Clinical and Economic burden of Caesarean-section

by

Mon Hnin Tun

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Abstract

Rising caesarean section (CS) rate remains a public health issue. Induction of labour (IOL) rates have been rising steadily in Canada from 12.9% in 1991 to 21.3% in 2004. Failed IOL occurs in 20% of induced pregnancies and is the major risk factor for CS. The purpose of this study was to investigate the impact of clinical and economic burden of CS. A rapid review of the literature was conducted to examine the risk factors for CS. Using data from the CHILD birth cohort, an emergency CS risk prediction tool was developed with six antennal factors: maternal age, height, BMI, pregnancy-induced hypertension, antenatal depression and birth order of the infant (area under the curve (AUC), 0.77 (0.71-0.82). This thesis also includes a retrospective cohort study of all singleton births in Alberta from 2005-2014 that evaluated the trends of CS, induction of labour (IOL), the association of IOL and CS, the impact of CS on childhood hospitalization or emergency department attendance with asthma or gastroenteritis. Understanding these associations will be beneficial in terms of offering the labour induction at appropriate gestation weeks in particular low-risk expectant mothers. Findings indicate that infants delivered by CS increased the healthcare service utilization by visiting emergency department with asthma and gastroenteritis than vaginally delivered infants. In addition, the results from the retrospective cohort demonstrated that IOL before reaching 39 weeks increased the risk of emergency CS when compared to expectant management. Moreover, IOL at 41 weeks is the most cost-effective strategy because it provides the most net health benefit (NHB) at a willingness-to-pay (WTP) threshold of $50,000 per QALY. This the first study conducting an economic evaluation of IOL at different gestation weeks in Canada. Implications of study results for clinicians and public health are discussed and future research directions are suggested.

Preface

This thesis is an original work by Mon H Tun. The thesis has been written in a paper format thesis according to the guidelines of the Faculty of Graduate Studies and Research at the University of Alberta. Manuscript composition and data analysis in all chapters are my original work.

This thesis consists of a literature review in relation to the caesarean section and tools for caesarean section risk prediction (Chapter 1). It is followed by four studies: prediction of risk for emergency caesarean section in the CHILD birth cohort study (Chapter 2), mode of delivery and risk of hospital care in childhood for asthma and gastroenteritis (Chapter 3), caesarean section rates in Alberta and association of labour induction and caesarean section (Chapter 4), and a cost-utility analysis of labour induction at different gestation weeks in nulliparous women in Alberta (Chapter 5). In the final chapter, Chapter 6, general discussion and conclusions are presented. This chapter highlights the main findings from the four studies, clinical significance of those findings, strengths and limitations of the studies and implications for future research.

Chapter 2 of this thesis has been submitted for publication as Mon H Tun, Radha Chari, Padma Kaul, Fabiana V Mamede, Mike Paulden, Diana L Lefebvre, Stuart E Turvey, Theo J Moraes, MD, Malcolm R Sears, Padmaja Subbarao, Piush J Mandhane. "Prediction of risk for emergency caesarean section; the CHILD birth cohort study" in the American Obstetric and Gynaecology Journal.

Chapter 5 of this thesis has been submitted for publication as Mon Tun, Piush Mandhane, Padma Kaul, Radha Chari, Mike Paulden. "Economic Evaluation of labour induction at different gestation weeks in nulliparous women in Alberta: cost-utility analysis" in the Canadian Medical Association Journal.

Mon H Tun was responsible for the study design, data analysis and preparation of the thesis. Professor Piush Mandhane and Professor Mike Paulden provided guidance to the study design, data analysis, and interpretation of the results and preparation of the thesis.

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Chapter 1. Introduction

1.1 Caesarean-section

Globally, the caesarean-section (CS) delivery rates have been increasing in recent decades (1,2). CS is a surgical procedure performed when a vaginal delivery would put the life or health of the fetus or mother at risk. CS is the most common type of inpatient surgery in Canada. The World Health Organization (WHO) has recommended a maximum CS rate of 15% (3) with the 2016 CS rate in Canada approaching 30% (4). An increase in the primary CS rate and a decrease in vaginal birth after CS (VBAC) (5) are the two main factors contributing to the rise in CS rates (6,7). There is evidence that the higher rate of CS is largely attributable to planned repeat CS (8,9). The repeat CS rate in Canada was 81.7% in 2012 (10) and 90.7% in the United States (11). Further, the rate of VBAC is down from 33.3% in 1994-1995 to 28.5% in 2000-2001 (12). There is a growing consensus that preventing primary CS is the most effective method to lower the overall CS rate given the increasing rates of repeat CS and lower VBAC rates (13,14). The Robson classification system classifies all deliveries into ten mutually exclusive and totally inclusive groups based on a set of predefined obstetric parameters (15). These include parity, previous CS, onset of labour, fetal presentation, number of fetuses and gestational age. The classification system is simple to use and it enables auditing and analyzing CS rates as it is based on routinely documented obstetric characteristics of individual woman without relying on the indication of CS. WHO recommends to utilize Robson Ten Group Classification System as a global standard for assessing, monitoring and comparing CS rates nationally, internationally and globally (16).

Unnecessary CS can lead to increased medical risks for mothers and infants and there is a lack of evidence that a CS rate greater than the WHO threshold provides substantial maternal and neonatal benefits. Few studies have reported on the increased healthcare costs associated with CS (17) and the increased immediate and long-term risk of maternal and neonatal morbidity and mortality associated with CS (18).

1.2 Benefits of caesarean-section

The CSs performed following medical indications are life-saving procedures and provide greater safety of the mothers and babies. Reported benefits of CS include reduced rates of urinary incontience, pelvic organ prolapse (19), pelvic organ damage and perineal and vaginal laceration (20). Avoidance of labour pain has also been cited as a potential benefit of CS (21). Other possible benefits of CS, particulary scheduled CS, include the convenience of scheduling the time and date of birth and also provide flexibility to the healthcare providers to plan for staffing efficiently (21).

1.3 Economic burden of caesarean-section

CS requires additional healthcare resources including operating room space, anaesthesiologists and longer stay in hospital for mothers and infants (22-24). As such, CS deliveries cost hospitals twice as much in obstetrical care compared to vaginal births ($2,2265 vs. $4,930). In Canada, the estimated total cost for all primary CS hospitalizations was $292 million (23). Additionally, CS delivery was associated with higher hospital readmission costs during the first two months postpartum compared to vaginal delivery (£3,200 vs. £1,698) (25). Furthermore, CS delivery after labour induction was more expensive than scheduled CS (26,27), spontaneous delivery and instrumental vaginal delivery (28,29).

1.4 Burden of caesarean-section on mothers

CS is associated with higher perinatal morbidity and mortality **(Table 1.2)**. CS is associated with an increased chances of maternal haemorrhage, blood transfusion, hysterectomy, placental problems (previa/accreta or uterine rupture (30) and complications arising from general anaesthetic (31). Long term sequalae of CS include pelvic adhesions, chronic pain, decreased fertility (32-34), perinatal depression (35), and increased risk of miscarriage, low birth weight, preterm birth and stillbirth (19) in subsequent pregnancies (34,36,37). Rauh and colleagues (2012) (35) demonstrated that women who underwent primary CS had lower self-esteem and

higher postnatal depressiveness scores. Mortality from emergency CS is four times higher than from vaginal delivery (38,39). An emergency CS in advanced labour increased the risk of maternal morbidity, mortality and psychological trauma (40,41).

1.5 Burden of caesarean-section on infants

While CS can prevent severe perinatal morbidity from intrapartum asphyxia, CS can have long-term consequences for the child. CS delivered infants are subject to different hormonal, physical, bacterial and medical interventions. The short-term and long-term health burden of CS on infants are listed in **Table 1.2** Of note, infants born by CS experienced a higher incidence of hypoglycemia, oxygen requirement, and respiratory distress compared with vaginally-delivered babies (30,42-44). Empirical studies have shown the negative impact of CS on the initiation and duration of lactation (45-47), and CS delivered babies are less likely to be exclusively breastfed for the first 6 months of life (48). Several meta-analyses, further, indicated that infants delivered by CS have a 20% increase in the likelihood of developing asthma (49,50), atopy, allergies (51,52), type 1 diabetes (53) and obesity up to the age of 5 years (19). In addition, CS delivered healthy term infants had higher rates of hospitalization with gastroenteritis (54,55) and asthma (56,57). One study highlighted that fetal complications rate were higher in emergency caesarean section than in elective caesarean section (58).

1.6 Risk factors and indications for caesarean-section

We completed a single-reviewer rapid review to identify factors associated with CS. Comprehensive literature searches were conducted in PubMed and keywords for cesarean section, risk factors or indications or determinants, nulliparous or first-time mothers, vaginal birth after cesarean section or trial of labour, systematic review or meta-analysis were used in the searches. **Appendix 1** provides the search terms used for the review. Studies were included if they were observational, systematic review or meta-analysis that identified the risk of CS delivery. One reviewer (MT) screened all the titles and abstracts. Studies were excluded if they were not primary research or were letters to the editor, case report or case-series studies. The risk

factors of CS in healthy nulliparous women were compiled and classified into maternal, fetal and pregnancy-related factors **(Table 1.3)**.

Maternal Factors

CS on maternal request has been attributed to rising CS rates comprising 6%-8% of all primary CS in the UK and Northern Europe (59,60). Increased maternal age, specifically with primigravida, multiple pregnancy, abnormal fetal presentation, low birth weight, arrest of labour, and gestational age (61) are the common contributing factors for primary CS. Maternal anthropometrics including higher pre-pregnancy weight (62), weight gain during pregnancy (61), higher maternal BMI (63), shorter maternal height (61,62,64) are also associated with CS. Studies have shown that 14% (one in seven) of CS deliveries were attributed to obesity (65-68) and the risk of CS delivery is increased by 7% with one-unit increase in maternal body mass index (BMI) (69). Patel (2005) reported that pregnancy complications including gestational hypertension, pre-pregnancy diabetes or gestational diabetes were also associated with increased risk of CS (70).

The rate of scheduled CS without medical indication increases with advanced maternal age (71).Women aged ≥ 35 were more likely to have a primary CS than younger women were. In a study done in the UK, increased maternal age contributed to 38% of the additional surgical procedures and the risk of CS is estimated to be increased by 50% with every 5-year increase in the mother's age at the time of delivery (72). Advanced maternal age is associated with an increased risk of obesity, diabetes and hypertensive disorders (73-75).

Parameters such as parity, prior uterine surgeries, and history of previous vaginal delivery are determinants of success of VBAC (61,66,68,76,77). Prior CS delivery was strongly associated with scheduled CS delivery whereas cephalopelvic disproportion had significant impact on emergency CS delivery (78).

Pregnancy-related factors

Patel (2005) reported that epidural use was highly associated with emergency CS (70) which was inconsistent with the findings from Segal (2000) (79,80) and Halpern (1998) (80). In addition, clinically and sonographically determined cervical dilation and low Bishop score on admission were associated with increased risk of CS delivery (61,81). Labour dystocia or failure to progress

are indicators for emergency CS (68,82). The association between induction of labour (IOL) and the risk of CS is controversial but studies have reported failed IOL is a major risk factor or emergency CS (83).

Fetal factors

Abnormal or indeterminate fetal heart rate, suspected fetal macrosomia (66,68,82,84-86) have been associated with increased CS risk. Breech presentation were strongly associated with scheduled CS than scheduled CS (78).

1.7 Induction of labour and caesarean section

Induction of labor (IOL), a common obstetric procedure, has increased gradually worldwide (87). IOL is generally a safe and effective procedure and carried out in approximately 20%-25% of pregnancies (88,89). However, failed IOL occurs in 20% of induced pregnancies and is the major risk factor for CS (83). IOL is defined as utilizing artificial methods to initiate labour and is considered when the benefits of induction outweigh the risk to continue with a pregnancy (90). IOL rates have been rising steadily in Canada from 12.9% to 21.3% (1991 to 2004) (91). Many international guidelines recommended inducing labour between 41 and 42 weeks of gestation without any indication (59,90,92,93). Some studies have shown that IOL at full term reduces stillbirth and severe pre-eclampsia (94-96). As a result, two studies suggest that there is an increase in the frequency of IOL without indication (97,98).

IOL has an associated cost and Kaimal et al (2011) found that IOL at 41 weeks was “cost-effective”, while Hersh et al. (2019) found that IOL at 39 weeks was “marginally cost-effective” when compared to EM (99,100). A trial of labour (TOL) is the most cost-effective mode of delivery following previous CS (26,101-103), with the probability of 74% or 67% success rate of vaginal delivery (26,101). A recent report by Grobman (2020) indicated that IOL is associated with longer duration in labour and delivery but resulted in lesser antepartum visits, tests and shorter post-partum hospital stay (104).

There have been inconsistent findings of an association between IOL and CS. The success of labour induction is determined by many maternal and fetal variables. Nulliparity and poor cervical conditions (bishop score <6) are known risk factors for CS after IOL (105-107). IOL in nulliparous women is six times more likely to fail when compared to multiparous women (98) and increased the CS rate by 20% in low-risk nulliparous women (108). Several factors considered as predictors of failed IOL are obesity (109,110), pregnancy complicated by preeclampsia (111), gestation age < 41 weeks, maternal age above 30 years, fetal macrosomia, premature rupture of membranes (PROM), gestational diabetes and hypertension (112,113). IOL increases pre-delivery hospital stay, labour time and cost (114). In observational studies, IOL increased the risk of CS when compared to expectant management (EM) (115-117). Caughey (2009) pointed out the lack of appropriate control group (spontaneous labour or expectant management) and confounding factors resulting from the indications for IOL are the factors for the controversial issue of IOL increased the risk of CS (118). Nonetheless, randomized trials and meta-analyses showed no increased risk of CS when IOL was compared to EM, with the majority of the trials including IOL after post-dates (≥ 41 weeks) (94,119-124). The ARRIVE trail randomized 3062 low-risk nulliparous women to IOL at 39 weeks vs. EM and reported no significant difference in composite perinatal outcome but a significantly lower rate of CS and hypertensive disorders of pregnancy in the IOL group. Notably, emergency CS after failed IOL carries a higher rate of complications than a vaginal delivery or scheduled CS (125).

1.8 Caesarean-section risk prediction tools

Prior CS prediction tools among low-risk nulliparous women utilize antenatal and intrapartum obstetric and non- obstetric characteristics (126-128). The inclusion of intrapartum factors such as augmentation of labour and meconium staining of the amniotic fluid (129-131)limits a caregiver's ability to counsel a patient about the likelihood of a CS delivery prior to labour occurring (132).

Janssen et al (2017) studied 1,302 nulliparous women and developed a CS model for low risk nulliparous pregnant women with area under the curve (AUC) of 0.71 (0.67-0.75) (131). However, the model included intrapartum factors such as cervical dilatation, station of baby and

intensity of contractions. Smith et al (2004) included only 4 characteristics: maternal age, height, gestational age and fetal sex in the combined logistic and Bayseian models (133). The model estimated the risk of CS delivery among nulliparous women and yielded an AUC of 0.67.Unfortunately, the model assessed the risk of CS after induction of labour with prostaglandin.

The validated prediction model for VBAC by Grobman et al found an AUC of 0.74 (66). The Grobman calculator is based on 6 characteristics including maternal age, body mass index (BMI), race/ethnicity, history of previous vaginal delivery and a recurring indication for previous CS. The FLAMM scoring system, developed to predict a VBAC included intrapartum factors such as cervical dilation and effacement (134). These models have limited generalizability as the tools are meant to predict the probability of a VBAC for term pregnant women with one prior CS.

Tools to predict emergency CS delivery have similarly incorporated antepartum and intrapartum factors (135,136). The emergency CS risk prediction model and classification tree (CTREE), with the area under the receiver operating characteristic curve (AUC) ranges from 0.74 to 0.81, included intrapartum factors such as scalp pH, and labour induction among women with history of previous CS (137).

1.9 Study Objective and structure

The overall purpose of this thesis was to examine the clinical and economic burden of CS among nulliparous and low-risk nulliparous women. The findings of this thesis could be informative to healthcare providers in providing antenatal care and aid the expectant mothers in labor induction and birth mode decision making. Specifically, this thesis consisted of four studies looking at the clinical and economic burden of CS. The following specific objectives were addressed for each chapter of the thesis.

Question 1: Which antenatal obstetric and non-obstetric factors predict the risk of emergency CS?

Question 2: Does CS delivery increase the risk of healthcare service utilization i) due to wheezing/ asthma in infants ii) due to gastroenteritis?

Question 3: Does IOL before 41 weeks of gestation increase the risk for emergency CS compared to expectant management?

Question 4: Which gestation week provides the most net health benefit to first offer the IOL among singleton pregnancy women?

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Table 1.1 Robson ten group delivery classification system

Groups	Description
Group 1	Nulliparous, single cephalic, ≥ 37 weeks, in spontaneous labor.
Group 2	Nulliparous, single cephalic, ≥ 37 weeks, induced or CS before labor 2a- Nulliparous, singleton, cephalic, ≥ 37 weeks' gestation, induced labor 2b- Nulliparous, singleton, cephalic, ≥ 37 weeks' gestation, caesarean section before labor.
Group 3	Multiparous (excluding previous caesarean section), singleton, cephalic, ≥ 37 weeks' gestation, in spontaneous labor.
Group 4	Multiparous without a previous uterine scar, with singleton, cephalic pregnancy, ≥ 37 weeks' gestation, induced or caesarean section before labor. 4a- Multiparous without a previous uterine scar, with singleton, cephalic pregnancy, ≥ 37 weeks' gestation, induced labor. 4b- Multiparous without a previous uterine scar, with singleton, cephalic pregnancy, ≥ 37 weeks' gestation, caesarean section before labor.
Group 5	Previous caesarean section, singleton, cephalic, ≥ 37 weeks' gestation.
Group 6	All nulliparous with a single breech.
Group 7	All multiparous with a single breech (including previous caesarean section).
Group 8	All multiple pregnancies (including previous caesarean section).
Group 9	All women with a single pregnancy in transverse or oblique lie (including those with previous caesarean section).
Group 10	All singleton, cephalic, < 37 weeks' gestation pregnancies (including previous caesarean section All singleton, cephalic, < 37 weeks' gestation pregnancies (including previous caesarean section).

Table 1.2 Burden of caesarean section on mothers and infants

	Short-term	Long-term
Maternal outcomes	Haemorrhage requring blood transfusion or emergency peripartum hysterectomy, uterine rupture (19,30,138) Infections (Urinary tract infection, Wound infection, Endometritis, Sepsis, Penumonia) (19,35,138,139), Anesthetic complications (31,138) Surgical injuries (uterine lacerations, bladder injury, ureteral injury, vesicouterine fistula, bowel injury, uterine atony (19,139) Post-partum depression, obstetric shock, cardia arrest, acute renal failure (19,138,140) Puerperal venous thromboembolism (19,139,141) Amniotic fluid embolism (138) Rehospitalization (19,138,139) Reoperation (19,138,139) Breast feeding problems Maternal death (38,39,138)	Adhesions (small bowel obstruction, pelvic adhesions) (138) Chronic pain, dysmenorrhea, menorrhagia, sexual dysfunction, (19,138,139) Infertility/ Subfertility (32-34,138) Maternal depression (19,35,139)
Infant or Childhood outcomes	Fetal injuries (19,139) Respiratory morbidity (19,138) Neonatal death (19,138) Wheeze, allergy, atopy (19,138,142) Altered intestinal gut microbiome diversity (143) Breastfeeding problems (48)	Wheeze, atopy, asthma, allergy, overweight, obesity, inflammatory bowel disease, type 1 diabetes (19,49,138,142,144) Cerebral palsy (19,138,139) Emotional, behavioral, cognitive and educational outcomes (19,138,142,143)

		Gastrointestinal disorder (Gastroenteritis, Crohn's disease, ulcerative colitis) (142,145)
Subsequent pregnancy outcomes	Perinatal death (19)	Placenta complications (previa, accreta, abruption) (19,138,139) Uterine rupture (19,30,138,139) Miscarriage, ectopic pregnancy (19,138,139) Hysterectomy (138) postpartum haemorrhage, antepartum haemorrhage, preterm labour, stillbirth, fetal growth restriction, neonatal death, low birth weight (19,34,36)

Table 1.3 Reference studies reporting the association of caesarean section in nulliparous and multiparous

	Obstetric	Non-obstetric
Antepartum	Maternal factors -gestational hypertension (68,70,146) -preeclampsia, eclampsia (68,146) -gestational diabetes (68,146,147) -premature rupture of membrane (148) -parity (68,149) -cephalo pelvis disproportion (66,68) -previous vaginal delivery (66,68) -in-vitro fertilization (IVF) (146,150) Others -gestation age (68)	Maternal factors -age (66,72,82,86,149,151-153) -height (66,68,82,86,151,154) -pre-pregnancy weight/ BMI and pregnancy weight gain (66-68,82,146,153,155,156) -socio economic status (149) -race/ethnicity (66,68) -education (149,157) -smoking (146) -maternal stress, anxiety, depression score (82,158) -chronic hypertension (68,159) -diabetes (68,147) -sleep disorder (obstructive sleep apnoea) (160) -maternal request (60) Fetal factors -macrosomia (68,82,161) -position (occiput posterior) (68,82) -presentation (breech) (68,82) -gender (86) Others -exercise, diet (162,163)

		-vitamin D supplementation (164,165) -senior healthcare professionals/ healthcare institution (68,166) -healthcare insurance (86)
Intrapartum	<u>Maternal factors</u> -cervical dilatation (Bishop score) (68,82,157) <u>Others</u> -epidural analgesia (82,167,168) -induction of labour (IOL) (68,82,110,119,121,169) -augmentation of labour (82) <u>Indications for Emergency CS</u> -dystocia or failure to progress (68,82) -fetal distress (68,157) -acupressure	<u>Others</u> -Cardiotocography monitoring (170)

Appendix 1: PubMed July 2020

Search	Query	Results
#7	#1 AND #2 AND #3 AND #5	1843
#6	#1 AND #2 AND #4 AND #5	356
#5	((systematic review) OR meta analysis) AND metaanalysis	125491
#4	(((((((nulliparous) OR (first time pregnant)) OR (first time mother)) OR (first time deliver)) OR (nonparturitive)) OR (first pregnancy)) OR (nonparturient)) OR (nonparous)	194232
#3	(((((((((vaginal birth after cesarean) OR (vbac)) OR (vaginal birth)) OR (vaginal deliver)) OR (trial of labor)) OR (postcesarean)) OR (postcaesarean)) OR (c section)) OR (abdominal deliver)) OR (uterine scar)	82725
#2	(((((((Cesarean Section) OR (cesarean)) OR (caesarean abdominal deliver)) OR (caesarea)) OR (cesarea)) OR (c section)) OR (CS)) OR (abdominal deliver)	519462
#1	(((((((((risk factors) OR (predict)) OR (model)) OR (predictors)) OR (indicators)) OR (determinants)) OR (risk score)) OR (risk management)) OR (factor)) OR (risk)	16614138

Chapter 2. Prediction of risk for emergency caesarean section; the CHILD birth cohort study

Mon H Tun[1], Radha Chari[2], Padma Kaul [3,4,5], Fabiana Mamede[1], Mike Paulden[4], Diana L Lefebvre[6], Stuart Turvey[7], Meghan Azad[8], Theo J Moraes[9], Malcolm R Sears[6], Padmaja Subbarao[9], Piushkumar Mandhane[1]

[1]Department of Pediatrics, University of Alberta, Edmonton AB, Canada

[2]Department of Obstetrics and Gynaecology, University of Alberta, Edmonton AB, Canada

[3]Canadian VIGOUR Centre, University of Alberta, Edmonton AB, Canada

[4]School of Public Health, University of Alberta, Edmonton AB, Canada

[5]Department of Medicine, University of Alberta, Edmonton AB, Canada

[6]Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

[7]Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada.

[8]Department of Pediatrics & Child Health, University of Manitoba, Winnipeg, Manitoba, Canada.

[9]Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

Abstract

Introduction

Prior cesarean section (CS) and emergency CS prediction tools use antenatal and intrapartum risk factors. We aimed to develop a predictive model for the risk of emergency CS before the onset of labour utilizing antenatal obstetric and non-obstetric factors.

Methods

We completed a secondary analysis of data collected from the CHILD Cohort Study. The CHILD subsample for this analysis was limited to term (37 weeks gestational age or greater) pregnant women carrying a singleton fetus with cephalic presentation. Data available included maternal demographics, obstetric history and birth modes. The sample was divided into a training dataset (80%) and validation dataset (20%). The emergency CS prediction model was developed using variables associated with CS delivery in the training dataset (multiple logistic regression). The predictive capacity of the emergency CS delivery model was assessed by the area under the receiver operating characteristic curve (AUC). The predictive ability of our final model was subsequently evaluated in the validation data set.

Results

The participant sample consisted of 2,836 pregnant women. Mean age of participants was 32 years, mean BMI of 25.4 kg/m2 and 39% were nulliparous. The scheduled CS rate was 6% (156/2836) while the emergency CS delivery rate was 13% (365/2836). Each year of increasing maternal age increased the odds of emergency CS by 6% (adjusted Odds Ratio (aOR) 1.06, 1.02-1.08) as did a 4% increase for each unit increase in BMI (aOR 1.04, 1.02-1.06). In contrast, maternal height was negatively associated with the risk of emergency CS delivery. The final emergency CS delivery predictive model included six variables (pregnancy induced hypertension, antenatal depression, birth order of the infant, age, height, BMI, when controlling for delivery hospital). The AUC for our final prediction model was 0.74 (0.72-0.77) in the training set with an AUC of 0.77 (0.71-0.82) in the validation dataset.

Conclusion

We developed and validated a prediction model for emergency CS delivery risk that deliberately did not include intrapartum factors. The tool may be used in counselling prospective parents around their CS risk and CS surgical operating room planning. Further validation of the tool in additional cohorts is suggested.

2.1 Background and Introduction

The World Health Organization (WHO) has raised concerns regarding the dramatic increase in cesarean section (CS) rates. CS is an effective means to resolve the medical and surgical complications of dystocia and serious complications of pregnancy. A number of maternal, antenatal and intrapartum factors have been associated with scheduled CS and emergency CS (1-4). Absolute indications for scheduled CS include cephalopelvic disproportion, placenta previa, abnormal lie and presentation whereas prior CS delivery is classified as a relative indication for scheduled CS (4). Emergency CS, performed to improve maternal or fetal outcomes, is associated with increased maternal morbidity and mortality, compared to a scheduled CS. Morbidity associated with emergency CS include severe hemorrhage, complications from rapid administration of general anesthesia and accidental injury to the mother and infant (5-8). A meta-analysis reported that the rates of maternal and fetal complications and mortality were higher in emergency CS when compared to scheduled CS (9). In addition to the additional morbidity and mortality, resource planning for an emergency CS is more difficult compared to scheduled CS resulting in higher infection rates (8). Emergency CS prediction tools utilizing intrapartum factors do not afford the patient or caregiver an opportunity to schedule a CS to avoid the morbidity associated with emergency CS.

The CS risk prediction model developed by Janssen et al utilized both antenatal and intrapartum factors for low risk nulliparous pregnant women (10). The FLAMM scoring system, developed to predict a VBAC (vaginal birth after prior caesarean section), included intrapartum factors including cervical dilation and effacement. The Grobman calculator, which included only antenatal factors, has limited generalizability as the tool is meant to predict the probability of a vaginal birth after cesarean section (VBAC) for term pregnant women with one prior CS. Tools to predict emergency CS delivery have incorporated antepartum and intrapartum factors (11,12). The emergency CS risk prediction model and classification tree (CTREE), with discriminatory accuracy ranges from 0.74 to 0.81, included intrapartum factors such as scalp pH, and labour induction among women with history of previous CS (13). We could not identify a tool or scoring system for emergency CS risk prediction utilizing prenatal factors only.

In this study, we used data from the CHILD Cohort Study to identify the main antenatal obstetric and non-obstetric risk factors for emergency CS and to subsequently develop an emergency CS prediction tool.

2.2 Methods

The CHILD Cohort Study is a large general-population recruited prospective observational pre-birth cohort study of 3,455 pregnant women enrolled in Edmonton, Winnipeg, rural Manitoba, Vancouver and Toronto between 2009 and 2012. We restricted our analysis to nulliparous and multiparous women carrying a singleton, cephalic presentation fetus at 37 completed weeks of gestation with available birth chart records (n=3,408). Women with a home birth, placenta previa, a prior CS delivery, multiple gestation and those who had their labour induced were excluded from this analysis. Our final sample size was 2,836 low-risk pregnant women **(Figure 2.1).** Details on the data collection methods and the characteristics of the cohort have been described previously (14) (www.childstudy.ca). Mothers were approached for enrollment in the study during the second or third trimester of their pregnancy. Infant, and their parents, were recruited if born at 34 weeks' gestation or later and with birth weight of 2,500 g or more. Ethics approval was obtained from local authorized review board of each CHILD study center and McMaster University. The pregnant women provided written informed consent to participate in the CHILD study. A separate ethics approval was obtained for this analysis (Pro00092920).

Mothers completed questionnaires on general health such as diabetes, hypertension and psychosocial factors at the time of recruitment and at 36 weeks of gestation. Information regarding maternal age, weight (kg), height (cm), parity, socioeconomic status, maternal education, ethnicity, maternal smoking status, medical comorbidities and risk factors including hypertensive disorder and diabetes mellitus complicating pregnancy were collected through standardized questionnaire. Maternal antenatal depression was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D). Participants were classified as depressed if their CESD-score was ≥10 points. The socioeconomic status (SES) was divided into two groups with a cut-off income of ≥ $60,000 which indicates higher socioeconomic status. Maternal pre-

pregnancy BMI was calculated using self-reported height and weight and classified by World Health Organization (WHO) criteria. Delivery information, including delivery mode, gestational age at birth and neonatal sex, were obtained from birth chart reviews.

2.2.1 Statistical Analysis

The primary outcome was emergency CS for any indication. The secondary outcome was scheduled CS. Variable selection for the CS risk prediction was based on combination of literature review (Supplementary Table 1 and Appendix) and clinical experience. All parametric data were expressed as mean ± standard deviation (SD), and non-parametric data as median ± interquartile range (IQR). Mean centering was employed to center the maternal age and height variables. Categorical variables were analyzed using the Chi-squared test or the Fisher's exact test. The selection of covariates was based on their clinical significance and association with emergency CS delivery. Our initial analyses examined predictors of all-indication (scheduled and emergency) CS. Subsequently, we completed a sensitivity multinomial logistic regression model to identify the risk factors for three different birth modes (vaginal, scheduled CS and emergency CS). We found differences in risk factors for scheduled and emergency CS. As a result, we developed separate prediction tools for emergency and scheduled CS. We completed a stratified sensitivity analysis in nulliparous and multiparous women.

Data analysis steps to develop an emergency CS score are described in **supplementary figure 2.1**. First, the data were randomly divided into two groups: a training dataset (80% of the sample) and a validation dataset (20% of the sample). Variables significant in univariate analysis were further tested by multiple logistic regression model. A prediction model (vaginal vs. emergency CS) was then developed with the training data set taking hospital and provincial difference of CS rate into account. The area under Receiver operating characteristic curve (AUC) was used to assess the performance of the prediction model based on the model's sensitivity and specificity. The predictive ability of the model was then evaluated in the validation data set. The *p*-values for all hypothesis tests were 2-sided and statistical significance was set at $p < 0.05$. Goodness-of-fit for the logistic regression models was assessed by using the Hosmer and Lemeshow test. Using a similar analytical methodology, we also developed a separate prediction

model and scoring system for scheduled CS. Data analysis was carried out using STATA version 14.

2.3 Results

The demographic and clinical characteristic of women in the study cohort are presented in **Table 2.1.** Of the 2,836 pregnant women included in the final analysis, 14% (365/2680) had an emergency CS delivery and 6% (156/2836) had a scheduled CS. The majority of women enrolled were Caucasians (73%). The mean age of women at enrollment was 32 years with a mean BMI of 25 kg/m^2. Among infants delivered by emergency CS, 59% (214/365) were male. Among the women delivered by emergency CS, 6% had gestational diabetes, 7% had pregnancy-induced hypertension and 20% of the infants were delivered at early term gestations (i.e. before reaching 39 weeks). Women delivered by emergency CS had greater depression symptoms (CESD-scores ≥ 10 points) than the vaginally delivered group (35% vs. 27%, p=0.0001). The women with scheduled CS and emergency CS were older and had higher BMI when compared to vaginally delivered women (33.70 vs. 31.99, p=0.01; 32.63 vs. 31.99, p=0.023). Women who underwent scheduled CS had higher SES when compared to vaginal delivery (86% vs. 79%, p=0.045).

Risk factors for CS: In multiple logistic regression, women with a higher antenatal depression score had a 43% increased risk of being delivered by CS (aOR 1.43, 1.10-1.84). Each additional year of maternal age increased the odds of CS by 5% (aOR 1.05, 1.02-1.08) and each unit increase in BMI increased the odds of CS by 4% (aOR 1.04, 1.02-1.06). In contrast, maternal height was negatively associated with the risk of CS delivery (aOR 0.95, 0.94-0.97). Not being first-born (aOR 0.46, 0.36-0.59) was significantly associated with decreased risk of CS. The CS rate varied across the 13 hospitals from 11% to 25%. For one percent increase in CS rate of the hospitals at which the delivery occurred, the mother's chances of being delivered by CS increased by 9% (aOR 1.09, 1.05-1.13) **(Table 2.2, Figure 2.2a)**. In our stratified analysis by parity, pregnancy induced hypertension was a significant predictor for CS in nulliparous but not multiparous women (aOR 1.93, 1.02-3.67 vs. aOR 1.09, 0.55-2.21) **(Supplementary Table 2.2)**.

We observed differences in the risk factors for scheduled and emergency CS in multinomial analysis **(Supplementary Table 2.3)**. Women who delivered at a hospital with higher CS rate had a higher risk for scheduled CS (aOR 1.19, 1.12-1.27); however, hospital CS rate was not a significant risk factor for emergency CS (aOR 1.04, 0.98-1.09) **(Table 2.2 & Supplementary Table 2.3)**. For each year of increase in maternal age, women had a 6% increased risk for scheduled CS (aOR 1.06, 1.01-1.09) and 5% for emergency CS (aOR 1.05, 1.02-1.08). Similarly, women with a higher BMI had a 4% increased risk of both scheduled CS (aOR 1.04, 1.01-1.08) and emergency CS (aOR 1.04, 1.02-1.07) **(Supplementary Table 2.3)**. Pregnant women who had an emergency CS were more likely to have pregnancy-induced hypertension (aOR 1.75, 1.01-3.07) and a higher CES-D score (aOR 1.45, 1.07-1.96). In contrast, taller pregnant women (aOR 0.94, 0.92-0.96) and women who had a previous vaginal delivery had lower odds of having an emergency CS (aOR 0.21, 0.15-0.30) **(Supplementary Table 2.3)**.

Development of scoring system for emergency CS (primary outcome): Our emergency CS model identified six predictors when controlling for hospital delivered: maternal age, height, BMI, pregnancy-induced hypertension, antenatal depression score (CES-D), and birth order of the infant (**Table 2)**. The AUC values for the development prediction models was 0.74 (0.72-0.77) while the AUC for the validation dataset was 0.77 (0.71-0.82) **(Table 2.2, Figure 2.2b)**. We subsequently developed a modified scoring system based on the logistic regression model coefficients that ranged from 0 to 14 **(Table 2.3a)**. The scores were further categorized into grade 0 (0-5 points), grade 1 (6-7 points), grade 2 (8-9 points), and grade 3 (≥ 10 points). With the increase in grade, there was an increase in odds of emergency CS risk **(Table 2.3b)**. For example, women with grade 2 had a 6.11 increased odds of having an emergency CS (95%CI; 3.06-12.19) while women with grade 3 scores had a 13.96 increased odds of an emergency CS (95%CI; 7.32-26.61) compared to women with grade 0 (baseline) risk scores. The developed modified scoring system provided a sensitivity of 11%, specificity of 91% and an AUC of 0.70 (0.68-0.73) **(Table 2.3b)**. Among women with a grade 1 risk of an emergency CS, the number needed to treat (NNT) is seven (i.e. schedule seven CS to prevent one emergency CS), while the NNT was three for emergency CS grade 2 while NNT=4 and women with a grade 3 emergency CS risk.

The results of the scheduled CS prediction model and the scoring system were described in the online supplementary material **(Supplementary Table 2.4, 2.5 and Appendix 2.2)**.

2.4 Discussion

We developed a score that identifies low-risk pregnant women at risk for an emergency cesarean using data from a large population based cohort from different sites in Canada. The score includes antenatal obstetric and non-obstetric factors, as well as birth order of the infant, and controls for the hospital CS rate. The yielded AUC are comparable to prediction models that included intrapartum factors (10,15), birth weight of the infants (15) and premature rupture of membrane (15). Most of the parameters in our predictive model are routinely collected as part of routine prenatal care except the CES-D (maternal depression) score. Furthermore, our model has good generalizability as the score was developed from deliveries from 13 different hospitals distributed across Canada. The emergency CS scores could be utilized in the overall context of clinical information to help patient with counseling, expectation and decision-making.

Several studies, including our own, have shown that advanced maternal age was associated with higher odds of having a CS delivery (10,15-17). Similarly, our finding of an inverse association between maternal height and CS delivery is consistent with prior studies (10,15,18,19). Furthermore, a higher maternal BMI has been associated with adverse obstetric outcome and increased the risk of CS delivery (20,21). A previous history of vaginal delivery decreased the risk of emergency CS were consistent with the findings from VBAC prediction models (16,22). In contrast to prior studies, we did not find that sociodemographic factors such as ethnicity, education and social class and employment and income status were associated with emergency CS (23).

Unique to our study, we observed that women with higher antenatal depression score had higher risk of emergency CS delivery. One study reported that mental health status, in particular stress, sleep disturbances and worry were associated with higher risk of emergency CS (24). Fear and anxiety of childbirth (25,26) and depressed mood (27) are common causes for preference for CS. Our study finding suggests clinicians should assess for the presence of antenatal depression in

routine antenatal screening for emergency CS risk. In addition, comprehensive mental health programs and the effective interventions of health promotion could reduce the fear and promote confidence with childbirth by vaginal delivery.

We were not able to develop a scoring system for scheduled CS with a significant predictive capacity. The Avon Longitudinal Study reported that the largest impact on scheduled CS was breech presentation and previous CS (11). Our exclusion of women with breech presentation, prior CS delivery, placenta previa and cephalopelvic disproportion, and abnormal lie and presentation from the analysis, known risk factors for a scheduled CS (4), may have resulted in the inability of our scoring system to predict the risk of scheduled CS. Additionally, the data on prior CS history is incomplete in our study population. Hence, we cannot be certain whether the observed increased in the risk of scheduled CS in the subsequent born children could be a confounding effect of prior CS history.

Strengths of our study include a nationwide, prospective design, conducted in a large birth cohort study from four sites in Canada. With the multinomial logistic regression model, the risk of scheduled and emergency CS were estimated simultaneously and the parameter estimates are more efficient with less error. Our study had access to the wide range of sociodemographic and pregnancy related variables beyond what would normally be available in a clinical chart review. In addition, many of the antenatal factors utilized for the prediction model were verified with birth chart review by research assistant. Finally, the large sample size provided us with sufficient power to predict emergency CS risk and develop the scoring system with internal validation.

Our research is not without limitation. The observational study design with self-reported items may introduce systematic error in the variance of the predictor variables. Our study did not have access to complete information on maternal weight change during pregnancy, presence of oligohydramnios and estimated fetal weight. We only included term infants in this analysis as the risk factors for CS are different in pre-term infants. Our prediction model included both nulliparous and multiparous pregnant women which may have impact on model. Nonetheless, we adjusted for birth order in our prediction model as well as undertaking sensitivity analysis in nulliparous and multiparous subgroups.

While we performed internal validation by splitting the data set, we lacked data for conducting external validity for our CS prediction model. Future research could include external validation

of the score in other large, prospectively cohort study. The lack of complete information on prior CS will be worth exploring as an explanation of the variation in scheduled CS and the role of women's preferences. Subsequent work may assess the impact of our prediction model in decision-making about timing and mode of delivery and thereby influence acute and long-term outcomes for women and their offspring. Our study indicated that women with a higher BMI were more likely to have an emergency CS delivery and weight control efforts before and during pregnancy may help to reduce the emergency CS rate (21).

2.5 Conclusion

We developed a model to predict the likelihood of emergency CS using prenatal obstetric and non-obstetric factors. The proposed prediction model has similar performance characteristics compared to other emergency CS prediction models without the need for intra-partum prediction factors. The tool may assist in delivery mode decision-making which in turn can assist in healthcare resource planning and allocation. Early identification of the women at an increased risk of emergency CS is important and will be allow time to counsel and to refer them for scheduled CS.

Table 2.1. Demographic, antenatal and obstetric characteristics associated with mode of delivery

Characteristics	Vaginal * (n= 2,315)	Emergency CS (n=365)	Scheduled CS (n=156)
Maternal Age (years) (mean ± SD)	31.99 ± 4.62	**32.63 ± 4.86**	**33.70 ± 4.30**
Maternal Height (cm) (mean ± SD)	165.53 ± 6.81	**162.79 ± 6.98**	164.60 ± 7.50
Maternal Weight (kg) (mean ± SD)	68.75 ± 16.42	**70.90 ± 18.37**	**73.06 ± 20.36**
BMI in kg/m^2 (mean ± SD)	25.07 ± 5.68	**26.71 ± 6.46**	**26.89 ± 6.89**
Hospitals CS rate CHILD cohort (mean ± SD)	5.93 ± 3.20	**6.57 ± 3.16**	**7.4 ± 3.30**
Increased CESD-score (Ref: <10)	614 (27%)	**128 (35%)**	49 (31%)
Gestational Age (weeks)			
37	133 (6%)	**29 (8%)**	**9 (6%)**
38	253 (11%)	**42 (12%)**	**35 (23%)**
39	551 (24%)	**65 (18%)**	**75 (49%)**
40	754 (33%)	**92 (26%)**	**29 (18%)**
41	514 (22%)	**104 (29%)**	**5 (2.5%)**
≥42	97 (4%)	**27 (7%)**	**1 (0.5%)**
Gravida			
G1	862 (37%)	**199 (55%)**	**38 (24%)**
G2	748 (32%)	**90 (25%)**	**56 (36%)**
G3	386 (17%)	**38 (10%)**	**34 (22%)**
G4	176 (8%)	**21 (6%)**	**14 (9%)**
≥G5	142 (6%)	**16 (4%)**	**14 (9%)**
Maternal Ethnicity			
Caucasian	1334 (74%)	**157 (67%)**	111 (74%)
Others	462 (26%)	**77 (33%)**	40 (26%)
Socioeconomic status			
<$60,000	418 (21%)	62 (19%)	**18 (14%)**
≥ $60,000	1592 (79%)	258 (81%)	**115 (86%)**
Maternal Education			
No education beyond high school	209 (9%)	30 (9%)	**6 (4%)**
Some post secondary/ college	448 (20%)	87 (25%)	**41 (28%)**
University degree	1559 (71%)	235 (67%)	**98 (68%)**
Maternal smoking history			
Yes	133 (7%)	19 (8%)	14 (9%)
Hypertensive Disorders of Pregnancy			
Yes	69 (3%)	**26 (7%)**	6 (4%)
Gestation Diabetes			
Yes	98 (4%)	23 (6%)	9 (6%)
Previous vaginal delivery			
First Born	1170 (51%)	**289 (79%)**	**47 (30%)**
Subsequent Born	1141 (49%)	**75 (21%)**	**109 (70%)**
Child Sex			
Male	1204 (52%)	**214 (59%)**	79 (51%)
Female	1111 (48%)	**151 (41%)**	77 49%)

*=Vaginal delivery was used as a reference and compared with emergency CS and scheduled CS**.**
p-values <0.05 in bold; SD=standard deviation; BMI=body mass index

Table 2.2a. Multiple logistic regression results include demographic, antenatal physical and obstetric characteristics in overall cohort independent of the parity: Training dataset

	CS (Scheduled + Emergency) (Training, n=2269)		Emergency CS (Training, n=2150)	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Centered Age (years)	**1.05**	**1.02-1.08**	**1.06**	**1.02-1.08**
Centered Height (cm)	**0.95**	**0.94-0.97**	**0.94**	**0.92-0.96**
BMI in kg/m^2	**1.04**	**1.02-1.06**	**1.04**	**1.02-1.06**
CESD-score (ref: <10)	**1.43**	**1.10-1.84**	**1.45**	**1.07-1.96**
Hospital CS rate (CHILD)	**1.09**	**1.05-1.13**	1.04	0.98-1.09
Hypertensive Disorders of Pregnancy	1.58	0.95-2.63	**1.75**	**1.99-3.08**
Previous vaginal delivery	**0.46**	**0.36-0.59**	**0.21**	**0.15-0.29**
AUC	0.70	0.66-0.72	0.74	0.72-0.77
Sensitivity	1.4%		1.2%	
Specificity	99%		99%	

P-values <0.05 in bold; AUC= area under curve; OR= odds ratio; CI= confidence interval;

Table 2.2b. Multiple logistic regression results include demographic, antenatal physical and obstetric characteristics in overall cohort independent of the parity: Validation dataset

	CS (Scheduled + Emergency) (Validation, n=567)		Emergency CS (Validation, n=530)	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Centered Age (years)	**1.13**	**1.06-1.19**	**1.14**	**1.07-1.22**
Centered Height (cm)	**0.96**	**0.92-0.99**	**0.94**	**0.90-0.98**
BMI in kg/m^2	**1.08**	**1.04-1.12**	**1.07**	**1.03-1.12**
CESD-score (ref: <10)	1.49	0.90-2.48	**1.66**	**1.01-3.15**
Hospital CS rate	**1.11**	**1.03-1.20**	1.17	0.98-1.28
Hypertensive Disorders of Pregnancy	0.96	0.28-3.35	1.32	0.36-4.80
Previous vaginal delivery	**0.46**	**0.28-0.75**	**0.20**	**0.10-0.38**
AUC	0.74	0.69-0.79	0.77	0.71-0.82
Sensitivity	11%		13%	
Specificity	98%		98%	

P-values <0.05 in bold; AUC= area under curve; OR= odds ratio; CI= confidence interval;

Table 2.3a. Modified antenatal scoring system for predicting the risk of Emergency CS

Age (years)		Height (cm)		BMI (kg/m2)		CES-D score		Previous vaginal delivery		Hypertensive Disorders of Pregnancy	
Value	Score	Value	Score	Value	Score	Value	Score	Value	Score	Value	Score
≤ 30	0	≤ 160	4	< 18.5	0	Low (<10)	0	Absent	5	Absent	0
31-35	2	161-165	2	18.5-25	1	High (≥10)	2	Present	0	Present	2
> 35	4	> 165	0	> 25	3						

Table 2.3b. Emergency CS prediction risk scoring system

Score	n (%)	Emergency CS (n, %)	Odds Ratio (95% CI)	Numbers Needed to Treat (NNT)
Grade 0 (0-5 points)	459 (22%)	10 (3%)	Reference	
Grade 1 (6-7 points)	353 (16%)	24 (8%)	3.28 (1.55-6.94)	7
Grade 2 (8-9 points)	434 (20%)	52 (18%)	6.11 (3.06-12.19)	3
Grade 3 (≥10 points)	898 (42%)	213 (71%)	13.96 (7.32-26.61)	4

Figure 2.1. Flow diagram of the selection of study cohort included in the prediction model

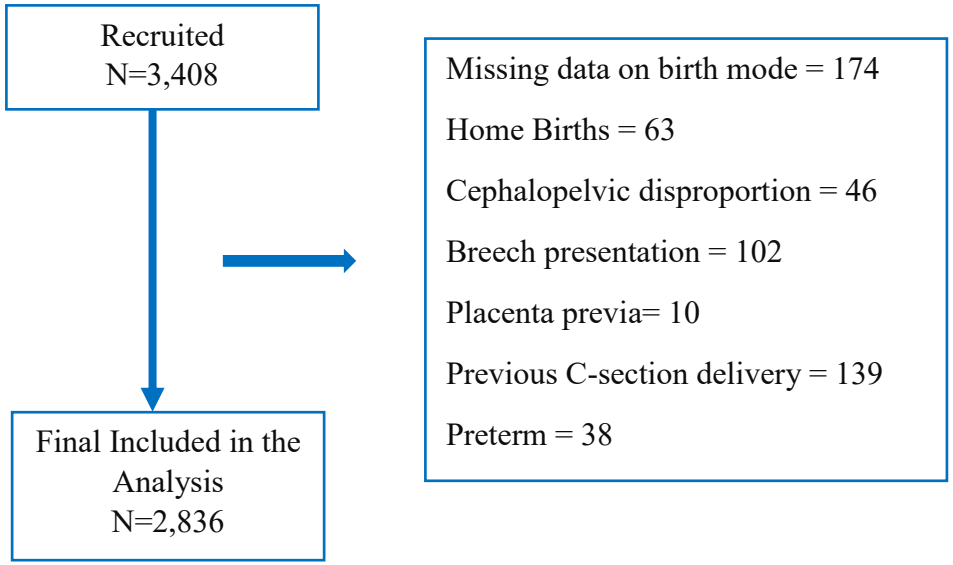
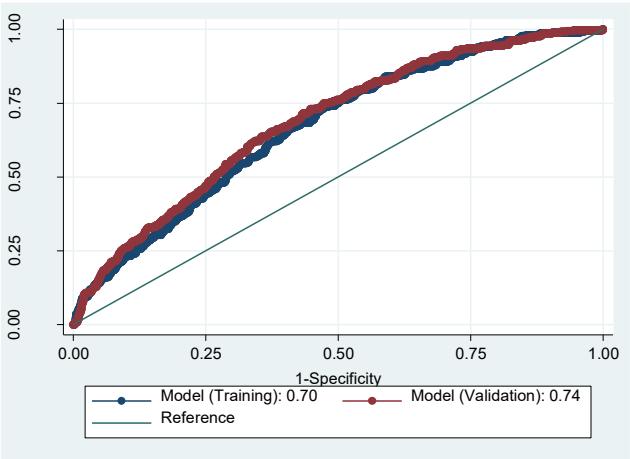
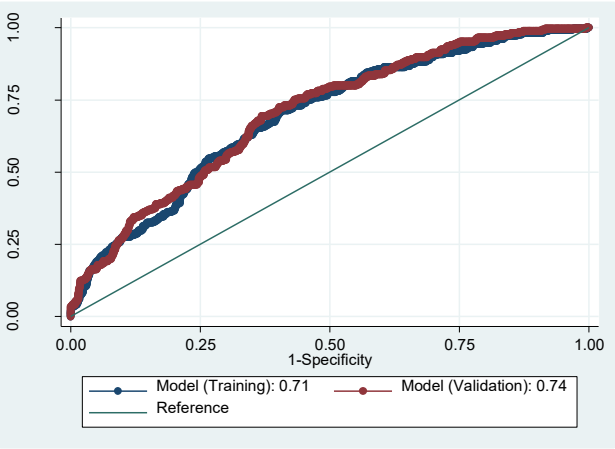


Figure 2.2. Comparison of the ROC curve for internal validation (training vs. validation) from multiple logistic regression a) CS b) Emergency CS c) Scheduled CS

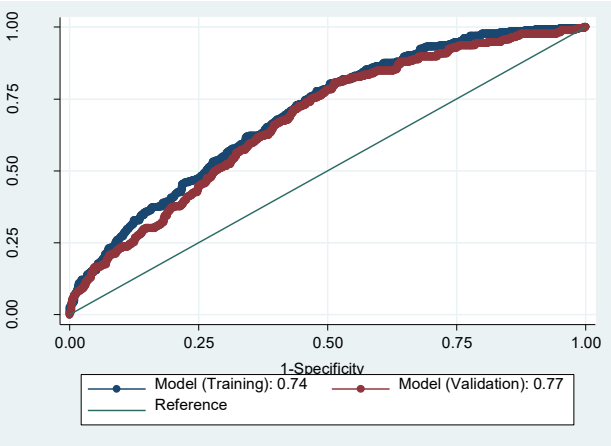
a)



b)



c)



Model (CS, Training): Value for area under the curve: 0.70 (95% CI: 0.66-0.72)

Model (CS, Validation): Value for area under the curve: 0.74 (95% CI: 0.69-0.79)

Model (Emergency CS, Training): Value for area under the curve: 0.71 (95% CI: 0.66-0.76)

Model (Emergency CS, Validation): Value for area under the curve: 0.73 (95% CI: 0.63-0.83)

Model (Scheduled CS, Training): Value for area under the curve: 0.74 (95% CI: 0.72-0.77)

Model (Scheduled CS, Validation): Value for area under the curve: 0.77 (95% CI: 0.71-0.82)

Supplementary Table 2.1. Reference studies reporting the association of caesarean section in nulliparous and multiparous

	Obstetric	Non-obstetric
Antepartum	Maternal factors -gestational hypertension (28-30) -preeclampsia, eclampsia (28,29) -gestational diabetes (28,29,31) -premature rupture of membrane (32) Others -gestation age (28)	Maternal factors -age (16,33-39) -height (16,28,34-36,40) -pre-pregnancy weight/ BMI and pregnancy weight gain (28,29,34,36,38,41-43) -parity (28,37) -socio economic status (37) -race/ethnicity (28,34) -education (37,44) -smoking (29) -maternal stress, anxiety, depression score (36,45) -cephalo pelvis disproportion (28,34) -chronic hypertension (28,46) -diabetes (28,31) -sleep disorder (obstructive sleep apnoea) (47) -maternal request (48) -previous vaginal delivery (28,34) -in-vitro fertilization (IVF) (29,49) Fetal factors -macrosomia (28,36,50) -position (occiput posterior) (28,36) -presentation (breech) (28,36)

		-gender (35) Others -exercise, diet (51,52) -vitamin D supplementation (53,54) -senior healthcare professionals/ healthcare institution (28,55) -healthcare insurance (35)
Intrapartum	Maternal factors -cervical dilatation (Bishop score) (28,36,44) Others -epidural analgesia (36,56,57) -induction of labour (IOL) (28,36,58-61) -augmentation of labour (36) Indications for emergency CS -dystocia or failure to progress (28,36) -fetal distress (28,44) -acupressure	Others -Cardiotocography monitoring (62)

Supplementary Table 2.2. Multiple logistic regression results of CS include demographic, antenatal physical and obstetric characteristics in nulliparous and multiparous cohort

	Nulliparous (n=1099)		Multiparous (n=1737)	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Centered Age (years)	**1.06**	**1.03-1.10**	**1.06**	**1.03-1.10**
Centered Height (cm)	**0.94**	**0.92-0.96**	**0.96**	**0.94-0.98**
BMI in kg/m^2	**1.05**	**1.02-1.07**	**1.05**	**1.03-1.08**
CESD-score (ref: <10)	**1.44**	**1.01-2.05**	**1.46**	**1.08-1.98**
Hospital CS rate (CHILD)	**1.09**	**1.05-1.14**	**1.06**	**1.03-1.09**
Hypertensive Disorders of Pregnancy	**1.93**	**1.02-3.67**	1.09	0.55-2.21
Previous vaginal delivery	**-**	**-**	**0.46**	**0.34-0.62**
AUC	0.69	0.65-0.73	0.70	0.66-0.73

P-values <0.05 in bold; AUC= area under curve; OR= odds ratio; CI= confidence interval;

Supplementary Table 2.3. Multiple logistic regression and multinomial logistic regression results include demographic, antenatal physical and obstetric characteristics in overall cohort independent of the parity: Training & Validation dataset

	Multiple logistic regression (Training, n=2269)		Multinomial logistic regression (Training, n=2269)			
	CS (Scheduled + Emergency)		Scheduled CS		Emergency CS	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Centered Age (years)	**1.05**	**1.02-1.08**	**1.06**	**1.01-1.09**	**1.05**	**1.02-1.08**
Centered Height (cm)	**0.95**	**0.94-0.97**	0.99	0.96-1.02	**0.94**	**0.92-0.96**
BMI in kg/m^2	**1.04**	**1.02-1.06**	**1.04**	**1.01-1.08**	**1.04**	**1.02-1.07**
CESD-score (ref: <10)	**1.43**	**1.10-1.84**	1.34	0.87-2.07	**1.45**	**1.07-1.96**
Hospital CS rate	**1.10**	**1.05-1.13**	**1.19**	**1.12-1.27**	1.04	0.99-1.09
Hypertensive Disorders of Pregnancy	1.58	0.95-2.63	1.14	0.45-2.88	**1.75**	**1.01-3.07**
Previous vaginal delivery	**0.46**	**0.36-0.59**	**2.03**	**1.31-3.15**	**0.21**	**0.15-0.30**

	Multiple logistic regression (Validation, n=567)		Multinomial logistic regression (Validation, n=567)			
	CS (Scheduled + Emergency)		Scheduled CS		Emergency CS	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Centered Age (years)	**1.13**	**1.06-1.19**	**1.11**	**1.01-1.22**	**1.14**	**1.07-1.22**
Centered Height (cm)	**0.95**	**0.92-0.99**	0.97	0.92-1.02	**0.95**	**0.91-0.98**
BMI in kg/m^2	**1.08**	**1.04-1.12**	**1.08**	**1.02-1.15**	**1.07**	**1.03-1.12**
CESD-score (ref: <10)	1.49	0.90-2.48	1.24	0.52-2.96	1.61	0.90-2.90
Hospital CS rate	**1.11**	**1.03-1.20**	1.03	0.91-1.17	**1.16**	**1.06-1.27**
Hypertensive Disorders of Pregnancy	0.96	0.28-3.35	-	-	1.36	0.38-4.91
Previous vaginal delivery	**0.46**	**0.28-0.75**	**2.54**	**1.02-6.30**	**0.20**	**0.10-0.38**

P-values <0.05 in bold; AUC= area under curve; OR= odds ratio; CI= confidence interval; Vaginal delivery was used as a reference and compared with emergency CS and scheduled CS in multinomial logistic regression

Supplementary Table 2.4. Multiple logistic regression results include demographic, antenatal physical and obstetric characteristics in overall cohort independent of the parity: Training & Validation dataset

	Scheduled CS (Training, n=1986)		Scheduled CS (Validation, n=485)	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Centered Age (years)	**1.05**	**1.01-1.10**	**1.10**	**1.01-1.21**
Centered Height (cm)	-	-	-	-
BMI in kg/m^2	**1.05**	**1.02-1.08**	**1.07**	**1.01-1.13**
CESD-score (ref: <10)	**-**	**-**	**-**	**-**
Hospital CS rate (CHILD)	**1.19**	**1.12-1.27**	1.03	0.91-1.16
Hypertensive Disorders of Pregnancy	-	-	-	-
Previous vaginal delivery	**2.08**	**1.34-3.21**	**2.71**	**1.11-6.68**
AUC	0.71	0.66-0.76	0.73	0.63-0.83
Sensitivity	0%		0%	
Specificity	100%		100%	

Supplementary Table 2.5. a) modified antenatal scoring system for predicting the risk of Scheduled CS and b) Scheduled CS risk prediction scoring system

a) Modified antenatal scoring system for Scheduled CS delivery

Age (years)		BMI (kg/m2)		Previous vaginal delivery		Hospital CS rate (CHILD)	
Value	Score	Value	Score	Value	Score	Value	Score
≤ 30	1	< 18.5	1	Absent	5	< 15%	1
31-35	2	18.5-25	2	Present	0	16-20%	3
> 35	5	> 25	5			21-25%	5
						> 25%	7

b) Scheduled CS prediction risk scoring system

Score	n (%)	Scheduled CS (n, %)	Odds Ratio (95% CI)
Grade 0 (0-5 points)	128 (8%)	7 (7%)	Reference
Grade 1 (6-7 points)	338 (22%)	17 (16%)	0.92 (0.37-2.26)
Grade 2 (8-9 points)	338 (22%)	29 (27%)	1.62 (0.69-3.80)
Grade 3 (10-11 points)	382 (25%)	31 (29%)	1.53 (0.66-3.56)
Grade 4 (≥12 points)	376 (23%)	22 (21%)	1.07 (0.45-2.58)

AUC=0.56 (0.51-0.62), Sensitivity= 5%, Specificity= 98%

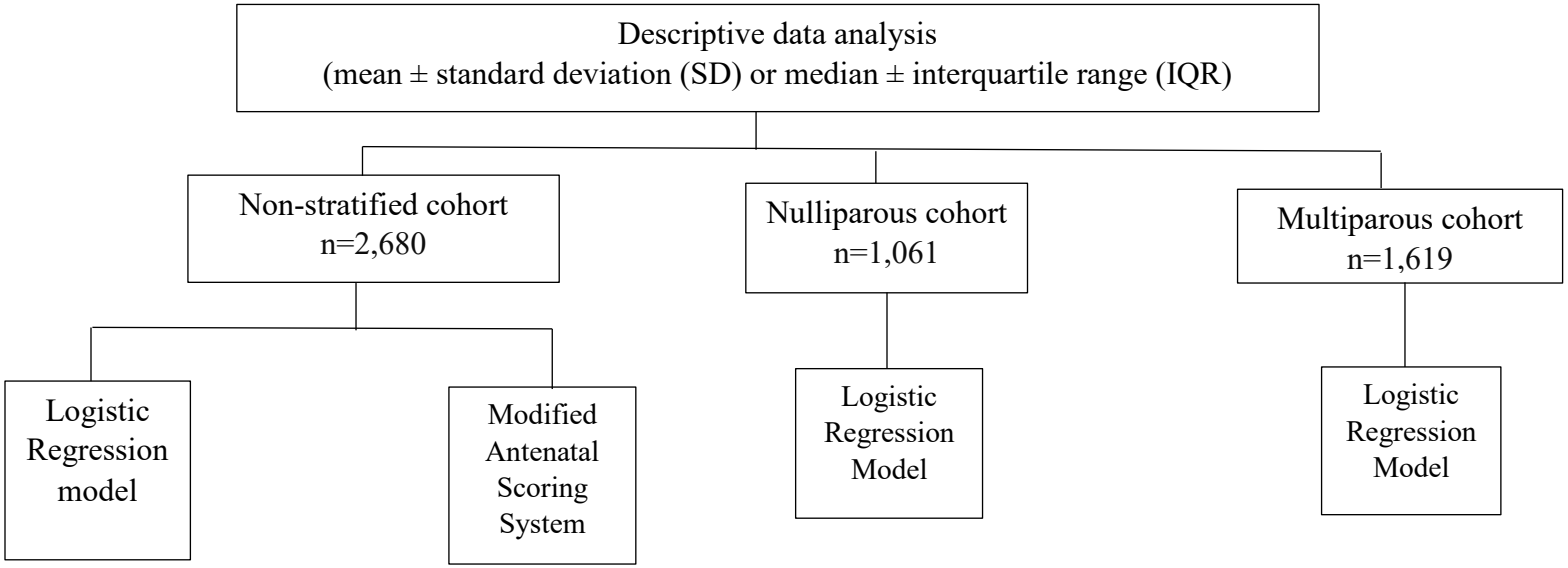
Supplementary Table 2.6. Demographic, antenatal and obstetric characteristics of Training and Validation data set

Characteristics	Training (n=2,150)	Validation (n=530)
Emergency CS (n, %)	283 (80%)	82 (20%)
Maternal Age (years) (mean ± SD)	32.14 ± 4.68	31.84 ± 4.60
Maternal Height (cm) (mean ± SD)	165.29 ± 6.92	165.59 ± 6.76
Maternal Weight (kg) (mean ± SD)	69.24 ± 16.72	68.24 ± 16.67
BMI in kg/m^2 (mean ± SD)	25.32 ± 5.81	25.17 ± 5.85
Hospitals CS rate CHILD cohort (mean ± SD)	5.94 ± 3.20	6.12 ± 3.17
Increased CESD-score (Ref: <10)	608 (28%)	134 (25%)
Gestational Age (weeks)		
37	132 (6%)	30 (6%)
38	248 (12%)	47 (9%)
39	480 (22%)	136 (26%)
40	687 (32%)	159 (30%)
41	492 (24%)	126 (24%)
≥42	99 (4%)	25 (5%)
Gravida		
G1	840 (39%)	221 (41%)
G2	676 (32%)	162 (31%)
G3	341 (16%)	83 (16%)
G4	161 (7%)	36 (7%)
≥G5	131 (6%)	27 (5%)
Maternal Ethnicity		
Caucasian	1197 (73%)	294 (73%)
Others	433 (27%)	106 (27%)
Socioeconomic status		
<$60,000	382 (20%)	98 (21%)
≥ $60,000	1483 (80%)	367 (79%)
Maternal Education		
No education beyond high school	197 (10%)	42 (8%)
Some post secondary/ college	427 (21%)	108 (21%)
University degree	1,433 (69%)	361 (71%)
Maternal smoking history		
Yes	68 (4%)	16 (4%)
Hypertensive Disorders of Pregnancy		
Yes	81 (4%)	14 (3%)
Gestation Diabetes		
Yes	97 (5%)	24 (5%)
Previous vaginal delivery		
First Born	1,157 (54%)	302 (57%)
Subsequent Born	993 (46%)	226 (43%)
Child Sex		
Male	1,130 (53%)	285 (54%)

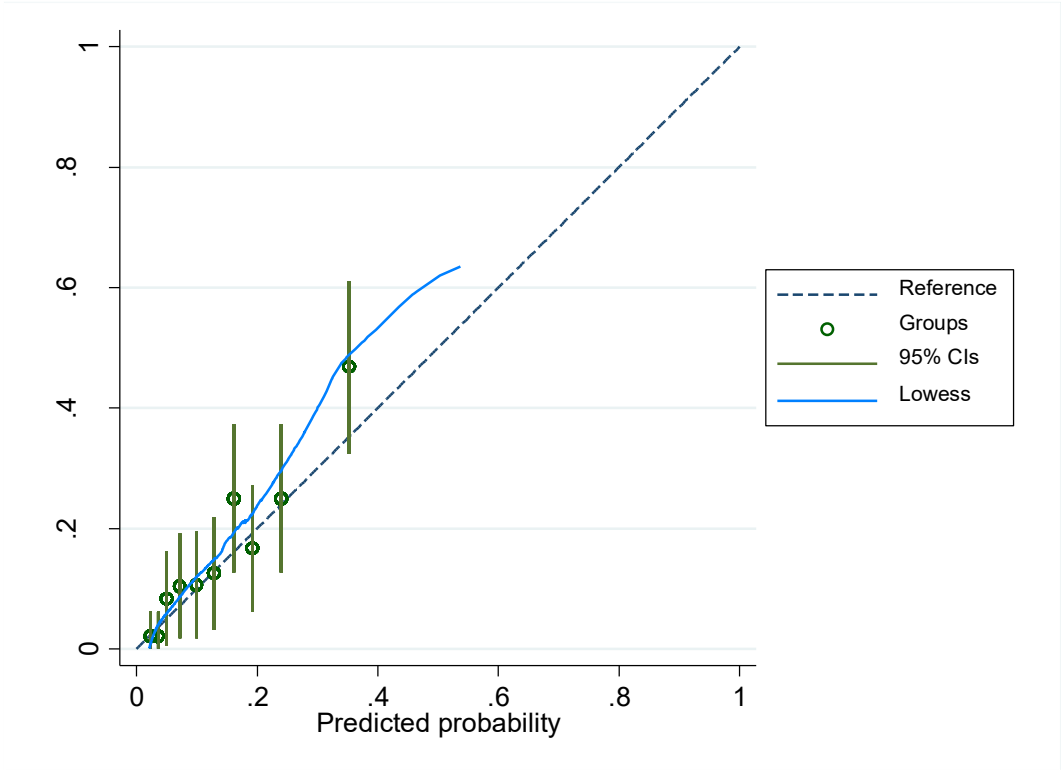
Female	1,017 (47%)	245 (46%)

*=Vaginal delivery was used as a reference and compared with emergency CS and scheduled CS.
p-values <0.05 in bold; SD=standard deviation; BMI=body mass index

Supplementary Figure 2.1. Flow diagram of the statistical analysis



Supplementary Figure 2.2. Calibration curve for Emergency CS prediction (Validation dataset)



Appendix 2.1: PubMed July 2020

Search	Query	Results
#7	#1 AND #2 AND #3 AND #5	1843
#6	#1 AND #2 AND #4 AND #5	356
#5	((systematic review) OR meta analysis) AND metaanalysis	125491
#4	(((((((nulliparous) OR (first time pregnant)) OR (first time mother)) OR (first time deliver)) OR (nonparturitive)) OR (first pregnancy)) OR (nonparturient)) OR (nonparous)	194232
#3	(((((((((vaginal birth after cesarean) OR (vbac)) OR (vaginal birth)) OR (vaginal deliver)) OR (trial of labor)) OR (postcesarean)) OR (postcaesarean)) OR (c section)) OR (abdominal deliver)) OR (uterine scar)	82725
#2	(((((((Cesarean Section) OR (cesarean)) OR (caesarean abdominal deliver)) OR (caesarea)) OR (cesarea)) OR (c section)) OR (CS)) OR (abdominal deliver)	519462
#1	(((((((((risk factors) OR (predict)) OR (model)) OR (predictors)) OR (indicators)) OR (determinants)) OR (risk score)) OR (risk management)) OR (factor)) OR (risk)	16614138

Appendix 2.2:

Development of scoring system for scheduled CS (secondary outcome): In the group with scheduled CS delivery, subsequent born children had higher risk of being delivered by scheduled CS (aOR 2.08, 1.34-3.21) **(Supplementary Table 4)**. The final model for scheduled CS included four predictors: maternal age, BMI, CS rate of the delivery hospital and birth order of the infant **(Supplementary Table 4)**. The AUC for the scheduled CS training model was 0.71 (0.66-0.76) and 0.73 (0.63-0.83) for the validation model **(Supplementary Table 4, Figure 2c)**. We modified the CS risk scoring system for scheduled CS (ranges from 3 to 16) **(Supplementary Table 5a)** using the regression coefficients from the multiple logistic regression models. For the scheduled CS, the scores were grouped into 5 grades: grade 0 (0-5 points), grade 1 (6-7 points), grade 2 (8-9 points), grade 3 (10-11 points), and grade 4 (≥ 12 points). We did not observe any significant associations between the scores and risk of scheduled CS delivery **(Supplementary Table 5b)**.

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Chapter 3. Mode of delivery and risk of hospital care in childhood for asthma and gastroenteritis

Mon Tun[1], Mike Paulden[2], Radha Chari[3], Piush Mandhane[1], Padma Kaul[2, 4, 5]

[1]Department of Pediatrics, University of Alberta, Edmonton AB.

[2]School of Public Health, University of Alberta, Edmonton AB.

[3]Department of Obstetrics and Gynaecology, University of Alberta, Edmonton AB.

[4]Canadian VIGOUR Centre, University of Alberta, Edmonton AB.

[5]Faculty of Medicine, University of Alberta, Edmonton AB.

Abstract

Background: There are currently limited data on the association between mode of delivery and asthma or acute gastroenteritis outcomes in early childhood in Canada Caesarean section (CS) alters the neonatal gut microbiota development.

Objective: To examine the association between different birth modes (vaginal, Caesarean section (CS), and emergency room visits or hospital admissions for gastroenteritis or asthma during early childhood in the offspring.

Methods: This population-based retrospective study cohort included term singleton live births in Alberta from 2005-2014. The study cohort was developed by linking multiple administrative health databases. Infants delivered by CS were compared to those delivered vaginally for emergency room visit or hospitalization with gastroenteritis or asthma. The children were followed up from the time of delivery to the study end period. We estimated adjusted hazard ratios (HRs) and 95% confidence intervals (CI) using Cox proportional hazard models. Analyses were adjusted for sex, gestational age at the time of delivery, maternal age, maternal asthma, small for gestational age and large for gestational age.

Results: In this study population of 438,659 children, CS accounted for 27% of the deliveries. CS significantly increased the risk of emergency room visit with both gastroenteritis (adjusted HR 1.21, 95% CI 1.16-1.26) and asthma (adjusted HR 1.12, 95% CI 1.07-1.17) compared to children delivered vaginally. We observed a significant increase in hospitalization with gastroenteritis (adjusted HR 1.22, 95% CI, 1.08-1.38) among CS children compared to vaginal delivery. There were no clear association between delivery mode and hospitalization with asthma.

Conclusion: There is a significant increased risk for emergency room visit and hospitalization with gastroenteritis among children born by CS. There is a significant increased risk for emergency room visit, but not hospitalizations, for asthma among CS born children. Further research is required to explore the underlying casual mechanisms including disturbances in gut microbial establishment.

3.1 Background and Introduction

Rising Caesarean section (CS) rate is a public health concern with the CS rate and many countries have a higher prevalence rate than the World Health Organization recommended rate of 15% (1). In Canada, CS rate is approaching 30% in 2018 (2). CS, a life-saving intervention, reduces maternal and infant morbidity when medically indicated (3); however, CS associated short and long-term consequences to the mothers and offspring are well described (4-8). CS may influence an infant's long-term health either through alterations in gut microbiome or through an impact on establishing breastfeeding. Several studies have shown that CS disturbs the normal establishment of gut microbiota (9,10) and reduced Th-1 response in the first 2 years of life (11). CS has been negatively associated with initiation and duration of lactation (12,13) and exclusive breast-feeding.

Asthma, a chronic inflammatory disease of the airways, is also in a rising trend during the last decades in developed countries and become a significant health burden in children (14). It is estimated to affect 1.1 million Canadian children (15) and is one of the leading causes of hospital stays among children and youth with the highest rate among the children 0 to 4 years old (16). Genetic and environmental factors are known risk factors of asthma (17) and recent studies have shown that CS delivery is associated with increased risk for asthma (18,19). A number of studies have reported that infants delivery by CS are also at greater risk of developing gastroenteritis (20-22) and asthma (18,23-25). Acute gastroenteritis is a leading cause of childhood morbidity worldwide and one of the most frequent causes of hospitalization in young children (26). Up to 10% of all the hospital admissions for the children in the United States (27) are due to

gastroenteritis. Almost 95% of Canadian children are affected by gastroenteritis at least once by 5 years of age (28).

To our knowledge, there is no study looking at the association of mode of delivery and hospitalization with asthma or acute gastroenteritis in early childhood in Canada. Our aim was to explore the association between CS delivery and healthcare utilization for gastroenteritis or asthma in relationship to delivery mode using data from a large provincial administrative birth cohort.

3.2 Methods

We used data from a population-based retrospective cohort of children born in Alberta, Canada from January 1, 2005 to December 31, 2014. The study cohort was developed by linking multiple administrative health databases, such as hospital admission, ambulatory care and the population health registry. The study population included all singleton live births of ≥ 37 weeks of gestation. Multiple births, infants delivered before 37 weeks, infants with missing data on gestation, and maternal age less than 12 or missing maternal age were excluded. The hospitalization database includes demographic information and International Classification of Diseases-10 (ICD-10) codes for all medical diagnoses made during hospitalization. Mode of delivery (vaginal or C-section) was ascertained from the Canadian Classification of Interventions (CCI) codes. Ethics approval was obtained from the University of Alberta's Health Research Ethics Board-Health Panel (PRO00056999).

Exposure: Birth mode was defined as vaginal delivery, scheduled CS and emergency CS. Delivery hospitalizations of women without the intervention diagnosis code 5MD60 were considered to be vaginal births. Both assisted and unassisted vaginal deliveries were grouped

together. Among women with CS intervention codes, scheduled CS was defined as CS code without labour codes whereas CS deliveries with labour codes were classified as emergency CS **(Appendix 3.1)**.

Outcome: Hospitalization or emergency room visit for gastroenteritis or asthma were ascertained from the inpatient hospitalization and ambulatory care databases using ICD-10 codes **(Appendix 3.1)**. Children were followed from the birth date to the event of interest or the end of follow-up on 31 December 2018 (censored) whichever came first.

Outcome: Hospitalization or emergency room visit for gastroenteritis or asthma were ascertained from the inpatient hospitalization and ambulatory care databases using ICD-10 codes **(Appendix 3.1)**. Children were followed from the birth date to the event of interest or the end of follow-up on 31 December 2018 (censored) whichever came first.

Covariates: Covariates obtained from the linked databases (Alberta pregnancy birth cohort, inpatient hospitalization data, and Alberta population registry) include: maternal age, maternal history of asthma, maternal perinatal complications (gestational diabetes, hypertension, pre-eclampsia, eclampsia), infant birth weight, gestational age, small for gestational age (SGA), large for gestational age (LGA), infant sex, infant birth hospitalization, infant length of stay in the hospital, NICU admission and socioeconomic status **(Appendix 3.1)**. Gestational age at birth was obtained from the birth registry database.

3.2.1 Statistical Analysis

Categorical data were expressed as frequency (n) and percent (%) and the differences in frequency between vaginal or CS delivery were tested using the Chi-squared. Continuous variables were expressed as mean ± SD or the median (and interquartile range). Differences in

the baseline characteristic between vaginal or CS delivery were tested using Student t-test for normally distributed data and Mann-Whitney test was used for non-normally distributed data.

We used a Cox proportional hazards model to estimate the risk of an emergency room visit (primary outcome) or first hospitalization with asthma or gastroenteritis. All analyses were adjusted for gestational age, infant sex, maternal age, and maternal asthma and small for gestational age based on expert knowledge and published literature. The proportional hazards assumption of the Cox model was tested using plots of the log of the negative log of the survival function against log of time for each comparison group. For sensitivity analysis, we employed a Generalized Estimating Equations (GEE) procedure, a population-average method accounting for correlation among measures within subjects, for the overall cohort. A two-sided p-value <0.05 was considered statistically significant. We conducted sensitivity analysis in two cohorts, nulliparous and singleton second pregnancy with one prior CS. All statistical analyses were performed using the SAS program, version 9.4 (SAS Institute, Inc, Cary, NC).

3.3 Results

The patient-selection is described in **Figure 3.1**. Of the 438,659 children aged 0 to 10 years included in the cohort, 27% were delivered by CS and 73% were delivered vaginally. Of those delivered via CS, 10% were delivered by scheduled CS and 17% were delivered by emergency CS. CS was more common for boys (53%) and older mothers. **Table 3.1** shows the basic demographic characteristics of the study population by different birth modes. About 50% of the children delivered by CS were born before 41 weeks and 26% of them were first-born infants.

Offspring delivered via CS, in particular, emergency CS were more likely to be admitted and stayed longer in NICU.

During 2005-2014, a total of 10,266 children visited emergency room and 2,130 children were admitted to hospital for asthma. There were 12,079 children with an emergency department visit and 1,329 children with a hospital admission for gastroenteritis. **(Table 3.2)**. The distribution of demographic characteristic according to the hospitalization or emergency room visit with gastroenteritis or asthma are presented in **Table 3.2**.

Overall, 186,696 of the children were born to primiparous women and 52,235 were born to multiparous women with at least one previous CS delivery. Demographic and clinical characteristics of the nulliparous group and women with one previous CS according to the outcome measures were presented in **Tables 3.3 and 3.4**. In nulliparous cohort, a higher proportion children with a diagnosis of asthma or gastroenteritis were delivered by emergency CS **(Table 3.3)**. However, in women with one previous CS cohort, a majority of the children with asthma or gastroenteritis diagnosis were delivered by scheduled CS **(Table 3.4)**.

The risk of emergency room visit with gastroenteritis was significantly higher following CS in overall cohort (21% increase), as well as in the nulliparous group (19% increase) and women with a previous CS (32% increase) group **(Table 3.5)**. The increased risk of emergency department visit with gastroenteritis was observed mainly in infants delivered via emergency CS but in women with previous CS, the positive association was found in scheduled CS delivered infants. In the nulliparous group, increased risk of gastroenteritis emergency room visit was observed in both scheduled and emergency CS children. We found that delivery by CS was associated with 22% increased risk of hospitalization with gastroenteritis in full and nulliparous cohort [adjusted HR 1.22 (95% CI 1.09-1.38) and adjusted HR 1.22 (95% CI 1.02-1.48)] but we

did not observe a statistically significant increase association with repeat CS in women with one previous CS cohort.

Table 3.6 shows the association of different birth modes with time to emergency room visit and hospital admission with asthma. Risk of emergency department attendance with asthma was found significantly increased in CS delivered infants in the overall (13% increase), nulliparous (16% increase) and second pregnancy with one previous CS (14% increase) cohorts. In the overall cohort, the detected increase in emergency department visit with asthma was found in both scheduled (8% increase) and emergency CS (13% increase); however, in nulliparous and second pregnancy with one previous cohort, the significant associations were only observed in emergency CS, 16% and 19% increase respectively. There was no significant difference in the risk of asthma requiring hospitalization in all three cohorts.

In the multivariate GEE logistic regression models **(Table 3.7)** for full cohort, we found that CS delivered children have higher risk of emergency room visit (5% increase) and hospital admission (20% increase) with gastroenteritis. The 5% increase risk of emergency department attendance with asthma was observed but we did observe the difference in risk of hospitalization with asthma in the infants delivered via CS.

Figure 3.2 shows the survival curves for time to the first emergency room visit and hospital admission with gastroenteritis according to gestation age categories. The HRs for both emergency department attendance and hospital admission with gastroenteritis up to age 10 increased as gestation age decreased. Likewise, increasing risk of emergency room visit and hospitalization with asthma was observed with decreasing gestational age for asthma **Figure 3.3**.

3.4 Discussion

Our study based on a provincial birth cohort of 438,659 children in the Alberta pregnancy birth cohort provides comprehensive examination on the association between mode of delivery (vaginal or CS) and asthma and gastroenteritis outcomes in the offspring. We observed a significant increase in emergency department visit with asthma but we found no difference in risk of asthma hospitalization in the CS delivered offspring. However, CS delivered children have a higher risk of both emergency room visit and hospital admission with gastroenteritis. Further examination of children born to nulliparous women (n=186,696) found a similar trend for emergency room visit or hospitalization with gastroenteritis and asthma. In the subgroup of multiparous women with a previous CS, the increase in emergency department attendance with gastroenteritis and asthma were also found in CS delivered infants; however, we did not observe a significant risk of hospitalization or emergency department visit with asthma or gastroenteritis.

Our findings based on the overall cohort are consistent with the results from previous Swedish (20) and Danish (21) studies showing that CS increased the risk of hospitalization with gastroenteritis in both scheduled and emergency CS. Besides, CS increased the risk of emergency department visit with gastroenteritis, particularly in emergency CS delivered infants in the overall cohort and primiparous subgroup but the positive association was found with scheduled CS only in the multiparous with a history of CS group. Although we did not observe a significant association across all subgroups, the estimates were in the direction of higher risk. A possible explanation for the increase in hospitalization or emergency department visits with gastroenteritis could be explained by the disturbance in the normal establishment of gut

microflora in CS delivered infants (9,10) that impairs the colonization resistance to microbial pathogens (29), postnatal maturation and development of the immune system (30).

In women with previous CS, the scheduled repeat CS prevents the risk of uterine scar rupture from attempting VBAC (31) but it forbids the infant from being exposed to labour process and maternal vaginal and bowel flora. CS is emerging as a risk factor for the development of metabolic and immune diseases. Lack of contact with maternal vaginal and intestinal bacteria during delivery may contribute to the susceptibility of children to a number of diseases such as asthma, atopic diseases, gastroenteritis, type 1 diabetes mellitus later in life (32). Moreover, the normal intestinal microbiota provides a resistance to pathogenic bacteria colonization and an imbalance in homeostasis between the immune system and gut microbiota can increase the risk of gastrointestinal infections (29).

Several cohort studies from Europe have assessed whether emergency and elective Caesarean sections have different associations with the risk of childhood asthma and found inconsistent results (33-37). In contrast, a few studies observed no association between CS and asthma and allergic diseases (36,38-40). Studies from Scotland reported that scheduled and emergency CS increased the risk of hospitalization with asthma in both nulliparous and women with one prior CS cohorts (23,41). However, our study could not confirm an effect of CS on the risk of hospitalization with asthma in both cohorts.

We discovered an increase in emergency room visit with asthma mainly in emergency CS delivered children in full, nulliparous and women with one prior CS cohorts. The hypothesis of lack of exposure to maternal bowel flora that affects the development of T-cell mediated asthma (42), fails to explain the significant increase in emergency department attendance with asthma in emergency CS. The significant increase in emergency room visit with asthma could be explained

by the fact that asthma exacerbations were not very severe but they might not have a primary care physician and seeking care in the emergency department. Another possible explanation for an increase in emergency room attendance and a decrease in hospital admission with asthma could be due to the fact that asthmatic children treated at emergency department were provided with good longitudinal discharge and care plan.

The strength of our study is that it is a large population-based design and large sample size using health administrative datasets of individual records that minimized the risk of selection bias. The sample size was large and sufficient for the estimation made. Second, the reliability of the Alberta hospital registers and the variables used in this study have been validated for accuracy enabling us to identify the risk of emergency department visit or hospitalization with gastroenteritis or asthma. Third, the perinatal characteristics and risk factors were available to adjust for multiple confounders in both the mothers and the offspring. Fourth, the data extended over a ten-year period as a longer follow-up is required for the asthma development and provides a valuable Lastly, we conducted the sensitivity analysis in two sub cohorts, first-born infant and second child whose mothers had a prior CS.

Our study has some limitations. Although we adjusted for potential confounding factors, there could be unmeasured confounding bias, misclassification of mode of delivery, and missing data. Moreover, the total burden of gastroenteritis and asthma in the community has not been ascertained in this study. Most episodes of gastroenteritis and mild exacerbation of asthma are managed at home or through family physicians without warranting hospital admission. Since we did not include primary care data, we only captured the severe end of the clinical spectrum – gastroenteritis and asthma requiring emergency room attendance or hospitalization. However, the observed increased in emergency room visit or hospital admission with gastroenteritis or asthma

precludes the underestimation of the association in this study cohort. In addition, lack of information on specific indications for CS (e.g. preterm birth and small for gestational age) may confound the associations we detected as those specific indications could affect the infant risk of asthma or gastroenteritis hospitalization or emergency department visit (43,44). Nevertheless, our study only included term infants and adjusted for SGA in our models. We also did not have information on breast feeding status and hence were not able to adjust for it. However, one meta-analysis reported a negative association between breast feeding and scheduled CS (45). Lastly, the findings from our study should be interpreted with caution because the association found in this study do not imply causality.

3.5 Conclusion

In conclusion, in this population-base retrospective cohort study, children delivered via CS are at greater risk of emergency department visit with gastroenteritis and asthma, and hospitalization with gastroenteritis. It provides a valuable addition to the existing evidence on the effects of CS on childhood outcomes. Given the observational nature of our study, more studies are needed to determine if there is truly an increased risk of asthma or gastroenteritis hospitalization or emergency department visit in CS delivered Canadian children and the role of the microbiome in the etiology of gastroenteritis and asthma.

Table 3.1. Baseline characteristics of the study population by mode of delivery (n=438,659 infants, n=289,025 mothers)

	Caesarean section					Caesarean section				
	No		Yes		p-value	Scheduled CS		Emergency CS		p-value
	n	%	n	%		n	%	n	%	
Age mother at birth (year)										
<25 years	75429	80.46	18319	19.54	<.0001	4609	14.62	13710	14.62	<.0001
25-29 years	106961	76.12	33559	23.88		11369	8.09	22190	15.79	
30-34 years	95723	71.14	38834	76.12		16078	11.95	22756	16.91	
35-39 years	38108	65.00	20516	35.00		9749	16.63	10767	18.37	
>= 40 years	6654	59.36	4556	65.00		2226	19.86	2330	20.79	
Gestational age (completed week)										
Early Term (37-38 weeks)	76119	64.74	41449	35.26	<.0001	21991	18.70	19458	16.55	<.0001
Full Term (39-40 weeks)	197271	77.09	58635	22.91		21026	8.22	37609	14.70	
Late Term (41 weeks)	48271	76.12	15147	23.88		975	1.54	14172	22.35	
Post Term (>= 42 weeks)	1214	68.70	553	31.30		39	2.21	514	29.09	
Maternal asthma	1918	64.54	1054	35.46	<.0001	358	12.05	696	23.42	<.0001
Socioeconomic status										
Human Services	8223	75.38	2686	24.62	<.0001	1111	10.18	1575	14.44	<.0001
Government Sponsored Programs	10510	75.85	3346	24.15		1334	9.63	2012	14.52	
Others	284951	73.15	104604	26.85		39443	10.13	65161	16.73	
Induction of Labour	89944	78.89	24070	21.11	<.0001	0	0.00	24070	21.11	<.0001
Infant Sex, male	162623	72.54	61555	27.46	<.0001	22727	10.14	38828	17.32	<.0001
Birth Weight (g)										
HBW (> 4500 g)	4214	58.60	2977	41.40	<.0001	949	13.20	2028	28.20	<.0001
LBW (< 2500 g)	5258	66.73	2621	33.27	<.0001	736	9.34	1885	23.92	<.0001
SGA	34987	75.32	11463	24.68	<.0001	3050	6.57	8413	18.11	<.0001
LGA	25548	62.98	15018	37.02	<.0001	6452	15.90	8566	21.12	<.0001
NICU admission at birth	15180	47.68	16659	52.32	<.0001	5653	17.75	11006	34.57	<.0001
NICU days (mean ± SD)	2.845	4.44	2.055	4.07	<.0001	1.675	3.96	2.251	4.11	<.0001

Table 3.2. Characteristics of children treated as inpatients/ emergency room visit with a diagnosis of asthma or gastroenteritis (Full cohort, n=438,659)

	Inpatients				Emergency Room visit			
	Asthma (n=2,130)		Gastroenteritis (n=1,329)		Asthma (n=10,266)		Gastroenteritis (n=12,079)	
	No	(%)	No	(%)	No	(%)	No	(%)
Mode of delivery								
Vaginal	1609	75.54	929	69.90	7365	71.74	8563	70.89
Caesarean section	521	24.46	400	30.10	2901	28.26	3516	29.11
Scheduled Caesarean section	211	9.91	156	11.74	1050	10.23	1189	9.84
Emergency Caesarean section	310	14.55	244	18.36	1851	18.03	2327	19.26
Maternal age at delivery								
<25 years	726	34.08	363	27.31	3113	30.32	3735	30.92
25-29 years	654	30.70	439	33.03	3258	31.74	3872	32.06
30-34 years	513	24.08	333	25.06	2634	25.66	2926	24.22
35-39 years	195	9.15	164	12.34	1058	10.31	1289	10.67
>= 40 years	42	1.97	30	2.26	203	1.98	257	2.13
Socioeconomic status								
Human Services (W)	100	5.87	70	6.13	410	4.54	460	4.20
Government Sponsored Programs (S)	62	3.65	46	4.03	398	4.40	485	4.43
Others (0)	1540	90.48	1026	89.84	8231	91.06	10008	91.37
Maternal Asthma	23	1.08	8	0.60	124	1.21	100	0.83
Gestation								
37 weeks	213	10.00	153	11.51	955	9.30	1068	8.84
38 weeks	444	20.85	285	21.44	2171	21.15	2380	19.7
39 weeks	584	27.42	381	28.67	2889	28.14	3579	29.63
40 weeks	592	27.79	350	26.34	2772	27.00	3336	27.62
41 weeks	289	13.57	155	11.66	1425	13.88	1668	13.81
42 weeks	8	0.38	5	0.38	54	0.53	48	0.4
Infant Sex								
Male	1368	64.23	674	50.71	6634	64.62	6503	53.84
Neonatal Characteristics								
LGA	224	10.52	119	8.95	1063	10.35	1140	9.44
SGA	242	11.36	164	12.34	1067	10.39	1335	11.05
HBW (> 4500 g)	35	1.64	29	2.18	206	2.01	207	1.71
NICU admission after Birth	261	12.34	222	16.78	1018	10.00	1073	8.92

Table 3.3. Characteristics of children treated as inpatients/ emergency room visit with a diagnosis of asthma or gastroenteritis (Nulliparous cohort, n=186,696)

	Inpatients				Emergency Room visit			
	Asthma (n=768)		Gastroenteritis (n=516)		Asthma (n=4,290)		Gastroenteritis (n=6,039)	
	No	(%)	No	(%)	No	(%)	No	(%)
Mode of delivery								
Vaginal	560	72.92	354	68.6	2986	69.6	4197	69.5
Caesarean section	208	27.08	162	31.4	1304	30.4	1842	30.5
Scheduled Caesarean section	17	2.21	14	2.71	90	2.1	144	2.38
Emergency Caesarean section	191	24.87	148	28.68	1214	28.3	1698	28.12
Maternal age at delivery								
<25 years	369	48.05	213	41.28	1853	43.19	2533	41.94
25-29 years	212	27.60	157	30.43	1297	30.23	1876	31.06
30-34 years	140	18.23	95	18.41	836	19.49	1146	18.98
35-39 years	39	5.08	46	8.91	260	6.06	416	6.89
>= 40 years	8	1.04	5	0.97	44	1.03	68	1.13
Socioeconomic status								
Human Services (W)	27	4.13	25	5.27	152	3.84	216	3.83
Government Sponsored Programs (S)	22	3.36	15	3.16	184	4.65	232	4.12
Others (0)	605	92.51	434	91.56	3622	91.51	5185	92.05
Maternal Asthma	13	1.69	4	0.78	67	1.56	67	1.11
Gestation								
37 weeks	60	7.81	51	9.88	366	8.53	487	8.06
38 weeks	116	15.10	80	15.5	730	17.02	973	16.11
39 weeks	184	23.96	131	25.39	1086	25.31	1658	27.45
40 weeks	261	33.98	153	29.65	1262	29.42	1833	30.35
41 weeks	142	18.49	98	18.99	815	19	1059	17.54
42 weeks	5	0.65	3	0.58	31	0.72	29	0.48
Infant Sex								
Male	503	65.49	266	51.55	2775	64.69	3284	54.38
Neonatal Characteristics								
LGA	50	6.51	37	7.17	363	8.46	498	8.25
SGA	103	13.41	75	14.53	557	12.98	768	12.72
HBW (> 4500 g)	10	1.30	11	2.13	73	3.01	96	1.59
NICU admission after Birth	114	14.96	93	18.09	479	11.26	634	10.54

Table 3.4. Characteristics of children treated as inpatients/ emergency room visit with a diagnosis of asthma or gastroenteritis (second pregnancy with one previous CS cohort, n=52,235)

	Inpatients				Emergency Room visit			
	Asthma (n=257)		Gastroenteritis (n=175)		Asthma (n=1,297)		Gastroenteritis (n=1,284)	
	No	(%)	No	(%)	No	(%)	No	(%)
Mode of delivery								
Vaginal	115	44.75	59	33.71	491	37.86	423	32.94
Caesarean section	142	55.25	116	66.29	806	62.14	861	67.06
Scheduled Caesarean section	106	41.25	87	49.71	575	44.33	640	49.84
Emergency Caesarean section	36	14.01	29	16.57	231	17.81	221	17.21
Maternal age at delivery								
<25 years	74	28.79	27	15.43	261	20.12	231	17.99
25-29 years	85	33.07	54	30.86	393	30.3	383	29.83
30-34 years	57	22.18	53	30.29	422	32.54	405	31.54
35-39 years	34	13.23	32	18.29	183	14.11	214	16.67
>= 40 years	7	2.72	9	5.14	38	2.93	51	3.97
Socioeconomic status								
Human Services (W)	7	3.06	9	5.52	39	3.23	48	4.00
Government Sponsored Programs (S)	7	3.06	7	4.29	37	3.07	51	4.25
Others (0)	215	93.89	147	90.18	1131	93.70	1101	91.75
Maternal Asthma	2	0.78	0	0	14	1.08	10	0.78
Gestation								
37 weeks	30	11.67	22	12.57	114	8.79	123	9.58
38 weeks	83	32.3	57	32.57	414	31.92	387	30.14
39 weeks	87	33.85	66	37.71	449	34.62	484	37.69
40 weeks	38	14.79	25	14.29	233	17.96	202	15.73
41 weeks	19	7.39	5	2.86	85	6.55	85	6.62
42 weeks	0	0	0	0	2	0.15	3	0.23
Infant Sex								
Male	152	59.14	83	47.43	824	63.53	686	53.43
Neonatal Characteristics								
LGA	43	16.73	20	11.43	161	12.41	154	11.99
SGA	22	8.56	19	10.86	108	8.33	115	8.96
HBW (> 4500 g)	3	1.17	5	2.86	23	1.77	29	2.26
NICU admission after Birth	39	15.35	30	17.24	164	12.75	127	9.95

Table 3.5. Hazard ratios for children with a) an emergency room visit b) a hospital admission diagnosis of gastroenteritis for each birth mode in Full cohort (n=438,659), Nulliparous cohort (n=186,696) and Second pregnancy with one previous CS (n=52,235)

a) Emergency room visit with gastroenteritis

	Full cohort				Nulliparous				Second pregnancy with one previous CS			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CS	**1.16**	**1.12-1.21**	**1.21**	**1.16-1.26**	**1.12**	**1.06-1.18**	**1.19**	**1.12-1.26**	**1.32**	**1.17-1.48**	**1.32**	**1.17-1.50**
Scheduled CS	1.00	0.94-1.06	1.05	0.99-1.12	**1.18**	**1.01-1.39**	**1.21**	**1.03-1.43**	**1.23**	**1.10-1.37**	**1.22**	**1.08-1.37**
Emergency CS	**1.23**	**1.18-1.29**	**1.25**	**1.20-1.31**	**1.10**	**1.04-1.17**	**1.17**	**1.11-1.24**	1.09	0.94-1.26	1.10	0.95-1.27

b) Hospital admission with gastroenteritis

	Full cohort				Nulliparous				Second pregnancy with one previous CS			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CS	**1.21**	**1.08-1.37**	**1.22**	**1.09-1.38**	1.16	0.96-1.40	**1.22**	**1.02-1.48**	1.21	0.89-1.66	1.10	0.79-1.53
Scheduled CS	**1.21**	**1.03-1.43**	**1.20**	**1.01-1.43**	1.34	0.79-2.28	1.36	0.80-2.33	1.19	0.88-1.59	1.08	0.79-1.47
Emergency CS	**1.16**	**1.01-1.33**	**1.18**	**1.02-1.35**	1.13	0.93-1.37	1.19	0.98-1.44	1.02	0.68-1.51	1.02	0.68-1.52

Adjusted: Adjusted for gestational age, sex, SGA, maternal asthma ad maternal age.

Table 3.6. Hazard ratios for children with a) an emergency room visit b) a hospital admission diagnosis of asthma for each birth mode in Full cohort (n=438,659), Nulliparous cohort (n=186,696) and Second pregnancy with one previous CS (n=52,235)

a) Emergency room visit with asthma

	Full cohort				**Nulliparous**				**Second pregnancy with one previous CS**			
	Crude		**Adjusted**		**Crude**		**Adjusted**		**Crude**		**Adjusted**	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
CS	**1.12**	**1.08-1.17**	**1.13**	**1.09-1.19**	**1.11**	**1.04-1.19**	**1.16**	**1.08-1.24**	**1.14**	**1.02-1.28**	**1.14**	**1.01-1.29**
Scheduled CS	**1.06**	**1.01-1.13**	**1.08**	**1.01-1.16**	1.05	0.85-1.29	1.06	0.86-1.31	1.04	0.93-1.16	1.01	0.90-1.14
Emergency CS	**1.13**	**1.08-1.19**	**1.13**	**1.08-1.19**	**1.11**	**1.04-1.19**	**1.16**	**1.08-1.24**	**1.18**	**1.02-1.36**	**1.19**	**1.03-1.37**

b) Hospital admission with asthma

	Full cohort				**Nulliparous**				**Second pregnancy with one previous CS**			
	Crude		**Adjusted**		**Crude**		**Adjusted**		**Crude**		**Adjusted**	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
CS	0.93	0.83-1.01	0.95	0.85-1.05	0.94	0.81-1.11	1.02	0.86-1.19	0.79	0.62-1.02	0.78	0.60-1.01
Scheduled CS	1.01	0.88-1.17	1.08	0.93-1.25	1.10	0.68-1.77	1.22	0.75-1.98	0.87	0.68-1.11	0.84	0.65-1.10
Emergency CS	0.88	0.78-1.01	0.91	0.81-1.03	0.93	0.79-1.10	0.99	0.84-1.17	0.85	0.60-1.21	0.87	0.61-1.24

Adjusted: Adjusted for gestational age, sex, SGA, maternal asthma ad maternal age.

Table 3.7. Multivariate Generalized Estimating Equation logistic regression models for the probability of the CS delivered children with a) an emergency room visit b) a hospital admission diagnosis of asthma in Full cohort (n=438,659)

a) Emergency room visit and Hospitalization with gastroenteritis

	Emergency room visit				Hospitalization			
	Crude		Adjusted		Crude		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CS	**1.05**	**1.01-1.09**	**1.08**	**1.04-1.13**	**1.20**	**1.07-1.36**	**1.14**	**1.01-1.29**
Scheduled CS	0.95	0.90-1.01	0.99	0.93-1.06	**1.23**	**1.04-1.47**	**1.18**	**1.01-1.41**
Emergency CS	**1.09**	**1.04-1.15**	**1.12**	**1.07-1.17**	1.13	0.97-1.30	1.07	0.92-1.24

b) Emergency room visit and Hospital admission with asthma

	Emergency room visit				Hospitalization			
	Crude		Adjusted		Crude		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CS	**1.05**	**1.01-1.10**	**1.06**	**1.01-1.12**	0.92	0.82-1.02	0.95	0.86-1.06
Scheduled CS	1.03	0.96-1.11	1.05	0.98-1.14	0.99	0.86-1.16	1.07	0.92-1.25
Emergency CS	1.05	0.99-1.11	1.05	0.99-1.12	0.88	0.78-1.01	0.89	0.79-1.01

Adjusted: Adjusted for gestational age, sex, SGA, maternal asthma ad maternal age.

Figure 3.1. Flow-chart for selection of cohort

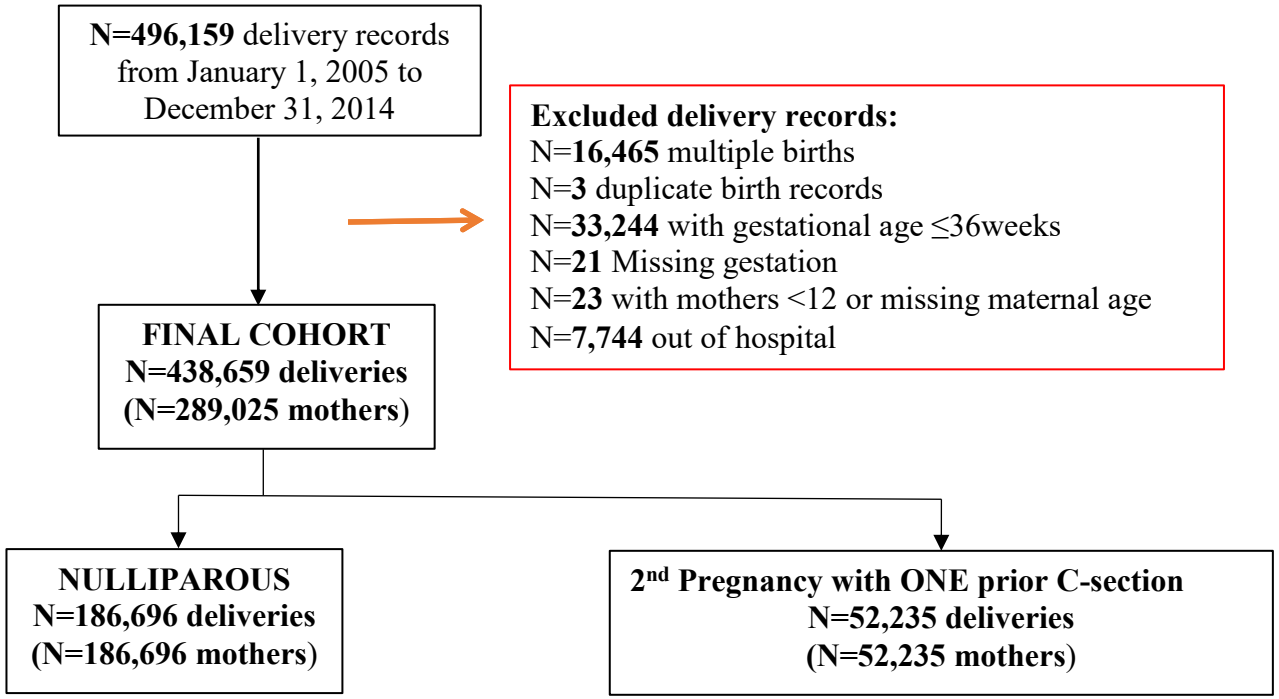
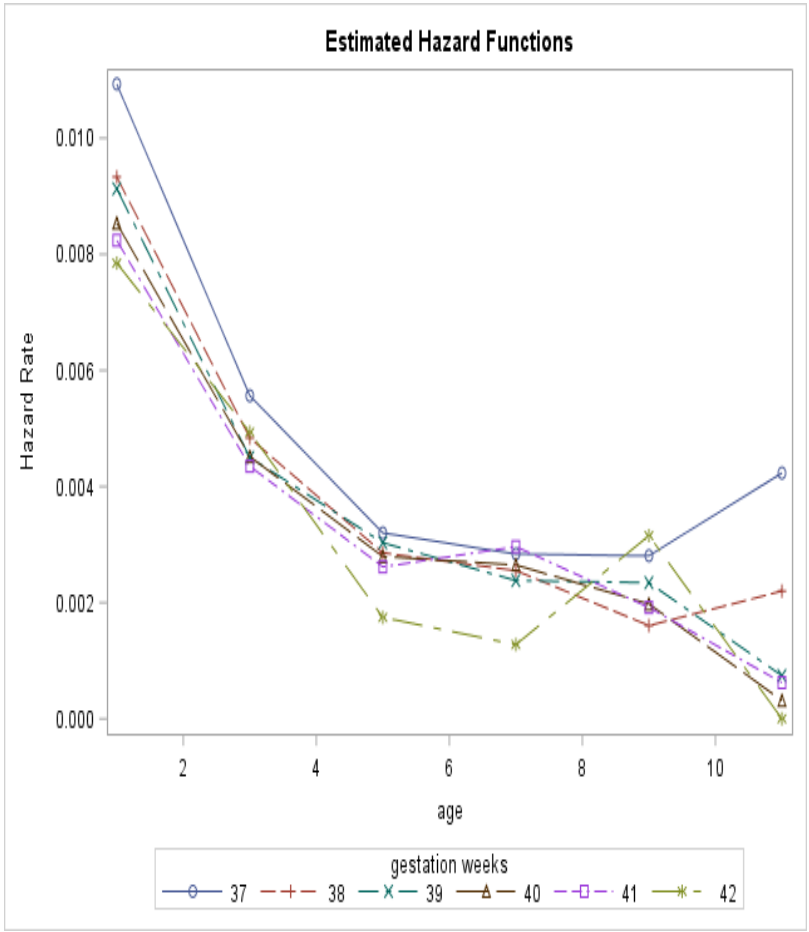


Figure 3.2: Time to fist a) emergency department visit b) hospital admission with gastroenteritis according to gestational age categories in full cohort

a)



b)

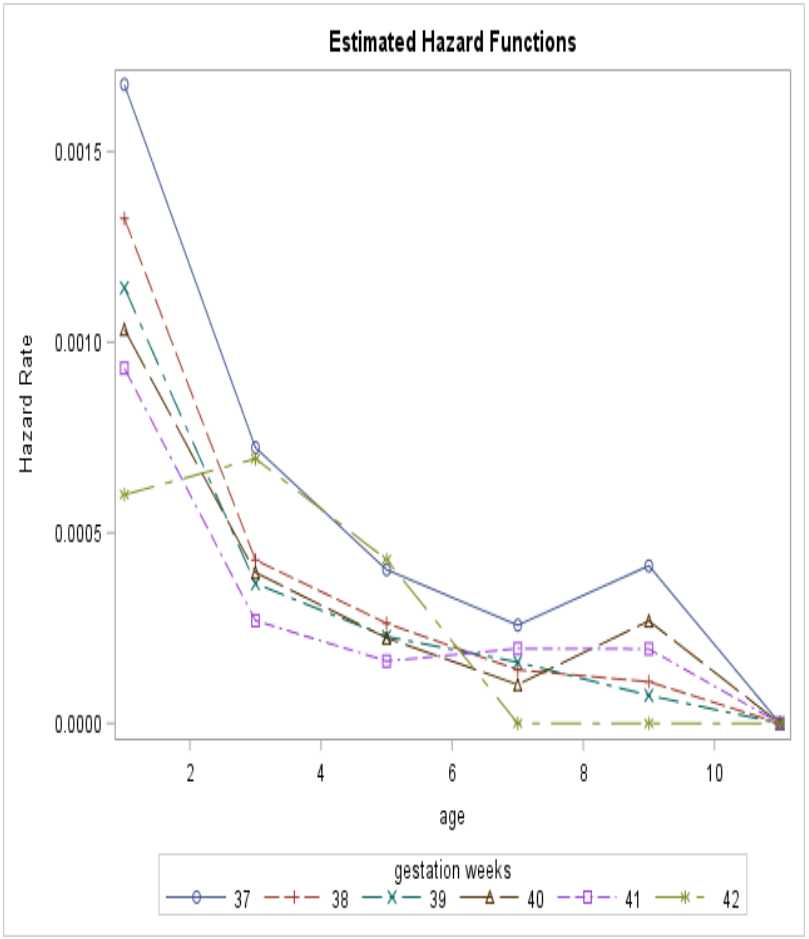
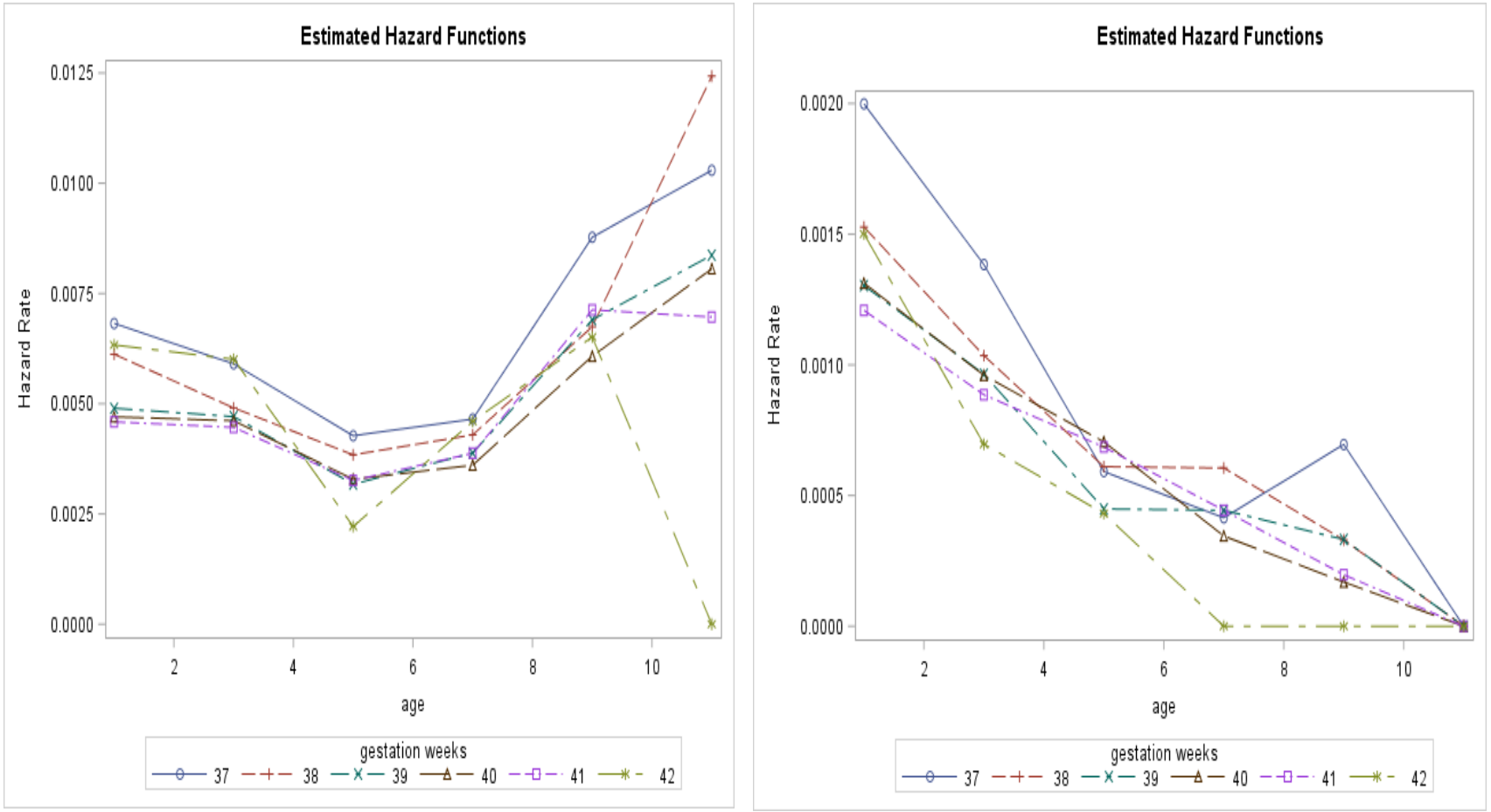


Figure 3.3: Time to fist a) emergency department visit b) hospital admission with asthma according to gestational age categories in full cohort

a) **b)**



Appendix 3.1: Definition and source of study variables

Study variables	Operational definitions	Data source
Exposure variable: Mode of delivery	Mode of delivery was the method used to deliver infants which can be either 1. Vaginal 2. Scheduled CS 3. Emergency CS 4. Vaginal birth after CS (VBAC)	Mode of delivery was determined from inpatient hospitalization data by CCI procedure codes & ICD-10-CA codes. CS was determined from the inpatient hospitalization data by CCI procedure codes. CS code: 5MD60 CS deliveries with ICD-10-CA labour codes were classified as emergency CS and without ICD-10-CA, labour codes were classified as scheduled CS. Labour codes: "O32101","O33001","O33101","O33201", "O33301","O33401","O33501","O33601", "O33701","O33801","O33901", "O4201","O4202","O4209", "O4211","O4212","O4219","O7110", "O7111","O7118", "O750","O751","O752","O753", "O757","O601","O602", "O80","O81","O61","O62","O63", "O64","O65","O66","O68","O69","O70") Repeat CS delivery was determined from the ICD-10-CA codes: VBAC codes: "O75701", "O75709"
Outcome variables: 1. Hospitalization / Emergency room attendance with gastroenteritis	Infant visit to emergency room or hospitalization with vomiting or diarrhea	Hospitalization/ Emergency room attendance with vomiting and diarrhea will be determined from the inpatient hospitalization data and ambulatory care data by ICD-10-CA codes. gastroenteritis codes: A02.0, A03–A05, A06.0–A06.3, A07, A08.1, A09.9, K52.8–K52.9, P78.3

2. Hospitalization/ Emergency room attendance with asthma at	Infant visit to emergency room or hospitalization with wheeze or asthma	Hospitalization/ Emergency room attendance with wheeze or asthma will be determined from the inpatient hospitalization data and ambulatory care data by ICD-10-CA codes. Asthma codes: J45.0-J45.9
Covariates: 1. Maternal asthma	Asthma status of mother	Mother history of asthma was determined from inpatient hospitalization data by ICD-10-CA codes. Maternal asthma: "J4500", "J4501","J4510", "J4511", "J4580","J4581","J4590","J4591", "J450", "J451", "J458", "J459", "J45"
2. Maternal Age	Maternal Age at the time of delivery	Maternal Age was determined from Alberta pregnancy birth cohort and/ or inpatient hospitalization data
3. Birth weight	The weight of an infant at birth. [<=4kg:normal & >4kg: high]	Birth weight was determined from Alberta pregnancy birth cohort
4. Gestation Age	Gestation age to determine Term or Preterm [>= 37 weeks: term and <37 weeks: preterm)	Gestational age was determined from Alberta pregnancy birth cohort
5. Large for Gestational Age (LGA)	Indicates whether the birth is large for gestational age (>90 percentile).	LGA was determined from Alberta pregnancy birth cohort
6. Small for Gestational Age (SGA)	Indicates whether the birth is small for gestational age (<90 percentile).	SGA was determined from Alberta pregnancy birth cohort
7. Infant Sex	Sex of the Newborn	Infant Sex was determined from Alberta pregnancy birth cohort
8. Birth hospitalization	Newborn admission to the hospital immediately after delivery	Newborn birth hospitalization was determined from inpatient hospitalization data (service code) Hospitalization service code: "51"
9. Length of stay in hospital	Infant duration of stay in the hospital	Infant length of stay in the hospital was determined from inpatient hospitalization data

10. NICU admission	Newborn admission to NICU	Newborn admission to NICU was determined from inpatient hospitalization data (care admit unit code) NICU admission: “50”
11. Gestational diabetes/ Hypertension/ Pre-eclampsia/ Eclampsia	Women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy/ high blood pressure during pregnancy/ high blood pressure during pregnancy with complication	Gestational diabetes/ Hypertension/ Pre-eclampsia/ Eclampsia was determined from inpatient hospitalization data by ICD-10-CA codes. Gestational diabetes codes: O24801", "O24803", "O24809", "O24501", "O24503", "O24509", "O24601", "O24603", "O24609", "O24701", "O24703", "O24709 Pre-eclampsia codes: "O111","O112","O113","O114","O119"," O11001", "O11003","O11009","O14001","O14101", "O14201","O14901","O14003", "O14103", "O14203","O14903","O14009","O14109", "O14209","O14909","O1400","O1402", "O1403", "O1404","O1410", "O1412", "O1413", "O1414", "O1420", "O1422", "O1423", "O1424", "O1490", "O1492", "O1493", "O1494" Eclampsia codes: "O15001", "O15003", "O15101", "O15103", "O15909"
12. Socioeconomic status	Socioeconomic status of the parents at the time of delivery	Socioeconomic status was determined from Alberta population registry

CCI: Canadian Classification of Health Interventions, 2012, Volume 4

ICD-10-CA: International Classification of Diseases-10-Canada

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Chapter 4. Caesarean-section Rates in Alberta: Term birth cohort from 2005-2014

Mon Tun[1], Mike Paulden[2], Piush Mandhane[1], Radha Chari[5], Padma Kaul[2, 4, 5]

[1]Department of Pediatrics, University of Alberta, Edmonton AB.

[2]School of Public Health, University of Alberta, Edmonton AB.

[3]Department of Obstetrics and Gynaecology, University of Alberta, Edmonton AB.

[4]Department of Medicine, University of Alberta, Edmonton AB.

[5]Canadian VIGOUR Centre, University of Alberta, Edmonton AB.

Abstract:

Introduction: Caesarean section (CS) rates are on the rise in Canada and other parts of the world. These is both an increase in primary CS rates as well as a decrease in vaginal births after caesarean (VBAC). Labour induction practices may also impact primary CS rate.

Objective: We examined temporal trends in overall CS and VBAC rates in non-nulliparous pregnancies. We then sought to determine whether induction of labour (IOL) between 37 through 41 weeks of gestation, as compared with expectant management (EM), is associated with emergency CS delivery in nulliparous pregnancies.

Methods: The patient population, nulliparous women with live-born, singleton, term pregnancies (≥ 37 weeks) births in Alberta from 2005 to 2014, was derived from linking multiple administrative health databases. The overall CS and IOL rates were calculated to determine the trend. Multiple logistic regression analysis was used to examine associations between the IOL and emergency CS rate at each gestation age after reaching term.

Results: The study cohort consisted of 438,659 birth events of singleton term infants (≥ 37 weeks) among 289,025 women over the ten-year period. The CS rate increased from 24.8% to 27.7%. There was a 1.3 fold increase in IOL from 23.7% to 30.8% over the ten-year study period. We analyzed data from186,696 (42.5%) birth events from nulliparous women. The primary CS rate in the nulliparous group had increased from 27.9% to 30.0%. An increase in emergency CS (25.9% to 27.5%) and IOL (28.3% to 39.0%) were also observed in nulliparous women. An IOL at 38 and 39 weeks of gestation was associated with an increased odds of emergency CS in both nulliparous and low-risk nulliparous cohort compared to EM. The risk of emergency CS was reduced if IOL was at 41 weeks in both cohorts.

Conclusion: IOL before reaching full term was associated with increased risk of emergency CS delivery when compared to EM group in both nulliparous and low-risk nulliparous pregnancies. Expectant mothers should be counselled for informed choice between early term vs. late term induction.

4.1 Background and Introduction

Caesarean-section (CS) rates have increased dramatically with some countries exceeding the World Health Organization (WHO) recommended rate of 15% (1,2). The Healthy People 2020 target CS rate to be 23.9% in low-risk full term pregnant women with a singleton, cephalic presentation (3). In Canada, CS is the most common inpatient surgery and CS rates approaching 30% in 2018 (4). There has been a gradual increase in primary CS from 18.5% to 19.4% while repeat CS has decreased from 83% to 81% between 2007-2008 and 2016-2017 (5). A decrease in vaginal births after caesarean (VBAC) is an additional factor contributing to the rise in total CS rates (6,7). Hospitals with higher rates of VBAC have lower rates of primary CS delivery among low-risk nulliparous women (8). There is a growing consensus that prevention of primary CS is important to lower the overall CS rates (9). Factors that may contributed to an increase in CS include breech presentation (10) and induction of labour (IOL) in the pregnant women with diabetes, hypertension, or obesity (11-13).

Induction of labour (IOL), a common obstetrical procedure, is performed when the benefits of delivery outweigh the risks of continuing the pregnancy (14) . Many international guidelines recommended IOL between 41 and 42 weeks of gestation to obviate the risks associated with post-term pregnancies (14-16). IOL rates have been rising steadily in Canada from 12.9% in 1991 to 21.3% in 2004 (5). A failed IOL is the major risk factor for CS. Nulliparity and poor cervical conditions are the known risk factors for CS after IOL (17-19). IOL in nulliparous women is six times more likely to fail when compared to non-nulliparous women (20) and has been shown to increase the CS rate by 13% in low-risk nulliparous women (without premature rupture of membrane, gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia,

placenta previa and placenta abruption) (21). In observational studies, there are conflicting findings on the associations between IOL and the increased risk of CS (22-26). Randomized controlled trials and systematic reviews found that IOL decreased the risk of CS when compared to expectant management (27-30). There is a concern about a higher frequency of CS delivery and other possible adverse maternal and perinatal outcomes when IOL is offered between 39 weeks and 41 weeks of gestation (31). We aimed to examine whether IOL between 37 through 41 weeks of gestation, as compared with expectant management, is associated with emergency CS delivery in nulliparous pregnancies, and to determine temporal trends in overall CS rates, VBAC rates in non-nulliparous pregnancies.

4.2 Methods

We analyzed data from an observational retrospective population-based cohort study generated from all pregnancies resulting in a live birth in Alberta, Canada between Jan 2005 and December 2014. The study cohort was developed by linking multiple administrative health databases, including hospitalization data, outpatient data, physician claims data, the Alberta Vital Status registry, and the population health registry. Women with live-born, singleton, term pregnancies (≥ 37 weeks) were included. Pregnancies that resulted in infants with non-cephalic presentations, were excluded. We limited our study to nulliparous and low-risk nulliparous women. Low-risk nulliparous cohort excluded pregnant women with premature rupture of membrane, gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, placenta previa, placenta abruption and cephalopelvic disproportion). Ethical approval was obtained from the University of Alberta Ethics Committee, Protocol No. Pro00056999

The integrated database included information regarding labour and delivery, maternal and infant characteristics, and diagnoses and interventions. Diagnoses in the database were coded using the Canadian version of the International Classification of Diseases (ICD-10-CA). Interventions and procedures were coded using the Canadian Classification of Interventions. The accuracy of the perinatal information in the database has been validated previously (32,33). Maternal characteristic included age, marital status, socioeconomic status, maternal pregnancy associated medical conditions (gestational diabetes, hypertension, preeclampsia, eclampsia). Obstetric factors included gestational age at IOL and parity while intrapartum outcomes included mode of birth, third or fourth degree perineal laceration and postpartum haemorrhage. Perinatal outcomes data included gestation at delivery, birth weight and neonatal intensive care unit (NICU) admission. IOL was identified by ICD-10 procedure codes 5AC30 and CS delivery was identified by ICD-10 procedure codes 5MD60. CS deliveries without ICD-10 labour codes were classified as scheduled CS and with labour codes were identified as emergency CS. Definitions of different birth modes, diagnostic and procedure codes used are in **Appendix 4.1**.

4.2.1 Statistical Methods

The primary outcomes of interest were temporal trends of CS rates in the total cohort and in the subgroup of non-nulliparous women. Additional analysis examined the temporal trend in VBAC rates. Frequency distributions in percentage were employed to describe the study population and the temporal trends using the Conchran-Armitage test was used to assess the linear trend in proportion of CS, VBAC and IOL by year. VBAC rates in non-nulliparous women were analyzed after restricting the population to second pregnancy with only one prior CS.

Our secondary objective was to examine the association between IOL and CS rates. This analysis was restricted to nulliparous women with live singleton births at term (between 37- and 41-weeks gestation). Furthermore, a low-risk nulliparous cohort was identified by excluding pregnant women with gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, premature rupture of membrane, placenta previa, placenta abruption and cephalopelvic disproportion. Analysis was conducted in four ways. First, we compared the CS rate after IOL and after spontaneous onset of labour (SOL) in overall population (overall comparison). Second, CS rate after IOL was compared with after SOL (week-to-week comparison) (34). Third, we employed the method recommended by Caughey et al comparing women who had their IOL in a specific gestational week with the group of women who were expectantly managed or waited for a later labor after that gestational week (all-above comparison) (35). The Caughey et al. method excluded a substantial number of women undergoing spontaneous labor in the IOL group from the analysis. We subsequently conducted a sensitivity analysis, suggested by Glantz et al., by changing the definition of expectant management group (at-or-above) to include women with spontaneous labour that occurred at the same week of IOL in the expectant management group (34) **(Appendix 4.2)**.

Multiple logistic regression was used to determine if IOL was associated with CS after controlling for potential confounding. Results were considered statistically significant at the p-value of <0.05 and interactions between the exposure variable and the confounders were tested. All statistical analyses were performed using the SAS program, version 9.4 (SAS Institute, Inc, Cary, NC).

4.3 Results

There were 438,659 birth events of singleton term infants (≥ 37 weeks) from 289,025 women in Alberta between 2005 and 2014 **(Figure 4.1)**. Maternal characteristics, medical conditions, obstetric conditions are shown in **Figure 4.1**. Of the 438,659 birth events, 115,784 (26%) were CS. The overall CS rate in Alberta term birth cohort increased from 24.8% to 27.7% **(Figure 4.1)**. There was a 1.3-fold increase in IOL (23.67% to 30.78%). The CS rate in the nulliparous group (n=186,696; 42.5% of all birth events) increased from 27.9% to 30.0% per annum. Emergency CS rates (25.93% to 27.54%) and IOL (28.3% to 39%) increased among nulliparous women. The rates of repeat CS and VBAC were 64% and 36% among women who had a previous CS (N=52,235 birth events; **Figure 4.1)**.

Nulliparous women scheduled for a CS were older than women undergoing SOL or IOL. Women in the IOL group were more likely to have gestational diabetes, hypertension and less likely to have vaginal delivery when compared to the spontaneous group **(Table 4.1)**. Among women who had an IOL, 68% of the labour was induced before 41 weeks **(Table 4.1)**. In low-risk nulliparous group, the majority of the pregnant women who underwent a scheduled CS were older and about 50% of them underwent IOL before reaching full term **(Table 4.2)**. Approximately 15% of pregnancies were induced at 37-38 weeks in low-risk nulliparous cohort **(Table 4.2)**.

IOL was significantly associated with increased risk of emergency CS both in nulliparous and low-risk nulliparous cohorts after controlling for maternal age, socioeconomic status, marital status, infant sex and maternal asthma **(Table 4.3)**. In the "all-above" analysis, when IOL was compared to expectant management group, IOL prior to 40-weeks was associated with an

increase in the emergency CS rate. However, a decrease in the risk of emergency CS was observed if IOL was done at 41 weeks in both nulliparous and low-risk nulliparous cohorts **(Table 4.4)**. IOL at 38 and 39 weeks of gestation was associated with 10% higher odds of CS in nulliparous cohort (aOR 1.10, 1.05-1.15; aOR 1.09, 1.04-1.13) compared to the expectant management group. In contrast, IOL at 41weeks was associated with 24% lower odds of CS (aOR 0.76, 0.66-0.78). We observed similar results in the low-risk nulliparous cohort with an increase in CS at 37, 38 and 39 weeks and a decrease in CS at 41 weeks **(Table 4.4)**. In a sensitivity analysis (at-or-above) with inclusion of spontaneous labour that occurred in the same week as the induction in the expectant management group, IOL was associated with significant increase in emergency CS at all gestational weeks in both nulliparous and low-risk nulliparous groups **(Table 4.5)**.

4.4 Discussion

This study examined the trends of CS rates, VBAC rates and the association between IOL and CS rates. In this population-based cohort study of term, singleton pregnancies, we found a steady increase in CS, IOL rate and a decline in VBAC rate over a ten-year study period. The CS rate in the nulliparous group increased from 27.9% to 30.0% per annum over the ten-year course of the cohort. IOL was associated with increased odds of emergency CS from 37 to 39 weeks of gestation in both nulliparous and low-risk nulliparous cohort compared to EM. The risk of emergency CS was reduced if labour was induced at 41 weeks in both cohorts. In addition, in a sensitivity analysis “at-or-above”, IOL was associated with higher rates of CS at all gestational weeks after reaching 37-weeks in both nulliparous and low-risk nulliparous cohorts.

The CS rates in our nulliparous study population were higher than the study by Glantz et al (34) 26.35% vs. 23%; however, IOL rates were similar, 33.8% vs. 32.75%. Similar to our analysis "at-or-above", Glantz et al found that IOL increased the risk of CS from 38 weeks of gestation onwards in nulliparous cohort (34). Zhao et al (24) reported consistent findings of increased in CS with IOL compared to EM.

Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends a trial of labour (TOL) in women with one previous transverse low-segment CS with no contraindications (36). The overall success rate of VBAC was 76% in 1996 (37) and a recent study reported that attempted VBAC rate was about 31% and VBAC success rate was stable at 50% (38). Studies have shown a decline in offering TOL to pregnant women due to concerns about the safety of VBAC and increasing influence of medicolegal liability (39,40). Those reasons could have explained a decline in VBAC rate and an increase in repeat CS rate, in particular, a rise in scheduled CS rate in our study.

Using "all-above" method, studies by Caughey et al (35) and Glantz et al (34) showed that IOL was not associated with increased risks of CS deliveries in nulliparous women which was in disagreement with our findings. The differences in findings of association between IOL and CS reflecting different study periods, study population and different care practices during pregnancy and labor in the United States and Canada. An observational study from Scotland, using large sample size of 25 years (23), reported that IOL increased the risk of CS at 39 weeks and reduced the risk of CS at 40 and 41 weeks of gestation with "all-above" method. The increased in CS rates were observed with IOL from 39 to 41 weeks when they used "at-or-above" method.

It is important to select the appropriate control group when examining associations between IOL and CS. In our study, approximately 50% of low-risk nulliparous women had IOL before 41

weeks. The available options in caring for a low-risk nulliparous pregnant women at term are between IOL and EM rather than IOL and spontaneous onset of labour. EM will either result in SOL or IOL at a later gestational age. Hence, we compared IOL with EM group.

The risk of CS associated with labour induction depends on the definition of EM group. In addition, the association between IOL and CS delivery may be biased by indications for induction and cervical ripening with intracervical or intravaginal prostaglandins in induction cohort compared to EM. The studies including pregnant women with obstetrical complications such as gestational hypertension, pre-eclampsia, gestational diabetes reported that IOL did not increase the risk of CS deliveries in the HYPITAT and DIGITAT trials (41). The findings from these studies could be biased by the timely cervical ripening and more favorable cervix in the induction group which biased their results towards the null. Likewise, Wood et al (42) pointed out that their meta-analysis was heavily influenced by the Canadian Mulitcentre Post-term Pregnancy Trial (43), where cervical ripening was offered to the induction group and not to the EM group. Hence, pregnant women with favorable cervix will be more likely to be in the IOL group and those with unfavorable cervix will be more likely to be in the expectant group which could bias the results in favor of induction.

Two randomized controlled trails reported IOL at 39 weeks when compared to EM improved the birth outcomes and did not increase the CS rate (29,30). Moreover, one recent observational study showing IOL at 39 weeks was associated with a decrease in CS rate when compared to EM (25). In contrast to those findings, we found an increase in CS if IOL was done at 39 weeks. The differences in findings between our study and that of Souter et al could be due to differences in the study period, labour induction guidelines, the estimation of gestational age and definition used for failed IOL. Currently, there is no standard criteria to diagnose failed IOL (44); the

variation in the definition adopted for labour induction in practice resulted in different CS rates. IOL also modified the normal progression of labour by increasing the duration of labour in both nulliparous and non-nulliparous women who had an unfavorable cervical status at baseline (45). The increased duration of labour may have resulted in more variability in the clinical judgement for CS delivery after IOL. There are evidences showing an increase in the frequency of IOL without indication (20,46). IOL is generally a safe and effective procedure; however, failed induction is the major risk factor that can result in CS.

The major strength of this study is the large longitudinally linked population-based data included community hospitals and with the high-level accuracy of the variables used in the analysis. Furthermore, the data extended over a ten-year period and there is less chance of variation in labour induction guidelines. In addition, we were able to explore other relevant potential confounding factors including age, parity, socioeconomic status and maternal asthma.

Our study lacks specific clinical information on indication of induction, cervical bishop scores, physician and patient attitudes and cultural influences on decision making which may have resulted in a selection bias for labour induction. To control for the lack of data on indication for induction, we conducted a stratified analysis in low-risk nulliparous group and observed a similar trend of increase in CS with IOL when compared to expectant management as in nulliparous cohort. Our findings may have limited generalizability as the study included pregnant women only from one province. Although, we adjusted for potential confounding factors in our multiple logistic regression models, there could still be residual confounding factors that could not be accounted by statistical models such as the women who were induced were fundamentally different from those who were in expectant management group.

4.5 Conclusion

In conclusion, our primary analysis “all-above” results showed that IOL at late term decreased the risk of emergency CS when compared to expectant management group in both nulliparous and low-risk nulliparous pregnancies. Nonetheless, if IOL was done at early and full-term, it increased the risk of emergency CS delivery in both study cohorts. Our findings are consistent with the recommendations from international and SOGC guidelines to conduct routine IOL at 41 weeks to reduce a woman’s chance of delivery by CS. This study supports the importance of providing counseling to the expectant mothers about the potential risk of CS delivery and the informed choice between early vs. late term induction.

Figure 4.1. Flow-chart for selection of cohort

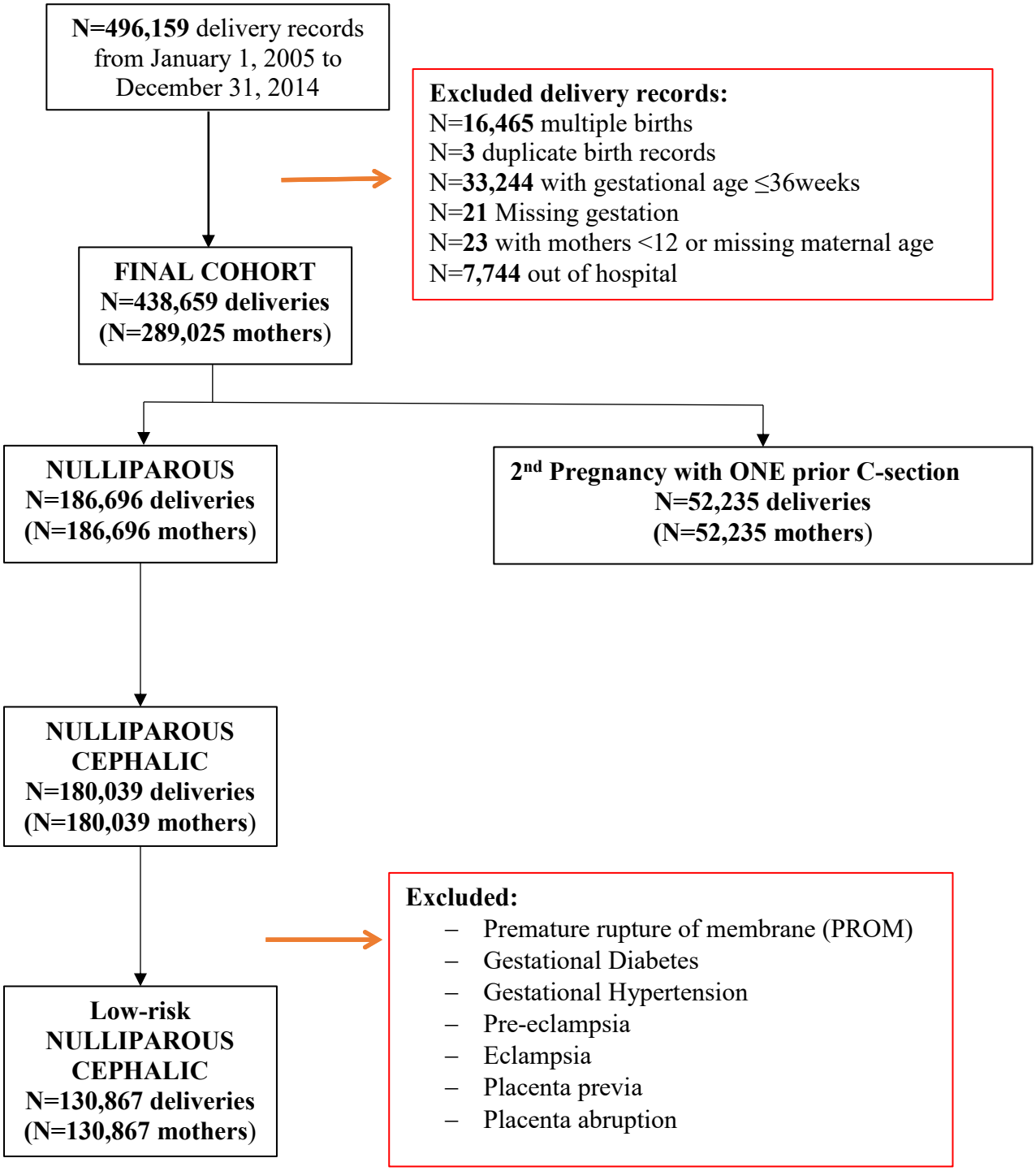
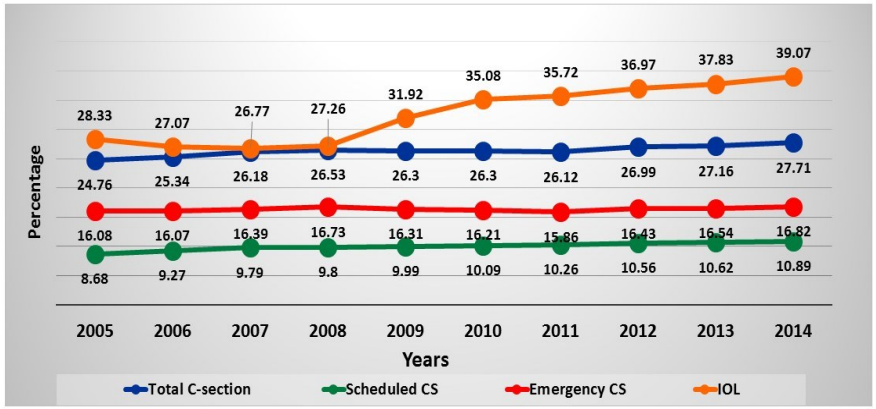
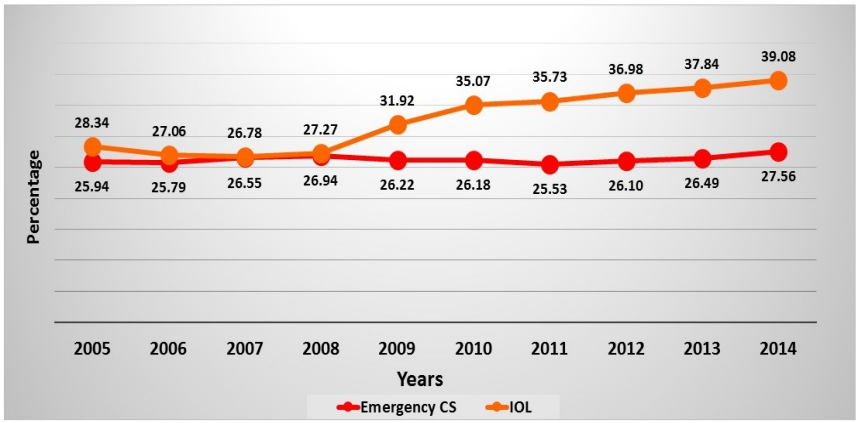


Figure 4.2. Caesarean section and Labour Induction Rates in Alberta Term Cohort, 2005-2014

a) Term cohort (≥ 37 weeks), Overall



b) Nulliparous cohort (≥ 37 weeks)



c) Pregnancy with one previous C-section cohort (≥ 37 weeks)

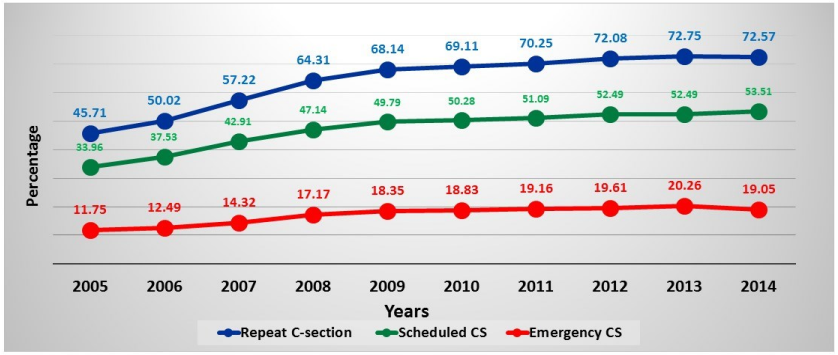


Table 4.1. Maternal characteristics, intrapartum outcomes and infant characteristics by onset of labour in nulliparous term birth cohort with cephalic presentation (n=180,039), 2005-2014

	Spontaneous Labor N=115,153		**Induction** N=60,991		**Scheduled Caesarean Section** N=3,895	
	N/ Mean	%/SD	N/ Mean	%/SD	N/ Mean	%/SD
Maternal Age						
<25 years	39011	33.88	17373	28.48	688	17.66
25-29 years	39894	34.64	20958	34.36	1011	25.96
30-34 years	27233	23.65	15862	26.01	1179	30.27
35-39 years	7990	6.94	5679	9.31	760	19.51
>= 40 years	1025	0.89	1119	1.83	257	6.60
Marital Status of Mother at Time of Birth						
Legally Married and Husband is the natural father of the child	72368	62.85	39520	64.80	2676	68.70
Legally Married and Husband is not the natural father of the child	435	0.38	225	0.37	23	0.59
Not Legally Married	42200	36.65	21147	34.67	1191	30.58
Socioeconomic status						
First Nations	3933	3.44	1871	3.08	99	2.56
Human Services	2335	2.04	1222	2.01	92	2.38
Government Sponsored Programs	3265	2.86	1610	2.65	95	2.46
Others	104813	91.66	55962	92.25	3580	92.60
Maternal Asthma	826	0.72	540	0.89	37	0.95
Pregnancy associated complications						
Gestational Diabetes	2904	2.52	4572	7.50	355	9.11
Gestational Hypertension	129	0.11	278	0.46	7	0.18
Preeclampsia/ Eclampsia	610	0.53	2134	3.50	134	3.44
Gestation						
37 weeks	6553	5.69	5334	8.75	523	13.43
38 weeks	16451	14.29	8832	14.48	1208	31.01
39 weeks	34223	29.72	12254	20.09	1416	36.35
40 weeks	42877	37.23	13763	22.57	489	12.55
41 weeks	14655	12.73	20281	33.25	250	6.42
42 weeks	394	0.34	527	0.86	9	0.23
Intrapartum outcomes						
Postpartum haemorrhage	12370	10.74	7839	12.85	207	5.31
3rd or 4th degree perineal laceration	8435	7.33	4201	6.89	NA	NA
Delivery Type						
Vaginal delivery	92307	80.16	41191	67.53	NA	NA
Instrumental vaginal delivery (Forceps)	7034	6.11	4108	6.74	NA	NA
Instrumental vaginal delivery (Vacuum)	17072	14.83	8427	13.82	NA	NA
Emergency caesarean section	22846	19.84	19800	32.46	NA	NA
Delivered Region						
Chinook	5356	4.65	2492	4.09	212	5.44
Palliser	3929	3.41	730	1.20	52	1.34
Calgary	41510	36.05	24897	40.82	1666	42.77
David Thompson	9683	8.41	4268	7.00	257	6.60

East Central	1600	1.39	760	1.25	49	1.26
Capital	39387	34.20	21406	35.10	1296	33.27
Aspen	4615	4.01	1482	2.43	151	3.88
Peace Country	5200	4.52	2755	4.52	100	2.57
Northern Lights	3873	3.36	2201	3.61	112	2.88
Infant Sex						
Female	56212	48.82	29561	48.47	1754	45.03
Male	58941	51.18	31430	51.53	2141	54.97
Neonatal Characteristics						
LGA	6854	5.95	4651	7.63	671	17.23
SGA	15344	13.33	8951	14.68	427	10.96
HBW (> 4500 g)	1137	0.99	1048	1.72	198	5.08
Birth Weight (g)	3381.78	440.09	3417.14	499.09	3441.68	584.22
Neonatal ICU admission after Birth						
Vaginal delivery	5367	5.87	2999	7.30	-	-
Scheduled C-section	-	-	-	-	575	14.80
Emergency C-section	3811	16.74	3116	15.78	-	-

Table 4.2. Maternal characteristics, intrapartum outcomes and infant characteristics by onset of labour in low-risk nulliparous term birth cohort with cephalic presentation (n=130,867), 2005-2014

	Spontaneous Labor N=91,552		**Induction** N=35,897		**Scheduled Caesarean Section** N=3,418	
	N/mean	%/SD	N/mean	%/SD	N/mean	%/SD
Maternal Age						
<25 years	32813	35.84	11510	32.06	612	17.91
25-29 years	31563	34.48	12335	34.36	907	26.54
30-34 years	20651	22.56	8479	23.62	1033	30.22
35-39 years	5817	6.35	2950	8.22	658	19.25
>= 40 years	708	0.77	623	1.74	208	6.09
Marital Status of Mother at Time of Birth						
Legally Married and Husband is the natural father of the child	56610	61.83	22573	62.88	2331	68.20
Legally Married and Husband is not the natural father of the child	345	0.38	138	0.38	22	0.64
Not Legally Married	34470	37.65	13129	36.57	1062	31.07
Unknown	126	0.14	57	0.16	3	0.09
Socioeconomic status						
First Nations	3282	3.61	1153	3.23	74	2.18
Human Services	1934	2.13	748	2.10	82	2.42
Government Sponsored Programs	2678	2.95	1000	2.80	82	2.42
Others	82986	91.31	32783	91.87	3157	92.99
Maternal Asthma	650	0.71	322	0.90	32	0.94
Pregnancy associated complications						
Gestational Diabetes	NA	NA	NA	NA	NA	NA
Gestational Hypertension	NA	NA	NA	NA	NA	NA
Preeclampsia/ Eclampsia	NA	NA	NA	NA	NA	NA
Gestation						
37 weeks	4159	4.54	2250	6.27	419	12.26
38 weeks	11748	12.83	3518	9.80	1025	29.99
39 weeks	26884	29.36	4769	13.29	1276	37.33
40 weeks	35709	39.00	7491	20.87	447	13.08
41 weeks	12703	13.88	17396	48.46	242	7.08
42 weeks	349	0.38	473	1.32	9	0.26
Intrapartum outcomes						
Postpartum haemorrhage	9707	10.60	4497	12.53	181	5.30
3rd or 4th degree perineal laceration	6680	7.30	2485	6.92	NA	NA
Delivery Type						
Vaginal delivery	74031	80.86	23937	66.68	NA	NA
Instrumental vaginal delivery (Forceps)	5425	5.93	2221	6.19	NA	NA
Instrumental vaginal delivery (Vacuum)	13715	14.98	5018	13.98	NA	NA
Emergency caesarean section	17521	19.14	11960	33.32	NA	NA

Delivered Region						
Chinook	4500	4.92	1772	4.94	185	5.41
Palliser	2971	3.25	432	1.20	41	1.20
Calgary	32214	35.19	13223	36.84	1522	44.53
David Thompson	8112	8.86	3051	8.50	235	6.88
East Central	1465	1.60	618	1.72	42	1.23
Capital	31112	33.98	12372	34.47	1090	31.89
Aspen	4178	4.56	1134	3.16	125	3.66
Peace Country	4070	4.45	1864	5.19	87	2.55
Northern Lights	2930	3.20	1431	3.99	91	2.66
Infant Sex						
Female	44826	48.96	17438	48.58	1549	45.32
Male	46726	51.04	18459	51.42	1869	54.68
Neonatal Characteristics						
LGA	5260	5.75	2743	7.64	521	15.24
SGA	12513	13.67	5721	15.94	369	10.80
HBW (> 4500 g)	910	0.99	763	2.13	146	4.27
Birth Weight (g)	3386.68	437.74	3463.58	511.90	3424.28	561.60
Neonatal ICU admission after Birth						
Vaginal delivery	4155	5.68	1738	7.28	-	-
Scheduled C-section	-	-	-	-	468	13.72
Emergency C-section	2849	16.32	1891	15.86	-	-

Table 4.3. Risk of emergency caesarean delivery associated with induction of labour (IOL) a) Method 1 (overall comparison) b) Method 2 (within-week comparison) in nulliparous and low-risk nulliparous term cohort with cephalic presentation (n=180,039 & n=130,867)

a) Method 1 (overall comparison)

	OR	95% CI	aOR***	95% CI	aOR**	95% CI	aOR*	95% CI
Nulliparous	**2.02**	**1.98-2.07**	**1.82**	**1.77-1.86**	**1.83**	**1.78-1.87**	**1.86**	**1.81-1.90**
Low-risk Nulliparous	**2.21**	**2.15-2.27**	**1.86**	**1.80-1.92**	**1.87**	**1.82-1.93**	**1.88**	**1.83-1.94**

***** Adjusted for maternal age, SES, marital status, LGA, infant sex, maternal asthma**
**** Adjusted for maternal age, SES, marital status, infant sex, maternal asthma**
*** Adjusted for maternal age, SES, marital status, infant sex, delivered hospital**

b) Method 2 (within-week comparison)

Nulliparous	OR	95% CI	aOR***	95% CI	aOR**	95% CI	aOR*	95% CI
37 weeks	1.79	1.64-1.95	**1.77**	**1.62-1.94**	**1.75**	**1.60-1.91**	**1.82**	**1.66-1.99**
38 weeks	2.05	1.93-2.18	**1.97**	**1.85-2.10**	**1.98**	**1.86-2.11**	**2.01**	**1.93-2.20**
39 weeks	2.11	2.01-2.21	**1.99**	**1.90-2.10**	**2.01**	**1.92-2.11**	**2.07**	**1.97-2.17**
40 weeks	2.05	1.97-2.14	**1.95**	**1.86-2.03**	**1.97**	**1.89-2.06**	**1.99**	**1.91-2.08**
41 weeks	1.50	1.43-1.57	**1.49**	**1.42-1.56**	**1.48**	**1.42-1.55**	**1.50**	**1.43-1.57**
42 weeks	1.55	1.19-2.02	**1.54**	**1.16-2.03**	**1.57**	**1.19-2.06**	**1.59**	**1.20-2.11**

Low-risk Nulliparous	OR	95% CI	aOR***	95% CI	aOR**	95% CI	aOR*	95% CI
37 weeks	1.97	1.74-2.23	**1.97**	**1.73-2.23**	**1.95**	**1.72-2.21**	**2.02**	**1.78-2.30**
38 weeks	2.25	2.06-2.46	**2.19**	**2.00-2.40**	**2.20**	**2.01-2.41**	**2.28**	**2.08-2.50**
39 weeks	2.29	2.14-2.46	**2.21**	**2.06-2.38**	**2.23**	**2.08-2.39**	**2.27**	**2.12-2.44**
40 weeks	2.14	2.02-2.26	**2.05**	**1.94-2.17**	**2.09**	**1.97-2.21**	**2.07**	**1.96-2.19**

41 weeks	1.50	1.43-1.58	**1.49**	**1.42-1.57**	**1.49**	**1.41-1.56**	**1.50**	**1.43-1.58**
42 weeks	1.54	1.16-2.04	**1.51**	**1.13-2.03**	**1.55**	**1.16-2.06**	**1.58**	**1.18-2.13**

***** Adjusted for maternal age, SES, marital status, LGA, infant sex, maternal asthma**
**** Adjusted for maternal age, SES, marital status, infant sex, maternal asthma**
*** Adjusted for maternal age, SES, marital status, infant sex, delivered hospital**

Table 4.4. Risk of emergency caesarean delivery associated with induction of labour (IOL) at a given gestational age compared with expectant management with a delivery at a later gestation in nulliparous women (All-above) a) nulliparous term cohort with cephalic presentation (n=180,039) b) low-risk nulliparous term cohort with cephalic presentation (n=130,867)

low-risk: pregnant women without gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia and premature rupture of membrane.

a)

Week	Induction of Labour		Expectant Management									
	N	Caesarean (%)	N	Caesarean (%)	OR	95% CI	aOR***	95% CI	aOR**	95% CI	aOR*	95% CI
37	5334	26.02	167629	23.92	**1.12**	**1.05-1.19**	1.06	0.99-1.13	1.06	0.99-1.13	1.09	1.02-1.16
38	8832	27.68	141138	24.7	**1.17**	**1.11-1.22**	**1.10**	**1.05-1.15**	**1.10**	**1.05-1.16**	**1.13**	**1.08-1.19**
39	12254	30.01	93245	26.99	**1.16**	**1.11-1.21**	**1.09**	**1.04-1.13**	**1.09**	**1.05-1.14**	**1.11**	**1.07-1.16**
40	13763	33.62	36116	33.1	1.02	0.98-1.07	0.99	0.95-1.03	0.99	0.95-1.04	0.99	0.96-1.04
41	20281	36.56	930	42.47	**0.78**	**0.68-0.89**	**0.76**	**0.66-0.87**	**0.77**	**0.68-0.89**	**0.79**	**0.69-0.92**

***** Adjusted for maternal age, SES, marital status, LGA, infant sex, maternal asthma**
**** Adjusted for maternal age, SES, marital status, infant sex, maternal asthma**
*** Adjusted for maternal age, SES, marital status, infant sex, delivered hospital**

b)

Week	Induction of Labour		Expectant Management									
	N	Caesarean (%)	N	Caesarean (%)	OR	95% CI	aOR***	95% CI	aOR**	95% CI	aOR*	95% CI
37	2250	25.87	124039	22.74	**1.19**	**1.08-1.30**	**1.16**	**1.05-1.28**	**1.14**	**1.04-1.26**	**1.19**	**1.08-1.31**
38	3518	26.92	107748	23.64	**1.19**	**1.10-1.28**	**1.15**	**1.07-1.25**	**1.15**	**1.06-1.24**	**1.18**	**1.09-1.27**
39	4769	30.34	74819	26.1	**1.23**	**1.16-1.32**	**1.18**	**1.10-1.26**	**1.18**	**1.11-1.26**	**1.20**	**1.12-1.28**
40	7491	33.47	31172	32.5	1.05	0.99-1.10	1.02	0.97-1.08	1.03	0.98-1.09	1.02	0.97-1.08
41	17396	35.95	831	42.84	**0.75**	**0.65-0.86**	**0.74**	**0.64-0.85**	**0.75**	**0.65-0.86**	**0.77**	**0.66-0.89**

***** Adjusted for maternal age, SES, marital status, LGA, infant sex, maternal asthma**
**** Adjusted for maternal age, SES, marital status, infant sex, maternal asthma**
*** Adjusted for maternal age, SES, marital status, infant sex, delivered hospital**

All-above induction gestation age: IOL at a specific gestation age was compared to expectantly managed pregnant women who delivered after that gestation by either spontaneously labour or induction of labour

Table 4.5. Risk of caesarean delivery associated with induction of labour (IOL) at a given gestational age compared with expectant management with a delivery at a later gestation in nulliparous women (At-or-above) a) nulliparous term cohort with cephalic presentation (n=180,039) b) low-risk nulliparous term cohort with cephalic presentation (n=130,867)

low-risk: pregnant women without gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia and premature rupture of membrane.

a)

Week	Induction of Labour		Expectant Management									
	N	Caesarean (%)	N	Caesarean (%)	OR	95% CI	aOR***	95% CI	aOR**	95% CI	aOR*	95% CI
37	5334	26.02	174182	23.69	**1.13**	**1.07-1.21**	**1.07**	**1.01-1.14**	**1.07**	**1.01-1.40**	**1.11**	**1.04-1.18**
38	8832	27.68	157589	23.89	**1.22**	**1.16-1.28**	**1.15**	**1.09-1.20**	**1.15**	**1.10-1.21**	**1.18**	**1.13-1.24**
39	12254	30.01	127468	24.47	**1.32**	**1.27-1.38**	**1.23**	**1.18-1.29**	**1.24**	**1.19-1.30**	**1.27**	**1.22-1.33**
40	13763	33.62	78993	26.00	**1.44**	**1.39-1.50**	**1.37**	**1.32-1.43**	**1.39**	**1.34-1.44**	**1.40**	**1.34-1.45**
41	20281	36.56	15585	29.12	**1.40**	**1.34-1.47**	**1.38**	**1.32-1.45**	**1.39**	**1.33-1.45**	**1.40**	**1.34-1.47**

***** Adjusted for maternal age, SES, marital status, LGA, infant sex, maternal asthma**
**** Adjusted for maternal age, SES, marital status, infant sex, maternal asthma**
*** Adjusted for maternal age, SES, marital status, infant sex, delivered hospital**

b)

Week	Induction of Labour		Expectant Management									
	N	Caesarean (%)	N	Caesarean (%)	OR	95% CI	aOR***	95% CI	aOR**	95% CI	aOR*	95% CI
37	2250	25.87	128198	22.54	1.20	1.09-1.32	**1.17**	**1.06-1.29**	**1.16**	**1.05-1.28**	**1.21**	**1.10-1.33**
38	3518	26.92	119496	22.81	1.25	1.16-1.34	**1.20**	**1.11-1.30**	**1.20**	**1.11-1.30**	**1.24**	**1.14-1.34**
39	4769	30.34	101703	23.62	1.41	1.32-1.50	**1.34**	**1.26-1.43**	**1.35**	**1.26-1.44**	**1.37**	**1.28-1.46**
40	7491	33.47	66881	25.45	1.47	1.40-1.55	**1.42**	**1.34-1.49**	**1.44**	**1.37-1.52**	**1.43**	**1.36-1.51**
41	17396	35.95	13534	28.66	1.40	1.33-1.47	**1.37**	**1.31-1.44**	**1.38**	**1.31-1.45**	**1.40**	**1.33-1.47**

Week	Induction of Labour		Expectant Management							
	N	Caesarea (%)	N	Caesarea (%)	OR	95% CI	aOR**	95% CI	aOR*	95% CI
37	2250	25.87	128198	22.54	1.20	1.09-1.32	**1.17**	**1.06-1.29**	**1.16**	**1.05-1.28**
38	3518	26.92	119496	22.81	1.25	1.16-1.34	**1.20**	**1.11-1.30**	**1.20**	**1.11-1.30**
39	4769	30.34	101703	23.62	1.41	1.32-1.50	**1.34**	**1.26-1.43**	**1.35**	**1.26-1.44**
40	7491	33.47	66881	25.45	1.47	1.40-1.55	**1.42**	**1.34-1.49**	**1.44**	**1.37-1.52**
41	17396	35.95	13534	28.66	1.40	1.33-1.47	**1.37**	**1.31-1.44**	**1.38**	**1.31-1.45**

***** Adjusted for maternal age, SES, marital status, LGA, infant sex, maternal asthma**
**** Adjusted for maternal age, SES, marital status, infant sex, maternal asthma**
*** Adjusted for maternal age, SES, marital status, infant sex, delivered hospital**

At-or-above induction gestation age: IOL at a specific gestation age was compared to expectantly managed pregnant women who delivered at the same gestation by spontaneous labor or after that gestation by either spontaneously labour or induction of labour

Appendix 4.1. Definition and source of study variables (Alberta pregnancy birth cohort)

Study variables	Operational definitions	Data source
Exposure variable: 1.Induction of Labour (IOL)	Induction of Labour (surgical/ medical)	IOL was determined from the inpatient hospitalization data by CCI procedure codes. IOL code: 5AC30
Outcome variables: 1. CS in labour (Emergency CS)	Mode of delivery was the method used to deliver infants which can be either 1. Vaginal 2. Scheduled CS 3. Emergency CS 4. Vaginal birth after CS (VBAC) - Emergency CS was the method used to deliver infants in emergency situation due to maternal / fetal distress	Mode of delivery was determined from inpatient hospitalization data by CCI procedure codes & ICD-10-CA codes. CS was determined from the inpatient hospitalization data by CCI procedure codes. CS code: 5MD60 CS deliveries with ICD-10-CA labour codes were classified as emergency CS and without ICD-10-CA, labour codes were classified as scheduled CS). Labour codes: "O32101","O33001","O33101","O33201", "O33301","O33401","O33501","O33601", "O33701","O33801","O33901", "O4201","O4202","O4209", "O4211","O4212","O4219","O7110", "O7111","O7118", "O750","O751","O752","O753", "O757","O601","O602", "O80","O81","O61","O62","O63", "O64","O65","O66","O68","O69","O70") Repeat CS delivery was determined from the ICD-10-CA codes: VBAC codes: "O75701", "O75709"
Covariates: 1. Maternal Age	Maternal Age at the time of delivery	Maternal Age was determined from Alberta pregnancy birth cohort
2. Birth weight	The weight of an infant at birth. [<=4kg:normal & >4kg: high]	Birth weight was determined from Alberta pregnancy birth cohort

3. Gestation Age	Gestation age to determine Term or Preterm [>= 37 weeks: term and <37 weeks: preterm)	Gestational age was determined from Alberta pregnancy birth cohort
4. Infant Sex	Sex of the Newborn	Infant Sex was determined from Alberta pregnancy birth cohort
5. Birth hospitalization	Newborn admission to the hospital immediately after delivery	Newborn birth hospitalization was determined from inpatient hospitalization data (service code) Hospitalization service code: "51"
6. Length of stay in hospital	Infant duration of stay in the hospital	Infant length of stay in the hospital was computed from inpatient hospitalization data
7. NICU admission	Newborn admission to NICU	Newborn admission to NICU was determined from inpatient hospitalization data (care admit unit code) NICU admission: "50"
8. Gestational diabetes/ Hypertension/ Pre-eclampsia/ Eclampsia/ PROM/ Placenta previa/ Placenta abruption	Women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy/ high blood pressure during pregnancy/ high blood pressure during pregnancy with complication	Gestational diabetes/ Hypertension/ Pre-eclampsia/ Eclampsia was determined from inpatient hospitalization data by ICD-10-CA codes. Gestational diabetes codes: O24801", "O24803", "O24809", "O24501", "O24503", "O24509", "O24601", "O24603", "O24609", "O24701", "O24703", "O24709 Pre-eclampsia codes: "O111","O112","O113","O114","O119"," O11001", "O11003","O11009","O14001","O14101", "O14201","O14901","O14003", "O14103", "O14203","O14903","O14009","O14109", "O14209","O14909","O1400","O1402", "O1403", "O1404","O1410", "O1412", "O1413", "O1414", "O1420", "O1422", "O1423", "O1424", "O1490", "O1492", "O1493", "O1494" Eclampsia codes: "O15001", "O15003", "O15101", "O15103", "O15909" PROM codes: "O42021", "O42023", "O42029", "O42091", "O42093", "O42099", "O42121",

		"O42123", "O42129", "O42191", "O42193", "O42199", "O42203", "O42209", "O42901", "O42903", "O42909", "O42011", "O42013", "O42019", "O42111", "O42113", "O42199" Placenta previa codes: "O4400","O4401", "O4402", "O4403","O4410", "O4411","O4412","O4413","O4420", "O4421", "O4422", "O4423", "O4430","O4431", "O4432","O4433","O4440","O4441","O4442", "O4443","O4450","O4451","O4452", "O4453", "P020","O44001","O44003", "O44009", "O44101","O44103", "O44109" Placenta abruption codes: "O45001","O45003", "O45009", "O45011", "O45013", "O45019", "O45081", "O45083", "O45089", "O45091", "O45093", "O45099", "O45801", "O45803", "O45809", "O45901", "O45903", "O45909"
9. Maternal intrapartum outcomes (Postpartum haemorrhage, 3rd and 4th degree perineal laceration)	Maternal intrapartum complications	Postpartum haemorrhage (PPH) and 3rd and 4th degree perineal tear were determined by ICD-10-CA codes. PPH codes: "O72002", "O72004", "O72009", "O72102","O72104", "O72109","O72202","O72204","O72209" 3rd and 4th degree perineal tear codes: "O70201", "O70204", "O70209", "O70301","O70304", "O70309"
10. Instrumental delivery	Type of instruments used to deliver infants which can be either 1. Forceps 2. Vacuum	Type of instruments will be determined from inpatient hospitalization data by CCI procedure codes. Forceps code: 5MD53 Vacuum code: 5MD54 Forceps and Vacuum codes: 5MD55
11. Maternal ICU admission	Maternal admission to ICU after delivery	Maternal admission to ICU after delivery was determined from inpatient hospitalization data (care admit unit code) ICU admission: “10”, “20”, “30”, “80”
12. Socioeconomic status	Socioeconomic status of the parents at the time of delivery	Socioeconomic status was determined from Alberta population registry
13. Maternal asthma	Asthma status of mother	Mother history of asthma was determined from inpatient hospitalization data by ICD-10-CA codes. Maternal asthma:

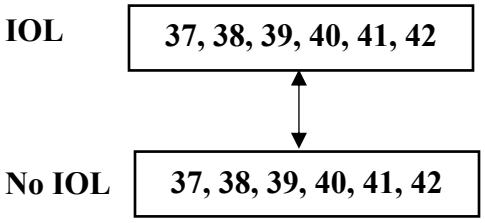
		"J4500", "J4501","J4510", "J4511", "J4580","J4581","J4590","J4591", "J450", "J451", "J458", "J459", "J45"
14. CPD (Cephalopelvic disproportion)	Cephalopelvic dispropotion	CPD will be determined from inpatient hospitalization data by ICD-10-CA codes. CPD code: O33.901

CCI: Canadian Classification of Health Interventions, 2012, Volume 4

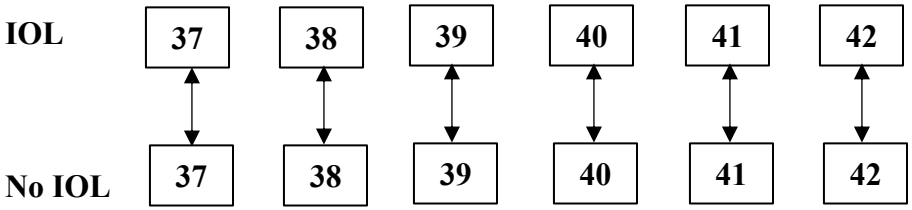
ICD-10-CA: International Classification of Diseases-10-Canada

Appendix 4.2. Comparison groups for induction of labour (IOL) a) Method 1 (Overall comparison) b) Method 2 (Within-week comparison) c) Method 3 (All-above) d) Method 4 (At-or-above)

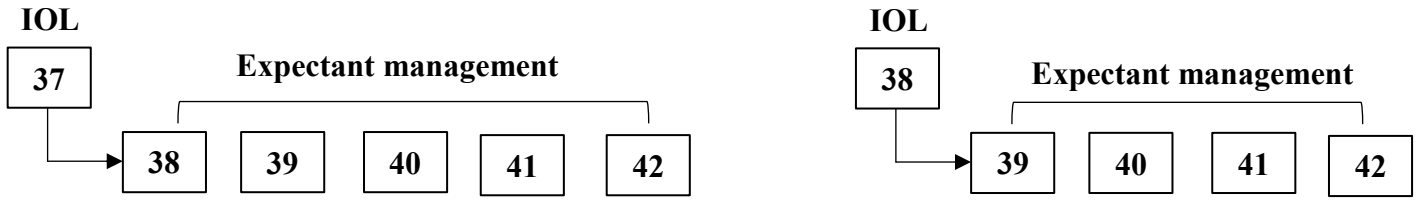
a) Method 1 (Overall comparison)



b) Method 2 (Within-week comparison)

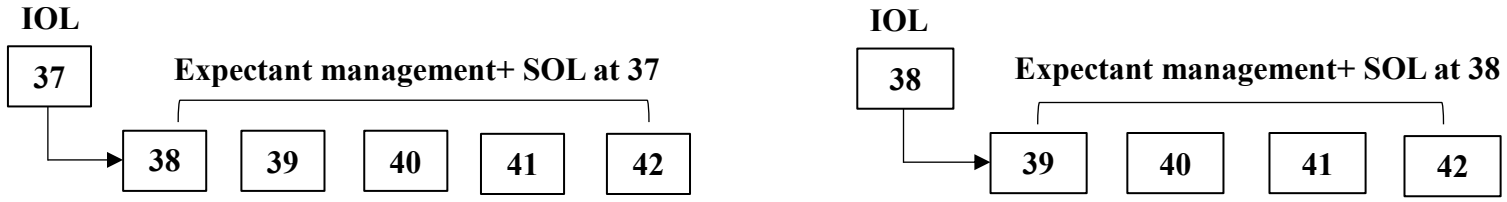


c) Method 3 (All-above)



All-above: IOL at a given gestational age compared with expectantly managed pregnant women who delivered after that gestation by either spontaneously labour or induction of labour

d) Method 4 (At-or-above)



At-or-above: IOL at a given gestational age compared with expectantly managed pregnant women who delivered at the same gestation by spontaneous labor or after that gestation by either spontaneously labour or induction of labour

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Chapter 5. A cost-utility analysis of labour induction at different gestation weeks in nulliparous women in Alberta

Mon Tun[1], Piush Mandhane[1], Padma Kaul[2, 3, 4] Radha Chari[5], Mike Paulden[2]

[1]Department of Pediatrics, University of Alberta, Edmonton AB.

[2]School of Public Health, University of Alberta, Edmonton AB.

[3]Faculty of Medicine, University of Alberta, Edmonton AB.

[4]Canadian VIGOUR Centre, University of Alberta, Edmonton AB.

[5]Department of Obstetrics and Gynaecology, University of Alberta, Edmonton AB.

Abstract:

Aim: To determine the most cost-effective gestation week to first offer induction of labour in nulliparous pregnant women with singleton pregnancy.

Methods: A decision tree model was used to determine the impact on public health care costs and child health outcomes associated with early labour induction, as an alternative to expectant management, between 37 and 42 weeks gestation. The main outcome measures were quality-adjusted life years (QALYs) and expected costs to the public health care system. These outcomes were used to estimate the expected net health benefit (NHB) associated with induction at each gestation week at a willingness-to-pay of CAD $50,000 per QALY. Estimates of expected NHB were then used to identify the gestation week at which early labour induction is most cost-effective. The analysis was conducted from the Alberta public health payer perspective and adopted a 1.5% discount rate and lifetime horizon, in accordance with current Canadian guidelines.

Data: Effectiveness parameters were informed by a 10-year population-based Alberta pregnancy birth cohort of 438,659 nulliparous pregnant women (>=37 weeks gestation) with singleton pregnancy in cephalic presentation. Hospital admission costs for labour induction and delivery were obtained from the Canadian Institutes for Health Information (CIHI). Health utility parameters were informed by literature estimates.

Results: Labour induction at 41 weeks provided the most expected NHB, followed by induction at 40 or 39 weeks. Accounting for parameter uncertainty, induction at 41 weeks had a 56% chance of being cost-effective, whereas induction at 39 weeks and 40 weeks had 27% and 14% chance of being cost-effective, respectively.

Conclusion: Elective labour induction is most cost-effective at 41 weeks gestation, with earlier or later induction appearing less cost-effective. Nevertheless, women should be provided with up-to-date information for an informed choice and induction should be a shared decision between the clinicians and the expectant mothers.

5.1 Background and Introduction

Induction of labour (IOL), a common obstetric intervention in childbirth, is recommended when the benefits to the mother or baby of an earlier planned birth outweigh the risks of induction and continuing the pregnancy (1). Induction of labour is defined as the artificial initiation of labour (1); the alternative is expectant management (EM) of the pregnancy where spontaneous onset of labour (SOL) is awaited. IOL should be considered when the vaginal delivery mode would be the most appropriate birth mode (2). While some indications for IOL such as premature rupture of membrane, preeclampsia, and gestational diabetes are supported by a high level of evidence to reduce the risk of stillbirth, maternal morbidity and mortality, others are not (3). Globally, IOL has become an increasingly common practice over recent decades: one in four pregnant women undergo IOL, with significant variation by country (4,5). Post-term pregnancy is associated with increased risk of placenta insufficiency, fetal distress and stillbirth (6). Many international guidelines and Society of Obstetricians and Gynaecologists of Canada (SOGC) recommend to offer induction of labour (IOL) between 41 and 42 weeks of gestation (7-10). In Canada, the proportion of women who undergo IOL has steadily increased, from 12.9% in 1992 to 21.8% in 2005 (11); in Alberta, this proportion had increased to 29.5% by 2013 (12). IOL increases pre-delivery hospital stay and labour time, and increases costs by 17% (13,14). One recent report from the ARRIVE trial showed that IOL at 39 weeks resulted in fewer antenatal visits and did not incur greater health care resource utilization when compared to EM (15).

Although there have been inconsistent findings of an association between IOL and cesarean section (CS) in observational studies (16-20), randomized controlled trials and systematic reviews have found that IOL decreases the risk of CS when compared to expectant management (EM) (21-24). Nevertheless, IOL has an associated cost, raising the question of whether IOL is cost-effective compared to EM. Kaimal et al (2011) found that IOL at 41 weeks was “cost-effective”, while Hersh et al. (2019) found that IOL at 39 weeks was “marginally cost-effective”; in both studies, IOL was found to improve health outcomes but increase costs when compared to EM (25,26). Both studies were comparing IOL at 39 weeks (25) and 41 weeks (26) to EM. The findings from each of these studies may not be generalizable to IOL at different gestational ages. To our knowledge, this is the first study to consider the cost-effectiveness of IOL at different gestational weeks.

5.2 Methods

A decision-tree analytic model was constructed in Microsoft Excel to compare IOL to EM at each gestation week after reaching early term (37 weeks). Six strategies were evaluated, under which IOL was scheduled at 37, 38, 39, 40, 41 or 42 weeks, respectively **(Table 5.1)**. Under the first of these strategies, all pregnant women were assumed to immediately undergo IOL at 37 weeks. For all other strategies, pregnant women were assumed to receive EM from 37 weeks while SOL was awaited; IOL was then performed at the scheduled week only for those women who did not experience SOL prior to this time. The latest at which IOL was scheduled under any strategy was 42 weeks, such that no women would continue to receive EM beyond this time if they had not previously experienced SOL.

For each strategy, if IOL was successful then the pregnant woman was assumed to deliver vaginally; however, if IOL failed then the pregnant woman was assumed to undergo emergency CS. **Figure 5.1** shows a simplified schematic of the decision tree model structure for IOL at different gestation weeks after reaching early term. The analysis was performed from a public health payer perspective, accounting for medical costs to the Alberta healthcare system (e.g. hospitalization costs with IOL and CS). The time horizon was lifetime of the neonate. Costs and outcomes were discounted at 1.5% per annum, in line with Canadian guidelines.(27)

The probability estimates for the model are summarized in **Table 5.2**. We obtained information regarding the probability of IOL at different gestation weeks, and the associated CS and health outcomes in neonates, from the Alberta birth cohort data set. This is a ten-year retrospective cohort of all term, singleton deliveries in Alberta from 2005-2014. The probabilities of stillbirth by gestation week were obtained from a systematic review and meta-analysis (28). Costing data for labour induction and different birth modes were obtained from Alberta Health (AH) 'Case Mix Group' health cost data (29), which includes all Alberta residents eligible for publicly funded healthcare. Alberta cost data is rigorously validated in accordance with provincial and national guidelines, ensuring high quality data. All costs were expressed in 2018 Canadian dollars and inflated where appropriate using the consumer price index (CPI) (30). Health state utility values at birth were obtained from the literature, and utilities for subsequent years were obtained from the Alberta PROMs and EQ-5D Research and Support Unit (APESRU) (31). The

utility of a stillbirth and neonatal death from the neonatal perspective was zero, by definition. The neonatal utility of NICU admission was obtained from Tan et al (32) and applied for the first 12 weeks post-delivery. The differences in utility between vaginal and CS delivery were applied from 12 weeks until 1 year of age, after which utilities were assumed to return to perfect health. Outcomes were expressed in quality-adjusted life-years (QALYs) gained from the neonatal perspective only, and calculated by multiplying the utility associated with each health state with time spent in the respective state (33).

The six strategies were compared on the basis of population 'net health benefit' (NHB), a measure that takes into account the health outcomes associated with each strategy (QALYs gained), the cost of each strategy, and the expected health opportunity costs (QALYs forgone) associated with these costs (34). Estimating these health opportunity costs requires specification of a willingness-to-pay (WTP) threshold. The most cost-effective strategy was defined as that providing the greatest NHB, based on a conventional WTP threshold of CAD $50,000 per QALY (35). Different WTP thresholds were considered in sensitivity analysis. Incremental cost-effectiveness ratio (ICERs) were also calculated sequentially and reported for each strategy (36).

Parameter uncertainty was accounted for using probabilistic analysis (100,000 Monte Carlo simulations). Probability and utility parameters were assigned beta distributions, while cost parameters were assigned gamma distributions. This allowed for 95% credible intervals to be reported around the NHB for each strategy, as well as estimation of the probability that each strategy is cost-effective at different WTP thresholds. The probabilities of the six strategies being cost-effective were calculated for WTP thresholds from zero to CAD $100,000 per QALY, and plotted using cost-effectiveness acceptability curves (CEACs). Additionally, expected value of perfect information (EVPI) analysis was conducted to estimate the cost-effectiveness of further research. EVPI accounts for the uncertainty surrounding decisions and provides a means for assessing research priorities in a fund-limited research environment (37). Finally, we conducted probabilistic one-way sensitivity analysis **(Supplementary Figure 5.1)** in the lifetime model (38).

5.3 Results

Our model suggests that IOL at 41 weeks resulted in the most NHB, followed by IOL at 40 weeks and 39 weeks. Labour induction at 37 weeks incurred the most cost, with a decreasing cost trend from 37 to 42 weeks. Labour induction at 39 weeks generated slightly higher QALYs. At a WTP threshold of CAD $50,000, IOL at 41 weeks had the highest probability of being cost-effective (56%), followed by IOL at 39 weeks (27%) and 40 weeks (14%). We found that IOL at 37 weeks showed the least NHB when compared with other strategies **(Table 5.3**).

Figure 5.2 shows the costs and QALYs associated with all six strategies. Induction of labour at 37 weeks incurred the most cost, mainly driven by the resource utilization from emergency CS resulted from labour induction. The strategy of IOL at 40 weeks was associated with the most QALYs gained. Two strategies, IOL at 37 and 38 weeks, were dominated by other strategies **(Table 5.4)**.

The results from the probabilistic analysis are presented in **Table 5.3** and **Figure 5.3**. At a threshold of CAD $50,000, IOL at 41 weeks has a 56% probability of being cost-effective. The EVPI results are shown in **(Supplementary Figure 5.2)**. At a WTP threshold of CAD $50,000 per QALY, the EVPI is CAD $446 per patient.

The 11 variables that resulted the greatest change in the probabilistic one-way sensitivity analysis are shown in **(Supplementary Fig 5.1).** The optimal strategy to offer IOL is highly sensitive to two parameters: cost of EMCS from IOL and cost of EMCS from SOL **(Supplementary Fig 5.1 & Supplementary Table 5.2)**. When varying the cost of EMCS from IOL, offering IOL at 40 weeks or 39 weeks became the most cost-effective strategy at the 3rd decile and at the 2nd and 1st deciles, respectively. When varying the cost of EMCS from SOL, offering IOL at 40 weeks or 39 weeks became the most cost-effective strategy at the 7th decile and at the 8th and 9th deciles, respectively. Varying the other input parameters had no influence on the optimal strategy.

5.4 Discussion

We found that the strategy of offering nulliparous women IOL at 41 weeks gestation is cost-effective, with the highest expected NHB. It also has the highest probability of being cost-

effective, accounting for uncertainty. This finding is in-line with the current recommendation from the SOGC to offer labour induction at 41 weeks. Nevertheless, the question of whether or not to offer IOL before reaching 41 weeks in nulliparous women remains widely debated.

We utilized the ten-year Alberta nulliparous cohort and the provincial utility and cost data to perform a cost-utility analysis. This is the first cost-utility analysis of comparing IOL at different gestation weeks after reaching term (37 weeks), and the time horizon was lifetime for the neonates. This study incorporated the IOL associated stillbirths of different gestational age. Our model integrates the utility of NICU admission of neonates and Alberta patient reported outcome measures (PROMS) and EQ-5D Research and Support Unit (APERSU) health utility for the lifetime. Many parameters were informed by provincial birth cohort and cost data and when data were not available, we obtained from the published literature. The probabilistic sensitivity analysis incorporates the uncertainty to determine how much if affects the overall results. The strategies of offering IOL at early-term (37-38 weeks) were dominated by other strategies. The findings were generalizable to the Albertans, as the cost and clinical parameters were mostly based on Alberta birth cohort data.

The previous economic evaluations of IOL at 39 weeks showed different findings when compared to expectant management in other populations. The study from Walker et al (2017) showed the results of IOL at 39 weeks in the advanced aged pregnant women would save money; however, the strategy did not prevent stillbirth (39). The study was conducted alongside a randomized controlled trial and the follow-up was only for 4 weeks. In a recent study from the United States, it was shown that the strategy of IOL at 39 weeks in low-risk nulliparous women generated better outcomes with greater costs, with an additional healthcare spending of 2 billion dollars per year (25). The study also pointed out that the IOL is a medical intervention and the decision should be shared between the pregnant woman and the healthcare provider. The delivery is a physiology process and one study showed that most expectant mothers prefer avoiding interventions unless medically indicated (40).

In a study published in 1992, Laupacis *et al*. suggested that decision thresholds for cost per QALY between $0 and $20,000 represented strong evidence for adoption; between $20,000 and $100,000 moderate evidence for adoption; and above $100,000 provided weak evidence for

adoption (41). In light of no formal Canadian benchmark, we assume that the WTP threshold we employed ($50,000) is acceptable for Canadian decision makers (35).

There are several limitations with our research. First, the gestation week utilized in our study cohort was in weeks and there could be a variation in the range of gestation weeks (± 1 week) due to the rounded value as well as the estimated gestational age obtained from the antenatal care. As with any cost-utility analysis, the reliability of our results depends on the strength of the probability, cost and utility inputs, which we took from our provincial cohort and from literature estimates. For example, we utilized the increased odds ratio of IOL association with CS, although randomized controlled trials and meta-analysis showing the reduced risk of IOL with CS (28,42). Likewise, the cost of stillbirth and neonatal deaths were obtained from a published study from the United States (25), whereas Canada has a different healthcare system. Due to the limited data, we assumed that the mortality rates of neonatal intensive care admission were the same between the neonates delivered at different gestation weeks. In addition, our model did not capture the full spectrum of neonatal outcomes associated with different birth modes. Despite these limitations, Monte Carlo simulations indicated that our model was robust even when inputs were varied significantly across plausible ranges. The transferability of our results is limited with regards to other countries, due to the healthcare reimbursement scheme, difference in labour induction practices and delivery mode decision-making. Canada has a publicly funded healthcare system and this result is from the public payer perspective.

This cost-utility analysis informs clinicians, policy makers and expectant mothers that early-term IOL at 41 weeks is the most cost-effective gestational weeks. The results from this study recommend not to offer IOL before reaching full-term (39-40 weeks).

5.5 Conclusion

Our study is the first to simultaneously compare the cost-effectiveness of IOL at different gestation weeks in Canada. The study findings suggest that IOL at 41 weeks is the most cost-effective strategy, and has a 56% chance of being cost-effective at WTP threshold of CAD $50,000. Incorporating the strategy of IOL before reaching 41 weeks into the current practice should be carefully evaluated, and the implications for healthcare resources should be considered. Nevertheless, it is important to provide the pregnant women with up-to-date

information for an informed choice to be made. Most importantly, IOL should be a shared decision between expectant mothers and their clinicians.

Table 5.1. Strategies considered in the cost-utility analysis

	37 weeks	38 weeks	39 weeks	40 weeks	41 weeks	42 weeks
Strategy 1	**IOL**					
Strategy 2	**EM**	**IOL**				
Strategy 3	**EM**	**EM**	**IOL**			
Strategy 4	**EM**	**EM**	**EM**	**IOL**		
Strategy 5	**EM**	**EM**	**EM**	**EM**	**IOL**	
Strategy 6	**EM**	**EM**	**EM**	**EM**	**EM**	**IOL**

IOL= induction of labour, EM= expectant management

37 weeks: 37 weeks and 0 days to 37 weeks and 6 days

38 weeks: 38 weeks and 0 days to 38 weeks and 6 days

39 weeks: 39 weeks and 0 days to 39 weeks and 6 days

40 weeks: 40 weeks and 0 days to 40 weeks and 6 days

41 weeks: 41 weeks and 0 days to 41 weeks and 6 days

42 weeks: 42 weeks and 0 days and beyond

Table 5.2. Decision-tree analytic model inputs for the cost-utility analysis of IOL at different gestation weeks compared with expectant management for nulliparous pregnant women

Variable	Value	SD	Source
Utilities (neonatal perspective)			
Utility of stillbirth	0	0	-
Utility of neonatal death	0	0	-
Utility of vaginal delivery	0.9960	0.00510	Caughey et al (2006)
Utility of cesarean section	0.9760	0.00610	Mrus et al (2000)
Utility for NICU admission, vaginal delivery (first 12 weeks)	0.7604	N/A	Tan et al (2010)
Utility of NICU admission, cesarean section (first 12 weeks)	0.7575	N/A	
Cost (CAD 2018)			
Cost of vaginal delivery with SOL	$1,033	$591	CMG 2018
Cost of vaginal delivery with IOL	$4,254	$834	CMG 2018
Cost of emergency CS delivery with IOL	$7,749	$3,602	CMG 2018
Cost of emergency CS delivery with SOL	$7,339	$3,359	CMG 2018
Cost of stillbirth	$12,592	$1,983	Hersh et al 2019 (21)
Cost of neonatal death	$136,825	$16,526	Hersh et al 2019 (21)
Cost of neonatal intensive care unit admission	$1,185	$839	Longo et al 2018
Probabilities			
Neonatal death without NICU admission (37-42 weeks)	0.0005	0.000031	Muglu et al (2019)
Neonatal death with NICU admission (37-42 weeks)	0.0355	0.009002	Simpson et al (2020)
<u>At 37 weeks</u>			
Stillbirth	0.0003	0.00001	Sinkey et al (2018)
Vaginal delivery with IOL	0.4509	0.00365	
Vaginal delivery with SOL	0.4383	0.00274	
NICU admission with IOL vaginal delivery	0.1163	0.00329	Alberta Birth Cohort
NICU admission with IOL emergency CS delivery	0.2203	0.00856	
NICU admission with SOL vaginal delivery	0.0728	0.00209	
NICU admission with SOL emergency CS delivery	0.1726	0.00540	
<u>At 38 weeks</u>			
Stillbirth	0.0003	0.00001	Sinkey et al (2018)
Vaginal delivery with IOL	0.4533	0.00271	
Vaginal delivery with SOL	0.4397	0.00169	Alberta Birth Cohort
NICU admission with IOL vaginal delivery	0.0641	0.00191	
NICU admission with IOL emergency CS delivery	0.1495	0.00585	
NICU admission with SOL vaginal delivery	0.0435	0.00102	
NICU admission with SOL emergency CS delivery	0.1308	0.00308	
<u>At 39 weeks</u>			
Stillbirth	0.0004	0.00001	Sinkey et al (2018)
Vaginal delivery with IOL	0.4480	0.00236	
Vaginal delivery with SOL	0.4548	0.00123	
NICU admission with IOL vaginal delivery	0.0467	0.0015	Alberta Birth Cohort

NICU admission with IOL emergency CS delivery	0.1223	0.00451	
NICU admission with SOL vaginal delivery	0.0354	0.00067	
NICU admission with SOL emergency CS delivery	0.1140	0.00246	
At 40 weeks			
Stillbirth	0.0005	0.00002	Sinkey et al (2018)
Vaginal delivery with IOL	0.4395	0.00232	
Vaginal delivery with SOL	0.4645	0.00118	
NICU admission with IOL vaginal delivery	0.0435	0.00140	
NICU admission with IOL emergency CS delivery	0.1230	0.00413	Alberta Birth Cohort
NICU admission with SOL vaginal delivery	0.0389	0.00066	
NICU admission with SOL emergency CS delivery	0.1325	0.00281	
At 41 weeks			
Stillbirth	0.0008	0.00003	Sinkey et al (2018)
Vaginal delivery with IOL	0.4278	0.00202	
Vaginal delivery with SOL	0.4456	0.00220	
NICU admission with IOL vaginal delivery	0.0409	0.00121	
NICU admission with IOL emergency CS delivery	0.1294	0.00337	Alberta Birth Cohort
NICU admission with SOL vaginal delivery	0.0435	0.00132	
NICU admission with SOL emergency CS delivery	0.1361	0.00428	
At 42 weeks			
Stillbirth	0.0013	0.00007	Sinkey et al (2018)
Vaginal delivery with IOL	0.4033	0.01268	
Vaginal delivery with SOL	-	-	
NICU admission with IOL vaginal delivery	0.0578	0.00922	
NICU admission with IOL emergency CS delivery	0.1574	0.01964	Alberta Birth Cohort
NICU admission with SOL vaginal delivery	-	-	
NICU admission with SOL emergency CS delivery	-	-	

Table 5.3. Expected Costs and QALYs of IOL at different gestation weeks (results from Probabilistic Sensitivity Analysis: base case analysis (1.5% discount rate) and scenario analysis (0% and 3% discount rate)

		Costs (CAD)	QALYs	NHB
PSA (1.5% Discount)	**37 weeks**	$7,274	42.518	42.372
	38 weeks	$6,797	42.611	42.475
	39 weeks	$6,419	42.634	42.506
	40 weeks	$5,877	42.633	42.515
	41 weeks	$5,283	42.625	**42.519**
	42 weeks	$5,121	42.606	42.503
PSA (0% Discount)	**37 weeks**	$7,313	71.711	71.565
	38 weeks	$6,833	71.866	71.729
	39 weeks	$6,448	71.905	71.776
	40 weeks	$5,893	71.902	**71.784**
	41 weeks	$5,284	71.889	71.783
	42 weeks	$5,118	71.857	71.755
PSA (3% Discount)	**37 weeks**	$7,311	28.438	28.292
	38 weeks	$6,830	28.501	28.364
	39 weeks	$6,441	28.517	28.388
	40 weeks	$5,879	28.516	28.398
	41 weeks	$5,264	28.511	**28.405**
	42 weeks	$5,095	28.498	28.396

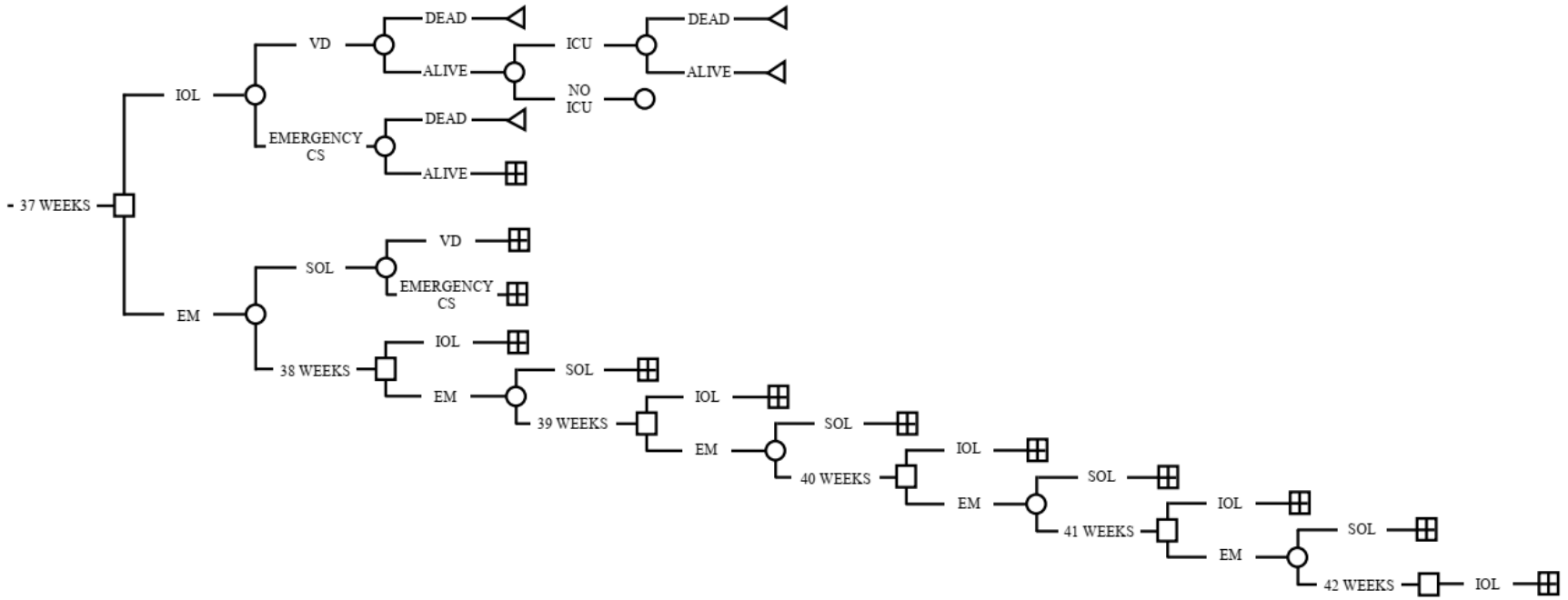
The NHB based on WTP of CAD $50,000, NHB= Net Health Benefit, QALYs= Quality-adjusted life years, PSA=Probabilistic sensitivity analysis

Table 5.4. Cost-effectiveness rankings for base case

Strategy	Cost (CAD)	Incremental Cost (CAD)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER (per QALYs)
42 weeks	$5,121	N/A	42.606	N/A	N/A
41 weeks	$5,283	$161	42.625	0.019	$8,593
40 weeks	$5,877	$594	42.633	0.008	$74,203
39 weeks	$6,419	$541	42.634	0.002	$327,525
38 weeks	$6,797	Dominated	42.611	Dominated	Dominated
37 weeks	$7,274	Dominated	42.518	Dominated	Dominated

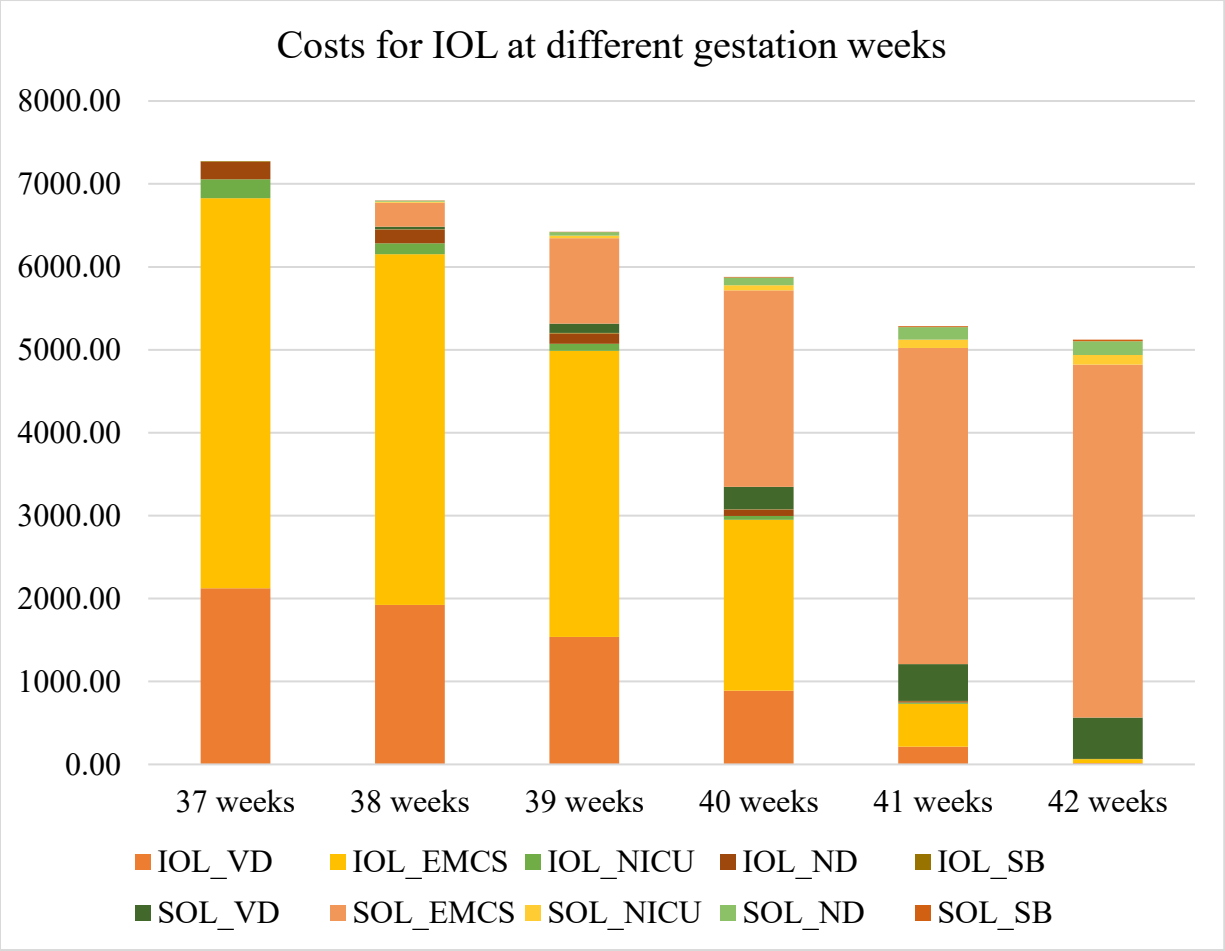
ICER= Incremental cost-effectiveness ratio

Figure 5.1. Decision-tree diagram



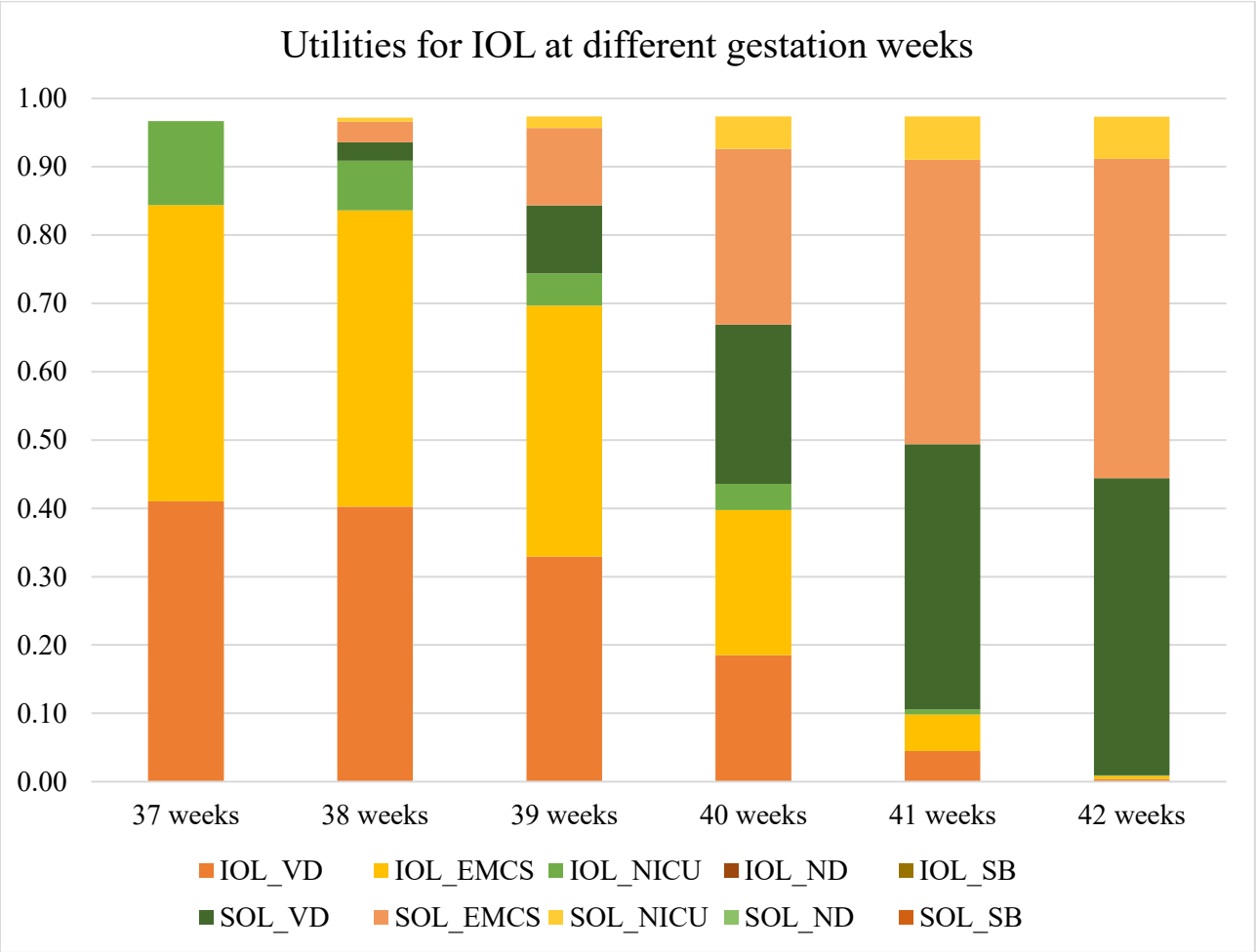
All branches not terminating in a triangle are collapsed to facilitate to display and are the same as branches already open

Figure 5.2 (a) Costs of IOL at different gestation weeks (Probabilistic Sensitivity Analysis)



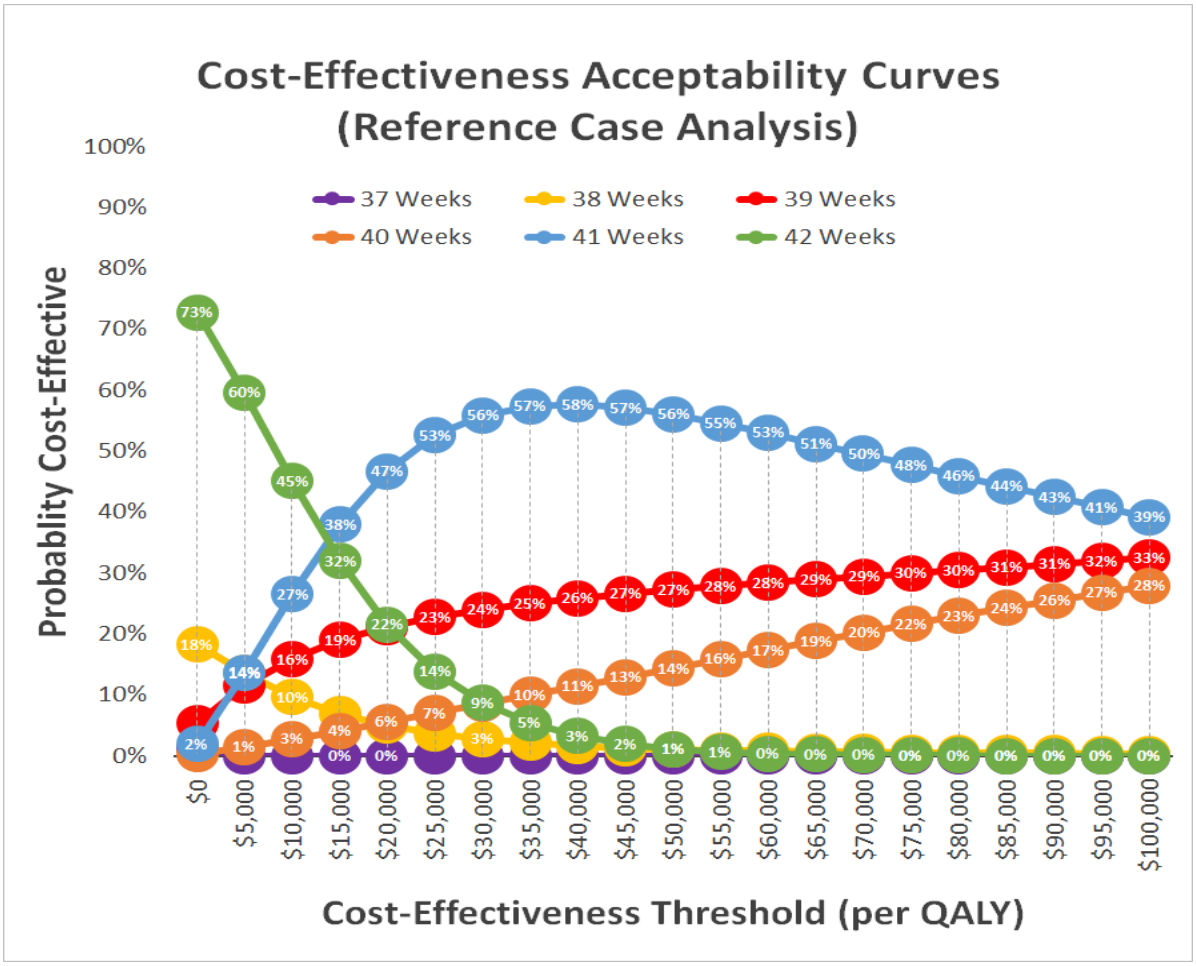
IOL= Induction of Labour, SOL= Spontaneous onset of Labour, VD= Vaginal delivery, EMCS= Emergency cesarean section, NICU= Neonatal ICU, ND= Neonatal death, SB= Stillbirth

Figure 5.2 (b) Utilities of IOL at different gestation weeks (Probabilistic Sensitivity Analysis)



IOL= Induction of Labour, SOL= Spontaneous onset of Labour, VD= Vaginal delivery, EMCS= Emergency cesarean section, NICU= Neonatal ICU, ND= Neonatal death, SB= Stillbirth

Figure 5.3. Cost-effectiveness Acceptability Curve of IOL at different gestation weeks



Supplementary Table 5.1. Parameters values for sensitivity analyses

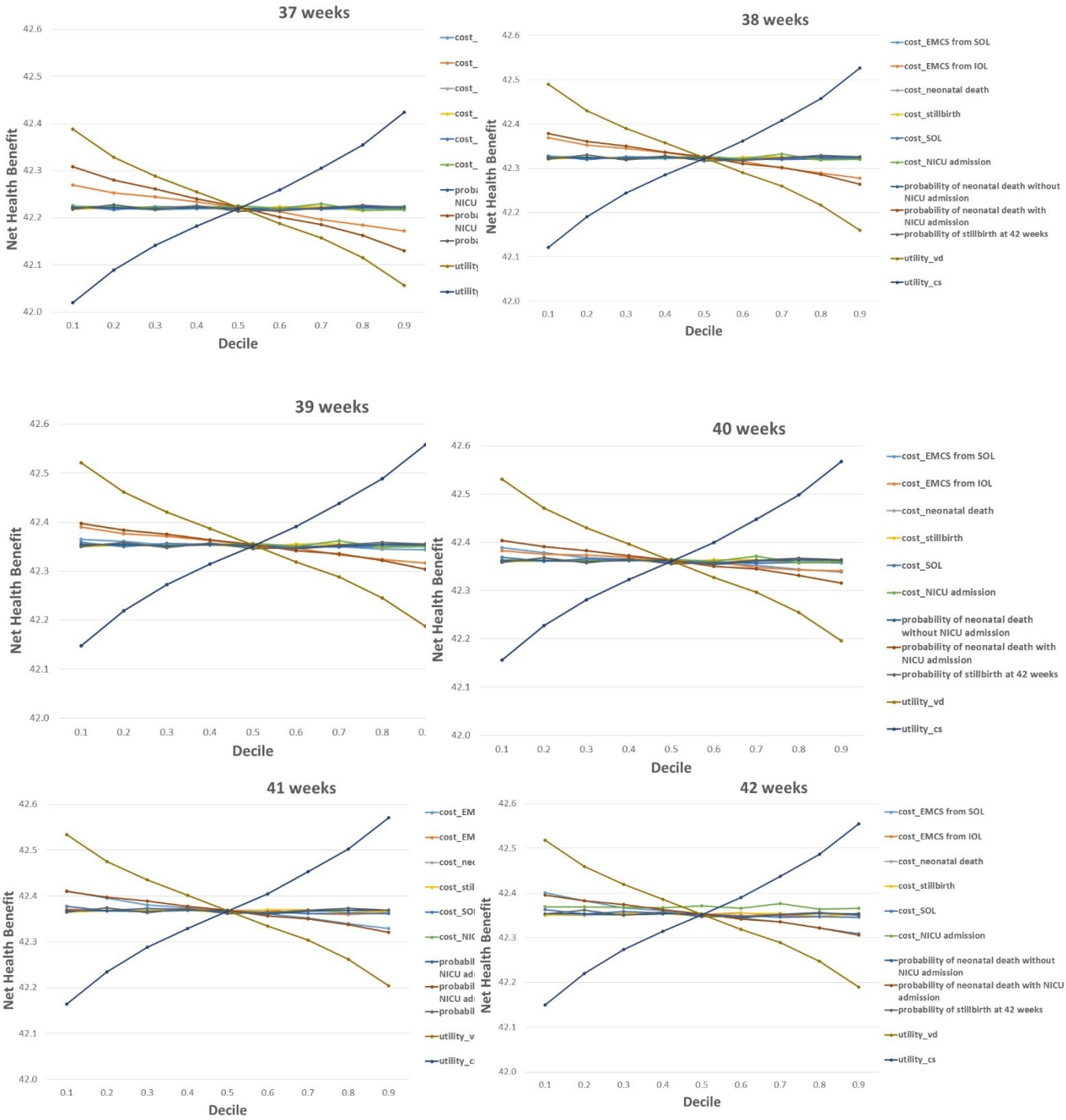
Variable	Base Case	Parameter Range	
		Lower 95%	Upper 95%
Cost (CAD 2018)			
Cost of vaginal delivery with SOL	$1,033	$217	$2,474
Cost of emergency CS delivery with IOL	$7,749	$2,377	$16,244
Cost of emergency CS delivery with SOL	$7,339	$2,300	$15,232
Cost of neonatal intensive care unit admission	$1,185	$142	$3,303
Probabilities			
At 37 weeks			
Vaginal delivery with IOL	0.4509	0.4438	0.4581
Vaginal delivery with SOL	0.4383	0.4329	0.4436
At 38 weeks			
Vaginal delivery with IOL	0.4533	0.4479	0.4586
Vaginal delivery with SOL	0.4397	0.4364	0.4431
At 39 weeks			
Vaginal delivery with IOL	0.4480	0.4433	0.4526
Vaginal delivery with SOL	0.4548	0.4523	0.4572
At 40 weeks			
Vaginal delivery with IOL	0.4395	0.4348	0.4526
Vaginal delivery with SOL	0.4645	0.4622	0.4668
At 41 weeks			
Vaginal delivery with IOL	0.4278	0.4238	0.4318
Vaginal delivery with SOL	0.4456	0.4412	0.4500
At 42 weeks			
Vaginal delivery with IOL	0.4033	0.3784	0.42383
Vaginal delivery with SOL	-	-	-

Supplementary Table 5.2. The optimal gestation weeks to offer IOL with highest NHB from probabilistic one-way sensitivity analysis

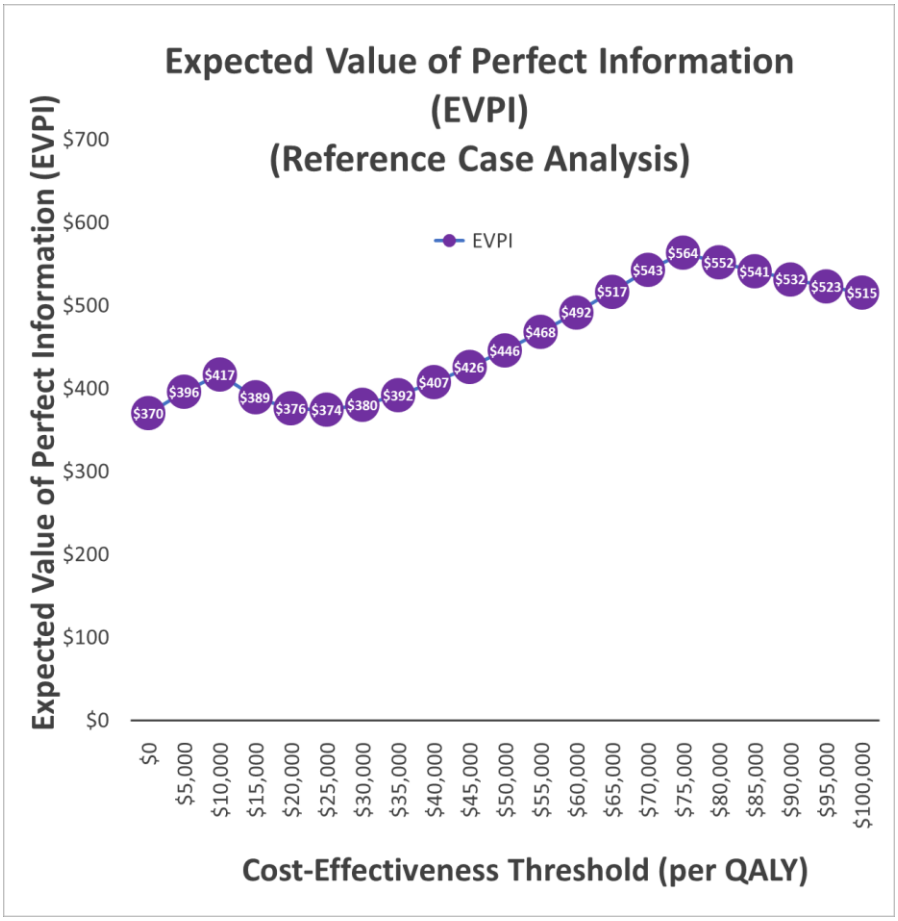
Strategy with highest NHB	**1st Decile**	**2nd Decile**	**3rd Decile**	**4th Decile**	**5th Decile**	**6th Decile**	**7th Decile**	**8th Decile**	**9th Decile**
Cost of EMCS from SOL	41	41	41	41	41	41	**40**	**39**	**39**
Cost of EMCS from IOL	**39**	**39**	**40**	41	41	41	41	41	41
Cost of neonatal death	41	41	41	41	41	41	41	41	41
Cost of stillbirth	41	41	41	41	41	41	41	41	41
Cost of SOL	41	41	41	41	41	41	41	41	41
Cost of NICU admission	41	41	41	41	41	41	41	41	41
Probability of neonatal death without NICU admission	41	41	41	41	41	41	41	41	41
Probability of neonatal death with NICU admission	41	41	41	41	41	41	41	41	41
Probability of stillbirth at 42 week	41	41	41	41	41	41	41	41	41
Utility of vaginal delivery	41	41	41	41	41	41	41	41	41
Utility of cesarean section	41	41	41	41	41	41	41	41	41

IOL= Induction of Labour, SOL= Spontaneous onset of Labour, EMCS= Emergency cesarean section, NICU= Neonatal ICU, NHB=net health benefit

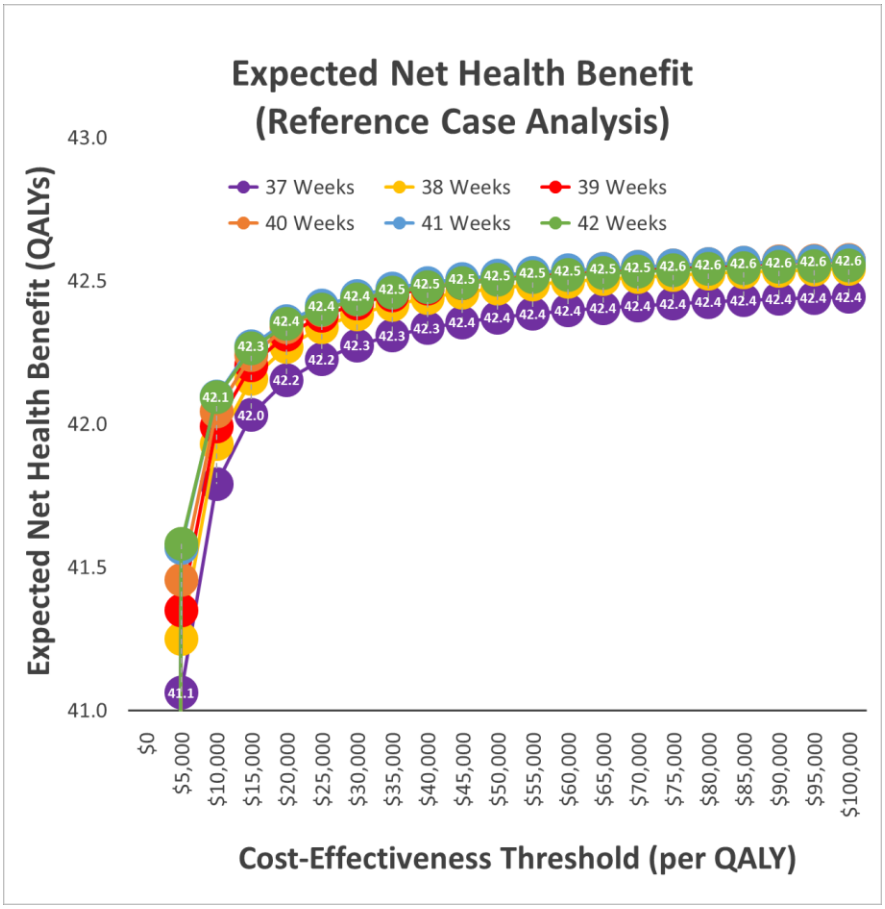
Supplementary Figure 5.1. Probabilistic one-way sensitivity analysis



Supplementary Figure 5.2. Expected Value of Perfect Information



Supplementary Figure 5.3. Expected Net Health Benefit



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Chapter 6. Summary and Future Directions

6.1 Summary of Findings

The rising CS rate remains a public health concern in the Canadian population. The overarching purpose of this thesis was to improve our understanding of clinical and economic burden of CS. The two main factors contributing to the rise in CS rates is an increase in the primary CS rate and a decrease in vaginal birth after CS (VBAC) as (1,2). CS risk prediction models incorporating intrapartum factors lacks the capability of utilization for counseling the expectant mother before labour. CS delivery is costly when compared to vaginal births (3-5) and a risk factor for increase health service utilization with gastroenteritis (6-8) and asthma (9-12),(13) in the children.

This thesis aimed to answer the questions regarding the clinical and economic burden of CS in term pregnancy cohorts. The four studies conducted concluded the following:

1. We identified six antenatal predictor factors for emergency CS delivery: maternal age, height, BMI, pregnancy-induced hypertension, antenatal depression and birth order of the infant.
2. We developed and validated an emergency CS prediction model that deliberately did not include intrapartum factors. The AUC for our final prediction model was 0.74 (0.72-0.77) in the training dataset and AUC of 0.77 (0.71-0.82) in the validation dataset. Our prediction model AUC was comparable to Janssen's model that included intrapartum factors (AUC=0.71) (14).
3. CS delivered offspring had a significant increase in emergency department visit and hospitalization with gastroenteritis. There is a significant increased risk for emergency room visit, but not hospitalizations, for asthma among CS born children.
4. IOL before reaching full-term (39 weeks) increased the risk of emergency CS when compared to expectant management.
5. IOL at 41 weeks is the most cost-effective strategy because it provides the most NHB at a willingness-to-pay threshold of $50,000 per QALY. To our knowledge, this is the first study conducting an economic evaluation of IOL at different gestation weeks in Canada.

We observed significant associations between CS delivery and increased risk of emergency room attendance and hospitalization with gastroenteritis and asthma in Albertan population. The findings provide new evidence of the adverse health outcomes of CS delivery on the infants. This is the first provincial-wide study on the effect of CS on the health service utilization in the children. In addition, this study highlighted the increased risk of emergency room visit with asthma and gastroenteritis and hospitalization with asthma in emergency CS delivered children. Studies have reported CS delivered babies are less likely to be breastfed (15,16) and formula-fed infants were more likely to be hospitalized with acute gastroenteritis for all types of delivery mode (17). Further studies are needed to find out the mediation effect of breastfeeding on disease development in the CS delivered children.

The relationship between IOL and CS delivery reported in this thesis provides evidence that IOL increased the risk of emergency CS when compared to expectant management if IOL was conducted between 37 to 39 weeks of gestation. In contrast, the risk of emergency CS was reduced if IOL was done at 41 weeks. The findings are consistent with the recommendations from international and SOGC guidelines to conduct routine IOL at 41 weeks without any indication to reduce a woman's chance of delivery by CS. In addition, we found that offering IOL at 41 weeks is the most cost-effective strategy as it provides the most NHB and with an ICER of $8,593 per QALY gained. This is the first provincial-based study in Canada comparing the IOL at different gestation weeks after reaching term, 37 weeks. Our study findings utilized the probability, health related quality of life, and the majority of the cost data from the Albertan population. Moreover, these study findings should be considered as recommendations to offer labour induction to nulliparous expectant mothers.

6.2 Strengths and Limitations

Strengths

This thesis has several strengths. First, we used data from the large population representative CHILD birth cohort for chapter 1. The participants from CHILD study were selected from four provinces across Canada; hence, it is considered representative of the Canadian general population. The emergency CS risk prediction model developed from the analysis of 2,836 low-risk pregnant women and the sample size utilized provides adequate statistical power. The data from CHILD cohort were collected prospectively with multiple checks ensuring the accuracy and overall integrity of the collected data. The large sample size allowed for consideration of a variety of potential confounders including sociodemographic factors. We were able to internally validate our emergency CS risk prediction model with the most routinely collected antenatal obstetric and non-obstetric factors and conduct a stratify analysis and build a separate emergency CS risk prediction model for nulliparous and multiparous.

Linked administrative health data and Alberta pregnancy ten-year birth cohort data was used for chapter 2, 3 and 4. The study samples help minimize the risk of selection bias. Alberta Health administrative data has routinely collected records on health services, frequency of health service utilization, diagnoses, medications and costs. The utilization of reliable and validated data from Alberta hospital registries provides the accurate assessment of emergency department visit or hospitalization with gastroenteritis or asthma.

As per Bradford Hill criteria for temporality, our study prospectively followed the study subjects in chapter 1 (emergency CS risk prediction) and 3 (the association of IOL and emergency CS risk), which is expected to be less subject to reporting bias as the antenatal risk factors and labour induction were collected before the delivery. Likewise, in chapter 2, the burden of healthcare service utilization with gastroenteritis and asthma were assessed after the infants were delivered. The longitudinal cohort design for chapter 1, 2 and 3 allowed for temporality between exposure and outcome. Consistent with other established studies, we observed the increased risk of asthma (18,19) and gastroenteritis (6-8) in CS delivered infants. Lastly, the cost-utility analysis incorporated the IOL associated stillbirths of different gestational ages and many model

probabilities were obtained from the provincial birth cohort and APERSU health utility for the lifetime was applied for the analysis and the uncertainty around all the parameters were reflected with the probabilistic sensitivity analysis of 10,000 simulations.

Limitations

However, this research study was not without limitations. Despite adjusted for broad set potential confounders, the possibility of residual confounding related to unmeasured potential confounders exists given the observational nature of all the studies. Firstly, the CHILD birth cohort and administrative health data provided the information on birth modes, sociodemographic and antenatal risk factors but both were not specifically designed for the purpose of the studies reported in the thesis. The data used for this thesis were secondary data from the CHILD birth cohort and administrative health data. This limits our ability to measure some important confounders of interest. For example, in administrative health data for the IOL association with CS delivery, reasons and indications for IOL was not captured. Likewise, information on prior history of CS, indication for CS, and weight gain during pregnancy were not available in the CHILD cohort. The assessment of maternal smoking status in CHILD cohort was based on self-report and may be subject to measurement error or bias. Lacking the specific clinical information on indication for IOL may result in our finding be subject to selection bias (chapter 4). The lack of specific clinical information may also confound the associations we observed in chapter 2 as those specific indications could affect the risk of development of asthma and gastroenteritis.

The emergency CS risk prediction model was based on low-risk pregnant women and may limit the generalizability to more heterogeneous and high-risk populations. The CHILD cohort excluded Aboriginal people living on reserves, institutional residents and people living in remote areas. The exclusion criteria used to develop the emergency CS risk prediction excluded women with higher risk of CS such as breech presentation, previous CS delivery and cephaolopelvic disproportion. However, in these high-risk groups, it would be necessary and beneficial to offer scheduled CS in order to reduce maternal and infant morbidity and mortality based on indication and without a prediction tool.

In the cost-utility analysis, we made the assumption that the mortality rates for neonatal intensive care admission were the same across the neonates delivered at different gestation weeks. Nonetheless, Monte Carlo simulations results indicated that our model was robust even when inputs were varied significantly across plausible ranges. Lastly, costs data were obtained from the provincial costing data and limited to single Canadian province and may not be generalizable to other health jurisdictions. Nonetheless, given the standardized case-mix group used, the findings from the study could be arguably to be generalizable across Canada.

6.3 Future direction

There are a number of potential areas of research topics for the improvement of antenatal care in Canada. Emergency CS was associated with higher risk of maternal and fetal morbidity and mortality when compared to scheduled CS (20) and emergency CS delivered infants had an increased risk of hospitalization or emergency department visit with asthma and gastroenteritis. Further studies externally validating the developed emergency CS risk prediction model for low-risk pregnant women are required. Incomplete information on previous CS in the CHILD birth cohort will be worth to explore the explanation of the variation in scheduled CS and the role of women's preferences and the various ways of making clinical decisions in different areas. Evaluating the role of comprehensive mental health programs and the effective interventions of health promotion may reduce the fear of a vaginal birth among those at low risk of emergency CS.

Models of antenatal care could be evaluated for an increase in IOL rate before reaching full-term in low-risk nulliparous women. Tailoring antenatal care and targeted investigations to understand the drivers of increase in IOL in nulliparous and low-risk nulliparous women may be helpful to reduce the CS rate and optimize the patient-centered outcomes. Early IOL has been shown to impact on cognitive outcome scores and school performance (21-23) in children. Monitoring the impact of offering IOL (before reaching 41 weeks) on healthcare system should be undertaken as well as on short and long-term outcomes of the women and the children. An economic evaluation of IOL incorporating long-term health outcomes in the children such as obesity and neurodevelopment could provide a more comprehensive assessment to inform decision making

in IOL. Women with a history of stillbirth are likely to utilize more health care services in the subsequent pregnancy (24) and future research incorporating the costs in the next pregnancy would be beneficial to widely assess the economic impact of stillbirth on the Canada healthcare system.

6.4 Conclusions

This research highlights the burden of CS associated health outcomes in CS delivered children on the Canadian healthcare system. This thesis also emphasized the findings of the impact of labour induction on CS rate in Alberta and the findings relevant to improvement of obstetric care. Early identification of those with increased risk of emergency CS is important and it will be helpful to provide counseling and refer them for a scheduled CS. Based on our findings, there may be benefit to assess antenatal depression among expectant mothers as part of routine antenatal screening. The low-risk expectant mothers should be fully informed of the unintended consequences of early IOL in order to make an informed decision-making.

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