	0.0
ERCD and NRFS and preeclampsia	6	0.0
Breech and IUGR and OMHP	6	0.0
Breech and OMHP and CDMR	6	0.0
ERCD and IUGR and OMHP	5	0.0
Dystocia and NRFS and OMHP	5	0.0
Breech and NRFS and cord	5	0.0
Breech and NRFS and OMHP	5	0.0
Breech and IUGR and preeclampsia	5	0.0
NRFS and IUGR and fetal anomaly	5	0.0
NRFS and abruption and preeclampsia	5	0.0
ERCD and dystocia and failed forceps	4	0.0
ERCD and NRFS and failed forceps	4	0.0
Dystocia and IUGR and preeclampsia	4	0.0
Breech and NRFS and LGA	4	0.0
Breech and NRFS and failed forceps	4	0.0
NRFS and previa and CDMR	4	0.0
Four indications[c]		
ERCD and CDMR and dystocia and NRFS and abruption	1	0.0
ERCD and CDMR and dystocia and breech and NRFS	1	0.0

Table C-1: Co-occurring, three or more indications for having overall CD in term singleton births		
Number of patients	**199,294**	
Category	**n**	**%**
ERCD and preeclampsia and OMHP and CDMR	1	0.0
Dystocia and NRFS and preeclampsia and OMHP and fetal anomaly	1	0.0
Other[d]	13,491	6.8

Abbreviations: NRFS-non-reassuring fetal status; other fetal health problem-OFHP; CD- cesarean delivery; LGA-large for gestational age baby; IUGR/SGA -intrauterine growth restriction/small for gestational age baby.

a. Each subject had two recorded indications and none of the other indications.

b. Each subject had three recorded indications and none of the other indications.

c. Each subject had four recorded indications and none of the other indications.

d. All other indications.

Appendix D. Co-occurring, three or more indications for having primary CD in term singleton births

Table D-1: Co-occurring, three or more indications for having primary CD in term singleton births		
Number of patients	**108,343**	
Category	**n**	**%**
Co-occurring indications [a]		
Breech and abruption	14	0.0
Failed forceps and OMHP	14	0.0
Dystocia and fetal anomaly	13	0.0
IUGR and preeclampsia	12	0.0
Dystocia and cord prolapse	10	0.0
NRFS and previa	10	0.0
Previa and CDMR	9	0.0
Abruption and OMHP	7	0.0
Breech and failed forceps	7	0.0
Dystocia and previa	7	0.0
IUGR and CDMR	7	0.0
LGA and failed forceps	7	0.0
IUGR and abruption	6	0.0
OMHP and fetal anomaly	6	0.0
Cord and OMHP	5	0.0
Preeclampsia and CDMR	5	0.0
Failed forceps and cord prolapse	4	0.0
LGA and fetal anomaly	4	0.0
Previa and preeclampsia	4	0.0
LGA and previa	3	0.0
Breech and abruption	14	0.0
Failed forceps and OMHP	14	0.0
Dystocia and fetal anomaly	13	0.0
IUGR and preeclampsia	12	0.0
Dystocia and cord prolapse	10	0.0

Table D-1: Co-occurring, three or more indications for having primary CD in term singleton births		
Number of patients	**108,343**	
Category	**n**	**%**
NRFS and previa	10	0.0
Previa and CDMR	9	0.0
Abruption and OMHP	7	0.0
Breech and failed forceps	7	0.0
Dystocia and previa	7	0.0
IUGR and CDMR	7	0.0
LGA and failed forceps	7	0.0
IUGR and abruption	6	0.0
OMHP and fetal anomaly	6	0.0
Cord and OMHP	5	0.0
Preeclampsia and CDMR	5	0.0
Failed forceps and cord prolapse	4	0.0
LGA and fetal anomaly	4	0.0
Previa and preeclampsia	4	0.0
LGA and previa	3	0.0
Three indications[b]		
Dystocia and NRFS and OMHP	357	0.3
Dystocia and NRFS and failed forceps	239	0.2
Dystocia and NRFS and CDMR	156	0.1
Dystocia and NRFS and LGA	119	0.1
Dystocia and NRFS and preeclampsia	72	0.1
Dystocia and breech and NRFS	68	0.1
Dystocia and NRFS and IUGR	51	0.0
Dystocia and NRFS and abruption	35	0.0
NRFS and IUGR and preeclampsia	20	0.0
NRFS and LGA and OMHP	18	0.0
NRFS and preeclampsia and OMHP	18	0.0
Breech and NRFS and IUGR	13	0.0

Table D-1: Co-occurring, three or more indications for having primary CD in term singleton births		
Number of patients	**108,343**	
Category	**n**	**%**
Dystocia and failed forceps and OMHP	12	0.0
Dystocia and OMHP and CDMR	9	0.0
Dystocia and breech and LGA	8	0.0
Dystocia and NRFS and cord prolapse	8	0.0
Dystocia and forceps and CDMR	7	0.0
Dystocia and NRFS and fetal anomaly	5	0.0
NRFS and abruption and preeclampsia	5	0.0
NRFS and abruption and OMHP	5	0.0
NRFS and preeclampsia and cord prolapse	2	0.0
NRFS and abruption and failed forceps	1	0.0
NRFS and abruption and cord prolapse	1	0.0
NRFS and abruption and CDMR	1	0.0
Four indications[c]		
Dystocia and NRFS and OMHP and LGA	10	0.0
Dystocia and breech and NRFS and CDMR	8	0.0
NRFS and OMHP and dystocia and preeclampsia	11	0.0
Preeclampsia and OMHP and IUGR and CDMR	1	0.0
NRFS and cord prolapse and OMHP and CDMR	4	0.0
Failed forceps and NRFS and cord prolapse and OMHP	1	0.0
NRFS and OMHP and failed forceps and abruption	1	0.0
Preeclampsia and OMHP and abruption and NRFS	1	0.0
Preeclampsia and OMHP and NRFS and IUGR	2	0.0
IUGR and CDMR and NRFS and abruption	1	0.0
NRFS and LGA and preeclampsia and OMHP	1	0.0
IUGR and OMHP and breech and NRFS	3	0.0
Breech and NRFS and LGA and CDMR	1	0.0
Other[d]	3,388	3.1

Abbreviations: NRFS-non-reassuring fetal status; other fetal health problem-OFHP; CD- cesarean delivery; LGA-large for gestational age baby; IUGR/SGA -intrauterine growth restriction/small for gestational age baby.

a. Each subject had two recorded indications and none of the other indications.
b. Each subject had three recorded indications and none of the other indications.
c. Each subject had four recorded indications and none of the other indications.
d. All other indications.

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