EPIDEMIOLOGIC INVESTIGATION OF AN INCREASE IN POSTPARTUM HEMORRHAGE

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

July 2014

Abstract

Increases in postpartum hemorrhage have been reported in several high income countries between 1991 and 2004. The purpose of this thesis was to investigate possible causes of recent increases in postpartum hemorrhage.

Data sources included a population-based database of deliveries in British Columbia, Canada, between 2000 and 2009 (n=371,193), and a hospitalization database of deliveries in Canada (excluding Quebec) between 2003 and 2010 (n=2,193,425). Postpartum hemorrhage was defined as a blood loss of ≥500 mL for a vaginal delivery or ≥1000 mL for cesarean delivery or as a diagnosis noted by a health care provider. The influence of changes in risk factors on temporal trends in postpartum hemorrhage was studied using logistic regression.

There was a significant increase in atonic postpartum hemorrhage in British Columbia from 4.8% in 2001 to 6.3% in 2009 (34% increase, 95% confidence interval [CI] 26-42%). This increase was not be explained by changes in the maternal, fetal and obstetric factors studied, including previously understudied factors such as maternal pre-pregnancy body mass index and labour augmentation with oxytocin. In Canada, rates of postpartum hemorrhage increased from 5.1% in 2003 to 6.2% in 2010 (22% increase, 95% CI 20% to 25%), driven by an increase in atonic postpartum hemorrhage. Placenta accreta was responsible for only a negligible fraction of postpartum hemorrhage. Temporal trends in severe postpartum hemorrhage in Canada showed a similar pattern; postpartum hemorrhage with blood transfusion increased from 36.7 in 2003 to 50.4 per 10,000 deliveries in 2010, while

postpartum hemorrhage with hysterectomy increased from 4.9 to 5.8 per 10,000 deliveries over the same period.

The temporal increase in postpartum hemorrhage did not explain a concurrent rise in obstetric acute renal failure in Canada. The increase in obstetric acute renal failure was restricted to women with hypertensive disorders of pregnancy.

In summary, postpartum hemorrhage and severe postpartum hemorrhage continued to increase in Canada in recent years, and the maternal, fetal and obstetric factors studied did not explain the rise. Further studies are required to identify the role of other risk factors that may explain the observed increase in postpartum hemorrhage.

Preface

This thesis is divided into 7 Chapters. The introductory chapter reviews the literature on postpartum hemorrhage. It describes recent increases in postpartum hemorrhage, followed by a discussion of the mortality and morbidity associated with postpartum hemorhage, the etiology of postpartum hemorrhage, the factors associated with the increase in postpartum hemorrhage, and the recent changes in maternal and fetal characteristics and in obstetric practice patterns. It also presents the rationale for the thesis, describes the data sources and study population (including the validity of the data sources) and the dissertation objectives. Further details on the dissertation structure are provided at the end of the introductory chapter (Chapter 1).

Chapters 2 to 6 of the dissertation are each composed of manuscripts published in, under review or in preparation for peer-reviewed publication. I was responsible for developing the study proposal, conceptual frameworks and analytic approaches for all analyses, with assistance from my thesis supervisor, Dr. K.S. Joseph, my thesis committee members Dr. Jennifer Hutcheon and Dr. Robert Liston, and the research collaborators (listed for each manuscript), including Ms. Lily Lee, Dr. Michael Kramer, Dr. Shiliang Liu, Ms. Sharon Bartholomew, and Dr. Laura Magee. I conducted all analyses involving data from the British Columbia Perinatal Data Registry, and wrote all statistical analysis code (as these data are not routinely available to researchers) for analyses involving data from the Canadian Institutes for Health Research, with the assistance of Dr. Shiliang Liu and Dr. K.S. Joseph. I wrote the first draft of all manuscripts. My supervisor, thesis committee members and the research collaborators made contributions to the study design, analysis and interpretation of

data and revised each article for intellectual content. My contribution was >90% for each manuscript of the dissertation.

CHAPTER 2. A version of this chapter was published as: Mehrabadi A, Hutcheon JA, Lee L, Liston RM, Joseph KS. Trends in postpartum hemorrhage from 2000 to 2009: a population-based study. BMC Pregnancy Childbirth 2012;12:108.

CHAPTER 3. A version of this chapter was published as: Mehrabadi A, Hutcheon JA, Lee L, Kramer MS, Liston RM, Joseph KS. Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-based retrospective cohort study. BJOG 2013;120:853-62.

CHAPTER 4. A version of this chapter was published as: Mehrabadi A, Liu S, Bartholomew S, Hutcheon JA, Kramer MS, Liston RM, Joseph KS, for the Canadian Perinatal Surveillance System (Public Health Agency of Canada). Temporal trends in postpartum hemorrhage and severe postpartum hemorrhage in Canada from 2003 to 2010. J Obstet Gynaecol Can 2014; 36:21-33.

CHAPTER 5. A version of this chapter is in preparation for peer-reviewed publication: Mehrabadi A, Hutcheon JA, Liu S, Bartholomew S, Kramer MS, Liston RM, Joseph KS, for the Canadian Perinatal Surveillance System (Public Health Agency of Canada). Impact of placenta accreta on the incidence of postpartum hemorrhage and severe postpartum hemorrhage.

CHAPTER 6. A version of this chapter is under review: Mehrabadi A, Liu S, Bartholomew S, Hutcheon JA, Magee LA, Kramer MS, Liston RM, Joseph KS, for the Canadian Perinatal Surveillance System (Public Health Agency of Canada) Hypertensive disorders of pregnancy and the recent rise in obstetric acute renal failure. 2014.

All studies included in the dissertation received ethics approval from the University of British Columba, Children & Women's Health Centre of British Columbia Research Ethics Board. Certificate number #H11-00307 was issued for analyses using data from the British Columbia Perinatal Data Registry, and certificate #H12-02551 was issued for analyses using data from the Canadian Institute for Health Information Discharge Abstract Database.

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List of Abbreviations

ARF – Acute Renal Failure

BCPDR – British Columbia Perinatal Data Registry

BMI – Body Mass Index

CIHI – Canadian Institute for Health Information

CI – Confidence Interval

CCI – Canadian Classification of Health Interventions

CCP – Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures

DAD – Discharge Abstract Database

ICD-9 – International Classification of Diseases, Ninth Revision

ICD-10-CA – International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canadian version

mL – Milliliter

NSAID – Non-steroidal anti-inflammatory drug

PAF – Population Attributable Fraction

PPH – Postpartum Hemorrhage

PSBC – Perinatal Services British Columbia

Glossary

This glossary summarizes certain terms not otherwise defined within the thesis.

Chorionamnionitis: Inflammation of the chorion and the amnion (the membranes that surround the fetus).

Ecclampsia: Eclampsia, a life-threatening complication of pregnancy that results when a pregnant women with hypertension in pregnancy develops seizures or coma.

Grand multipara: A woman who has given birth to a viable fetus 5 or more times.

Macrosomia: Term used to describe a newborn with excessive birth weight (>=4,000 g or >=4,500 g).

Oxytocin: A synthetic hormone typically given by the intravenous (or intramuscular) route in order to initiate labour or cause the uterus to contract more strongly.

Parity: Refers to the number of viable births a woman has had. Nulliparous refers to a woman who has had 0 previous viable births, while multiparous refers to a woman who has had 1 or more previous viable births.

Placental abruption: One form of premature separation of the placenta from its attachment to the uterus before the fetus/infant is delivered. Placental abruption is typically associated with painful contractions unlike placenta previa which is associated with painless bleeding.

Placenta accreta: A serious complication that results when placental tissue grows too deeply into the uterus/womb, attaching to the muscle layer and resulting in difficulty in separation of the placenta from the uterus at delivery.

Placenta previa: A complication of pregnancy which leads to premature separation of the placenta from the uterus and which causes painless bleeding (see also placental abruption). Placenta previa occurs when the placenta implants in the lowest part of the uterus and covers all or part of the opening to the cervix.

Polyhydramnios: An abnormally large amount of amniotic fluid in the amniotic sac.

Pre-eclampsia: A complication of pregnancy which typically occurs after 20 weeks of gestation and is characterized by an increase in blood pressure (hypertension) and systemic complications (typically renal complications as evidenced by increased levels of protein in the urine (proteinuria)). May be accompanied by swelling of the feet (pedal edema), elevation in liver enzymes and in severe cases by visual problems, abdominal pain and seizures.

Rate: The probability that an event will occur in a given time frame. Used in this dissertation synonymously to the epidemiologic term risk.

Rate ratio: The ratio of the rate of disease among the exposed group to the rate of the disease among the unexposed group. Used in this dissertation synonymously to relative risk, i.e. does not imply a time element in the denominator.

Sheehan Syndrome: A rare condition that may occur in a woman who bleeds severely during childbirth. This complication is related to tissue death in the pituitary gland, which may cause the gland to lose its ability to function properly. The pituitary gland produces hormones that stimulate breast milk production, growth, reproductive function, the thyroid, and the adrenal glands.

Acknowledgements

This dissertation was made possible by the exceptional support and contribution of my thesis supervisor and committee members, our co-authors and the agencies that provided critical data access and support. I would like to express my sincerest gratitude to my supervisor Dr. K.S. Joseph for his outstanding guidance and mentorship in all aspects of this thesis; his unconditional encouragement and extensive experience were essential to this work. I would also like to thank Dr. K.S. Joseph for providing me with ongoing opportunities for knowledge translation through speaking opportunities, and ongoing training and education in many aspects of Maternal and Child Health and Perinatal Epidemiology that contributed a great deal to this work and to my overall understanding of the field. I am tremendously thankful to my thesis committee members, Dr. Jennifer Hutcheon for providing resources and direction in novel methods for regression modeling, including the use of restricted cubic splines and multiple imputation for missing data, as well as always being available for conversations about methodological challenges and other obstacles I encountered, and Dr. Robert Liston for his substantial support and wisdom on all clinical matters addressed in the thesis.

I would like to acknowledge Dr. K.S. Joseph, Dr. Robert Liston, Dr. Michael Kramer, and Dr. Shiliang Liu, Sharon Bartholemew, the Public Health Agency of Canada, and the International Postpartum Hemorrhage Collaborative Group for their essential work in identifying the problem of an increase in postpartum hemorrhage and the rise in obstetric acute renal failure in Canada. Thank you to the Public Health Agency of Canada, Dr.

Shiliang Liu and Sharon Bartholemew for access to the Canadian Institute for Health Information Data and their indispensable knowledge of the database, as well as important guidance in the analysis and interpretation of data. I am particularly thankful to Dr. Shiliang Liu for his tremendous patience in helping to troubleshoot the problems we encountered. I would like to recognize the support of Kim Williams and Perinatal Services British Columbia, and thank them for understanding that the rising rates of postpartum hemorrhage are an important clinical and population health concern and for facilitating access to the British Columbia data. The contribution of Lily Lee in the interpretation and understanding of the data in British Columbia has been essential, as has the assistance provided by all staff at Perinatal Services BC, particularly the direct assistance of Cathe Johnson, Terri Pacheco, Brooke Kinniburgh, Linda Lee, and Kenny Der. I would like to thank Dr. Michael Kramer for his important contribution as a co-author and for providing me with the experience of participating as a co-author on a related study on the rise in postpartum hemorrhage in the United States. I would also like to thank Dr. Laura Magee for her contribution as co-author and her critical input and clinical expertise on the topic of hypertensive disorders of pregnancy and obstetric acute renal failure.

This work was supported by a Canadian Institutes of Health Research Team grant in Severe Maternal Morbidity (MAH - 115445) and was carried out under the auspices of Perinatal Services BC and the Public Health Agency of Canada Canadian Perinatal Surveillance System.

Dedication

Dedicated to my true love J.C. and to baby Azarito

Chapter 1: Introduction

1.1 Background and problem statement

Reports indicate that postpartum hemorrhage has increased in Canada and elsewhere over the last two decades.[1] An initial report from Canada identified the problem as a temporal increase in rates of severe postpartum hemorrhage, specifically an increase in rates of hysterectomy for postpartum hemorrhage between 1991 and 2000.[2] This was followed by reports from New South Wales, Australia, which showed that rates of postpartum hemorrhage had increased,[3] and another report from Canada that showed that the rising rates were restricted to one type of postpartum hemorrhage namely, atonic postpartum hemorrhage.[4] In Canada, postpartum hemorrhage is defined in International Classification of Diseases (ICD) 9 and 10 codes as an estimated blood loss of ≥500 mL after vaginal birth or ≥1000 mL after cesarean delivery, or as a diagnosed noted by a health care provider.[5] Despite varying definitions internationally, several studies from high income countries have documented increases in rates of postpartum hemorrhage over the past decade; increases in postpartum hemorrhage have also been reported in the United States, Norway, Scotland, Sweden, and Ireland during a similar time period.[6-10] Table 1.1 summarizes the different outcome definitions and rate changes reported among high income countries internationally.

In Canada, rates of postpartum hemorrhage with hysterectomy increased from 24.0 in 1991 to 41.7 per 100,000 deliveries in 2004,[4] and rates of postpartum hemorrhage with blood transfusion increased from 36.6 in 2003 to 44.3 per 10,000 deliveries in 2007.[11] Rates of atonic postpartum hemorrhage in Canada (defined as postpartum hemorrhage within 24 hours of delivery, following delivery of the placenta and generally due to inadequate uterine contraction) increased from 2.9 to 4.0 per 100 deliveries from 1991 to 2004.[4] Adjustment for known risk factors (e.g., maternal age,

previous cesarean delivery, prenatal diagnosis of a large fetus, epidural analgesia, medical induction of labour, and cesarean delivery) did not explain the temporal increase in atonic postpartum hemorrhage.[4] In British Columbia, atonic postpartum hemorrhage increased from 3.8 to 5.2 per 100 deliveries from 1991 to 2004, an increase of 34%.[12] In the United States, a recent national, population-based study reported that rates of severe postpartum hemorrhage (defined as postpartum hemorrhage in conjunction with receipt of blood transfusion, hysterectomy or surgical repair of the uterus) increased from 1.9 to 4.2 per 1000 deliveries between 1999 and 2008, and that the increase was not explained by maternal and obstetric factors.[13] The study found that the increase in postpartum hemorrhage was restricted to atonic postpartum hemorrhage, and no increase occurred among the non-atonic postpartum hemorrhage subtypes.[13]

Table 1.1. Increase in postpartum hemorrhage (PPH) in high income countries.

Author/ Publication Year	**Country**	**Outcome definition**	**Rate**
Ford et al 2007[3]	Australia	PPH (≥500 mL vaginal, ≥750 mL cesarean)	1994: 4.7 per 100 2002: 6.0 per 100
Joseph et al 2007[4]	Canada	PPH (≥500 mL vaginal, ≥1000 mL cesarean)	1991: 4.1 per 100 2004: 5.1 per 100
Bateman et al 2010[6]	United States	PPH (≥500 mL vaginal, ≥1000 mL cesarean)	1995: 2.2 per 100 2004: 2.9 per 100
Rossen et al 2010[7]	Norway	PPH (≥1000 mL)	1998/99: 2.5 per 100 2006/07: 3.3 per 100
Scottish Confidential Audit 2011[8]	Scotland	Major obstetrical hemorrhage (≥2500 mL, transfused ≥5 units, or treatment for coagulopathy)	2004: 32 per 10,000 2009: 52 per 10,000
Blomberg et al 2011[9]	Sweden	PPH (>1000 mL)	1997: 3.4 per 100 2008: 5.3 per 100
Lutomski et al 2011[10]	Ireland	PPH (>500 mL)	1999: 1.5 per 100 2009: 4.1 per 100

The international increase in other countries was also reported to be due to an increase in the atonic subtype of postpartum hemorrhage.[1,6,10] Other population-based studies, which included details about labour induction, fetal weight, parity, and long duration of labour, from Australia, the United States and Ireland were also unable to explain the increase in postpartum hemorrhage.[3,10,14]

1.2 Postpartum hemorrhage mortality and morbidity

The increase in postpartum hemorrhage in Canada and among other high income countries is concerning because of the considerable morbidity associated with postpartum hemorrhage.[1,15] Postpartum hemorrhage is a leading cause of maternal death in developing countries, and the primary cause of maternal death in Africa and Asia.[16] Postpartum hemorrhage is not the main cause of maternal death in high income countries. The maternal mortality ratio in Canada was 5.5 (95% CI 4.2-7.2) per 100,000 live births in 2002-04, and not significantly different from the mortality ratio in 1981-83 (4.5 per 100,000, 95% CI 3.3-5.9).[17] The maternal mortality ratio for postpartum hemorrhage in Canada in fact decreased from 5.3 per 1,000,000 in 1981-86 to 2.5 per 1,000,000 live births in 1999-2004.[17] Maternal mortality associated with hemorrhage also did not increase significantly between 1994-96 and 2003-05 in Australia, between 1997-99 and 2000-02 in France, between 1985-87 and 2003-05 in the United Kingdom, or between 1998 and 2004 in the United States.[1]

Nevertheless, postpartum hemorrhage is among the leading causes of severe maternal morbidity among high income countries.[1,8,11] In Canada, severe postpartum hemorrhage (as defined by postpartum hemorrhage in conjunction with blood transfusion) occurs at a higher rate than puerperal sepsis, cardiac arrest, cardiac failure or myocardial infarction, eclampsia, and rupture of uterus during labour, and is one of the most common severe maternal morbidities in Canada.[11]

Rates of the leading subtypes of severe maternal morbidity in Canada are summarized in Table 1.2.

Table 1.2. Common subtypes of severe maternal morbidity in Canada (excluding Quebec), 2003 to 2007.

Severe maternal morbidity	Rate per 100,000 deliveries (95% confidence interval)
Postpartum hemorrhage with blood transfusion	39.8 (38.8 to 40.9)
Puerperal sepsis	11.3 (10.7 to11.8)
Cardiac arrest, cardiac failure, or myocardial infarction	10.4 (9.9 to 11.0)
Eclampsia	8.9 (8.8 to 8.9)
Rupture of uterus during labour	7.8 (7.3 to 8.3)

From Liu et al. 2010[11]

Consequences of postpartum hemorrhage can include events related to an extreme drop in blood volume and the inability of vital organs to function as a result. Such events include adult respiratory distress syndrome, coagulopathy, shock, Sheehan syndrome (damage to the pituitary gland and related hormonal function), and acute renal failure.[18] In Canada, Sheehan's syndrome increased from 3.7 to 12.6 per million deliveries between 1991-93 and 2002-04 (a 241% increase, 95% CI -8% to 1158%, p=0.008 for linear trend in proportions).[4]

Acute renal failure among obstetric patients increased in both Canada and the United States over the last decade, concurrent with the increase in postpartum hemorrhage.[11,19] It is unclear whether postpartum hemorrhage, hypertensive disorders of pregnancy, or another risk factor underlied the rise in obstetric acute renal failure. Obstetric acute renal failure increased significantly in Canada from 1.6 to 2.3 per 10,000 deliveries between 2003 and 2007,[11] while obstetric acute renal failure increased significantly in the United States from 2.3 per 10,000 in 1998 to 5.5 per 10,000

deliveries in 2008, concurrently with increases in both hysterectomies and blood transfusions, both markers of severe blood loss.[19] No published study to date has examined whether the rise in acute renal failure is due to the increase in postpartum hemorrhage.

Mild forms of postpartum hemorrhage can also have a health impact, leading to anemia and extreme physical fatigue.[20] Besides the somatic consequences of postpartum hemorrhage on organ function and physical fitness, a growing body of literature documents the psychological effects of postpartum hemorrhage.[21-24] The fear associated with an obstetric emergency can have lasting effects.[21] After severe postpartum hemorrhage, some women report ongoing long-term distress, including post-traumatic stress symptoms such as anxiety, re-experiencing the traumatic event, and avoiding people or places that remind them of the traumatic experience.[22,24]

1.3 Etiology of uterine atony

The etiology of postpartum hemorrhage can be broadly classified into uterine and non-uterine causes. Uterine causes include atony, retained placenta, abnormal placentation, uterine or cervical lacerations and uterine rupture.[5] Non-uterine causes include bleeding from lacerations either in the genital tract and/or associated structures, or from coagulation defects. Uterine atony is the most common cause of postpartum hemorrhage, accounting for approximately 75-80% of cases, and has been identified as underlying the increases in postpartum hemorrhage in Canada, the United States, Ireland and Australia.[1,4,10,14] Atony is defined as "the condition wherein the uterine smooth muscle fails to contract sufficiently after delivery of the fetus [and placenta], resulting in hemorrhage from dilated venous and arterial bleeders within the placental bed."[25] A woman's spiral arteries carry approximately 600 mL/min of blood through the intervillous space to the fetus during late pregnancy.[26] In the third stage of labour, the many large blood vessels which supplied

the placenta are compressed following myometrial contraction leading to separation and expulsion of the placenta.

Table 1.3. Etiology of uterine atony.

Disorder	Example	Possible mechanism
Uterine over distension	Multiple gestation Macrosomia Polyhydramnios	Excessive stretch of actin-myosin complexes
Intrinsic uterine dysfunction	Prolonged labour Prolonged second stage	Poor contractility, poor coordination
Extrinsic uterine dysfunction	Retained placenta Placental fragments Blood and clots Bladder distension	Physical barrier to contraction
Uterine or placental abnormalities	Surgical scars Placenta accreta Endometritis Chorioamnionitis	Noncontractile tissue
Iatrogenic	Prolonged exposure to oxytocin through induction and/or augmentation of labour	Receptor desensitization
	Magnesium sulfate, tocolytics	Direct antagonism

Adapted from Roberts 1995[5] and Webster 2005[25]

Factors that impede uterine contraction can cause postpartum hemorrhage from uterine atony through overdistension of the uterus in cases of multi-fetal (multiple) pregnancy, macrosomia or polyhydramnios or through physical barriers to contraction such as with blood clots and placental fragments.[5] Excess uterine activity in the form of prolonged or augmented labour may cause the uterus to become hypotonic, as can surgical scar tissue from a previous cesarean delivery.[26] Infections of the uterus such as chorioamnionitis also increase the risk of uterine atony, possibly by interfering with the ability of the uterine muscle tissue to contract.[5] Prolonged exposure to oxytocin through labour induction or augmentation is reported to increase the risk of uterine atony through desensitization of the receptors during the third stage of labour.[27] Several drugs (e.g., magnesium sulfate and tocolytics) may also interfere with uterine contraction in the third stage of

labour through their muscle relaxant effects.[28,29] Table 1.3 summarizes some factors thought to be causally associated with uterine atony and the possible mechanisms for the associations.

Postpartum hemorrhage is further classified into primary and secondary postpartum hemorrhage, with primary hemorrhage defined as that occurring within the first 24 hours of delivery and secondary hemorrhage defined as that occurring between 24 hours and 6 weeks.[30] Uterine atony is classified as primary postpartum hemorrhage, along with third stage hemorrhage (that due to retained, adherent or trapped placenta) and postpartum hemorrhage due to coagulation.[30] The etiology of secondary postpartum hemorrhage is somewhat different than that caused by uterine atony, being generally caused by retained products of conception and infection.[18]

1.4 Factors potentially associated with the increase in postpartum hemorrhage

Hypotheses to explain the recent increase in atonic postpartum hemorrhage centre around changes in two broad sets of factors, namely, maternal/fetal characteristics and obstetric management. Both maternal/fetal characteristics and obstetric practice have undergone substantial change in the past two decades.

1.4.1 Changes in maternal and fetal characteristics

Maternal and fetal factors thought to be causing the increase in postpartum hemorrhage in Canada include increases in maternal age at delivery (i.e., delayed childbearing), maternal body mass index/obesity, multi-fetal pregnancies (due to assisted reproductive techniques and older maternal age), fetal/infant weight, and primiparity (i.e., increases in the proportion of women having their first child).[4,11]

Maternal age at childbirth has been increasing in Canada, Australia, New Zealand, the United States, the United Kingdom and other Western European countries.[31] In particular, advanced maternal age (≥35 years) has increased in the countries where postpartum hemorrhage has also increased.[1] At and after the age of 35 years, women are more likely to use assisted reproductive technologies such as in vitro fertilization (IVF) to become pregnant.[31] Women using assisted reproductive technologies and older mothers are more likely to have multi-fetal pregnancies, a known risk factor for postpartum hemorrhage.[26,32] Advanced maternal age is also associated with adverse fetal/infant outcomes, including increases in miscarriages, stillbirth, low birth weight, and preterm birth.[31] Prior spontaneous abortion has been associated with a slightly increased risk of postpartum hemorrhage (adjusted odds ratio 1.1, 95% CI 1.0-1.2).[33] Increases in both pre-existing and pregnancy-related maternal medical conditions are more common at advanced ages, with type 2 diabetes and gestational diabetes, pre-existing hypertension and gestational hypertension and other chronic conditions (e.g., systemic lupus erythematosus) becoming more common at advanced maternal age.[34-36] Finally, the frequency of obstetric interventions such as cesarean delivery, induction of labour, and peripartum hysterectomy increase with advanced maternal age.[4,34-37] The increase in advanced maternal age among high income countries has therefore likely led to an increase in pregnancy complications and associated obstetric intervention, potentially increasing the risk of postpartum hemorrhage and severe postpartum hemorrhage.

Increases in body mass index (BMI), overweight and obesity have been apparent at the population level in Canada and other Western countries; these changes have also affected women of reproductive age.[9,38] Obesity is associated with increases in maternal complications, including pre-eclampsia and gestational diabetes, and has been reported to be associated with postpartum hemorrhage in some studies.[32,33,39] However, other studies have not found an increased risk of

postpartum hemorrhage with obesity,[40] or have reported a non-significant protective effect.[41] The possibility remains that the association of postpartum hemorrhage with obesity arises from confounding by maternal factors (such as gestational and pre-existing diabetes, hypertensive disorders), fetal factors (large for gestational age and macrosomia).[39] In addition, rates of obstetric interventions (e.g., labour induction and augmentation) for obesity, which are also risk factors for postpartum hemorrhage, may vary by provider and region.

The in utero diagnosis of a 'large fetus' and the delivery of a large infant has increased in Canada in recent years.[4] Macrosomia (fetal/infant weight ≥4000 g or ≥4500 g) is a known risk factor for postpartum hemorrhage.[3,32] However, even excluding cases of macrosomia, increased fetal/infant weight has been associated with higher rates of postpartum hemorrhage.[42] Finally, both nulliparity and grand multiparity (i.e., parity ≥5) have been associated with postpartum hemorrhage.[4,7,9,32] Nulliparity has been increasing among deliveries in Canada, while grand multiparity has been decreasing.[4] Nulliparity is associated with uterine atony compared with multiparity, possibly because multiparous women generally have more efficient uterine contractions.[26] The association of grand multiparity with postpartum hemorrhage is more controversial, with some studies suggesting that grand multiparity is associated with a higher rate of premature separation of the placenta (a strong risk factor for postpartum hemorrhage) and uterine rupture, due to a weaker uterine wall and other risk factors.[43] Other evidence indicates that the adverse outcomes with grand multiparity are strongly confounded by socioeconomic status and related maternal factors, including access to and use of prenatal care, nutrition status, psychosocial stress and adverse living conditions.[44]

1.4.2 Changes in obstetric practice patterns

Obstetric factors hypothesized to be associated with the increase in postpartum hemorrhage include increases in epidural analgesia, labour induction, labour augmentation and cesarean delivery. A related factor is the increase in pregnant women with previous cesarean deliveries. The presence of a uterine scar is known to increase uterine and placental complications during pregnancy and delivery and is a risk factor for postpartum hemorrhage.[33] Specifically, a scar can interfere with appropriate contraction of the uterine muscles, predisposing a woman to uterine atony or uterine rupture, and can lead to adherent, retained or trapped placental fragments.[26] Another hypothesis relates to increased and prolonged oxytocin use during labour augmentation. The mechanism suggested for atony after prolonged exposure to oxytocin is uterine muscle receptor desensitization to the effects of oxytocin, which prevents the muscle tissue from contracting normally following childbirth.[27]

Induction of labour has been reported as a risk factor for postpartum hemorrhage in many studies,[3,4,7,33] although one study found a negative association with postpartum hemorrhage.[45] Other studies suggest that the type of induction is important, with one study reporting that oxytocin induction is more likely to cause postpartum hemorrhage than induction with prostaglandin.[42] Epidural analgesia is often associated with postpartum hemorrhage in crude analyses, but loses its significant effect upon adjustment for labour characteristics.[3,7] The study of the association of epidural analgesia with postpartum hemorrhage demonstrates the complexity of some of these associations, as epidural analgesia often leads to a prolonged second stage of labour and increased use of oxytocin augmentation. A systematic review reported an association between prolonged second stage of labour and postpartum hemorrhage among four of the five studies where the association was recorded.[46] However, limitations included a narrow definition of the

second stage (two hour limit regardless of parity or use of anesthesia) and the potential for confounding that was not addressed. Nevertheless, factors such as prolonged second stage and oxytocin augmentation may be better viewed as lying in the causal pathway between epidural analgesia and postpartum hemorrhage (and hence not requiring adjustment in studies on the effect of epidural analgesia on postpartum hemorrhage).

1.5 Study rationale

In 2009, the International Postpartum Hemorrhage Collaborative Group recommended that studies be carried out into the increase in postpartum hemorrhage observed in high income countries over the last decades.[1] Although various hypotheses have been proposed to explain the increasing rates of postpartum hemorrhage in Canada and elsewhere, no published study had identified the risk factors responsible for the increase.[1] Identifying the cause of the increase is an important research endeavor as postpartum hemorrhage, both mild and severe, has a negative impact on maternal health. Although postpartum hemorrhage is not the main cause of maternal death in high income countries, the morbidity associated with severe postpartum hemorrhage and related complications can lead to death, severe morbidity and long-term disability.[11] Mild postpartum hemorrhage can lead to anemia and attendant consequences such as fatigue, lethargy, and suboptimal fitness.[20] In addition, postpartum hemorrhage may have lasting psychological effects that affect a woman's quality of life for years after the event.[21-23]

Canadian studies on the etiology of postpartum hemorrhage have been limited by their reliance on the Discharge Abstract Database of the Canadian Institute for Health Information, a large administrative health database. The Discharge Abstract Database has the advantage of including a large number of hospital deliveries, enabling the study of rare outcomes, such as placenta accreta

and obstetric acute renal failure (addressed in this dissertation). The Discharge Abstract Database also allows the study of maternal morbidity at the national level and by province and territory. However, the Discharge Abstract Database does not include information on important demographic and clinical risk factors for postpartum hemorrhage such as labour augmentation and maternal pre-pregnancy body mass index.

This dissertation was motivated by the need to carry out a detailed study on the etiology of postpartum hemorrhage in order to identify potential causes for increases in atonic postpartum hemorrhage and to address other gaps in the literature identified above. A more detailed investigation was therefore proposed, using data from the British Columbia Perinatal Data Registry, a population-based perinatal database with detailed information that is routinely used for perinatal surveillance. The British Columbia Perinatal Data Registry is an important perinatal data resource in British Columbia and contains information on all deliveries in British Columbia, with information on risk factors such as pre-pregnancy body mass index and labour augmentation (factors not included in previous studies on postpartum hemorrhage). It is, therefore, likely to provide insights and new information regarding the cause of the increase in postpartum hemorrhage. Additionally, it serves as an ideal data source for investigating objective markers of severity through its high quality information on the management of severe postpartum hemorrhage (including the receipt of blood transfusion, the amount of blood transfused, the procedures to control bleeding, etc). On the other hand, the Canadian Institute for Health Information's Discharge Abstract Database, which has been validated for the major outcomes of interest,[47] provides information on postpartum hemorrhage at the national level. In addition, the Discharge Abstract Database is ideal for studying rare and important risk factors for postpartum hemorrhage such as placenta accreta and assessing the magnitude of their associations with the most severe

forms of postpartum hemorrhage. Placenta accreta has not been systematically studied in previous population-based research. Finally, the Discharge Abstract Database is well-suited for studying risk factors associated with the rare occurrence of obstetric acute renal failure and the observed increase in obstetric acute renal failure in Canada.

1.6 Dissertation objectives

The primary purpose of this doctoral thesis was to describe the increase in postpartum hemorrhage and severe postpartum hemorrhage (by subtype) by maternal, fetal and obstetric characteristics, and to determine the underlying cause or causes of the increase in postpartum hemorrhage and severe postpartum hemorrhage using a detailed population-based database from British Columbia, Canada. The secondary objectives were 1) to determine if previously observed increases in postpartum hemorrhage in Canada between 1991 and 2004 continued after 2004, 2) to describe the postpartum hemorrhage rates in Canada by province and territory, and by maternal, fetal and obstetric factors, 3) to explore whether placenta accreta could explain the increase in postpartum hemorrhage using a diagnostic code introduced in 2009, and 4) to determine whether the increase in obstetric acute renal failure in Canada was explained by the concurrent increase in postpartum hemorrhage.

The specific objectives of the dissertation therefore were:

1) To describe temporal trends in postpartum hemorrhage (including severe postpartum hemorrhage such as postpartum hemorrhage associated with blood transfusion, hysterectomy and other surgical and non-surgical procedures) in British Columbia between 2000 and 2009.

2) To determine the risk factors associated with the temporal increase in postpartum hemorrhage, atonic postpartum hemorrhage, severe postpartum hemorrhage and severe atonic postpartum hemorrhage in British Columbia between 2001 and 2009.
3) To determine if the increase in postpartum hemorrhage continued to occur in Canada between 2003 and 2010 and whether there were regional differences across Canadian provinces and territories.
4) To determine the impact of placenta accreta on the incidence of postpartum hemorrhage and severe postpartum hemorrhage in Canada.
5) To determine whether the temporal increase in postpartum hemorrhage explained the concurrent increase in obstetric acute renal failure in Canada.

1.7 Data sources and study population

The data sources used for analyses in this dissertation are the British Columbia Perinatal Data Registry and the Canadian Institute for Health Information's Discharge Abstract Database. The British Columbia Perinatal Data Registry contains information for approximately 99% of stillbirths or live births in British Columbia, from approximately 60 hospitals and health centres across the province and includes home births attended by registered midwives. The Canadian Institute for Health Information's Discharge Abstract Database includes all hospital deliveries in Canada (excluding Quebec) that resulted in a live birth or stillbirth, and includes approximately 98% of all Canadian births. Both databases register stillbirths and live births at 20 weeks of gestation or greater. Data used in this database from the Discharge Abstract Database was based on International Statistical Classification of Diseases and Related Health Problems (ICD-10-CA), and the Canadian Classification of Interventions (CCI) codes, while the British Columbia Perinatal Data Registry data used contained both ICD-9, Therapeutic and Surgical Procedures (CCP)

procedure codes, ICD-10-CA and CCI codes, as well as additional data abstracted from the antenatal records, labour and delivery records, and birth records using standardized forms filled out by care providers from across the province of British Columbia. Both the Discharge Abstract Database and the British Columbia Perinatal Data Registry were abstracted from women's medical records by trained data abstractors.

1.7.1 Validity of data sources

The British Columbia Perinatal Data Registry incorporates routine quality checks for the data, including programmed logic and consistency checks and validation rules to ensure that the measures entered are plausible. The data are also reviewed at the hospital-level and through the analyses of key indicators. Currently, a validation study is underway, and preliminary results have been promising.[48] In particular, pre-pregnancy body mass index appears valid, despite missing data, and mode of delivery and labour induction also have high validity.[48] Preliminary analyses also reveal that pre-pregnancy body mass index appears to be missing at random, which supports the use of multiple imputation techniques to improve modeling, as outlined in Chapter 3.

Table 1.4. Validity of maternal data from the Discharge Abstract Database of the Canadian Institute for Health Information.

Maternal indicator (based on ICD-10-CA)	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
Postpartum hemorrhage	90.2 [86.2-93.3]	98.2 [97.8-98.5]
Blood transfusion	85.7 [42.1-99.6]	99.8 [99.6-99.9]
Induction of labour	89.2 [87.7-90.6]	96.9 [96.4-97.4]
Cesarean delivery	99.8 [99.5, 100.0]	98.7 [98.3-99.0]
3rd degree perineal laceration	97.1 [92.7-99.2]	99.9 [99.8-100.0]
4th degree perineal laceration	94.7 [74.0-99.7]	99.9 [99.8-100.0]
Hypertension (chronic)	83.3 [73.6-90.6]	99.9 [99.8-100.0]
Gestational hypertension with proteinuria (pre-eclampsia)	75.2 [67.5-81.8]	99.5 [99.3-99.7]
Any gestational hypertensive disorder	87.9 [85.0-90.4]	99.6 [99.4-99.8]

ICD-10-CA denotes International Statistical Classification of Diseases and Related Health Problems (Canadian version). CI denotes confidence interval.

The Discharge Abstract Database of the Canadian Institute for Health Information has been validated for accuracy with the Nova Scotia Atlee Perinatal Database (a relatively small, clinically-focused perinatal database) used as the gold standard.[47] The national database demonstrated high validity for key maternal indicators used in this dissertation. Key variables were highly accurate; postpartum hemorrhage had a sensitivity of 90.2% and a specificity of 98.2%, while blood transfusion had a sensitivity of 85.7% and a specificity of 99.8% (Table 1.4). The sensitivity and specificity of other important maternal indicators are summarized in Table 1.4. In order to account for measurement error in the estimation of blood loss, throughout the dissertation, several measures of severity were incorporated, including postpartum hemorrhage in conjunction with a blood transfusion, hysterectomy and other procedures to control bleeding. Analyses incorporated these more objective markers of severe blood loss to ensure that the results were not biased by measurement error.

1.8 Dissertation structure

The second and third chapters of this thesis provide detailed epidemiologic analyses of changes in postpartum hemorrhage and severe postpartum hemorrhage in British Columbia, Canada between 2000 and 2009. The second chapter involves a descriptive initial analysis of trends in postpartum hemorrhage including analyses by postpartum hemorrhage subtypes and by risk factors. The third chapter of the thesis provides the results of an etiologic analysis using multivariable regression to identify whether changes in specific, previously unexamined risk factors (such as pre-pregnancy body mass index and labour augmentation) explain the temporal increase in postpartum hemorrhage. This etiologic analysis was restricted to the years 2001 to 2009 since ICD-10 codes were available for this entire period (ICD-9 codes were used in 2000). The fourth chapter presents the results of analyses carried out to determine whether the increase in postpartum hemorrhage

continued across Canada in more recent years, and whether the increase occurred across all Canadian provinces and territories. The fifth chapter is an exploratory analysis of the impact of placenta accreta on the incidence of postpartum hemorrhage and severe postpartum hemorrhage, and includes a discussion about whether placenta accreta could potentially explain the increase in atonic postpartum hemorrhage. The sixth chapter presents the results of a study to determine whether the recent increase in obstetric acute renal failure in Canada could be explained by the simultaneous increase in postpartum hemorrhage and severe postpartum hemorrhage. Finally, the concluding chapter summarizes the study findings and discusses implications for clinical practice, surveillance, and further investigation.

Chapter 2: Epidemiologic investigation of an increase in postpartum hemorrhage in British Columbia: Descriptive epidemiology

2.1 Synopsis

Background: Postpartum hemorrhage, a major cause of maternal death and severe maternal morbidity, increased in frequency in Canada between 1991 and 2004. We carried out a descriptive study to describe the epidemiology of postpartum hemorrhage in British Columbia, Canada, between 2000 and 2009.

Methods: The study population included all women who were residents of British Columbia and delivered between 2000 and 2009. Data on postpartum hemorrhage by subtypes and severity were obtained from the British Columbia Perinatal Data Registry. Among women with postpartum hemorrhage, severe cases were identified as those requiring blood transfusions or procedures to control bleeding. Rates of postpartum hemorrhage and changes over time were assessed using rates, rate ratios and 95% confidence intervals (CI).

Results: The rate of postpartum hemorrhage increased by 27% (95% CI 21-34%) between 2000 and 2009 (from 6.3% to 8.0%), while atonic postpartum hemorrhage rates increased by 33% (95% CI 26-41%) from 4.8% to 6.4%. Atonic postpartum hemorrhage with blood transfusion increased from 17.8 to 25.5 per 10,000 deliveries from 2000 to 2009 and atonic postpartum hemorrhage with either suturing of the uterus, ligation of pelvic vessels or embolization increased from 1.8 to 5.6 per 10,000 deliveries from 2001 to 2009. The increase in atonic postpartum hemorrhage was most evident between 2006 and 2009 and occurred across regions, hospitals and various maternal, fetal and obstetric characteristics.

Conclusions: Atonic postpartum hemorrhage and severe atonic postpartum hemorrhage increased in British Columbia between 2000 and 2009. Further research is required to identify the cause or causes of the increase.

2.2 Background and objectives

This Chapter provides a preliminary descriptive analysis of trends in postpartum hemorrhage and severe postpartum hemorrhage in British Columbia, Canada, between 2000 and 2009. Included was an analysis of postpartum hemorrhage and severe postpartum hemorrhage rates by potential risk factors of interest, including region and hospital volume. The next chapter, Chapter 3, builds on this study with an etiologic analysis of factors associated with the rise in atonic and severe atonic postpartum hemorrhage, using multivariable regression modeling.

Postpartum hemorrhage is a major cause of maternal death worldwide and an important cause of severe maternal morbidity in high income countries.[49] In its severe form, postpartum hemorrhage represents a life-threatening obstetrical emergency.[5] Postpartum hemorrhage rates have increased in Canada and elsewhere from 1991 to 2004.[4] Initial reports from Canada identified the problem as a rise in rates of severe postpartum hemorrhage, specifically an increase in rates of postpartum hemorrhage requiring hysterectomy between 1991 and 1999.[2] This was followed by reports which showed that the increases were restricted to one type of postpartum hemorrhage, namely, atonic postpartum hemorrhage.[4] Increases in postpartum hemorrhage and severe postpartum hemorrhage have also been reported in Australia, Ireland, Scotland, Sweden, Norway and the United States during the same time period.[7,9,10,14,50] The increase in postpartum hemorrhage has occurred against a background of increases in older maternal age, obesity, multiple births, deliveries to women with a previous cesarean, induction and augmentation of labour, and cesarean deliveries.[4,7,14] However, the cause or causes for the increase in atonic postpartum hemorrhage remain unclear.[3,4,33] We carried out this study to characterize continuing trends in postpartum hemorrhage using data from British Columbia, Canada, with the goal of identifying potential causative factors and the clinical and population health implications. In this chapter of

the dissertation, our objective was to estimate the incidence of overall postpartum hemorrhage and its subtypes in British Columbia, Canada, between 2000 and 2009 and to describe the epidemiologic features of postpartum hemorrhage and severe postpartum hemorrhage.

Our choice of this sub-national population was motivated by the high quality and detailed nature of the data available for analysis. This enabled an examination of the impact of changes in several maternal characteristics (such as pre-pregnancy weight) and obstetric practice (such as the role of labour induction and augmentation) not previously examined in a population-based study.

2.3 Methods

The study population included all women residents of British Columbia, who delivered between 2000 and 2009. Data were obtained from the British Columbia Perinatal Data Registry, a population-based registry whose purpose is to collect perinatal data for research, surveillance and planning. The database contains information on approximately 99% of births in the province, including detailed clinical and diagnostic information. Standardized forms were filled-out by care providers (physicians, midwives, obstetricians, and nurses) during pregnancy, labour and delivery and postpartum, and then compiled and coded by trained data abstractors. Accuracy and validity of data were ensured through ongoing quality checks by staff, automated data rules and ongoing use in research and surveillance. All women who gave birth between April 1st, 2000 and March 31st, 2010 (hereafter referred to as years 2000 to 2009) and who resided in British Columbia were included in the study.

Postpartum hemorrhage in Canada was defined as an estimated blood loss of ≥500 mL after vaginal delivery or ≥1000 mL after cesarean delivery or as otherwise diagnosed by a care provider. Postpartum hemorrhage diagnoses were based on International Classification of Diseases (ICD) codes recorded in the Perinatal Database (ICD-9 from 2000 to 2003 and ICD-10 from 2004 to 2009). Subtypes of postpartum hemorrhage identified with ICD-9 or ICD-10 diagnostic codes included: 1) third stage hemorrhage (postpartum hemorrhage due to retained placenta), 2) postpartum hemorrhage due to uterine atony (following delivery of the placenta and occurring within 24 hours of delivery), 3) delayed and secondary postpartum hemorrhage (occurring after the first 24 hours following delivery) and 4) postpartum hemorrhage due to coagulation defects. Code details for postpartum hemorrhage did not change between ICD-9 and ICD-10.

Severe cases of postpartum hemorrhage were defined as postpartum hemorrhage occurring in conjunction with blood transfusion, hysterectomy, or other procedures to control bleeding. Blood transfusion was defined as receipt of one or more units of whole blood or packed red blood cells. Hysterectomy and procedures to control bleeding were identified using the Canadian Classification of Health Interventions (CCI) codes from April 1st, 2001 onwards. Interventions and procedures to control bleeding in conjunction with a diagnosis of postpartum hemorrhage included hysterectomy, bimanual uterine compression and massage, uterine (and vaginal) packing, ligation of pelvic vessels, and embolization of pelvic vessels (see Supplementary Table A.1 for all diagnostic codes and procedures). Between 2001 and 2003, 2,156 of 118,987 women (1.8%) were missing CCI procedure codes for procedures to control bleeding and so equivalent Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) codes were

used for a diagnosis of hysterectomy (Supplementary Table A.1). For other procedures to control bleeding, equivalent CCP codes were not available. However, exclusion of the 2,156 records made very little difference to either rates or statistical test results, so all women were included in the reported results.

Maternal, fetal and obstetrical characteristics were identified according to fields recorded in the Perinatal Database. Maternal characteristics included age, parity, and body mass index (BMI) and fetal characteristics included plurality, birth weight and gestational age. Obstetrical factors included spontaneous or instrumental vaginal delivery (with vacuum or forceps), cesarean delivery with or without labour, previous cesarean delivery, any method of labour induction, augmentation with oxytocin, and administration of epidural analgesia. Geographic regions of British Columbia were defined by the regional health authority of the mother's residence, and hospital volume was defined by number of deliveries per year, in the year of delivery. Length of hospital stay greater than 4 days and hospital stay greater than 7 days were used as a measure of the burden of illness associated with postpartum hemorrhage. The 4 day cut-off was chosen as it is greater than the average stay for both cesarean and vaginal deliveries, while the 7 days postpartum cut-off has previously been used as an indicator for severe maternal morbidity.[6,51]

Rates with exact binomial 95% confidence intervals were estimated for overall postpartum hemorrhage, postpartum hemorrhage subtypes, severe postpartum hemorrhage, and severe atonic postpartum hemorrhage for the period 2000 to 2009 and for each year within this time period. Temporal trends were assessed both by contrasting the rates in 2000 or 2001 with rates in 2009 using rate ratios (RR) and 95% confidence limits (95% CI). Temporal trends were also examined across all the years in the study using a chi-square test for linear trends in proportions. All rates

were expressed per 100 deliveries, except for rare outcomes such as severe postpartum hemorrhage, which were expressed per 10,000 deliveries. Statistical significance of differences was assessed based on two-sided p values and a p value <0.05 was considered statistically significant. Stata SE version 11 was used to model smoothed rates and 95% confidence intervals overlaid on observed semi-annual rates.[52] Calendar time was modelled using a restricted cubic spline, thereby avoiding linearity assumptions and loss of information from categorizing the continuous time variable.[53] For all other analysis, we used SAS version 9.2 statistical software and Epi Info (*wwwn.cdc.gov/epiinfo/*).

2.4 Results

Between 2000 and 2009, 412,093 women residents of British Columbia delivered either a live birth or stillbirth and were included in the study. Postpartum hemorrhage rates increased from 6.3% in 2000 to 8.0% in 2009, a 27% increase (95% CI 21-34%), while atonic postpartum hemorrhage increased from 4.8% in 2000 to 6.4% in 2009, a 33% increase (95% CI 26-41%, Table 2.1). The increase in postpartum hemorrhage and atonic postpartum hemorrhage was particularly evident between 2006 and 2009 (Figure 2.1). Overall postpartum hemorrhage and atonic postpartum hemorrhage showed an increasing linear trend between 2000 and 2009 ($p<0.001$). Other subtypes of postpartum hemorrhage did not show similar increasing trends (Figure 2.1); there was a 40% (95% CI 9-81%) increase in secondary postpartum hemorrhage from 0.25% in 2000 to 0.35% in 2009, but the temporal trend using information for all years was not significant ($p=0.27$, Table 2.1).

Severe postpartum hemorrhage increased significantly according to every indicator analyzed except for postpartum hemorrhage with hysterectomy. Postpartum hemorrhage with blood

transfusion increased from 29.1 to 42.5 per 10,000 deliveries from 2000 to 2009 (an increase of 46%, 95% CI 16-84%), while postpartum hemorrhage with uterine (and vaginal) packing increased by 102% (95% CI 12-263%) from 2001 to 2009. Postpartum hemorrhage with either suturing of the uterus, ligation of pelvic vessels or embolization increased by 297% (95% CI 75-801%, Table 2.1). Severe atonic postpartum hemorrhage demonstrated a trend similar to trends in severe overall postpartum hemorrhage; all procedures indicating severe atonic postpartum hemorrhage increased significantly over time (Table 2.1). Atonic postpartum hemorrhage with blood transfusion increased from 17.8 per 10,000 deliveries in 2000 to 25.5 per 10,000 deliveries in 2009 (43% increase, 95% CI 7-93%), while atonic postpartum hemorrhage with either suturing of the uterus, ligation of pelvic vessels or embolization increased from 1.8 in 2001 to 5.6 per 10,000 deliveries in 2009 (220% increase, 95% CI 38-640%). Most of the observed increase in overall postpartum hemorrhage with blood transfusion occurred between 2006 and 2009, while atonic postpartum hemorrhage with blood transfusion rates increased at a constant rate between 2003 and 2009 (Figure 2.1).

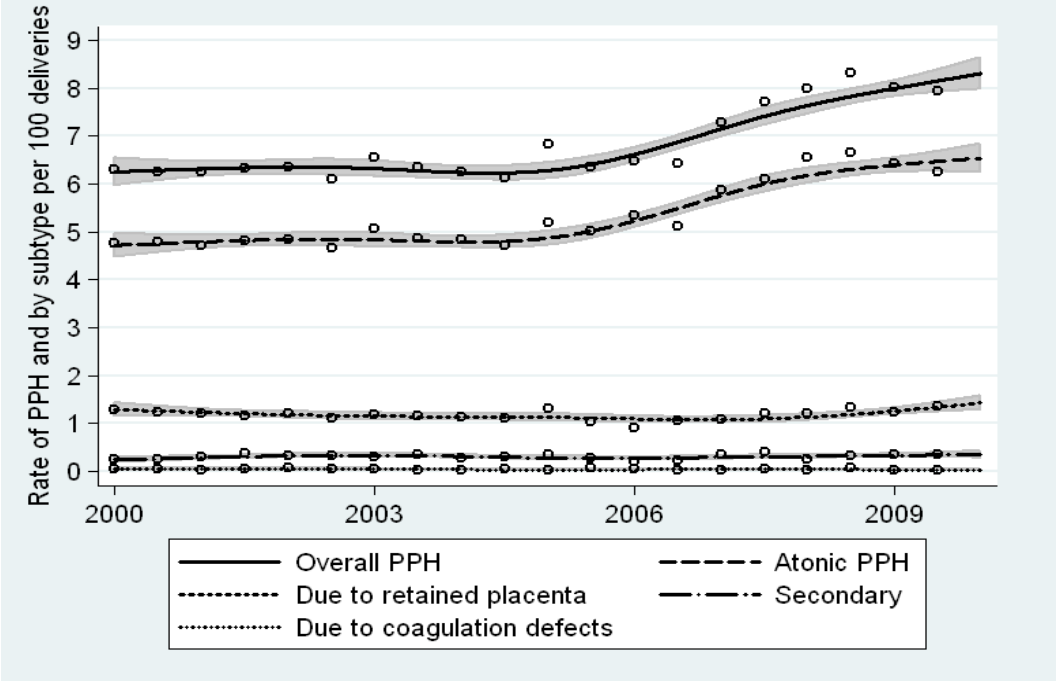


Figure 2.1. Temporal trends in postpartum hemorrhage (PPH) by subtype. Smoothed rates with 95% confidence interval overlaid on observed semi-annual rates

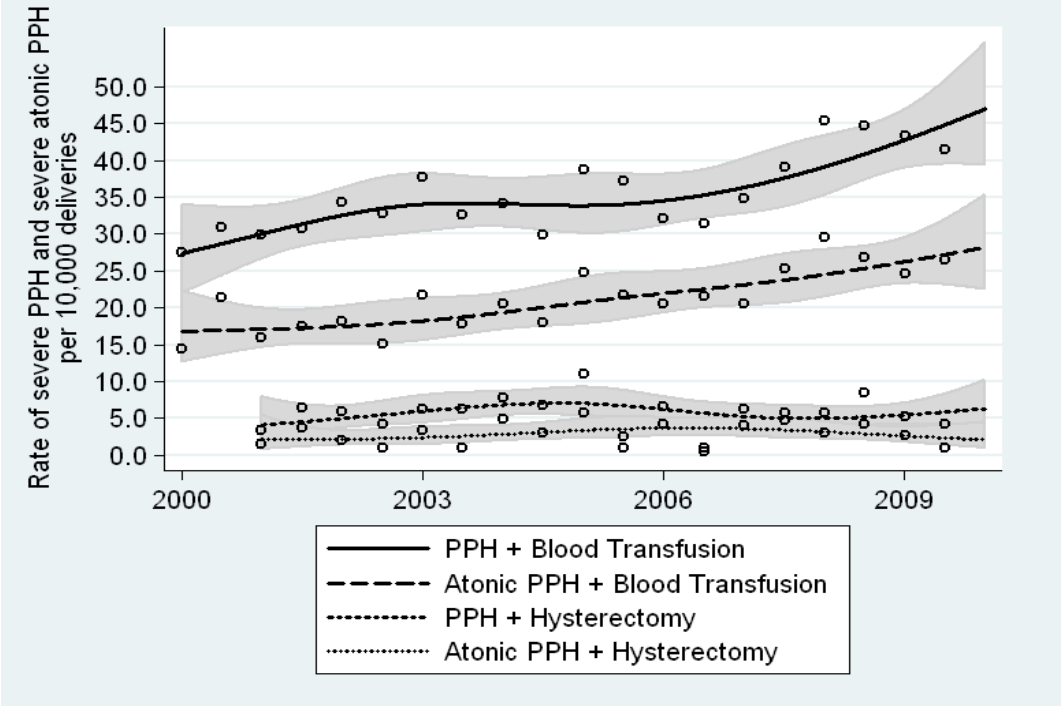


Figure 2.2. Temporal trends in severe postpartum hemorrhage (PPH) and severe atonic PPH. Smoothed rates with 95% confidence interval overlaid on observed semi-annual rates.

Table 2.1. Temporal trends in postpartum hemorrhage (PPH), PPH subtypes, severe PPH and severe atonic PPH in British Columbia, 2000-2009.

	All years	PPH rate				2009 vs. 2000/2001		
	n[1]	2000	2001	2008	2009	RR	95% CI	P for trend[2]
PPH (rates per 100 deliveries):								
All PPH	28221	6.3	6.3	8.2	8.0	1.27	1.21 - 1.34	<0.001
Third stage	4859	1.3	1.2	1.3	1.3	1.02	0.90 - 1.15	0.81
Atonic	22100	4.8	4.8	6.6	6.3	1.33	1.26 - 1.41	<0.001
Secondary	1276	0.25	0.34	0.29	0.35	1.40	1.09 - 1.81	0.27
Due to coagulation defects	178	0.05	0.05	0.05	0.03	0.51	0.25 - 1.05	0.14
Severe PPH (rates per 10,000 deliveries):								
PPH + blood transfusion	1468	29.1	30.3	45.1	42.5	1.46	1.16 - 1.84	<0.001
PPH + hysterectomy	215	-	4.8	7.1	4.7	0.99	0.53 - 1.84	0.76
PPH + suturing of uterus	65	-	0,0	3.4	3.2	-	-	<0.001
PPH + bimanual compression and massage	2255	-	27.7	98.1	95.6	3.45	2.79 - 4.25	<0.001
PPH + uterine (and vaginal) packing	223	-	4.0	6.4	8.1	2.02	1.12 - 3.63	0.02
PPH + ligation of pelvic vessels	81	-	1.3	3.9	4.5	3.58	1.34 - 9.55	<0.001
PPH + embolization of pelvic vessels	60	-	0.50	2.5	1.4	2.69	0.54 - 13.32	0.01
PPH + suturing, ligation, or embolization	186	-	1.8	9.1	7.0	3.97	1.75 - 9.01	<0.001
Severe atonic PPH (rates per 10,000 deliveries)								
Atonic PPH + blood transfusion	876	17.8	16.6	28.2	25.5	1.43	1.07 - 1.93	<0.001
Atonic PPH + hysterectomy	108	-	2.5	3.6	1.8	0.72	0.28 - 1.81	0.37
Atonic PPH + suturing of uterus	55	-	0.0	2.7	2.9	-	-	<0.001
Atonic PPH + bimanual compression and massage	1964	-	23.5	85.3	81.8	3.49	2.78 - 4.38	<0.001
Atonic PPH + uterine (and vaginal) packing	174	-	3.0	5.9	5.9	1.93	0.97 - 3.82	0.02
Atonic PPH + ligation of pelvic vessels	68	-	1.3	3.9	3.6	2.87	1.05 - 7.83	<0.001
Atonic PPH + embolization of pelvic vessels	43	-	0.50	2.0	1.1	2.24	0.43 - 11.55	0.01
Atonic PPH + uterine suturing, ligation, or embolization	150	-	1.8	8.0	5.6	3.20	1.38 - 7.40	<0.001

[1]n refers to number of cases of the outcome of interest.
[2]P value based on data for all years between 2000 (or 2001) and 2009.
RR denotes rate ratio and 95% CI denotes 95% confidence intervals.

Atonic postpartum hemorrhage increased significantly between 2000 and 2009 across all regions except for the Northern Health Authority which showed a decrease, and increased significantly across hospitals irrespective of hospital volume (except for those with 1000-1499 deliveries per year, Table 2.2). Atonic postpartum hemorrhage rates were higher among the large volume hospitals as compared with the small volume hospitals (6.1% compared with 4.5%). Supplementary analysis showed that women residing in the Northern Health Authority were younger, more likely to be multiparous, and less likely to receive epidural analgesia or undergo an instrumental vaginal delivery. Rates of epidural analgesia also decreased slightly ($p<0.05$) in this region, while rates increased significantly in all other regions.

Table 2.2. Atonic postpartum hemorrhage by region and hospital volume, British Columbia, 2000-2009.

Region (by health authority of woman's residence)	All years		Rate per 100 deliveries by year				2009 vs. 2000		P for trend[2]
	n[1]	rate	2000	2001	2008	2009	RR	95% CI	
Fraser	8340	5.2	5.0	4.9	6.6	6.0	1.19	1.09-1.30	<0.001
Interior	2769	4.7	3.9	3.4	5.8	7.0	1.81	1.54-2.11	<0.001
Northern	1694	4.9	5.2	4.8	5.6	4.1	0.79	0.64-0.97	0.03
Vancouver Coastal	6995	7.1	5.4	6.0	8.8	8.3	1.55	1.39-1.72	<0.001
Vancouver Island	2206	3.7	3.8	3.8	4.4	4.9	1.29	1.09-1.53	<0.001
Hospital Volume (by deliveries per year)									
<500	2537	4.5	5.0	4.1	5.6	5.2	1.04	0.88-1.23	<0.001
500-999	2363	4.6	3.8	4.0	5.6	5.6	1.49	1.27-1.75	<0.001
1000-1499	3369	4.2	5.6	4.4	5.3	4.0	0.71	0.61-0.84	0.88
1500-2499	3851	6.3	1.5	4.9	8.4	8.2	5.45	4.30-6.92	<0.001
≥2500	9980	6.1	5.6	5.5	6.8	6.5	1.15	1.05-1.25	<0.001

[1]n refers to number of cases of atonic postpartum hemorrhage.
[2]P value based on data for all years between 2000 and 2009.
RR denotes rate ratio and 95% CI denotes 95% confidence intervals.

Atonic postpartum hemorrhage increased significantly between 2000 and 2009 across all maternal, fetal and obstetric characteristics under study with the exception of birth weight <2500 grams, and gestational ages <28 weeks or ≥42 weeks (Table 2.3). An increase in atonic

postpartum hemorrhage was observed both among women with vaginal deliveries and cesarean deliveries, and regardless of whether a women had a previous cesarean delivery. Among cesarean deliveries, atonic postpartum hemorrhage increased significantly among all cesarean sub-categories, including cesareans without labour, those with spontaneous labour and those who had labour induction. Among women with a vaginal delivery, atonic postpartum hemorrhage increased more markedly among those with an instrumental vaginal delivery. Atonic postpartum hemorrhage increased significantly regardless of whether a woman had her labour induced, was augmented with oxytocin, or received epidural analgesia. The percent increase, however, was higher among women receiving these procedures.

Table 2.3. Temporal Trends in atonic postpartum hemorrhage by maternal, fetal and obstetrical characteristics, British Columbia, 2000-2009.

	All years		Rate per 100 deliveries				2009 vs. 2000		P for trend[2]
	n[1]	rate	2000	2001	2008	2009	RR	95% CI	
Parity									
Nulliparous	12,237	6.5	5.5	5.5	8.1	7.6	1.39	1.29-1.51	<0.001
Parous	9,863	4.4	4.2	4.2	5.3	5.2	1.24	1.14-1.35	<0.001
Maternal age (years)									
<20	953	6.2	6.1	5.0	8.5	7.6	1.26	0.97-1.62	<0.001
20-34	16,641	5.4	4.8	4.8	6.6	6.4	1.34	1.26-1.43	<0.001
≥35	4,506	5.2	4.4	4.7	6.3	5.9	1.34	1.18-1.53	<0.001
BMI									
Underweight	1,032	6.0	4.8	5.2	7.4	6.8	1.43	1.09-1.87	<0.001
Normal	9,960	5.7	5.1	5.1	6.9	6.8	1.33	1.22-1.47	<0.001
Overweight	2,977	5.1	4.5	4.5	6.2	6.2	1.39	1.19-1.62	<0.001
Obese	1,583	4.9	4.2	4.4	6.4	5.5	1.31	1.06-1.63	<0.001
Missing	6,548	5.1	4.5	4.4	6.4	6.1	1.36	1.21-1.53	<0.001
Plurality									
Singleton	21,529	5.3	4.7	4.7	6.5	6.3	1.33	1.25-1.41	<0.001
Multiple	571	9.2	7.1	10.8	11.3	9.4	1.33	0.91-1.95	<0.001
Birth weight (grams)									
<2500	794	3.7	3.2	4.0	5.0	3.7	1.17	0.85-1.61	0.03
2500-3999	17,353	5.2	4.5	4.5	6.3	6.2	1.37	1.29-1.47	<0.001
≥4000	3,939	7.2	6.6	6.4	9.1	8.2	1.24	1.09-1.41	<0.001
Gestational age (weeks)									
<28	68	2.0	2.1	0.69	3.13	1.5	0.71	0.25-2.01	0.53
28-36	1,477	4.5	3.3	4.2	6.0	5.2	1.55	1.21-1.97	<0.001
37-41	20,115	5.5	4.9	4.8	6.7	6.5	1.33	1.25-1.41	<0.001
≥42	396	6.2	5.8	5.3	6.9	5.9	1.03	0.68-1.57	0.52
Vaginal delivery									
Spontaneous	14,400	5.8	5.1	5.2	7.1	6.8	1.33	1.24-1.42	<0.001
Instrumental	5,141	11.5	8.9	10.3	14.6	14.2	1.59	1.42-1.79	<0.001
Cesarean delivery									
No labour	912	1.7	1.6	1.3	2.1	2.1	1.28	0.94-1.73	<0.001
With labour, no induction	1,001	2.4	1.6	1.5	3.5	3.0	1.92	1.43-2.58	<0.001
With induction	646	2.9	1.9	1.5	3.9	3.5	1.74	1.20-2.54	<0.001
Previous cesarean									
Yes	1,426	2.5	2.7	2.3	3.2	2.9	1.08	0.86-1.34	0.001
No	20,674	5.8	5.1	5.1	7.2	6.9	1.37	1.30-1.46	<0.001
Induction of labour									
Yes	5,648	6.4	5.4	5.4	8.4	7.7	1.41	1.26-1.58	<0.001
No	16,452	5.1	4.6	4.6	6.1	6.0	1.31	1.22-1.40	<0.001
Augmentation of labour (oxytocin)									
Yes	4,561	7.2	5.7	6.1	8.9	8.1	1.41	1.24-1.61	<0.001
No	17,539	5.0	4.6	4.5	6.1	6.0	1.31	1.23-1.39	<0.001
Epidural analgesia									
Yes	8,096	7.0	5.4	6.0	9.0	7.8	1.44	1.30-1.59	<0.001
No	14,004	4.7	4.6	4.3	5.6	5.8	1.27	1.19-1.36	<0.001

[1]n refers to number of cases of atonic postpartum hemorrhage.
[2]P value based on data for all years between 2000 and 2009.
RR denotes rate ratio and 95% CI denotes 95% confidence intervals.

Trends in atonic postpartum hemorrhage with blood transfusion were more variable over time across maternal, fetal and obstetric characteristics, likely due to smaller numbers for this outcome (Table 2.4). Significant and non-significant increases were observed across many maternal, fetal and obstetric categories. Notably, increases in atonic postpartum hemorrhage with blood transfusion were evident among both spontaneous and instrumental vaginal deliveries, although the increase was greater for instrumental vaginal births. Additionally, increases were evident among women irrespective of use of labour induction, oxytocin augmentation, or epidural analgesia. Increases in atonic postpartum hemorrhage with blood transfusion among women with a cesarean delivery were only observed among cesareans following labour induction. Although atonic postpartum hemorrhage rates were higher for vaginal as compared with cesarean deliveries (Table 2.3), rates of atonic postpartum hemorrhage with blood transfusion (as well as all other types of severe atonic postpartum hemorrhage – data available upon request) were higher among cesarean as compared with vaginal deliveries (Table 2.4).

Women with postpartum hemorrhage were more likely to have long hospital stays; 9.5% of women with postpartum hemorrhage had a length of stay greater than 4 days compared with 7.2% of women without postpartum hemorrhage (RR=1.32, 95% CI 1.27-1.37), and 1.3% had a length of stay greater than 7 days as compared with 0.7% of women without postpartum hemorrhage (RR=1.88, 95% CI 1.69-2.10).

Table 2.4. Temporal Trends in atonic postpartum hemorrhage with blood transfusion by maternal, fetal and obstetrical characteristics, British Columbia, 2000-2009.

	All years		Rate per 10,000 deliveries				2009 vs. 2000		P for trend[2]
	n[1]	rate	2000	2001	2008	2009	RR	95% CI	
Parity									
Nulliparous	342	15.3	20.1	19.9	39.5	31.3	1.56	1.04-2.34	<0.001
Parous	534	28.3	16.0	14.1	18.3	20.4	1.28	0.83-1.98	0.04
Maternal Age (in years)									
<20	56	36.6	27.3	28.6	47.7	55.8	2.05	0.67-6.24	0.07
20-34	612	19.8	15.8	15.0	27.3	25.5	1.61	1.13-2.30	<0.001
≥35	208	23.8	23.4	20.4	28.4	21.2	0.91	0.48-1.70	0.41
BMI									
Underweight	41	23.9	10.4	26.4	25.5	18.4	1.78	0.30-10.62	0.10
Normal	362	20.6	16.3	19.1	30.4	20.4	1.25	0.77-2.03	0.03
Overweight	115	19.8	17.3	13.6	25.0	24.1	1.39	0.62-3.08	0.02
Obese	58	17.8	10.1	6.5	27.3	18.6	1.85	0.48-7.14	0.09
Missing	300	23.4	24.8	15.3	27.6	34.7	1.40	0.89-2.30	0.001
Plurality									
Singleton	832	20.5	17.0	15.3	27.0	24.8	1.46	1.07-1.97	<0.001
Multiple	44	70.7	76.3	113.9	105.6	68.0	0.89	0.24-3.30	0.84
Birth weight (in grams)									
<2500	59	27.8	5.1	59.2	39.4	29.9	5.92	0.73-48.08	0.69
2500-3999	637	19.0	17.2	13.8	22.5	22.0	1.28	0.91-1.81	0.002
≥4000	177	32.3	26.0	18.8	58.3	45.4	1.75	0.92-3.32	<0.001
Gestational age (in weeks)									
<28	7	20.1	0.0	34.5	24.0	21.8	-	-	0.69
28-36	110	33.8	25.1	36.6	45.7	46.4	1.85	0.77-4.45	0.05
37-41	739	20.0	17.1	15.3	27.0	23.3	1.37	0.99-1.89	<0.001
≥42	17	26.6	35.2	0.0	16.5	34.0	0.96	0.16-5.75	0.61
Vaginal delivery									
Spontaneous	321	12.9	11.8	10.2	17.6	16.4	1.39	0.87-2.21	0.004
Instrumental	244	54.7	31.2	41.4	73.3	73.6	2.36	1.29-4.32	<0.001
Cesarean delivery									
No labour	110	20.7	26.9	18.1	21.5	24.7	0.92	0.41-2.04	0.57
With labour, no induction	129	30.4	31.2	30.0	33.7	29.0	0.93	0.43-2.01	0.59
With induction	72	32.2	20.3	9.3	65.0	28.8	1.42	0.42-4.83	0.01
Previous cesarean									
Yes	111	19.8	29.5	18.4	27.6	29.1	0.99	0.50-1.97	0.60
No	765	21.5	16.2	16.4	28.3	24.9	1.53	1.10-2.13	<0.001
Induction of labour									
Yes	236	26.9	19.9	18.9	44.3	31.3	1.57	0.86-2.86	0.002
No	640	19.7	17.3	16.0	24.1	24.0	1.39	0.99-1.96	<0.001
Augmentation of labour (oxytocin)									
Yes	172	27.3	23.2	15.4	38.4	38.0	1.64	0.86-3.12	<0.001
No	704	20.2	16.9	16.9	26.2	23.1	1.37	0.98-1.92	<0.001
Epidural analgesia									
Yes	340	29.4	23.4	20.9	40.2	35.4	1.51	0.92-2.48	<0.001
No	536	18.1	15.9	15.1	23.2	21.4	1.35	0.93-1.96	0.003

[1]n refers to number of cases of atonic postpartum hemorrhage with blood transfusion.
[2]P value based on data for all years between 2000 and 2009.
RR denotes rate ratio and 95% CI denotes 95% confidence intervals.

2.5 Discussion

Previous studies have reported an increase in postpartum hemorrhage between 1991 and 2004 and in severe postpartum hemorrhage between 2003 and 2007 in Canada.[4,11] Our population-based study from British Columbia demonstrated that postpartum hemorrhage rates continued to increase until 2009 with a steep increase between 2006 and 2009. The increase was driven by a 33% rise in atonic postpartum hemorrhage. There was a 43% increase in atonic postpartum hemorrhage with blood transfusion and a 220% increase in atonic postpartum hemorrhage with either uterine suturing, ligation of pelvic vessels or embolization.

The increase in overall and atonic postpartum hemorrhage since 2006 coincided with a change in the definition of postpartum hemorrhage in the Canadian Institute for Health Information 2006 coding standards.[30] The coding standards were modified in 2006 when the definition of postpartum hemorrhage (diagnosis of postpartum hemorrhage noted by a care provider) was expanded to include women with an estimated blood loss of ≥500 mL after vaginal delivery or ≥1000 mL after cesarean delivery, even if a diagnosis of postpartum hemorrhage was not noted in the medical chart. Increases in postpartum hemorrhage diagnoses around this time period were also reported elsewhere in Canada. A recent database report from Nova Scotia documented a 24% increase in postpartum hemorrhage from 2004 to 2005, from 5.0% to 6.2%, followed by a 29% increase between 2006 and 2007, from 6.2% to 8.0%.[54] Although these increases may be partly explained by this definition change, the increase was also observed for severe postpartum hemorrhage and severe atonic postpartum hemorrhage (as measured by concurrent blood transfusion or procedures to control bleeding). The latter are considered objective and clinically important measures of severity. Additionally, the increase did not occur for all subtypes of

postpartum hemorrhage as would be expected if the increase was solely due to a change in the definition of postpartum hemorrhage.

Postpartum hemorrhage rates increased across the majority of maternal, fetal and obstetric characteristics and this finding does not point to any single cause. Notably, atonic postpartum hemorrhage increased even among cesarean deliveries with no labour and no labour induction. One mechanism suggested for uterine atony (and for the current postpartum hemorrhage epidemic[3]) is desensitization of uterine tissue to oxytocin due to its liberal administration during labour induction and augmentation.[27] However, the observed increase in postpartum hemorrhage occurred even among women not induced or augmented, highlighting the fact that other causes may be responsible. Factors not associated with an increasing trend in postpartum hemorrhage (such as gestational age <28 weeks) typically had a low frequency and such findings are not inconsistent with an across-the-board increase in postpartum hemorrhage. The higher rates of atonic postpartum hemorrhage among vaginal deliveries (as opposed to cesarean deliveries) may be related to differing definitions of postpartum hemorrhage for these two routes of delivery. Cesarean deliveries were associated with higher rates of severe atonic postpartum hemorrhage than vaginal deliveries (Table 2.4).

The declining trend in postpartum hemorrhage among women from the Northern Health Authority may provide some etiologic insight into the increases seen elsewhere. The inter-relationship between risk factors for postpartum hemorrhage such epidural analgesia, oxytocin induction and instrumental vaginal delivery require further investigation in order to delineate their relative contributions to the change in postpartum hemorrhage rates. On the other hand, the

Northern Health Authority represented one of the smaller regions and rates by year fluctuated somewhat even though the linear trend was statistically significant (Table 2.2). The fact that postpartum hemorrhage with hysterectomy did not increase over the latter half of the study period is a welcome development as Canada (and British Columbia in particular) has higher postpartum hemorrhage with hysterectomy rates as compared with other countries.[1,11] Increasing use of procedures other than hysterectomy to control bleeding may be responsible for the stable trend in hysterectomy for postpartum hemorrhage.

Key strengths of our study include use of procedure code definitions for procedures to control bleeding that did not change over time, and postpartum hemorrhage code definitions that remained unchanged between ICD-9 and ICD-10. However, as noted, there was a change in the definition of postpartum hemorrhage in 2006. Besides blood transfusions and hysterectomies, other interventions with postpartum hemorrhage have not been reported in previous studies and it is unclear to what extent they have been consistently documented over time. Limitations of our study include use of information from a large perinatal database, which could contain some coding and transcription errors. In addition, multiple comparisons may increase the probability of falsely significant findings. Other limitations include problems with the clinical diagnosis of postpartum hemorrhage since estimation of blood loss during childbirth is difficult to standardize. Our use of different measures of severe postpartum hemorrhage was important for identifying increasing trends in clinically relevant cases of postpartum hemorrhage.

Atonic postpartum hemorrhage and severe atonic postpartum hemorrhage rates continued to increase in British Columbia across a range of maternal, fetal and obstetric characteristics. The

46% increase in atonic postpartum hemorrhage with blood transfusion between 2000 and 2009 is substantial. Given that these increases were similar to findings from other countries and jurisdictions employing different definitions and distinct markers of severity, further research is required to identify and address the cause or causes of the increase in atonic postpartum hemorrhage.

Chapter 3: Epidemiologic investigation of an increase in postpartum hemorrhage in British Columbia: Etiologic analysis

3.1 Synopsis

Objective: Increases in atonic postpartum hemorrhage have been reported from several countries in recent years. We attempted to determine the potential cause of the increase in atonic and severe atonic postpartum hemorrhage.

Methods: Detailed clinical information was obtained for 371,193 women from the British Columbia Perinatal Data Registry, which included all live births or stillbirths from hospital or home deliveries in British Columbia, Canada between 2001 and 2009. A population-based retrospective cohort study was carried out where the outcomes of interest were atonic postpartum hemorrhage and severe atonic postpartum hemorrhage (atonic postpartum hemorrhage with blood transfusion ≥1 unit; atonic postpartum hemorrhage with blood transfusion ≥3 units or procedures to control bleeding), while determinants studied included maternal characteristics (e.g., age, parity, body mass index) and obstetrics practice factors (e.g., labour induction, augmentation, cesarean delivery). Year-specific unadjusted and adjusted odds ratios for the outcomes were compared using logistic regression.

Results: Atonic postpartum hemorrhage increased from 4.8% in 2001 to 6.3% in 2009, atonic postpartum hemorrhage with blood transfusion ≥1 unit increased from 16.6 in 2001 to 25.5 per 10,000 deliveries in 2009 and atonic postpartum hemorrhage with blood transfusion ≥3 units or procedures to control bleeding increased from 11.9 to 17.6 per 10,000 deliveries. The crude 34% (95% CI 26-42) increase in atonic postpartum hemorrhage between 2001 and 2009 remained unchanged (42% increase, 95% 34-51) after adjustment for determinants of

PPH. Similarly, adjustment did not explain the increase in severe atonic postpartum hemorrhage.

Conclusion: Changes in maternal characteristics and obstetric practice do not explain the recent increase in atonic and severe atonic postpartum hemorrhage.

3.2 Background and objectives

Chapter 3 builds on the work in Chapter 2 to include several other risk factors for postpartum hemorrhage, and comprises of an etiologic multivariable analyses. Risk factors for atonic and severe atonic postpartum hemorrhage were modeled using logistic regression analyses to determine whether changes in the risk factors over time explained the rise in atonic and severe atonic postpartum hemorrhage. This etiologic analysis was restricted to years 2001 to 2009 as ICD-10 codes could be used throughout this period.

Increases in postpartum hemorrhage and severe postpartum hemorrhage have been reported in Australia, Canada, Ireland, Scotland, Norway, Sweden, and the United States over the last two decades.[1,3,4,6-10,14] The increases were driven by rising rates of atonic and other early postpartum hemorrhage following delivery of the placenta.[3,4,6] Although maternal deaths are rare in developed countries,[55] the observed increase in postpartum hemorrhage is concerning because postpartum hemorrhage is an important cause of maternal death and the most common severe maternal morbidity.[56] Isolating the cause of the rise in atonic postpartum hemorrhage is key to identifying prevention strategies.

Recent studies have examined various potential causes for the temporal increase in postpartum hemorrhage including changes in maternal and pregnancy characteristics, such as

increases in older maternal age, obesity, and multiple pregnancies, and changes in obstetric practice, including increases in labour induction and cesarean delivery.[3,6,7,9,33,41] However, the cause(s) for the temporal increase in atonic postpartum hemorrhage remains unclear and as discussed in Chapter 2 there is some suspicion that changes in the diagnosis of postpartum hemorrhage may have been partly responsible for the rising rates.

We carried out a population-based study to identify the potential cause or causes of the temporal increase in atonic postpartum hemorrhage using data from British Columbia, Canada, where atonic postpartum hemorrhage has increased in recent years.[57] Several risk factors not available at the national level were included in our study, including pre-pregnancy body mass index, birth weight, gestational age and augmentation of labour contractions with oxytocin. Finally, we examined changes in both atonic postpartum hemorrhage and severe atonic postpartum hemorrhage (measured using two different markers of severity) in order to ascertain if over-diagnosis of borderline atonic postpartum hemorrhage was potentially responsible for the increases in rates.

3.3 Methods

The study population included all women residents of British Columbia who delivered between April 1st, 2001 and March 31st, 2010 (hereafter referred to as years 2001 to 2009). Analyses for this study were restricted to the years 2001 and onwards as this is when ICD-10 coding was implemented across the province. Data were obtained from the British Columbia Perinatal Data Registry, a population-based registry which contains information on approximately 99% of births in the province including home births attended by registered midwives.

The outcomes of interest were any atonic postpartum hemorrhage and severe atonic postpartum hemorrhage. Postpartum hemorrhage was defined as an estimated blood loss of ≥500 mL after vaginal delivery or >1000 mL after cesarean delivery or as otherwise diagnosed and documented by the health care provider. Estimated postpartum blood loss was routinely collected by health care providers as a range of <500, 500-1000 or >1000 and then used by the data abstracters in conjunction with other chart information to code postpartum hemorrhage. The ICD-9 code 666.1 and the ICD-10 code O72.1 were used to identify atonic postpartum hemorrhage (hemorrhage occurring within the first 24 hours of delivery not including postpartum hemorrhage caused by retained placenta or coagulation defects). Temporal trends were also examined for the other subtypes of postpartum hemorrhage including postpartum hemorrhage due to retained placenta, secondary postpartum hemorrhage (postpartum hemorrhage more than 24 hours after delivery) and postpartum hemorrhage due to coagulation defects.

Maternal, fetal and obstetrical characteristics of interest included maternal age (<20, 20-24, 25-29, 30-34, 35-39, and ≥40 years), parity (0, 1-2, 3-4 and ≥5), body mass index (BMI) (defined as underweight, normal range, overweight and obese based on the World Health Organization classification system),[58] birth weight (<1500, 1500-2499, 2500-3999, 4000-4499, and ≥4500g), gestational age (<28, 28-31, 32-36, 37-41, and ≥42 weeks), whether or not the woman was a current smoker, had multiple (multi-fetal) pregnancy, a cesarean delivery, a previous cesarean delivery, received epidural analgesia, or had her labour induced or augmented. Other characteristics of interest were occurrence of a uterine rupture, 3rd or 4th degree perineal tear, high vaginal laceration, cervical laceration, placenta previa, placental abruption, breech presentation or transverse lie at delivery, polyhydramnios, diagnosis of a

prolonged first stage of labour, diagnosis of a prolonged second stage of labour, pre-eclampsia, chorioamnionitis, and forceps, vacuum or forceps and vacuum delivery.

Two binary measures of severe atonic postpartum hemorrhage included, first, atonic postpartum hemorrhage in conjunction with blood transfusion of one or more units of whole blood or packed red blood cells following delivery, and a composite outcome which represented very severe atonic postpartum hemorrhage. The second composite outcome comprised atonic postpartum hemorrhage with any of the following (1) receipt of three or more units of whole blood or packed red blood cells, (2) emergency hysterectomy, (3) uterine (and vaginal) packing, (4) suturing of uterus, (5) ligation of pelvic vessels, or (6) embolization of pelvic vessels. The composite outcome was used to account for potential changes in obstetric practice that may have reduced the threshold for blood transfusion. Hysterectomy and procedures to control bleeding were identified using the Canadian Classification of Health Interventions codes (Supplementary Table A.1 provides the diagnosis and procedure codes used).

Temporal trends in rates of atonic postpartum hemorrhage, severe atonic postpartum hemorrhage, and maternal, fetal and obstetric characteristics were assessed both by contrasting the rates in 2009 versus 2001 (using rate ratios and 95% CIs) and by examining the trend across all years using a chi-square test for linear trend in proportions. Calendar time was also modelled using restricted cubic splines in order to explore a non-linear relationship with the outcome. Graphs presented 95% confidence intervals unless their presentation reduced the clarity of findings. Covariates were modeled using continuous or categorical variables after assessing assumptions regarding linearity and assessing ease of interpretation.

In order to account for missing pre-pregnancy body mass index (BMI) data, multiple imputation was used to impute 20% missing data for height and 23% missing data for pre-pregnancy weight. Multiple imputation assumed an underlying multivariate normal model, comprised of 20 imputed datasets, and included all study covariates and outcomes as model covariates using MI Estimate command in Stata SE version 11 (Appendix A provides more detail of the justification for our choice of multiple imputation modeling).

The three outcomes (atonic postpartum hemorrhage, atonic postpartum hemorrhage with blood transfusion ≥1 unit, and atonic postpartum hemorrhage with blood transfusion ≥3 unit or a procedure to control bleeding) were modeled separately using logistic regression. Since the definition of postpartum hemorrhage varied by mode of delivery (≥500 mL for vaginal and >1000 mL for cesarean delivery), sensitivity analyses modeling atonic postpartum hemorrhage separately among vaginal and cesarean deliveries were also carried out. We further carried out sensitivity analyses in which covariates were added incrementally to the model starting with maternal pre-pregnancy factors, followed by maternal pregnancy factors, and lastly obstetric factors, namely, labour induction and labour augmentation, epidural analgesia and mode of delivery.

The crude odds ratio and 95% CI expressing the period effect (2009 vs 2001) was compared with the adjusted odds ratio and 95% CI to determine if the adjustment for changes in maternal characteristics and obstetric practice explained the temporal trend in atonic and severe atonic postpartum hemorrhage. We anticipated that the crude odds ratios expressing the temporal increase in atonic postpartum hemorrhage and severe atonic postpartum hemorrhage would be attenuated (i.e., closer to 1) after adjustment for risk factors that were

responsible for the rise in atonic postpartum hemorrhage and severe atonic postpartum hemorrhage. Generalized estimating equations, with an assumed unstructured correlation structure, were used to account for repeat pregnancies to the same woman during the study period. Statistical significance was assessed based on two-sided P values and a P-value of <0.05 was considered statistically significant. Analyses were carried out using SAS version 9.2 and Stata SE version 11.

3.4 Results

There were 372,259 deliveries to residents of British Columbia between 2001 and 2009. We restricted our analyses to 371,193 deliveries which had had complete information for gestational age and birth weight (0.3% missing). The rate of atonic postpartum hemorrhage increased from 4.8% in 2001 to 6.3% in 2009 (34% increase in unadjusted odds, 95% CI 26-42%). Among vaginal deliveries, atonic postpartum hemorrhage increased by 35% (95% CI 27-44%) from 6.0% in 2001 to 7.9% in 2009, while atonic postpartum hemorrhage among cesarean deliveries increased by 95% (95% CI 61-137%) from 1.4% to 2.7% (Figure 3.1A). The rate of atonic postpartum hemorrhage with blood transfusion ≥1 unit increased by 51% (95% CI 11-104%) from 16.6 to 25.5 per 10,000 deliveries from 2001 to 2009, while the composite outcome for severe atonic postpartum hemorrhage with blood transfusion ≥3 units or procedures to control bleeding increased by 47% (95% CI 2-112) from 11.9 in 2001 to 17.6 per 10,000 deliveries in 2009. Atonic postpartum hemorrhage with blood transfusion ≥1 unit increased steadily between 2001 and 2009 while uterine suturing, ligation or embolization increased most markedly between 2007 and 2009. Hysterectomy for atonic postpartum hemorrhage increased until 2006, and then decreased (Figure 3.1B).

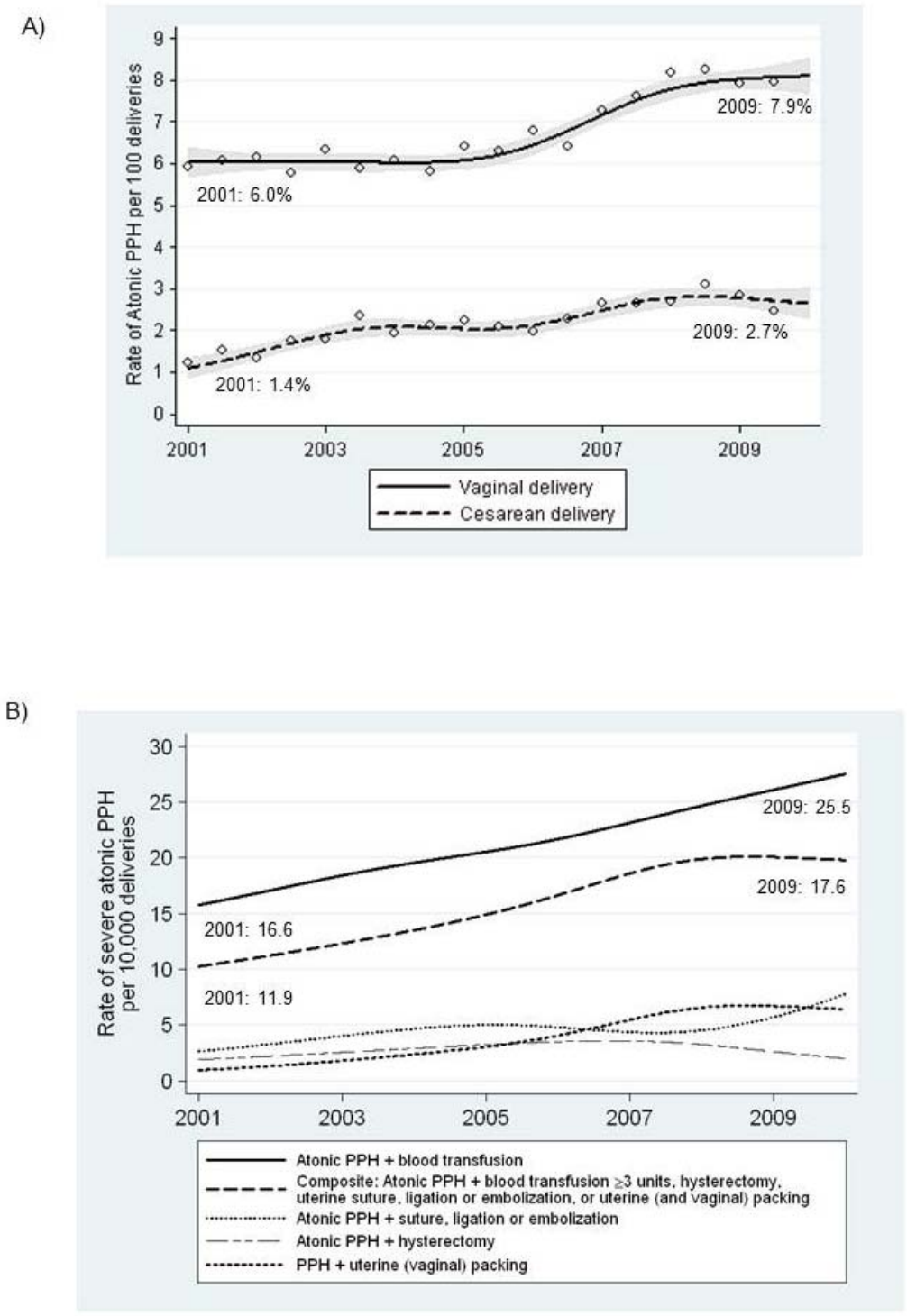


Figure 3.1. Temporal trends in atonic postpartum hemorrhage (PPH) by vaginal versus cesarean delivery, smoothed rates with 95% confidence intervals overlaid on observed semi-annual rates (Panel A), and severe atonic PPH as measured by PPH in conjunction with various markers of severity, smoothed rates (Panel B).

No significant changes were observed for other subtypes of postpartum hemorrhage, including third stage hemorrhage, secondary postpartum hemorrhage and postpartum hemorrhage due to coagulation defects (all P values for linear trend in proportions >0.05). Nor were marked non-linear trends observed for non-atonic postpartum hemorrhage (Supplementary Table A.2). For postpartum hemorrhage with blood transfusion, only atonic postpartum hemorrhage with blood transfusion increased significantly (analyses by postpartum hemorrhage subtypes and rates of blood transfusion by subtype are summarized in Supplementary Tables A.2 and A.3).

Changes between 2001 and 2009 in maternal, fetal and obstetric factors are summarized in Table 3.1. Risk factors for atonic postpartum hemorrhage that increased over the study period included maternal age ≥35 years, primiparity, overweight and obese pre-pregnancy BMI, gestational age <28 weeks and 32-36 weeks, multiple pregnancy and previous cesarean delivery. Obstetric factors that increased significantly were cesarean delivery, oxytocin augmentation, epidural analgesia, polyhydramnios, pre-eclampsia, prolonged second stage of labour, 3rd or 4th degree perineal tears, combined forceps and vacuum deliveries and chorioamnionitis.

Table 3.2 shows the crude and adjusted temporal increase in atonic postpartum hemorrhage and the effects of various risk factors for atonic postpartum hemorrhage. Known determinants of atonic postpartum hemorrhage did not explain the temporal increase in atonic postpartum hemorrhage; the crude 34% (95% CI 26-42) increase in atonic postpartum hemorrhage between 2001 and 2009 was not attenuated (42% increase, 95% 34-51) after adjustment for

changes in the listed determinants of postpartum hemorrhage. Factors associated with atonic postpartum hemorrhage are also shown in Table 3.2.

Table 3.3 summarizes the crude and adjusted temporal increase in atonic postpartum hemorrhage in conjunction with blood transfusion ≥1 unit. Known determinants of atonic postpartum hemorrhage did not explain the 51% (95% CI 11-104%) increase in atonic postpartum hemorrhage with blood transfusion between 2001 and 2009 (adjusted increase 57%, 95% CI 15-115%). Similar results were observed for severe atonic postpartum hemorrhage as measured by the composite outcome of blood transfusion of ≥3 units or the use of procedures to control bleeding (Table 3.4); the crude 47% (95% CI 2-112) increase in this composite outcome was not reduced upon adjustment for known determinants of severe atonic postpartum hemorrhage (adjusted increase 47%, 95% CI 2-113). Additional analyses carried out to assess temporal trends and adjustment for temporal trends among vaginal and cesarean deliveries showed the same patterns.

Table 3.1. Temporal trends in maternal, fetal and obstetric characteristics, British Columbia, Canada, 2001 to 2009 (n=371,193 deliveries).

	Rate per 100		2009 vs. 2001		P for trend
	2001	2009	RR	(95% CI)	
Maternal age <20 years	4.40	3.23	0.73	(0.68-0.79)	<0.001
20-24	15.5	13.9	0.90	(0.87-0.92)	<0.001
25-29	28.5	28.5	1.00	(0.99-1.02)	0.84
30-34	31.9	32.0	1.01	(0.99-1.02)	0.005
35-39	16.5	18.3	1.11	(1.08-1.15)	<0.001
≥40	3.28	4.08	1.24	(1.16-1.33)	<0.001
Parity 0	44.5	46.9	1.06	(1.04-1.07)	<0.001
1-2	49.9	47.9	0.96	(0.95-0.97)	<0.001
3-4	4.80	4.45	0.92	(0.87-0.98)	0.003
≥5	0.82	0.72	0.88	(0.74-1.01)	0.72
BMI* Underweight (<18.5 kg/m^2)	6.49	5.56	0.86	(0.80-0.91)	<0.001
Normal range (18.5-24)	62.7	60.3	0.96	(0.94-0.97)	<0.001
Overweight (25-29)	20.2	21.3	1.05	(1.02-1.09)	<0.001
Obese (≥30)	10.6	12.9	1.21	(1.15-1.27)	<0.001
Missing	33.8	26.4	0.78	(0.76-0.80)	<0.001
Birth weight <1500 g	1.11	1.28	1.15	(1.01-1.31)	0.02
1500-2499	3.57	4.01	1.12	(1.04-1.20)	0.002
2500-3999	80.5	82.2	1.02	(1.01-1.02)	<0.001
4000-4499	12.3	10.4	0.85	(0.11-0.18)	<0.001
≥4500	2.51	2.05	0.82	(0.74-0.89)	<0.001
Gestational age <28 weeks	0.70	0.91	1.30	(1.11-1.50)	0.001
28-31	0.58	0.64	1.10	(0.93-1.31)	0.06
32-36	6.30	7.63	1.21	(1.15-1.27)	<0.001
37-41	90.7	89.5	0.99	(0.98-0.99)	<0.001
≥42	1.72	1.34	0.78	(0.70-0.87)	<0.001
Current Smoker	12.3	8.86	0.72	(0.69-0.75)	<0.001
Multiple pregnancy	1.33	1.65	1.24	(1.11-1.39)	0.001
Cesarean delivery	26.7	30.2	1.13	(1.11-1.16)	<0.001
Previous cesarean	12.3	14.8	1.20	(1.16-1.24)	<0.001
Epidural analgesia	26.6	29.4	1.10	(1.08-1.13)	<0.001
Induction	21.2	20.0	0.94	(0.92-0.97)	<0.001
Oxytocin augmentation	14.8	16.1	1.09	(1.05-1.12)	<0.001
Uterine rupture	0.15	0.10	0.67	(0.43-0.97)	0.3
Perineal tear (3/4th degree)	2.79	3.06	1.10	(1.01-1.18)	0.001
High vaginal laceration	0.39	0.20	0.51	(0.39-0.66)	0.001
Cervical laceration	0.21	0.20	0.95	(0.69-1.25)	0.97
Placenta previa	0.63	0.68	1.08	(0.90-1.26)	0.18
Placental abruption	1.16	1.00	0.86	(0.76-0.98)	0.023
Breech	4.44	4.32	0.97	(0.91-1.03)	0.99
Transverse lie	0.39	0.33	0.85	(0.67-1.05)	<0.001
Polyhydramnios	0.58	0.77	1.33	(1.11-1.55)	<0.001
Prolonged first stage	4.33	3.53	0.82	(0.76-0.87)	<0.001
Prolonged second stage	7.88	8.35	1.06	(1.01-1.11)	0.004
Pre-eclampsia	1.07	1.20	1.12	(0.99-1.28)	<0.001
Chorioamnionitis	1.16	2.01	1.73	(1.56-1.97)	<0.001
Forceps	4.04	2.71	0.67	(0.62-0.72)	<0.001
Vacuum	7.17	7.13	0.99	(0.94-1.04)	0.28
Forceps and vacuum	0.37	0.63	1.70	(1.40-2.08)	<0.001

*BMI rates by category exclude missing category.
Rates expressed per 100 deliveries. RR denotes rate ratio, CI confidence interval and BMI body mass index. Subjects with missing data were excluded from calculations.

Table 3.2. Crude and adjusted effects of year and maternal, fetal and obstetric factors on atonic postpartum hemorrhage, British Columbia, Canada, 2009 versus 2001 (n=371,193 deliveries).

Determinant	Crude			Adjusted		
	OR	95% CI	P value	OR[†]	95% CI	P value
Year 2002	0.99	0.93-1.06	0.88	1.01	0.95-1.08	0.71
2003	1.05	0.98-1.11	0.17	1.08	1.01-1.15	0.03
2004	1.00	0.94-1.07	0.95	1.05	0.98-1.12	0.18
2005	1.07	1.00-1.14	0.04	1.12	1.05-1.19	0.001
2006	1.10	1.04-1.17	<0.001	1.16	1.08-1.23	<0.001
2007	1.26	1.18-1.33	<0.001	1.34	1.26-1.43	<0.001
2008	1.39	1.31-1.48	<0.001	1.49	1.40-1.58	<0.001
2009	1.34	1.26-1.42	<0.001	1.42	1.34-1.51	<0.001
Maternal age <20 years	1.11	1.02-1.20	0.01	1.04	0.96-1.13	0.30
25-29	0.94	0.90-0.98	0.01	0.95	0.91-1.00	0.04
30-34	0.94	0.90-0.98	0.01	1.00	0.95-1.04	0.84
35-39	0.91	0.87-0.96	<0.001	1.05	0.99-1.11	0.08
≥40	0.90	0.83-0.98	0.02	1.13	1.04-1.24	0.005
Parity 0	1.51	1.47-1.56	<0.001	1.29	1.24-1.34	<0.001
3-4	1.00	0.93-1.08	0.98	0.95	0.88-1.02	0.16
≥5	1.03	0.86-1.24)	0.73	0.94	0.78-1.12	0.48
Birth weight <1500 g	0.45	0.37-0.55	<0.001	0.58	0.40-0.85	0.005
1500-2499	0.80	0.73-0.86	<0.001	0.71	0.64-0.78	<0.001
4000-4499	1.37	1.31-1.43	<0.001	1.49	1.43-1.56	<0.001
≥4500	1.59	1.46-1.73	<0.001	1.95	1.79-2.13	<0.001
BMI (kg/m^2)	0.99	0.98-0.99	<0.001	1.00	0.99-1.00	0.04
Gestational age <28 wks	0.33	0.26-0.43	<0.001	0.46	0.29-0.73	0.001
28-31	0.77	0.64-0.94	0.01	1.16	0.88-1.53	0.28
32-36	0.84	0.79-0.89	<0.001	0.92	0.86-0.98	0.01
≥42	1.13	1.01-1.26	0.03	1.01	0.90-1.14	0.81
Current Smoker	0.78	0.74-0.82	<0.001	0.83	0.79-0.88	<0.001
Multiple pregnancy	1.81	1.66-1.98	<0.001	3.55	3.20-3.94	<0.001
Cesarean delivery	0.31	0.30-0.33	<0.001	0.30	0.29-0.32	<0.001
Previous cesarean	0.43	0.40-0.45	<0.001	1.02	0.96-1.10	0.49
Epidural analgesia	1.54	1.50-1.59	<0.001	1.05	1.02-1.09	0.005
Induction	1.29	1.24-1.33	<0.001	1.16	1.12-1.20	<0.001
Oxytocin augmentation	1.49	1.44-1.54	<0.001	1.09	1.04-1.14	<0.001
Uterine rupture	1.27	0.87-1.85	0.21	2.59	1.67-4.02	<0.001
Perineal tear (3^{rd} / 4^{th})	3.48	3.29-3.67	<0.001	1.82	1.71-1.93	<0.001
High vaginal laceration	6.07	5.28-6.97	<0.001	3.07	2.63-3.58	<0.001
Cervical laceration	10.40	8.90-12.16	<0.001	8.37	7.00-9.99	<0.001
Placenta previa	1.34	1.15-1.56	<0.001	3.91	3.32-4.61	<0.001
Placental abruption	1.14	1.01-1.30	0.04	1.62	1.41-1.86	<0.001
Breech	0.32	0.29-0.36	<0.001	0.84	0.74-0.95	0.005
Transverse lie	0.66	0.49-0.89	0.01	1.41	1.03-1.93	0.03
Polyhydramnios	0.80	0.65-0.97	0.03	0.95	0.77-1.16	0.60
Prolonged first stage	1.73	1.63-1.84	<0.001	1.32	1.24-1.41	<0.001
Prolonged second stage	2.40	2.30-2.49	<0.001	1.39	1.32-1.46	<0.001
Pre-eclampsia	1.55	1.39-1.73	<0.001	1.81	1.61-2.04	<0.001
Chorioamnionitis	1.41	1.27-1.56	<0.001	1.63	1.46-1.82	<0.001
Forceps	3.68	3.50-3.86	<0.001	1.80	1.69-1.91	<0.001
Vacuum	1.88	1.79-1.96	<0.001	1.23	1.17-1.29	<0.001
Forceps and vacuum	3.38	2.99-3.81	<0.001	1.69	1.48-1.92	<0.001

[†]Adjusted for all variables in the table. OR denotes odds ratio, CI confidence interval and BMI body mass index. Reference categories: calendar year 2001, age 20-24 years, parity 1-2, birth weight 2500-3999 g, gestational age 37-41 weeks and absence of specified factor.

Table 3.3. Crude and adjusted effects of year and maternal, fetal and obstetric factors on atonic postpartum hemorrhage and blood transfusion ≥ 1 unit, British Columbia, Canada, 2009 versus 2001 (n=371,193 deliveries).

Determinant	Crude			Adjusted		
	OR	95% CI	P value	OR†	95% CI	P value
Year 2002	1.00	0.71-1.40	0.99	1.04	0.74-1.47	0.81
2003	1.19	0.86-1.66	0.28	1.24	0.89-1.73	0.20
2004	1.15	0.83-1.59	0.42	1.19	0.85-1.66	0.32
2005	1.40	1.02-1.92	0.04	1.43	1.04-1.98	0.03
2006	1.25	0.91-1.72	0.17	1.30	0.94-1.80	0.11
2007	1.37	1.00-1.87	0.05	1.44	1.05-1.98	0.03
2008	1.68	1.25-2.27	<0.001	1.77	1.30-2.40	<0.001
2009	1.51	1.11-2.04	0.01	1.57	1.15-2.15	0.004
Maternal age <20 years	1.81	1.30-2.51	<0.001	1.75	1.25-2.45	0.001
25-29	0.86	0.68-1.09	0.21	0.82	0.65-1.04	0.10
30-34	1.01	0.81-1.25	0.95	0.93	0.74-1.16	0.52
35-39	1.03	0.80-1.31	0.83	0.94	0.73-1.22	0.66
≥40	1.59	1.13-2.23	0.01	1.29	0.90-1.85	0.17
Parity 0	2.00	1.73-2.33	<0.001	1.30	1.06-1.60	0.01
3-4	1.28	0.88-1.84	0.19	1.29	0.88-1.90	0.19
≥5	2.33	1.24-4.37	0.01	2.53	1.33-4.80	0.005
Birth weight <1500 g	1.40	0.79-2.48	0.25	0.84	0.23-3.03	0.79
1500-2499	1.64	1.21-2.21	<0.001	0.81	0.56-1.17	0.261
4000-4499	1.68	1.39-2.02	<0.001	1.78	1.46-2.16	<0.001
≥4500	2.00	1.39-2.89	<0.001	2.15	1.46-3.17	<0.001
BMI (kg/m^2)	0.98	0.97-1.00	0.08	0.98	0.97-1.00	0.11
Gestational age <28 wks	0.98	0.44-2.21	0.97	1.06	0.23-4.83	0.94
28-31	1.87	0.97-3.60	0.06	1.37	0.46-4.01	0.57
32-36	1.67	1.34-2.08	<0.001	1.42	1.10-1.85	0.008
≥42	1.24	0.73-2.10	0.43	0.94	0.53-1.67	0.84
Current Smoker	0.93	0.73-1.17	0.52	0.99	0.78-1.27	0.96
Multiple pregnancy	3.22	2.32-4.47	<0.001	2.79	1.93-4.06	<0.001
Cesarean delivery	1.34	1.16-1.55	<0.001	1.74	1.39-2.18	<0.001
Previous cesarean	0.85	0.69-1.05	0.14	0.95	0.70-1.29	0.75
Epidural analgesia	1.64	1.43-1.89	<0.001	0.90	0.74-1.08	0.25
Induction	1.42	1.22-1.67	<0.001	1.22	1.02-1.46	0.03
Oxytocin augmentation	1.36	1.14-1.62	<0.001	0.93	0.76-1.14	0.51
Uterine rupture	12.59	6.90-22.97	<0.001	8.45	3.90-18.32	<0.001
Perineal tear (3rd / 4th)	4.50	3.63-5.58	<0.001	2.75	2.13-3.55	<0.001
High vaginal laceration	18.66	13.45-25.89	<0.001	7.72	5.09-11.72	<0.001
Cervical laceration	41.15	30.75-55.06	<0.001	24.83	17.28-35.67	<0.001
Placenta previa	6.55	4.61-9.30	<0.001	6.38	4.35-9.37	<0.001
Placental abruption	2.49	1.63-3.81	<0.001	1.81	1.14-2.88	0.01
Breech	0.86	0.60-1.24	0.42	0.75	0.51-1.11	0.15
Transverse lie	2.71	1.28-5.70	0.01	1.71	0.80-3.64	0.17
Polyhydramnios	1.82	0.94-3.51	0.08	1.34	0.68-2.62	0.40
Prolonged first stage	1.57	1.17-2.11	<0.001	1.25	0.91-1.71	0.17
Prolonged second stage	2.79	2.34-3.34	<0.001	1.46	1.17-1.82	0.001
Pre-eclampsia	3.97	2.84-5.56	<0.001	2.88	1.98-4.20	<0.001
Chorioamnionitis	3.29	2.37-4.57	<0.001	2.27	1.58-3.27	<0.001
Forceps	4.71	3.85-5.76	<0.001	3.32	2.49-4.41	<0.001
Vacuum	1.96	1.59-2.41	<0.001	2.22	1.73-2.86	<0.001
Forceps and vacuum	4.13	2.55-6.69	<0.001	3.11	1.79-5.39	<0.001

†Adjusted for all variables in the table. OR denotes odds ratio, CI confidence interval and BMI body mass index. Reference categories: calendar year 2001, age 20-24 years, parity 1-2, birth weight 2500-3999 g, gestational age 37-41 weeks and absence of specified factor.

Table 3.4. Crude and adjusted effects of year and maternal, fetal and obstetric factors on severe atonic postpartum hemorrhage (PPH) defined using a composite outcome, British Columbia, 2009 versus 2001.

Determinant	Crude			Adjusted		
	OR	95% CI	P value	OR†	95% CI	P value
Year 2002	0.83	0.54-1.27	0.39	0.86	0.56-1.32	0.49
2003	1.02	0.68-1.53	0.92	1.03	0.69-1.55	0.87
2004	1.48	1.02-2.14	0.04	1.49	1.03-2.17	0.04
2005	1.26	0.86-1.84	0.24	1.23	0.83-1.81	0.31
2006	1.26	0.86-1.85	0.23	1.27	0.86-1.86	0.22
2007	1.77	1.25-2.52	<0.001	1.80	1.26-2.58	0.001
2008	1.89	1.33-2.67	<0.001	1.89	1.33-2.69	<0.001
2009	1.47	1.02-2.12	0.04	1.47	1.02-2.13	0.04
Maternal age <20 years	1.25	0.79-2.00	0.34	1.24	0.77-1.99	0.37
25-29	0.79	0.59-1.06	0.12	0.73	0.54-0.99	0.04
30-34	1.25	0.96-1.62	0.10	1.08	0.82-1.42	0.58
35-39	1.42	1.07-1.88	0.02	1.20	0.88-1.62	0.24
≥40	2.55	1.78-3.66	<0.001	1.87	1.28-2.74	0.001
Parity 0	1.85	1.56-2.20	<0.001	1.39	1.09-1.77	0.008
3-4	1.44	0.97-2.13	0.07	1.44	0.96-2.18	0.08
≥5	1.20	0.45-3.23	0.71	1.24	0.45-3.37	0.68
Birth weight <1500 g	1.38	0.71-2.67	0.34	1.08	0.22-5.35	0.93
1500-2499	1.77	1.27-2.47	<0.001	0.93	0.63-1.38	0.73
4000-4499	1.36	1.08-1.73	0.01	1.45	1.13-1.85	0.003
≥4500	1.75	1.12-2.74	0.01	1.85	1.16-2.95	0.01
BMI (kg/m^2)	0.99	0.97-1.01	0.19	0.98	0.96-1.00	0.13
Gestational age <28 wks	0.89	0.33-2.39	0.82	0.66	0.09-5.07	0.69
28-31	1.96	0.93-4.14	0.08	0.88	0.25-3.09	0.84
32-36	1.73	1.35-2.22	<0.001	1.16	0.87-1.56	0.32
≥42	1.08	0.56-2.09	0.82	0.92	0.47-1.84	0.82
Current Smoker	0.73	0.54-0.98	0.04	0.86	0.63-1.17	0.33
Multiple pregnancy	3.57	2.49-5.13	<0.001	2.80	1.85-4.23	<0.001
Cesarean delivery	2.01	1.71-2.37	<0.001	2.07	1.60-2.67	<0.001
Previous cesarean	1.08	0.86-1.35	0.52	0.97	0.69-1.36	0.86
Epidural analgesia	1.86	1.58-2.19	<0.001	1.27	1.03-1.57	0.03
Induction	1.11	0.92-1.35	0.28	0.95	0.76-1.18	0.62
Oxytocin augmentation	1.35	1.10-1.65	<0.001	0.87	0.68-1.10	0.25
Uterine rupture	22.04	12.86-37.77	<0.001	12.95	6.82-24.59	<0.001
Perineal tear (3^{rd} / 4^{th})	3.46	2.62-4.56	<0.001	2.66	1.90-3.72	<0.001
High vaginal laceration	17.23	11.66-25.48	<0.001	7.61	4.65-12.44	<0.001
Cervical laceration	39.78	28.37-55.78	<0.001	25.12	16.69-37.81	<0.001
Placenta previa	12.62	9.29-17.15	<0.001	9.89	7.00-13.97	<0.001
Placental abruption	3.74	2.48-5.63	<0.001	2.67	1.73-4.11	<0.001
Breech	1.02	0.69-1.51	0.94	0.73	0.48-1.12	0.15
Transverse lie	2.61	1.08-6.30	0.03	1.13	0.46-2.75	0.79
Polyhydramnios	3.04	1.67-5.52	<0.001	2.27	1.24-4.15	0.01
Prolonged first stage	1.46	1.03-2.07	0.04	1.13	0.78-1.65	0.52
Prolonged second stage	2.49	2.01-3.08	<0.001	1.50	1.15-1.96	0.003
Pre-eclampsia	2.64	1.65-4.22	<0.001	1.88	1.11-3.18	0.02
Chorioamnionitis	2.79	1.86-4.21	<0.001	1.65	1.05-2.60	0.03
Forceps	3.63	2.81-4.71	<0.001	2.25	1.55-3.26	<0.001
Vacuum	1.25	0.93-1.67	0.13	1.42	1.01-2.00	0.05
Forceps and vacuum	3.26	1.74-6.10	<0.001	2.15	1.06-4.35	0.03

Composite outcome: Blood transfusion ≥3 units, hysterectomy, or use of a procedure to control bleeding.
†Adjusted for all variables in the table. OR denotes odds ratio, CI confidence interval and BMI body mass index. Reference categories: calendar year 2001, age 20-24 years, parity 1-2, birth weight 2500-3999 g, gestational age 37-41 weeks and absence of specified factor.

Sensitivity analyses revealed that maternal pre-pregnancy factors (age, BMI, parity, smoking status, and previous cesarean delivery) and maternal pregnancy factors (multi-fetal gestation, pre-eclampsia, placenta previa, placental abruption, chorioamnionitis and polyhydramnios) attenuated the odds ratio for the rise in postpartum hemorrhage with blood transfusion slightly (from unadjusted OR=1.50, 95% CI 1.11-2.04 to adjusted OR=1.45, 95% 1.06-1.96). The addition of the obstetric factors such as labour induction and labour augmentation, followed by epidural analgesia and cesarean delivery, made little difference to the odds ratio for the temporal increase in postpartum hemorrhage with blood transfusion (Supplementary Table A.4). Results were similar for the other two outcomes (atonic postpartum hemorrhage and the composite outcome). The study results did not differ when cases of missing BMI were included in the logistic regression analysis using multiple imputation techniques as compared with complete case analysis.

3.5 Discussion

Atonic postpartum hemorrhage and severe atonic postpartum hemorrhage increased in British Columbia, Canada, between 2001 and 2009. The rate of atonic postpartum hemorrhage increased by 34% from 4.8% in 2001 to 6.3% in 2009, atonic postpartum hemorrhage with blood transfusion ≥1 unit increased by 51% from 16.6 in 2001 to 25.5 per 10,000 deliveries in 2009 and atonic postpartum hemorrhage with blood transfusion ≥3 units or use of procedures to control bleeding increased by 47% from 11.9 to 17.6 per 10,000 deliveries from 2001 to 2009. Logistic regression adjustment for the known determinants of postpartum hemorrhage did not explain the above-mentioned increase in atonic postpartum hemorrhage.

It is unclear why atonic postpartum hemorrhage and severe atonic postpartum hemorrhage have increased as the determinants examined accounted for little of the temporal increase. One possibility is that changes in diagnostic or coding practices were responsible for an artifactual increase in atonic postpartum hemorrhage. Although there was no change in codes between ICD-9 and ICD-10 for postpartum hemorrhage and its subtypes, there was a change in the chart abstraction methodology in Canadian hospitals with regard to postpartum hemorrhage that was implemented in 2006. The diagnosis of postpartum hemorrhage, which was previously postpartum hemorrhage as diagnosed and noted in the medical chart by the physician, obstetrician or midwife, was expanded to also include documented blood loss in the medical chart of ≥500 mL for a vaginal delivery and >1000 mL for a cesarean delivery. This change in reporting may partly account for the increasing trend in atonic postpartum hemorrhage among vaginal births after 2006, but cannot explain the steady pattern of the increase in atonic postpartum hemorrhage prior to 2006 among cesarean deliveries (Figure 3.1A) or the steady increase in severe postpartum hemorrhage prior to 2006, as measured by several objective markers of severity (Figure 3.1B). Also, a general increase in the diagnosis of postpartum hemorrhage would have led to similar increases in other subtypes of postpartum hemorrhage such as third stage hemorrhage, secondary postpartum hemorrhage, or that due to coagulation defects (Supplementary Table A.2).

The increase in atonic postpartum hemorrhage may have occurred due to changes in unmeasured risk factors or obstetric management. The Perinatal Data Registry began reporting cases of adherent placenta in 2009 and studies have reported increasing rates especially in women with a previous cesarean delivery.[59,60] However, given its rarity (16 per 10,000 deliveries in British Columbia in 2009) and since it should be classified as third-stage

hemorrhage according to current coding standards, it is unlikely that changes in the frequency of adherent placenta underlie the increase in atonic postpartum hemorrhage. Further study is required to determine the role of placenta accreta in more severe forms of postpartum hemorrhage. More liberal use of oxytocin during labour has been reported as a risk factor for postpartum hemorrhage secondary to uterine atony (possibly due to uterine muscle receptors becoming desensitized).[41] We did not have information on dose of oxytocin used for labour induction and/or augmentation. Additionally, we did not have information on use of magnesium sulfate, although we did control for pre-eclampsia. Magnesium sulfate has been associated with a fourfold increased risk of postpartum hemorrhage among women with mild pre-eclampsia in one study and hypotonic uterus may be a possible side effect.[28,61] Further, no information was available about management of the 3rd stage of labour and it is unknown to what extent practice patterns changed over time, although increases in active rather than expectant management may be expected, especially in the most recent years since the first identification of increases in atonic postpartum hemorrhage in Canada in 2007.[4,62,63]

Medications or environmental exposures during pregnancy may potentially underlie the increase in atonic postpartum hemorrhage. Selective serotonin reuptake inhibitors (SSRI) are commonly used in pregnancy (5% of pregnant women in British Columbia used these drugs in 2001[64]) and have been reported to increase hemorrhage risk due to impaired platelet aggregation.[65] Studies have shown a 30% (95% CI 0.98-1.72) increased risk of postpartum hemorrhage as compared to a 12% (95% CI 0.62-2.01) increased risk for non-SSRI antidepressant use.[66] There also remains the disquieting possibility that a difficult-to-identify drug interaction underlies the increase in atonic postpartum hemorrhage.

The increase in severe postpartum hemorrhage may partly represent practice pattern changes. In particular, there may be a more liberal use of blood transfusion at a lower threshold of postpartum hemorrhage. However, blood transfusion in conjunction with other subtypes of postpartum hemorrhage (third stage hemorrhage, secondary postpartum hemorrhage, and postpartum hemorrhage due to coagulation defects) did not increase significantly (Supplementary Tables A.2 and A.3). Similarly, the composite outcome in our study (which combined procedures to control bleeding, along with blood transfusion ≥3 units, in order to partly account for potential practice pattern changes) and several of the individual procedures to control postpartum hemorrhage also showed substantial increases. Currently, the relative efficacy of the various procedures to control bleeding have not been adequately evaluated, although case series have reported that these alternative strategies reduce rates of hysterectomy.[32] This is confirmed by the small temporal reduction in atonic postpartum hemorrhage with hysterectomy observed in our study when other procedures to control bleeding increased.

The literature on the relationship between body mass index and postpartum hemorrhage is conflicting, with some studies showing an increased risk of postpartum hemorrhage among overweight and obese women[9] and other studies showing no excess risk.[40,41] Our study indicated that increased BMI was not associated with an increased risk of atonic PPH or severe atonic postpartum hemorrhage. More importantly, controlling for BMI did not explain the temporal increase in atonic postpartum hemorrhage and severe atonic postpartum hemorrhage. Our analysis on BMI was limited by missing data, although multiple imputation techniques for addressing this problem did not change the findings.

The strengths of our study include its population-based nature, the large study size and the constancy of codes for postpartum hemorrhage and its subtypes in ICD-9 and ICD-10. Our study was also able to examine the various surgical procedures used to control postpartum hemorrhage. Reporting of blood transfusion is consistent in the database as transfused women receive a specific form in their charts, so it is unlikely that reporting changes affected temporal trends. The limitations of our study include the retrospective nature of the study design and the potential for transcription and other errors in the database. Another minor limitation arises because the definition of atonic postpartum hemorrhage in ICD-9 and ICD-10 potentially include postpartum hemorrhage from causes other than atony (e.g., postpartum hemorrhage due to a high vaginal laceration). Improvements in coding to isolate atonic postpartum hemorrhage from other causes of postpartum hemorrhage would aid future surveillance efforts.

In summary, our study confirms previous studies[3,4,6,8] reporting increased rates of atonic postpartum hemorrhage and indicates that postpartum hemorrhage, previously observed to have increased in the 1990s and early 2000s[3,7,14] has continued to increase in the late 2000s. Besides previously examined risk/protective factors for atonic postpartum hemorrhage, we also controlled for pre-pregnancy BMI and other factors such as labour induction and oxytocin augmentation but were unable to explain the temporal increase in atonic postpartum hemorrhage and severe atonic postpartum hemorrhage. Given the consistent findings across studies employing different definitions and markers of severity, improved postpartum hemorrhage management strategies should be incorporated into routine clinical practice to reduce the severity of postpartum hemorrhage and prevent long-term illness and disability.[32]

Future studies should continue to investigate novel risk factors for the increase in atonic postpartum hemorrhage in order to identify and address causes.

Chapter 4: Temporal trends in postpartum hemorrhage and severe postpartum hemorrhage in Canada from 2003 to 2010

4.1 Synopsis

Objective: Increases in postpartum hemorrhage have been reported from several countries. We assessed temporal trends in postpartum hemorrhage and severe postpartum hemorrhage in Canada between 2003 and 2010.

Methods: We carried out a population-based cohort study of all hospital deliveries in Canada (excluding Quebec) from 2003 to 2010 (n = 2 193 425), using data from the Canadian Institute for Health Information. Postpartum hemorrhage was defined as a blood loss of ≥500 mL following vaginal delivery or ≥ 1000 mL following cesarean delivery, or as noted by the care provider. Severe postpartum hemorrhage was defined as postpartum hemorrhage plus blood transfusion, hysterectomy, or other procedures to control bleeding (including uterine suturing or ligation/embolization of pelvic arteries). Temporal trends were assessed using the chi-square test for trend, rate ratios, and logistic regression.

Results: Postpartum hemorrhage increased by 22% (95% CI 20 to 25) from 5.1% in 2003 to 6.2% in 2010 ($P < 0.001$), driven by a 29% increase (95% CI 26 to 33) in atonic postpartum hemorrhage (3.9% in 2003 vs. 5.0% in 2010, $P < 0.001$). Postpartum hemorrhage with blood transfusion increased from 36.7 to 50.4 per 10,000 deliveries ($P < 0.001$), while postpartum hemorrhage with hysterectomy increased from 4.9 to 5.8 per 10,000 deliveries ($P < 0.01$). Postpartum hemorrhage with uterine suturing, or ligation/embolization of pelvic arteries, increased from 4.1 to 10.7 per 10,000 deliveries ($P < 0.001$). These increases occurred in most provinces and territories, and could not be explained by changes in maternal, fetal, and

obstetric factors.

Conclusion: Rates of postpartum hemorrhage and severe postpartum hemorrhage continued to increase in Canada between 2003 and 2010.

4.2 Background and objectives

Chapter 2 and 3 provided detailed analyses of risk factors for postpartum hemorrhage in British Columbia, some of which were not available nationally. Chapter 4 is a national study which focuses on differences by province and territory. Knowledge about whether the rise in postpartum hemorrhage occurred across different regions in Canada is important in understanding the scope of the problem and, in addition, to understanding whether the rise in postpartum in Canada continued in recent years.

Rates of postpartum hemorrhage in Canada increased by 23% between 1991 and 2004 (from 4.1% to 5.1%), and atonic postpartum hemorrhage was identified as the subtype of postpartum hemorrhage underlying the increase.[4] Increasing rates of postpartum hemorrhage have been reported in several high income countries.[1,3,4,7,9,10,14] Postpartum hemorrhage can lead to death and serious complications that follow an extreme drop in blood volume and related organ failure, including acute renal failure, adult respiratory distress syndrome, coagulopathy, and shock.[6,18] However, the reasons for the increase in postpartum hemorrhage have not been identified despite several studies that have examined the role of various maternal, fetal, and obstetric factors (including changes in maternal age, pre-pregnancy weight, multi-fetal pregnancy, birth weight, epidural anaesthesia, labour induction and augmentation, and cesarean delivery).[4,6,10]

It is unclear if the observed increases in rates of postpartum hemorrhage and severe postpartum hemorrhage in Canada between 1991 and 2004 stabilized or continued. Also, regional variations in the temporal trends in postpartum hemorrhage within Canada have not been adequately explored. The purpose of this study was to determine whether the rate of postpartum hemorrhage continued to increase in Canada after 2004. We further explored temporal patterns in postpartum hemorrhage rates by provinces and territories, and by maternal, fetal, and obstetric factors. Finally, we examined temporal changes in severe postpartum hemorrhage using objective markers of severity such as blood transfusion, emergency hysterectomy, and other procedures to control bleeding (including uterine suturing, or ligation/embolization of pelvic blood vessels).

4.3 Methods

The data source for this study was the Canadian Institute for Health Information's Discharge Abstract Database, which contains information on women delivering in all hospitals in Canada (excluding Quebec). Information in the database is abstracted by trained health records personnel using standardized definitions and includes information on maternal characteristics, medical history, and details of all diagnoses and procedures. Validation studies have shown that the perinatal information in the database is accurate.[47] In particular, the diagnosis of postpartum hemorrhage had a sensitivity of 90.2% and specificity of 98.2%, and blood transfusion had a sensitivity of 85.7% and specificity of 99.8%.[47]

All hospital deliveries (n = 2 193 425) in Canada (excluding Quebec) which resulted in a live birth or stillbirth between April 1, 2003, and March 31, 2011 (hereafter referred to as years

2003 to 2010) were included in the study. The primary outcome of postpartum hemorrhage was defined using ICD-10 codes 072.0 to 072.3, which identified postpartum hemorrhage as a blood loss of ≥ 500 mL following vaginal delivery or ≥ 1000 mL following cesarean delivery, or as a diagnosis noted by a health care provider. Atonic postpartum hemorrhage was defined as postpartum hemorrhage within 24 hours of delivery (ICD-10 code 072.1) excluding that caused by retained placenta or coagulation defects. Non-atonic postpartum hemorrhage excluded deliveries with an atonic postpartum hemorrhage diagnosis and comprised third stage hemorrhage, secondary postpartum hemorrhage (occurring more than 24 hours after delivery), and postpartum hemorrhage due to coagulation defects. Severe postpartum hemorrhage was defined as postpartum hemorrhage in conjunction with a procedure code for blood transfusion, hysterectomy, or other procedures to control bleeding (including suturing of the uterus, e.g., B-Lynch suture, or ligation/embolization of pelvic blood vessels for the purpose of controlling postpartum hemorrhage).

Postpartum hemorrhage rates were examined according to maternal and fetal characteristics, pregnancy complications, medical interventions, and labour complications. This included maternal age, previous cesarean delivery, multi-fetal gestation, antepartum diagnosis of large fetus, hypertensive disorders, diabetes mellitus, chorioamnionitis, polyhydramnios, placenta previa, placental abruption, induction of labour, epidural anaesthesia, instrumental delivery, caesarean section, uterine rupture, third or fourth degree perineal tear, cervical laceration, and high vaginal laceration. All diagnostic and procedure codes used in the study are listed in Supplementary Table B.1. Rates of postpartum hemorrhage within the provinces and territories were based on the location of delivery hospitalization rather than maternal

residence.

Temporal trends were assessed using the chi-square test for linear trend in proportions by year, and by comparing rates in 2010 with those in 2003 using rate ratios and 95% confidence intervals. Temporal changes in postpartum hemorrhage rates according to province or territory and maternal, fetal, and obstetric factors were also quantified using rate ratios and 95% CIs (rates in 2009–2010 divided by rates in 2003–2004). To test for regional variations, rate ratios and 95% CIs were used to compare the overall rate of postpartum hemorrhage with blood transfusion in the period 2003 to 2010 in each province or territory relative to the rest of the country. Logistic regression analysis was used to obtain unadjusted and adjusted odds ratios for potential determinants of postpartum hemorrhage with blood transfusion. Year of delivery was entered in the model using indicator variables, and crude and adjusted year effects were contrasted to determine whether controlling for changes in maternal, fetal and obstetric factors attenuated the increase in postpartum hemorrhage between 2003 and 2010. Sensitivity analyses were used to determine if results differed when the outcome of postpartum hemorrhage with hysterectomy or postpartum hemorrhage with other procedures to control bleeding was modelled. A two-sided P value of < 0.05 was considered statistically significant.

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). This study was carried out under the auspices of the Public Health Agency of Canada, which has a federal mandate to monitor the health of the Canadian population. The data source included denominalized information, and ethics review board approval was therefore not required.

4.4 Results

Between 2003 and 2010, there were a total of 122,676 cases of postpartum hemorrhage among 2,193,425 deliveries (5.6 per 100 deliveries). The incidence of postpartum hemorrhage increased by 22% (95% CI 20 to 25) from 5.1% in 2003 to 6.2% in 2010 (*P* for trend < 0.001), driven by a 29% increase (95% CI 26 to 33) in the incidence of atonic postpartum hemorrhage (3.9% in 2003 vs. 5.0% in 2010; *P* for trend < 0.001) (Figure 4.1). The rate of non-atonic postpartum hemorrhage did not change significantly; it was 1.18% in both 2003 and 2010. While the incidence of third stage hemorrhage did not change significantly (0.89% in 2003 and 0.85% in 2010; *P* for trend = 0.71), the incidence of secondary postpartum hemorrhage increased by 12% (95% CI 2 to 23) from 0.29% in 2003 to 0.32% in 2010 (*P* for trend < 0.001). The rate of postpartum hemorrhage due to coagulation defects increased by 24% (95% CI −2 to 57), from 0.05% in 2003 to 0.06% in 2010 (*P* for trend = 0.01).

A total of 9575 cases of postpartum hemorrhage with blood transfusion occurred between 2003 and 2010 (43.7 per 10,000 deliveries). The rate of postpartum hemorrhage with blood transfusion increased by 37% (95% CI 26 to 49) from 36.7 in 2003 to 50.4 per 10,000 deliveries in 2010 (*P* for trend < 0.001), while the rate of postpartum hemorrhage with hysterectomy increased by 16% (95% CI −7.8 to 47) from 4.9 to 5.8 per 10,000 deliveries (*P* for trend = 0.01). The rate of postpartum hemorrhage with procedures to control bleeding (uterine suturing or ligation/embolization of uterine blood vessels) increased by 164% (95% CI 111 to 231) from 4.1 to 10.7 per 10,000 deliveries (*P* for trend < 0.001, Figure 4.1).

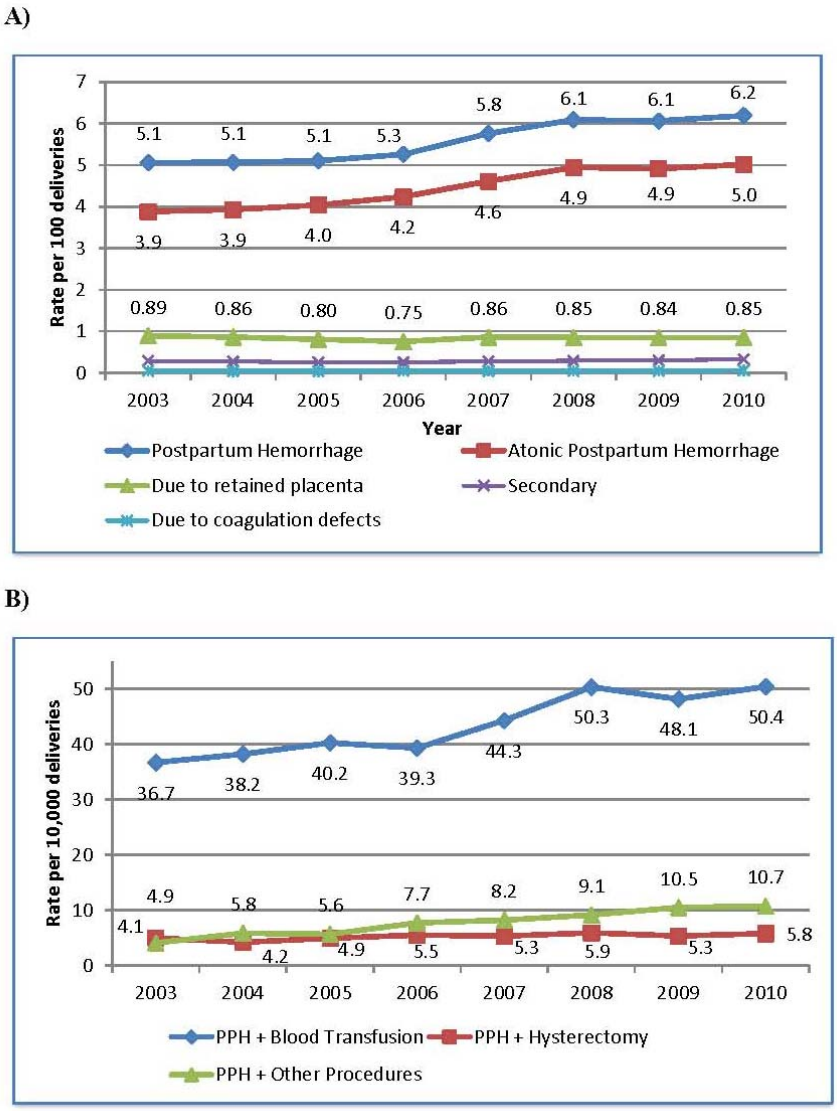


Figure 4.1. Temporal trends rates of postpartum hemorrhage (PPH) by subtype (Panel A) and severe PPH (Panel B) in Canada (excluding Quebec).

Table 4.1. Number of cases and rates of postpartum hemorrhage per 100 deliveries, Canada and provinces and territories (excluding Quebec), 2003 to 2010.

Province/territory	All years n	All years Rate (95% CI)	2003–2004	2005–2006	2007–2008	2009–2010	% increase	*P* for trend
Newfoundland and Labrador	1571	4.2 (4.0–4.5)	3.7	4.6	4.5	4.2	14.0	0.07
Prince Edward Island	397	3.6 (3.3–4.0)	2.9	3.1	4.3	4.2	44.8	<0.001
Nova Scotia	4816	6.9 (6.8–7.1)	4.9	6.5	8.4	7.9	61.6	<0.001
New Brunswick	2238	3.9 (3.8–4.1)	3.1	4.0	4.0	4.6	50.1	<0.001
Ontario	40590	3.7 (3.6–3.7)	3.7	3.6	3.6	3.8	4.5	0.001
Manitoba	6917	6.5 (6.4–6.7)	4.8*	5.5	7.2	7.5	57.8	<0.001
Saskatchewan	8633	8.3 (8.1–8.5)	10.0	7.1	7.9	8.3	-17.2	<0.001
Alberta	32045	8.8 (8.7–8.9)	7.5	8.1	9.6	9.8	29.8	<0.001
British Columbia	23913	7.3 (7.2–7.3)	6.4	6.6	7.9	8.0	24.5	<0.001
Northwest Territories	611	9.7 (9.0–10.5)	8.7	9.0	9.6	11.5	32.0	0.01
Nunavut	510	17.1 (15.8–18.5)	8.1	17.0	17.2	25.1	209.7	<0.001
Yukon	435	15.7 (14.4–17.1)	16.0	14.6	18.5	13.7	-14.5	0.88
Canada	122676	5.6 (5.6–5.6)	5.1	5.2	5.9	6.1	21.0	<0.001

*Data for 2003 not available for Manitoba.

Table 4.2. Number of cases and rates of postpartum hemorrhage with blood transfusion per 10,000 deliveries, Canada and provinces and territories (excluding Quebec), 2003 to 2010.

Province/territory	All years n	All years Rate (95% CI)	2003–2004	2005–2006	2007–2008	2009–2010	% increase	*P* for trend
Newfoundland and Labrador	260	70.2 (62.0–79.3)	48.6	66.8	75.8	88.6	82.5	<0.001
Prince Edward Island	42	38.4 (27.7–51.9)	36.5	22.5	46.9	47.1	29.3	0.40
Nova Scotia	284	40.9 (36.3–46.0)	37.1	34.3	49.2	42.6	14.8	0.17
New Brunswick	203	35.6 (30.8–40.8)	22.3	29.6	40.9	48.4	117.4	<0.001
Ontario	4132	37.4 (36.3–38.6)	32.6	34.5	40.2	42.2	29.5	<0.001
Manitoba	529	49.8 (45.7–54.2)	42.8*	45.6	51.1	55.5	29.6	0.05
Saskatchewan	612	58.8 (54.2–63.6)	50.6	59.9	63.7	59.9	18.3	0.09
Alberta	2178	60.1 (57.6–62.6)	52.3	52.6	66.1	66.9	28.0	<0.001
British Columbia	1249	37.9 (35.8–40.1)	34.3	35.3	40.3	41.1	19.8	0.02
Northwest Territories	34	54.1 (37.5–75.5)	87.8	56.6	30.9	43.8	-50.2	0.05
Nunavut	37	124.2 (87.6–171)	43.4	114.3	62.7	266	513.2	<0.001
Yukon	15	54.2 (30.4–89.3)	73.4	45.7	70.2	27.9	-62.0	0.40
Canada	9575	43.7 (42.8–44.5)	37.4	39.8	47.3	49.2	31.5	<0.001

*Data for 2003 not available for Manitoba.

Table 4.3. Rates of postpartum hemorrhage (PPH) with blood transfusion per 10,000 deliveries by maternal, fetal and obstetric factors, Canada (excluding Quebec), 2003 to 2010.

	2003–2004	2005–2006	2007–2008	2009–2010	2009–10 vs. 2003–04		*P* for trend
	Rate per 10,000				RR	95% CI	
Maternal age, years							
<20	47.8	49.8	75.9	76.0	1.59	1.26–2.00	<0.001
20–24	38.4	39.9	47.9	47.3	1.23	1.07–1.42	<0.001
25–29	32.3	35.9	42.6	45.8	1.42	1.27–1.59	<0.001
30–34	35.7	37.6	43.6	44.7	1.25	1.13–1.39	<0.001
35–39	44.4	44.3	50.4	54.6	1.23	1.07–1.41	<0.001
≥40	50.2	60.1	65.2	68.9	1.37	1.04–1.82	0.02
Previous cesarean delivery	39.4	40.4	46.2	52.0	1.32	1.12–1.55	<0.001
Multi-fetal gestation	167	175	206	191	1.15	0.90–1.46	0.13
Large fetus	72.4	77.2	94.7	74.8	1.03	0.76–1.40	0.21
Hypertensive disorders	85.7	89.3	95.0	99.6	1.16	0.99–1.36	0.02
Diabetes	46.6	53.9	59.7	49.2	1.06	0.83–1.35	0.48
Chorioamnionitis	124	151	150	157	1.26	0.93–1.71	0.19
Polyhydramnios	52.4	111	82.4	96.9	1.85	0.96–3.59	0.08
Placenta previa	404	390	516	534	1.32	1.05–1.66	0.004
Placental abruption	152	161	161	172	1.14	0.87–1.49	0.36
Induction of labour	47.4	49.4	60.6	61.3	1.29	1.16–1.44	<0.001
Epidural analgesia	36.8	40.1	44.0	45.5	1.24	1.13–135	<0.001
Instrumental delivery	62.7	69.3	78.2	91.6	1.46	1.28–1.67	<0.001
Cesarean delivery	50.4	56.8	62.5	63.5	1.26	1.14–1.39	<0.001
Uterine rupture	483	521	700	628	1.30	0.80–2.12	0.14
High vaginal laceration	232	259	274	457	1.97	1.32–2.94	<0.001
Cervical laceration	1053	1135	1259	1375	1.31	0.99–1.73	0.03
Perineal tear (3rd/4th)	84.8	101	113	120	1.42	1.13–1.77	<0.001

RR denotes rate ratio; CI denotes confidence interval.

Table 4.4. Results of logistic regression showing unadjusted and adjusted odds ratios of factors associated with postpartum hemorrhage with blood transfusion, Canada (excluding Quebec), 2003 to 2010.

	Rate per 10,000	Unadjusted OR (95%CI)	Adjusted OR (95% CI)
Year 2003	36.7	Reference	Reference
2004	38.2	1.04 (0.95–1.14)	1.06 (0.96–1.16)
2005	40.2	1.10 (1.01–1.20)	1.11 (1.01–1.21)
2006	39.3	1.07 (0.98–1.17)	1.10 (1.00–1.20)
2007	44.3	1.21 (1.11–1.32)	1.24 (1.14–1.35)
2008	50.3	1.37 (1.26–1.49)	1.40 (1.29–1.53)
2009	48.1	1.31 (1.21–1.43)	1.33 (1.22–1.44)
2010	50.4	1.38 (1.27–1.50)	1.38 (1.26–1.50)
Maternal age, years			
<20	62.8	1.45 (1.32–1.58)	1.47 (1.34–1.61)
20–24	43.5	Reference	Reference
25–29	39.4	0.91 (0.85–0.96)	0.87 (0.81–0.92)
30–34	40.6	0.93 (0.88–0.99)	0.86 (0.81–0.92)
35–39	48.7	1.12 (1.04–1.20)	0.98 (0.91–1.05)
≥40	61.7	1.42 (1.27–1.58)	1.10 (0.98–1.23)
Previous cesarean delivery	44.9	1.03 (0.97–1.10)	0.97 (0.91–1.04)
Multi-fetal gestation	186	4.54 (4.17–4.95)	3.77 (3.45–4.12)
Large fetus	79.5	1.86 (1.68–2.07)	1.78 (1.60–1.98)
Hypertensive disorder	92.7	2.30 (2.17–2.45)	1.92 (1.80–2.04)
Diabetes	52.6	1.22 (1.12–1.33)	0.99 (0.91–1.08)
Chorioamnionitis	147	3.49 (3.13–3.88)	2.66 (2.38–2.97)
Polyhydramnios	86.8	2.01 (1.64–2.46)	1.47 (1.19–1.81)
Placenta previa	466	11.8 (10.9–12.9)	10.9 (10.0–12.0)
Placental abruption	162	3.88 (3.51–4.28)	3.02 (2.73–3.35)
Induction of labour	55.2	1.37 (1.31–1.43)	1.31 (1.25–1.38)
Epidural	41.9	0.93 (0.90–0.97)	0.84 (0.80–0.87)
Instrumental delivery	75.5	1.90 (1.81–2.00)	1.98 (1.87–2.10)
Cesarean delivery	58.7	1.55 (1.48–1.61)	1.39 (1.32–1.47)
Uterine rupture	581	14.2 (11.9–17.1)	10.6 (8.67–12.9)
High vaginal laceration	289	6.90 (5.99–7.96)	5.27 (4.52–6.14)
Cervical laceration	1207	32.5 (29.0–36.4)	26.7 (23.6–30.1)
Perineal tear (3rd/4th)	105	2.54 (2.34–2.75)	2.35 (2.15–2.34)

Severe atonic postpartum hemorrhage showed a similar trend to that of severe postpartum hemorrhage. The rate of atonic postpartum hemorrhage with blood transfusion increased by 48% (95% CI 33 to 64), from 21.8 per 10,000 deliveries in 2003 to 32.2 per 10,000 deliveries in 2010, and the rate of atonic postpartum hemorrhage with procedures to control bleeding increased by 171% (95% CI 109 to 251) from 3.1 per 10,000 deliveries in 2003 to 8.3 per 10,000 deliveries in 2010. Atonic postpartum hemorrhage with hysterectomy showed a less pronounced change, increasing in rate by 24% (95% CI −11 to 74) from 2.3 to 2.9 per 10,000 between 2003 and 2010 (*P* for trend = 0.03). The rate of non-atonic postpartum hemorrhage with blood transfusion increased by 22% (95% CI 7 to 40), from 14.9 to 20.7 per 10,000 deliveries (*P* for trend < 0.001). The rate of non-atonic postpartum hemorrhage with hysterectomy increased by 9.5% (95% CI −21 to 52), from 2.6 to 2.9 per 10,000 deliveries (*P* for trend = 0.19), while non-atonic postpartum hemorrhage with other procedures to control bleeding increased in rate by 143% (95% CI 53 to 283) from 1.0 to 2.4 per 10,000 deliveries (*P* for trend < 0.001). Temporal trends in postpartum hemorrhage and severe postpartum hemorrhage by subtype are summarized in Supplementary Table B.2. Maternal death rates did not change significantly during the study period, with a rate of 64 per 1,000,000 deliveries in 2003 and 42 per 1,000,000 deliveries in 2010 (*P* = 0.27). Similarly, maternal deaths among cases of postpartum hemorrhage did not change, remaining at 0.03 per 100 cases of postpartum hemorrhage in 2003 and 2010 (*P* = 0.90).

Absolute rates of postpartum hemorrhage for the period 2003 to 2010 varied widely across provinces and territories, ranging from lows of 3.6% in Prince Edward Island and 3.7% in

Ontario to highs of 15.7 % in the Yukon and 17.1% in Nunavut (Table 4.1). Rates of postpartum hemorrhage with blood transfusion were markedly higher in Nunavut (124 per 10,000 deliveries) than in the rest of Canada (44 per 10,000 deliveries). Rates of postpartum hemorrhage with blood transfusion were also significantly higher in Newfoundland and Labrador, Manitoba, Saskatchewan, and Alberta than in the rest of Canada (Table 4.2). Most provinces and territories showed significant temporal increases in postpartum hemorrhage rates, except for Saskatchewan (which showed a significant decrease) and Newfoundland and Labrador and the Yukon (which showed no significant changes, Table 4.1). Rates of postpartum hemorrhage with blood transfusion also increased in most provinces and territories, except for the Northwest Territories, where they decreased significantly, and the Yukon, where there was a non-significant decrease. Significant increases in rates of postpartum hemorrhage with blood transfusion were observed in Newfoundland and Labrador, New Brunswick, Ontario, Manitoba, Alberta, British Columbia, and Nunavut (Table 4.2).

Rates of several maternal, fetal, and obstetric factors changed significantly between 2003–04 and 2009–10 (P for trend < 0.001 for each). Deliveries to women aged ≥ 35 years increased from 17.7% to 19.2%, maternal hypertensive disorder rates increased from 6.0% to 6.3%, and maternal diabetes rates increased from 4.4% to 6.0%. Rates of multi-fetal gestation increased from 1.3% to 1.6%, the incidence of women delivering with an antepartum diagnosis of a “large fetus” decreased from 2.5% to 1.8%, and the incidence of women delivering with a previous cesarean delivery increased from 11.8% to 13.6%. Epidural anaesthesia rates increased from 40.7% to 45.3%, and rates of induction of labour increased

from 21.0% to 24.4%. Rates of instrumental deliveries decreased from 11.3% to 10.2%, while cesarean delivery rates increased from 26.3% to 27.9%. Rates of third or fourth degree perineal tears increased from 2.8% to 2.9%.

Maternal, fetal and obstetric characteristics by province are summarized in Supplementary Table B.3. Rates of several maternal and obstetric risk factors differed in Nunavut (where absolute rates of postpartum hemorrhage were highest) compared with the Canadian average. Deliveries to teenage mothers were more common in Nunavut, while rates of several obstetric factors and interventions in Nunavut were lower than the Canadian average, including rates of previous cesarean delivery, epidural anaesthesia, labour induction, and cesarean delivery.

Rates of postpartum hemorrhage with blood transfusion increased significantly among most maternal, fetal, and obstetric factors under study (Table 4.3), including different categories of maternal age, and among women with previous cesarean delivery, epidural anaesthesia, labour induction, instrumental delivery, and cesarean delivery. Significant increases in rates of postpartum hemorrhage with blood transfusion also occurred among women with placenta previa and severe perineal tears. Significant increases occurred among women with hypertensive disorders and cervical lacerations according to the test for linear trend in proportions, but the confidence intervals comparing rates in 2009–10 with those in 2003–04 crossed unity. However, non-significant increases in rates of postpartum hemorrhage with blood transfusion were observed among deliveries with multi-fetal gestation, chorioamnionitis, placental abruption, and uterine rupture, and in women with diabetes and

those with an antepartum diagnosis of a large fetus.

In unadjusted analyses all risk factors under study were significantly associated with postpartum hemorrhage with blood transfusion (Table 4.4), except for previous cesarean delivery (which was not significant) and epidural anaesthesia (which was significantly protective). Maternal ages 35 to 39 years and ≥ 40 years were significantly associated with postpartum hemorrhage with blood transfusion, as was maternal age < 20 years. Adjusted analyses showed that older maternal age and diabetes were not associated with postpartum hemorrhage with blood transfusion. All other factors were significantly associated with postpartum hemorrhage with blood transfusion but could not explain the unadjusted 38% increase (95% CI 27 to 50) in the odds of postpartum hemorrhage with blood transfusion between 2003 and 2010 (adjusted increase 38%, 95% CI 26 to 50). Sensitivity analyses revealed that the unadjusted 164% increase (95% CI 111 to 231) in rates of postpartum hemorrhage with procedures to control bleeding could not be explained by controlling for risk factors (adjusted increase 149%, 95% CI 99 to 212). Postpartum hemorrhage with hysterectomy showed a non-significant increase in rate between 2003 and 2010, and this remained non-significant after adjusting for risk factors (unadjusted increase 16%, 95% CI −8 to 47; adjusted increase 3%, 95% CI −19 to 30).

4.5 Discussion

Our study showed that the increases in postpartum hemorrhage observed in Canada in the 1990s have continued in more recent years. Postpartum hemorrhage rates increased between 2003 and 2010, driven by a 29% increase (95% CI 26 to 33) in rates of atonic postpartum

hemorrhage, from 3.9% in 2003 to 5.0% in 2010. Despite wide variation in regional rates of postpartum hemorrhage, increases in rates occurred in most provinces and territories. In addition, the rising trend in postpartum hemorrhage in Canada was accompanied by a simultaneous increase in the incidence of severe postpartum hemorrhage as measured by postpartum hemorrhage in conjunction with blood transfusion, hysterectomy, and other procedures to control bleeding. Although numerous maternal, fetal, and obstetric factors were significantly associated with severe postpartum hemorrhage, the temporal increase remained after controlling for these factors.

Increases in rates of postpartum hemorrhage have been documented in Canada and several other countries.[1,3,4,6,8,9,13] Nevertheless, it is important to exclude the possibility that the increases are an artifact resulting from changes in the diagnosis of postpartum hemorrhage or changes in patterns of practice in treating postpartum hemorrhage. Accurate estimation of blood loss is challenging, and this makes the diagnosis of postpartum hemorrhage more prone to error, especially in cases of mild hemorrhage. Additionally, the diagnostic criteria for postpartum hemorrhage in Canada changed slightly in 2006; the previous criteria required a diagnosis of postpartum hemorrhage to be noted in the medical chart by the health care provider, and this was expanded to also include a documented blood loss of ≥ 500 mL for a vaginal delivery and ≥ 1000 mL for a cesarean delivery.[57] However, there are several reasons to suggest that the observed increase represents an actual increase in rates of postpartum hemorrhage. If changes in diagnostic criteria were responsible for the 29% increase in atonic postpartum hemorrhage from 2003 to 2010, a similar temporal increase should have occurred in rates of non-atonic postpartum hemorrhage as well. In fact, rates of non-atonic postpartum

hemorrhage and its principal component (third stage hemorrhage), did not show a temporal increase, even though our study had > 99% statistical power to demonstrate a 29% increase in these two subtypes of postpartum hemorrhage (alpha = 0.05). Reports from the United States show a similar phenomenon, with temporal increases observed in atonic postpartum hemorrhage but not in the non-atonic subtype.[13,14]

Another key finding of this study that suggests that the observed increase in postpartum hemorrhage is not an artifact resulting from changes in diagnosis was the marked increase in severe postpartum hemorrhage rates. Rates of postpartum hemorrhage with blood transfusion and rates of postpartum hemorrhage with invasive procedures to control bleeding, including hysterectomy, uterine suturing, or ligation/embolization of pelvic vessels, all increased significantly between 2003 and 2010. Although the increase in such emergency procedures to manage severe postpartum hemorrhage suggests that postpartum hemorrhage rates are in fact increasing, it is encouraging to note that increases in rates of postpartum hemorrhage with hysterectomy (a 16% increase) have trailed increases in postpartum hemorrhage with blood transfusion (a 37% increase) and uterine suturing or ligation/embolization of pelvic vessels (a 164% increase). Previous studies have noted relatively higher rates of hysterectomy and relatively lower rates of blood transfusion in Canada than in other countries.[11] However, our data show that rates of postpartum hemorrhage with hysterectomy stabilized between 2006 and 2010, while rates of postpartum hemorrhage with blood transfusion and uterine suturing or ligation/embolization of pelvic blood vessels continued to increase (Figure 4.1B). Procedures to control bleeding are unlikely to be used in cases of mild hemorrhage. Therefore these temporal increases in postpartum hemorrhage with procedures to control

bleeding also contradict the argument that increases in severe postpartum hemorrhage, specifically increases in postpartum hemorrhage with blood transfusion, were merely due to a more liberal use of blood transfusion. Finally, case fatality rates among women with postpartum hemorrhage remained constant between 2003 and 2010, highlighting the efficacy of these interventions in assuring patient safety despite increases in rates of severe postpartum hemorrhage.

Regional rates and patterns of postpartum hemorrhage show striking differences and a common thread. True variation across the country cannot be ruled out. However, striking variations in absolute rates of postpartum hemorrhage were substantial, and suggest differences in assessment of blood loss, diagnosis of postpartum hemorrhage, or documentation and coding issues. Variability in diagnosis is not surprising given the difficulties in assessing the volume of postpartum blood loss. Despite these regional variations, rates of postpartum hemorrhage and postpartum hemorrhage with blood transfusion showed an increasing temporal trend in most provinces and territories. The extremely high rates of postpartum hemorrhage in Nunavut require attention, especially given the rising rates and remarkably high rates of postpartum hemorrhage with blood transfusion (Tables 4.1 and 4.2).

The strengths of this study are that it is population-based and includes detailed demographic and clinical information on procedures to control bleeding and several important risk factors for postpartum hemorrhage. The limitations of the study include the lack of information on labour augmentation, third stage management, and medication use in pregnancy. In addition,

as mentioned, regional variations in the diagnosis of postpartum hemorrhage are likely. Despite these shortcomings, previous studies have found that the diagnosis of postpartum hemorrhage in perinatal databases is accurate;[67,68] in particular, information in our data source had high specificity and sensitivity for both postpartum hemorrhage and blood transfusion.[47] Our study was restricted to deliveries in the hospital setting. Although it is possible that an increasing temporal trend towards non-hospital deliveries by low risk women could have artificially increased rates of postpartum hemorrhage among hospital deliveries, this is an unlikely explanation for the increase in postpartum hemorrhage rates between 2003 and 2010. Previous studies from British Columbia that included non-hospital deliveries have showed similar temporal increases in the rate of postpartum hemorrhage.[69,70] In addition, rates of non-hospital births in Canada increased from 0.8% in 2003 to 1.5% in 2010,[71] and sensitivity analyses show that such a change cannot explain the substantial increase in postpartum hemorrhage in hospital deliveries observed in our study. Assuming that 7 per 1,000 deliveries were non-hospital deliveries, and none of them experienced postpartum hemorrhage, the denominator in 2010 would increase from 282,695 to 284,688 (non-hospital deliveries added to the denominator). However, the rate of postpartum hemorrhage in 2010 would be essentially unchanged at 61 per 1,000 deliveries (17 497 cases / 284,688 total deliveries), constituting a 21% increase (instead of the observed rate of 62 per 1000 deliveries and the observed increase of 22%). In addition, it is unlikely that non-hospital deliveries experienced no postpartum hemorrhages.

Another limitation of the study is that we were unable to access Quebec data for our study because Quebec does not submit data to the Canadian Institute for Health Information's

Discharge Abstract Database. The previous publication on postpartum hemorrhage in Canada also suffered from this limitation.[4]

Rates of postpartum hemorrhage and severe postpartum hemorrhage continued to increase in Canada between 2003 and 2010. The increase occurred in most provinces and territories in Canada, and could not be explained by maternal, fetal, or obstetric factors. The specificity of the increase in rates of the atonic subtype of postpartum hemorrhage and of severe postpartum hemorrhage, as defined by objective markers of severity, suggests that the increase in postpartum hemorrhage represents a real increase. However, the factors underlying the increase remain unidentified, and more detailed research to clarify the etiology is required. Routine audits of severe postpartum hemorrhage are recommended for ensuring optimal management and patient safety.

Chapter 5: Impact of placenta accreta on the incidence of postpartum hemorrhage and severe postpartum hemorrhage

5.1 Synopsis

Objective: To quantify the impact of placenta accreta on the rate of postpartum hemorrhage and severe postpartum hemorrhage.

Methods: All hospital deliveries in Canada (excluding Quebec) for the years 2009 and 2010 (n=570,637) were included in the study using data from the Canadian Institute for Health Information. Placenta accreta included placental adhesion to the uterine wall, musculature, and surrounding organs (accreta/increta/percreta). Severe postpartum hemorrhage included postpartum hemorrhage with blood transfusion, hysterectomy, or other procedures to control bleeding (including uterine suturing or ligation/embolization of pelvic arteries). Rates, rate ratios (RR), population attributable fractions (PAF i.e., incidence of postpartum hemorrhage attributable to placenta accreta) and 95% confidence intervals (CI) were estimated.

Results: The incidence of placenta accreta was 14.4 per 10,000 deliveries (819 cases among 570,637 deliveries), while the incidence of placenta accreta with postpartum hemorrhage was 7.2 per 10,000 deliveries. Most cases of placenta accreta were associated with third stage hemorrhage (41%). Although placenta accreta was strongly associated with postpartum hemorrhage (RR 8.3, 95% CI 7.7-8.9), its low frequency relative to postpartum hemorrhage resulted in a small PAF (1.0%, 95% CI 0.93-1.16). However, the very strong association between placenta accreta and postpartum hemorrhage with hysterectomy (RR 286, 95% CI: 226-361) resulted in a PAF of 29%, 95% CI 24.3-34.3.

Conclusion: Placenta accreta is too infrequent to account for the recent temporal increase in postpartum hemorrhage, but contributes substantially to the proportion of postpartum hemorrhage with hysterectomy.

5.2 Background and objectives

This chapter explores the impact of placenta accreta on the incidence of postpartum hemorrhage and severe postpartum hemorrhage. The goal of this study was to provide information about whether placenta accreta could potentially explain the increase in atonic and severe atonic postpartum hemorrhage in Canada. We were, however, restricted to the years 2009 and 2010 when routine collection of a placenta accreta diagnosis became available.

As discussed in previous chapters, several high income countries such as Australia, Canada, Ireland, Norway, Scotland and the United States have reported increases in postpartum hemorrhage over the last two decades that remain unexplained.[1,3,4,7,8,10,14] The subtype of postpartum hemorrhage underlying the increase was identified as atonic postpartum hemorrhage;[4,10,14] in Canada, the rate of atonic postpartum hemorrhage increased by 29% (95% CI 26 to 33%) from 3.9% in 2003 to 5.0% in 2010.[8] However, this increase could not be explained by changes in maternal age, obesity, multi-fetal gestation, labour induction, oxytocin augmentation and other maternal, fetal/infant and obstetric factors.[70] The International Postpartum Hemorrhage Collaborative Group recommended an investigation into the role of placenta accreta,[1] a severe and potentially life-threatening pregnancy complication, reported to have increased as a consequence of the increase in cesarean deliveries over the last 20-30 years.[60,72]

The purpose of this study was to describe the association between placenta accreta and postpartum hemorrhage and severe postpartum hemorrhage, and then to determine the population attributable fraction (PAF) of placenta accreta related to postpartum hemorrhage and severe postpartum hemorrhage. We discuss possible implications of the findings for explaining the recent increases in postpartum hemorrhage rates that have been observed in Canada and other high income countries.

5.3 Methods

The study was carried out using data from the Canadian Institute for Health Information's Discharge Abstract Database. The database contains demographic information, medical history, and diagnoses and procedures associated with all hospitalizations in Canada excluding Quebec. The database has been validated for the accuracy of maternal and other perinatal information; postpartum hemorrhage had high sensitivity (90.2%, 95% confidence interval [CI] 86.2-93.3) and specificity (98.2%, 95% CI 97.8-98.5) and procedures such as blood transfusion had reasonably high sensitivity 85.7% (42.1-99.6) and very high specificity (99.8%, 95% CI 99.6-99.9).[47] Our study used a retrospective cohort design, including all hospital deliveries in Canada (excluding Quebec) that resulted in a live birth or a stillbirth between April, 2009 and March, 2011 (referred to as 2009-2010). The years of study were chosen because in 2009, the Canadian Institute for Health Information began to routinely collect diagnostic information on placenta accreta.

Placenta accreta was defined using the International Statistical Classification of Diseases and Related Health Problems (Canadian version, ICD-10-CA) code for morbidly adherent placenta,

O43.2, and included placenta accreta, increta, and percreta. The outcome of postpartum hemorrhage was defined (using ICD-10-CA codes O72.0 to O72.3) as a blood loss of ≥500 mL following vaginal delivery or ≥1000 mL following cesarean delivery, or as noted in the medical record by the health care provider. Subtypes of postpartum hemorrhage included atonic postpartum hemorrhage (occurring within 24 hours after delivery), third stage hemorrhage (which included retained, trapped or adherent placenta occurring in the third stage of labour), delayed and secondary postpartum hemorrhage (occurring between 24 hours and 6 weeks after delivery), and postpartum hemorrhage due to coagulation defects. Severe postpartum hemorrhage was defined as postpartum hemorrhage occurring in conjunction with blood transfusion, hysterectomy, or other procedures to control bleeding (i.e., uterine suture, pelvic ligation or pelvic embolization).

Risk factors examined for placenta accreta included maternal age (<20, 20-24, 25-29, 30-34, 35-39, ≥40 years), parity (nulliparous, 1, 2-4, ≥5, missing), multi-fetal gestation, placenta previa plus previous cesarean delivery, placenta previa without previous cesarean delivery, and previous cesarean delivery without placenta previa. ICD-10-CA codes used for the study are summarized in Supplementary Table B.1. Rates and 95% confidence intervals (CIs) were calculated for placenta accreta, placenta accreta with postpartum hemorrhage, placenta accreta with severe postpartum hemorrhage, and placenta accreta by subtype of postpartum hemorrhage. Logistic regression analyses were used to estimate crude and adjusted odds ratios for risk factors of placenta accreta. The rate ratios and 95% confidence intervals for the association between placenta accreta and postpartum hemorrhage and severe postpartum hemorrhage were estimated, as was the population attributable fraction (PAF) of postpartum hemorrhage and severe

postpartum hemorrhage due to placenta accreta. The PAF refers to the proportion of the incidence of any disease/outcome (e.g., postpartum hemorrhage) in the population that is attributable to the determinant (e.g., placenta accreta), and is affected by both the population-level rates of the determinant and the strength of association between the determinant and the disease/outcome. The PAF in this context provides an estimate of the fraction of postpartum hemorrhage or severe postpartum hemorrhage that would be prevented if placenta accreta was eliminated from the population.

The statistical software SAS version 9.3, Stata version 12.1, and OpenEpi (www.OpenEpi.com**)** version 3.01 were used for the analyses. This study was carried out under the auspices of the Public Health Agency of Canada's Canadian Perinatal Surveillance System, which is mandated to monitor maternal and infant health in the Canadian population. The data source included denominalized information.

5.4 Results

The incidence of placenta accreta was 14.4 per 10,000 deliveries (819 cases among 570,637 deliveries), and the case fatality rate for placenta accreta was 0.12%. The incidence of placenta accreta with postpartum hemorrhage was 7.2 per 10,000 deliveries (Table 5.1). One-quarter of all cases of placenta accreta required a blood transfusion (incidence=3.5 per 10,000 deliveries); 19% had postpartum hemorrhage and a blood transfusion (incidence=2.8 per 10,000 deliveries). Among cases of placenta accreta, 17% underwent a hysterectomy (incidence 2.4 per 10,000), while 11.2% had both postpartum hemorrhage and a hysterectomy (incidence 1.6 per 10,000 deliveries). Retained placenta without hemorrhage occurred in 17% of cases. While 50% of

women with placenta accreta had postpartum hemorrhage, the majority of cases of placenta accreta had third stage postpartum hemorrhage (41%), while a minority (7%) had atonic postpartum hemorrhage. Most cases of atonic postpartum hemorrhage with placenta accreta were severe; 0.63 per 10,000 women had atonic postpartum hemorrhage with either blood transfusion, hysterectomy or other procedures to control bleeding. Table 5.1 summarizes the rate of placenta accreta, postpartum hemorrhage and related complications.

Table 5.1. Rate of placenta accreta, postpartum hemorrhage, and related complications, Canada (excluding Quebec), 2009-2010 (n=570,637 deliveries).

	N	Rate per 10,000 deliveries	% of placenta accreta
Placenta accreta	819	14.4 (13.4-15.4)	100.0
Placenta accreta with:			
Postpartum hemorrhage	412	7.22 (6.54-7.95)	50.3
Postpartum hemorrhage with blood transfusion	157	2.75 (2.34-3.22)	19.2
Postpartum hemorrhage with hysterectomy	92	1.61 (1.30-1.98)	11.2
Postpartum hemorrhage with procedures to control bleeding*	47	0.82 (0.61-1.10)	5.7
Severe postpartum hemorrhage†	185	3.24 (2.79-3.74)	22.6
Atonic postpartum hemorrhage	59	1.03 (0.79-1.33)	7.2
Atonic postpartum hemorrhage with blood transfusion	29	0.51 (0.34-0.73)	3.5
Atonic postpartum hemorrhage with hysterectomy	17	0.30 (0.17-0.48)	2.1
Atonic postpartum hemorrhage with procedures to control bleeding*	10	0.18 (0.08-0.32)	1.2
Severe atonic PPH†	36	0.63 (0.42-0.87)	4.4
Non-atonic postpartum hemorrhage	353	6.19 (5.56-6.87)	43.1
Third stage hemorrhage	338	5.92 (5.31-6.59)	41.3
Severe third stage hemorrhage†	143	2.49 (2.11-2.95)	17.3
Secondary postpartum hemorrhage	29	0.51 (0.34-0.73)	3.5
Postpartum hemorrhage due to coagulation defects	9	0.16 (0.07-0.30)	1.1
Retained placenta without hemorrhage	132	2.31 (1.94-2.74)	16.1
Blood transfusion	202	3.54 (3.07-4.06)	24.7
Hysterectomy	137	2.40 (2.02-2.84)	16.7
Cesarean hysterectomy	71	1.24 (0.97-1.57)	8.7
Other procedures to control bleeding	66	1.16 (0.90-1.47)	8.1
Placental abruption	30	0.53 (0.36-0.75)	3.7

*Includes uterine suturing, pelvic artery ligation or pelvic artery embolization
†In conjunction with either blood transfusion, hysterectomy, or procedures to control bleeding

Table 5.2. Placenta accreta by maternal and obstetric characteristics, Canada (excluding Quebec), 2009-2010.

Risk factors	Placenta accreta n=819	Total Deliveries n=570,637	Rate of placenta accreta per 10,000	% of cases	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Maternal Age (in years)						
<20	23	25667	8.96	2.81	1.09 (0.68-1.74)	1.10 (0.69-1.76)
20-24	73	87892	8.31	8.91	Reference	Reference
25-29	160	168296	9.51	19.5	1.21 (0.92-1.60)	1.16 (0.88-1.53)
30-34	293	179305	16.3	35.8	2.08 (1.61-2.69)	1.87 (1.44-2.42)
35-39	213	90328	23.6	26.0	3.09 (2.37-4.03)	2.44 (1.86-3.20)
≥40	57	19147	29.8	6.96	4.06 (2.87-5.74)	2.81 (1.97-4.01)
Parity						
Nulliparous	271	207036	13.1	33.1	1.04 (0.86-1.25)	1.48 (1.22-1.81)
1	186	153428	12.1	22.7	Reference	Reference
2	145	81762	17.7	17.7	1.46 (1.18-1.80)	1.41 (1.13-1.74)
≥5	18	6906	26.1	2.20	2.27 (1.40-3.67)	1.70 (1.04-2.77)
Missing	199	121505	16.4	24.3	1.27 (1.05-1.55)	1.41 (1.16-1.72)
Multi-fetal gestation						
Yes	41	8830	46.4	5.01	3.73 (2.72-5.10)	3.14 (2.29-4.31)
No	778	561807	13.9	95.0	Reference	Reference
Cesarean/placenta previa						
Previous cesarean only	125	76888	16.3	15.3	1.49 (1.23-1.81)	1.44 (1.17-1.77)
Placenta previa only	51	2836	179.0	6.23	16.2 (12.2-21.6)	13.3 (10.0-17.8)
Placenta previa plus previous cesarean delivery	72	685	1051.1	8.79	107.8 (84.1-138.2)	91.6 (70.5-119.1)
No previa or previous cesarean delivery	571	490228	11.7	69.7	Reference	Reference

Risk factors for placenta accreta were older maternal age (30-34 years, 35-39 years, and ≥40 years compared with 20-24 years, Table 5.2) and increased parity (parity 2-4 and ≥5). Multi-fetal gestation was also associated with a higher risk of placenta accreta. Placenta previa (in the current pregnancy) in conjunction with a previous cesarean delivery was most strongly associated with placenta accreta (adjusted OR=91.6, 95% CI 70.5-119.1) followed by placenta previa without previous cesarean delivery (adjusted OR=13.3, 95% CI 10.0-17.8). Previous

cesarean delivery without placenta previa was also associated with a significantly increased risk of placenta accreta (adjusted OR=1.44, 95% CI 1.17-1.77).

Although placenta accreta was strongly associated with postpartum hemorrhage (rate ratio 8.3, 95% CI 7.7-8.9, Table 5.3), the population attributable fraction was only 1.0%, i.e. only 1.0% of the incidence of postpartum hemorrhage was attributable to placenta accreta. On the other hand, placenta accreta was strongly associated with postpartum hemorrhage with hysterectomy (rate ratio 286, 95% CI (226-361) and had a population attributable fraction of 29% i.e., 29% of the incidence of postpartum hemorrhage with hysterectomy was due to placenta accreta. Placenta accreta was strongly associated with all severe forms of postpartum hemorrhage; however, the population attributable fraction was only 7.6% for postpartum hemorrhage with procedures to control bleeding and 5.5% for postpartum hemorrhage with blood transfusion. Table 5.3 presents the rate ratios and population attributable fractions for postpartum hemorrhage and severe postpartum hemorrhage by subtype.

Of all the subtypes of postpartum hemorrhage, placenta accreta was most strongly associated with third stage postpartum hemorrhage (RR 52.4, 95% CI: 48.0-57.1), and the population attributable fraction was the highest at 6.9%. The population attributable fraction for third stage postpartum hemorrhage with hysterectomy was 63.2%, for third stage postpartum hemorrhage with other procedures to control bleeding it was 36.8%, and for third stage postpartum hemorrhage with blood transfusion it was 18.1%.

Table 5.2. Rate ratios and population attributable fractions for the effect and impact of placenta accreta on postpartum hemorrhage (PPH) and severe postpartum hemorrhage by subtype, Canada (excluding Quebec), 2009-2010.

Outcome	Women with placenta accreta n=819		Women without placenta accreta n=569,818		Rate ratio (95% CI)	Population Attributable Fraction (95% CI)
	No	%	No	%		
PPH	412	50.3	34543	6.06	8.30 (7.75-8.89)	1.0 (0.93-1.16)
PPH with blood transfusion	157	19.2	2653	0.47	41.2 (35.6-47.6)	5.5 (4.7-6.4)
PPH with hysterectomy	92	11.2	224	0.04	285.8 (226 -361)	29.0 (24.3-34.3)
PPH with other procedures	47	5.7	558	0.10	58.6 (43.9-78.3)	7.6 (5.8-10.1)
Atonic PPH	59	7.2	28253	4.96	1.45 (1.14-1.86)	0.07 (0.02-0.13)
Atonic PPH with blood transfusion	29	3.5	1797	0.32	11.2 (7.83-16.1)	1.4 (0.96-2.1)
Atonic PPH with hysterectomy	17	2.1	156	0.03	75.8 (46.2-124.5)	9.7 (6.1-15.1)
Atonic PPH with other procedures	10	1.22	470	0.08	14.8 (7.94-27.6)	1.9 (0.98-3.7)
Third stage PPH	338	41.3	4489	0.79	52.4 (48.0-57.1)	6.9 (6.2-7.6)
Third stage PPH with blood transfusion	121	14.8	542	0.1	155 (129-187)	18.1 (15.4-21.3)
Third stage PPH with hysterectomy	74	9	43	0.01	1198 (827-1733)	63.2 (54.1-71.4)
Third stage PPH with other procedures	35	4.3	60	0.01	405.9 (269-612)	36.8 (27.7-46.9)
Secondary PPH	29	3.54	1757	0.31	11.5 (8.01-16.5)	1.5 (0.99-2.2)
Secondary PPH with blood transfusion	12	1.47	293	0.05	28.5 (16.1-50.5)	3.8 (2.1-6.7)
Secondary PPH with hysterectomy	4	0.49	11	0	253.0 (80.7-793)	26.6 (10.3-53.2)
Secondary PPH with other procedures	2	0.24	20	0	69.6 (16.3-297)	9.0 (2.1-29.9)
PPH due to coagulation defects	9	1.1	288	0.05	21.7 (11.2-42.1)	2.9 (1.44-5.6)
PPH due to coagulation defects with blood transfusion	7	0.85	122	0.02	39.9 (18.7-85.2)	5.3 (2.5-10.8)
PPH due to coagulation defects with hysterectomy	8	0.98	41	0.01	135.8 (63.8-289)	16.2 (8.3-29.3)
PPH due to coagulation defects with other procedures	4	0.49	37	0.01	75.2 (26.9-211)	9.6 (3.6-23.2)

PPH denotes postpartum hemorrhage; CI denotes confidence interval

5.5 Discussion

Our study showed that approximately 50% of the cases of placenta accreta experienced postpartum hemorrhage, 22.6% experienced a severe form of postpartum hemorrhage (either postpartum hemorrhage with hysterectomy, blood transfusion or other procedures to control bleeding). Placenta accreta was strongly associated with postpartum hemorrhage (rate ratio 8.30, 95% CI: 7.75-8.89) and most strongly associated with third stage hemorrhage (rate ratio 52.4 (95% CI: 48.0-57.1); its relative infrequency (14.4 per 10,000 deliveries) resulted in a low population attributable fraction for postpartum hemorrhage (1%). Given that recent increases in post-partum hemorrhage have been predominantly driven by increases in atonic postpartum hemorrhage (e.g., a 29% increase in Canada from 3.9% in 2003 vs. 5.0% in 2010[73]) and the modest association between placenta accreta and atonic postpartum hemorrhage (rate ratio of 1.45, 95% CI 1.14 to 1.86; PAF 0.01, 95% CI 0.0 to 0.1), increases in placenta accreta cannot explain the recent increases in postpartum hemorrhage. The relatively low frequency of placenta accreta and postpartum hemorrhage (7.2 per 10,000 deliveries) and the magnitude of the absolute temporal increase in atonic postpartum hemorrhage (1.1% between 2003and 2010) also suggests that temporal increases placenta accreta frequency cannot explain the recent rise in atonic postpartum hemorrhage.

Our study showed that placenta accreta accounted for 29% of the incidence of postpartum hemorrhage with hysterectomy, which increased significantly in Canada from 4.9 to 5.8 per 10,000 deliveries between 2003 and 2010.[73] Thus an increase in placenta accreta could have contributed significantly to the rising incidence of postpartum hemorrhage with hysterectomy in Canada. Our study also suggests that increases in placenta accreta could have partly

contributed to changes in the incidence of other severe forms of postpartum hemorrhage such as postpartum hemorrhage with blood transfusion, and postpartum hemorrhage with other procedures to control bleeding. Changes in placenta accreta rates may have also contributed to severe forms of third stage hemorrhage, although the absolute rates of such postpartum hemorrhage were low overall.

The strengths of our study were the population-based design that included all hospital deliveries in Canada (excluding Quebec), whereas most studies on this topic have been restricted to tertiary care centres.[74-77] Postpartum hemorrhage and several other obstetric outcomes have been shown to have high validity in our database.[47] Some of the limitations of our study included potential underdiagnoses or under-reporting of placenta accreta which could have led to their under-representation among cases of postpartum hemorrhage. While this is possible, the rate of placenta accreta in our study (14.4 per 10,000 deliveries) was higher than that reported in another population-based study from Ireland which reported a rate of 8.5 per 10,000 deliveries between 2005 and 2009.[10] The rate of placenta accreta is expected to vary based on the prevalence of previous cesarean deliveries, combined with the fertility rate of women with previous cesarean deliveries.[75] Other study limitations included the restricted time frame for the study which precluded our ability to study changes in placenta accreta frequency over time. This limitation was due to routine collection of placenta accreta diagnosis only becoming instituted in our data source in 2009. Finally, we could not ascertain whether postpartum hemorrhage occurred before or after the hysterectomy, the procedures to control bleeding or blood transfusion. For instance, some hysterectomies, uterine suturing, and ligation and embolization of pelvic blood vessels may

have represented pre-emptive strategies to control bleeding or could have followed antepartum hemorrhage. Regardless, our interest was in the population rates of placenta accreta and associated postpartum hemorrhage, and in all cases it is clear that placenta accreta preceded postpartum hemorrhage.

Our study revealed a case fatality rate of 0.12%, while previous studies have reported mortality rates that range from 0% to 0.3%, and 7% for the most severe forms of placenta accreta.[74-76] In addition, half the cases in our study did not have accompanying postpartum hemorrhage. This finding may be a result of less severe forms of placenta accreta being diagnosed, or prompt or prophylactic intervention to prevent bleeding. Currently, the appropriate management of placenta accreta remains controversial, particularly with regard to the use of treatments designed to preserve fertility.[78]

Similar to other research, our study found that concurrent placenta previa with a previous cesarean delivery was most strongly associated with placenta accreta. This finding supports the American College of Obstetricians and Gynecologists' recommendation to offer ultrasound screening for placenta accreta to women with a uterine scar and placenta previa.[78] However, only 8.8% of the placenta accreta cases in our study had both risk factors, while a larger proportion of the cases of placenta accreta (15%) had only a previous cesarean delivery with no placenta previa (implying that such risk-based screening would miss most cases). This finding supports the recommendation of the Confidential Enquiries into Maternal Deaths in the United Kingdom to screen all women with a previous cesarean delivery to have their placental site determined.[79] We did not have information on the number of previous

cesarean deliveries for each woman, but previous research has found an increasing risk of placenta accreta with increasing number of previous cesarean deliveries. For example women with placenta previa had a 4 times greater risk of placenta accreta given one previous cesarean delivery, and this risk increased to an 11 times higher risk with two or more previous cesarean deliveries. Risk factors other than placenta previa and previous cesarean delivery examined in previous studies include previous curettage, Asherman's syndrome, history of abortion or miscarriage, other prior uterine surgery or trauma and female fetal sex.[72,74,76,77,80]

In conclusion, placenta accreta is too infrequent a condition to account for the increase in postpartum hemorrhage observed in Canada and elsewhere in recent decades. However, potential temporal increases in placenta accreta may have contributed to temporal increases in postpartum hemorrhage with hysterectomy and other severe forms of postpartum hemorrhage. Future studies and population surveillance are necessary for monitoring the rates of placenta accreta and its contribution to severe postpartum hemorrhage. In addition, studies should explore other potential causes of the increase in postpartum hemorrhage observed in high income countries.

Chapter 6: Does the increase in postpartum hemorrhage explain the recent rise in obstetric acute renal failure?

6.1 Synopsis

Objectives: Rates of obstetric acute renal failure have increased in Canada and the United States in recent years. We examined whether changes in postpartum hemorrhage, hypertensive disorders of pregnancy or other risk factors explained this phenomenon.

Methods: Information on all hospital deliveries in Canada (excluding Quebec) between 2003 and 2010 (n=2,193,425) was obtained from the Canadian Institute for Health Information. Temporal trends in obstetric acute renal failure were assessed among women with and without postpartum hemorrhage, hypertensive disorders of pregnancy, or other risk factors. Logistic regression was used to determine if changes in risk factors explained the temporal increase in obstetric acute renal failure.

Results: Obstetric acute renal failure rates rose from 1.66 to 2.68 per 10,000 deliveries between 2003-04 and 2009-10 (61 percent increase, 95% confidence interval [CI] 24 to 110 percent). Adjustment for postpartum hemorrhage, hypertensive disorders and other factors did not attenuate the increase. The temporal increase in acute renal failure was restricted to deliveries with hypertensive disorders (adjusted increase 95 percent, 95% CI 38 to 176 percent), and was especially pronounced among women with gestational hypertension with significant proteinuria (adjusted increase 171 percent, 95% CI 71 to 329 percent). No significant increase occurred among women without hypertensive disorders (adjusted increase 12 percent, 95% CI -28 to 72 percent).

Conclusions: The rise in obstetric acute renal failure in Canada between 2003 and 2010 was restricted to women with hypertensive disorders, and was especially pronounced among women with pre-eclampsia. Further study is required to determine the cause of the increase in obstetric acute renal failure among women with pre-eclampsia.

6.2 Background and objectives

Obstetric acute renal failure, also referred to as pregnancy-related acute kidney injury, is a serious and potentially life-threatening pregnancy complication.[81-83] During the past half-century, substantial declines in obstetric acute renal failure occurred in high income countries, owing to improvements in obstetric care, and the legalization of abortion and an associated decrease in septic abortions.[84-86] In recent years, however, rates have increased in both Canada and the United States.[11,19] In Canada, obstetric acute renal failure increased significantly from 1.6 per 10,000 deliveries in 2003 to 2.3 per 10,000 deliveries in 2007,[11] while the rate in the United States increased from 2.3 in 1998 to 4.5 per 10,000 deliveries in 2008.[19] These increases are concerning because obstetric acute renal failure is associated with high rates of maternal morbidity and a case-fatality rate of 2.9%.[81] Major risk factors for obstetric acute renal failure include chronic hypertensive disease, pre-eclampsia, postpartum hemorrhage, antepartum hemorrhage, sepsis and other infections.[6,82,84,87]

Since rates of postpartum hemorrhage have increased in Canada (see Chapter 4) and several high income countries,[1,3,4,7,9,10,14] we hypothesized that the hypovolemia and related organ failure associated with postpartum hemorrhage may have been responsible for the observed increase in obstetric acute renal failure. An alternative hypothesis was related to hypertensive

disorders of pregnancy, which represent the most important risk factor for obstetric acute renal failure.[84,87] Although the rate of hypertensive disorders of pregnancy has not changed substantially in recent years in Canada,[73] there have been marked changes in the management of hypertension in pregnancy.[88] In particular, guidelines promoting fluid restriction to prevent pulmonary edema and changes in pharmacotherapy for control of hypertension may have had the secondary effect of increasing acute renal failure through hypovolemia, renal hypoperfusion, or nephrotoxicity.[88-91]

The purpose of this study was to determine whether the temporal increase in postpartum hemorrhage in Canada described in Chapter 4 explained the concurrent increase in obstetric acute renal failure. A secondary objective was to examine whether changes in hypertensive disorders of pregnancy (particularly pre-eclampsia) or other risk factors explained the rise in obstetric acute renal failure.

6.3 Methods

Data were obtained from the Discharge Abstract Database of the Canadian Institute for Health Information, a national database that contains information on all hospitalizations in Canada (excluding Quebec). Information in the database included demographic details, medical history, diagnoses and procedures associated with each hospitalization. The database has been validated and is routinely used for surveillance and research purposes.[47] The study cohort included all hospital deliveries (n=2,193,425) in Canada (excluding Quebec), that resulted in a live birth or stillbirth from April, 2003 to March, 2011 (hereafter referred to as 2003 to 2010).

Postpartum hemorrhage was defined using International Statistical Classification of Diseases and Related Health Problems (Canadian version, ICD-10-CA) codes O72.0 to O72.3, as a blood loss of ≥500 mL following vaginal delivery or ≥1000 mL following cesarean delivery, or as noted in the medical record by a care provider. Subtypes of postpartum hemorrhage included were similarly identified using appropriate codes (Supplementary Table C.1). Severe postpartum hemorrhage was defined as postpartum hemorrhage plus blood transfusion, hysterectomy, or other procedures to control bleeding. A validation study of the Discharge Abstract Database reported a sensitivity of 90.2% and specificity of 98.2% for postpartum hemorrhage, and a sensitivity of 85.7% and specificity of 99.8% for blood transfusion.[47]

Hypertensive disorders of pregnancy included pre-existing hypertension with or without superimposed proteinuria (O10-O11), gestational hypertension without significant proteinuria (O13), gestational hypertension with significant proteinuria (O14), eclampsia (O15), and unspecified maternal hypertension (O16). The validation study of the Discharge Abstract Database found a sensitivity of 87.9% and a specificity of 99.6% for gestational hypertension and a sensitivity of 83.3% and a specificity of 99.9% for pre-existing hypertension.[47]

Acute renal failure among women admitted for childbirth was defined using standard ICD-10 codes, including those for postpartum acute renal failure (O90.4), post-procedural renal failure (N99.0), acute renal failure (N17) or unspecified kidney failure (N19).[6,11,19] The

outcome of acute renal failure was based on the health care provider's documentation of this diagnosis in the woman's medical chart. In order to avoid potential temporal ambiguity between the determinant and the outcome (i.e., acute renal failure preceding postpartum hemorrhage), we repeated our analyses after restricting the study to cases of postpartum acute renal failure (O90.4). Temporal trends in obstetric acute renal failure were estimated by year and also in 2-year periods to enhance the stability of rate estimates. Rates of maternal death, dialysis, and intensive care admission among women with obstetric acute renal failure were examined to ensure that any temporal changes did not merely reflect changes in the occurrence or reporting of milder cases.

Other determinants of acute renal failure examined in the study were maternal age and parity, multi-fetal gestation, cesarean delivery, and induction of labor. Maternal co-morbidities examined included diabetes (pre-existing or gestational), gestational edema and proteinuria without hypertension, sepsis, other puerperal infection, placenta previa, placental abruption, unspecified antepartum hemorrhage, uterine rupture, and cardiac failure.

We first assessed temporal trends in annual rates of postpartum hemorrhage, hypertensive disorders and other risk factors using the chi-square test for linear trend in proportions. Among cases of obstetric acute renal failure, the frequency of these risk factors was quantified in both the first (2003-2006) and second half (2007-2010) of the study period (the test for linear trend in proportions was based on the rate for each year of study). Acute renal failure rates were also quantified among women with and without postpartum hemorrhage, with and without hypertensive disorders, and other risk factors.

Logistic regression was used to compare the annual increase in obstetric acute renal failure rates after adjusting for postpartum hemorrhage, hypertensive disorders of pregnancy, and other risk factors for acute renal failure. Unadjusted and adjusted odds ratios for the temporal increase in obstetric acute renal failure were compared to determine whether the temporal increase was explained (i.e., controlled for) by changes in postpartum hemorrhage and other risk factors. Year was modeled as a continuous covariate based on each year between 2003 and 2010. To facilitate interpretation, calendar time was also modeled in two-year intervals and acute renal failure rates in 2009-10 were compared with rates in 2003-04. A separate category was used in logistic models for missing information on parity (22% of deliveries). Based on preliminary descriptive analyses of rates of acute renal failure among the risk factors of interest, we added *post hoc* analyses of interaction terms to evaluate whether the rate of acute renal failure over time differed based on whether women experienced postpartum hemorrhage or hypertensive disorder of pregnancy. Sensitivity analyses were carried out to explore whether temporal trends in obstetric acute renal failure were better explained by changes in severe postpartum hemorrhage (instead of any postpartum hemorrhage) or by modeling age as a continuous covariate using restricted cubic splines.[53,92] We also carried out a *post hoc* assessment of temporal trends in rates of pulmonary edema. Finally, we assessed if adjustment for other potential confounders, namely, previous cesarean delivery, chronic kidney disease, obesity, and obstetric shock, accounted for temporal changes in obstetric acute renal failure. All analyses were conducted using the statistical software package SAS version 9.3 and Stata SE version 11. This study was carried out under the auspices of the Public Health Agency of Canada's Canadian Perinatal Surveillance

System. The data source included denominalized information, and the Public Health Agency of Canada, which is mandated to monitor maternal and infant health in the Canadian population, is not required to obtain ethics review board approval for such studies.

6.4 Results

Among the 2,193,425 hospital deliveries in Canada between 2003 and 2010, 502 cases of obstetric acute renal failure were observed; rates increased by 61% (95% confidence interval [CI] 24-110%) between 2003-04 and 2009-10, from 1.66 to 2.68 per 10,000 deliveries (Table 6.1). The increase in obstetric acute renal failure coincided with a 21% (95% CI 19-23%) increase in postpartum hemorrhage (Table 6.1). Hypertensive disorders of pregnancy increased slightly from 6.0% of deliveries in 2003-04 to 6.3% in 2009-10 (P value for trend <0.001), while gestational hypertension with significant proteinuria remained at 1.1% throughout the study period (P for trend 0.44). The frequency of older maternal age in the cohort increased from 17.7% in 2003-04 to 19.2% in 2009-10. A small temporal decline was observed in nulliparity, while multi-fetal pregnancy and history of previous cesarean delivery rose over the same period. Demographic and obstetric characteristics (including rates of labour induction and cesarean delivery) are summarized in Table 6.1.

Table 6.2 summarizes the characteristics of the acute renal failure cases in the first and second half of the study period. The proportion of acute renal failure cases with atonic postpartum hemorrhage increased significantly from 12.3% in 2003-06 to 19.3% in 2007-10 (P for trend=0.03, Table 6.2). Similarly, the proportion of women with any hypertensive disorder increased significantly among cases; in particular, the proportion of women with

gestational hypertension with proteinuria increased from 33% in 2003-06 to 41% in 2007-10 (P for trend <0.01, Table 6.2). Rates of maternal death, intensive care unit admission, and dialysis among cases of acute renal failure did not change significantly between the first and second half of the study period (Table 6.2).

Table 6.1. Temporal trends in obstetric acute renal failure and in postpartum hemorrhage, hypertensive disorders of pregnancy and other risk factors for obstetric acute renal failure, Canada (excluding Quebec), 2003 to 2010 (N=2,193,425).

Outcome/Risk factor	All years N (cases)	2003-04	2005-06	2007-08	2009-10	P value for trend*
Acute renal failure - per 10,000 deliveries	502	1.66	2.35	2.40	2.68	<0.001
Risk factors - per 100 deliveries						
Postpartum hemorrhage	122,676	5.06	5.18	5.92	6.13	<0.001
Atonic postpartum hemorrhage	97,920	3.90	4.14	4.78	4.96	<0.001
Non-atonic postpartum hemorrhage	24,756	1.16	1.04	1.15	1.16	0.08
Severe postpartum hemorrhage (PPH)						
Postpartum hemorrhage + blood transfusion	9,575	0.37	0.40	0.47	0.49	<0.001
Postpartum hemorrhage + hysterectomy	1,150	0.05	0.05	0.06	0.06	<0.01
Postpartum hemorrhage + other procedures	1,714	0.05	0.07	0.09	0.11	<0.001
Any hypertensive disorder	134,490	6.03	6.09	6.13	6.26	<0.001
Pre-existing hypertension	9,695	0.41	0.44	0.45	0.46	<0.001
Pre-existing hypertension with proteinuria	2,543	0.11	0.11	0.12	0.13	0.001
Gestational hypertension no proteinuria	92,528	4.10	4.19	4.22	4.35	<0.001
Gestational hypertension with proteinuria	24,851	1.12	1.13	1.15	1.14	0.44
Unspecified hypertension	4,268	0.25	0.19	0.17	0.17	<0.001
Eclampsia	1,684	0.12	0.08	0.06	0.06	<0.001
Other risk factors - per 100 deliveries						
Maternal age ≥35 years	404,529	17.7	18.2	18.6	19.2	<0.001
Nulliparous†	763,115	45.1	44.6	44.3	44.4	<0.001
Multi-fetal gestation	30,608	1.27	1.33	1.42	1.55	<0.001
Previous cesarean	281,862	11.8	12.6	13.3	13.6	<0.001
Diabetes	112,951	4.37	4.87	5.28	5.98	<0.001
Gestational edema and proteinuria	2,454	0.11	0.07	0.12	0.14	<0.001
Sepsis	2,557	0.16	0.12	0.10	0.09	<0.001
Other puerperal infection	8,615	0.48	0.41	0.35	0.33	<0.001
Antepartum hemorrhage/placenta previa	20,712	0.91	0.94	0.94	0.98	<0.001
Placental abruption	25,783	1.24	1.15	1.15	1.17	<0.001
Polyhydramnios	10,939	0.45	0.45	0.51	0.58	<0.001
Induction of labour	471,515	21.0	20.4	20.1	24.4	<0.001
Cesarean delivery	600,128	26.3	27.3	27.9	27.9	<0.001
Uterine rupture	2,153	0.11	0.10	0.09	0.09	<0.01
Obstetric shock	544	0.02	0.02	0.03	0.03	0.04
Cardiac failure	1,837	0.08	0.09	0.08	0.10	<0.001
Amniotic Fluid Embolism	136	0.01	0.01	0.01	0.01	0.33
Chronic Kidney disease	172	0.01	0.01	0.01	0.01	0.75

*Test for linear trend in proportions based on each year between 2003 and 2010.
†Proportion calculated excludes women with missing information for parity.

Table 6.2. Proportion of obstetric acute renal failure cases (n=502) with postpartum hemorrhage, hypertensive disorders, other risk factors, and mortality/morbidity, Canada (excluding Quebec), 2003-06 and 2007-10.

	All years N (cases)	2003-06 n=212 %	2007-10 n=290 %	P value for trend*
Postpartum hemorrhage	148	26.9	31.4	0.34
Atonic postpartum hemorrhage	82	12.3	19.3	0.03
Non-atonic postpartum hemorrhage	66	14.6	12.1	0.27
Non-atonic postpartum hemorrhage†				
Due to retained placenta	19	3.8	3.8	0.85
Secondary	9	2.4	1.4	0.37
Due to coagulation defects	55	12.3	10.0	0.31
Severe postpartum hemorrhage				
Postpartum hemorrhage + blood transfusion	93	17.5	19.3	0.64
Postpartum hemorrhage + hysterectomy	25	3.3	6.2	0.22
Postpartum hemorrhage + other procedures	15	1.9	3.8	0.23
Any hypertensive disorder	316	59.0	65.9	0.05
Pre-existing hypertension	11	1.9	2.4	0.57
Pre-existing hypertension with proteinuria	33	6.1	6.9	0.76
Gestational hypertension without proteinuria	70	15.6	12.7	0.21
Gestational hypertension with proteinuria	190	33.0	41.4	<0.01
Unspecified hypertension	11	3.3	1.4	0.08
Eclampsia	16	2.8	3.5	0.66
Maternal age ≥35 years	143	23.6	32.1	0.07
Nulliparous‡	257	68.2	62.6	0.23
Multi-fetal gestation	50	10.4	9.7	0.66
Previous cesarean	52	9.0	11.4	0.27
Diabetes	77	15.6	15.2	0.58
Gestational edema and proteinuria	8	1.9	1.4	0.98
Sepsis or other puerperal infection	60	11.3	12.4	0.93
Antepartum hemorrhage/placenta previa	22	4.3	4.5	0.83
Placental abruption	56	11.3	11.0	0.67
Polyhydramnios	12	2.4	2.4	0.88
Induction of labour	158	27.8	34.1	0.30
Cesarean delivery	335	70.8	63.8	0.38
Uterine rupture	5	0.9	1.0	0.69
Obstetric shock	25	3.3	6.2	0.19
Cardiac failure	35	6.6	7.2	0.29
Amniotic fluid embolism	6	1.4	1.0	0.46
Chronic kidney disease	13	2.8	2.4	0.60
Maternal death	14	3.3	2.4	0.81
ICU admission	191	41.0	35.9	0.24
Dialysis	44	10.4	7.6	0.21

*Test for linear trend in proportions based on each year between 2003 and 2010.
†Subcategories include women with more than one subtype of non-atonic postpartum hemorrhage.
‡Proportion calculated excludes women with missing information for parity.

Rates of obstetric acute renal failure increased among women with and women without postpartum hemorrhage (Table 6.3). Among women with postpartum hemorrhage, rates of acute renal failure increased by 79% (95% CI 5-206%) from 2003-04 to 2009-10 (P for trend=0.06), while among women without postpartum hemorrhage, rates of acute renal failure increased by 47% (95% CI 8-100%) between 2003-04 and 2009-10 (P for trend=0.005).

A significant increase in obstetric acute renal failure occurred only among women with hypertensive disorders (Table 6.3). Among women with hypertensive disorders, obstetric acute renal failure increased by 85% (95% CI 32-161%) from 15.6 per 10,000 deliveries in 2003-04 to 28.8 per 10,000 in 2009-10. There was no significant increase in obstetric acute renal failure among women without hypertension (21% increase, 95% CI -21 to 86%). The increase in obstetric acute renal failure among women with gestational hypertension with proteinuria was striking; acute renal failure rates increased by 141% (95% CI 54-277%) from 45.5 per 10,000 in 2003-04 to 109.6 per 10,000 in 2009-10. Obstetric acute renal failure did not increase significantly among subtypes of hypertensive disorders other than gestational hypertension with significant proteinuria. Analyses restricted to women without hypertensive disorders of pregnancy showed no statistically significant increase in obstetric acute renal failure among women with or without postpartum hemorrhage (Table 6.3).

Table 6.3. Temporal trends in obstetric acute renal failure among women with and without postpartum hemorrhage and women with and without hypertensive disorders of pregnancy, Canada (excluding Quebec), 2003 to 2010.

	All years	Acute renal failure Rate per 10,000 deliveries				2009-10 vs 2003-04	P value for trend
	N (cases)	2003-2004	2005-2006	2007-2008	2009-2010	Rate ratio (95% CI)	
Deliveries with postpartum hemorrhage (n=122,676)							
Acute renal failure	148	7.34	13.6	13.29	13.16	1.79 (1.05-3.06)	0.06
Deliveries without postpartum hemorrhage (n=2,070,749)							
Acute renal failure	354	1.36	1.74	1.71	2.00	1.47 (1.08-2.00)	0.005
Deliveries with hypertensive disorders (n=134,490)							
Acute renal failure	316	15.6	23.4	25.1	28.8	1.85 (1.32-2.61)	<0.001
Deliveries without hypertensive disorders (n=2,058,935)							
Acute renal failure	186	0.77	0.99	0.91	0.93	1.21 (0.79-1.86)	0.39
Deliveries with gestational hypertension with proteinuria (n=24,851)							
Acute renal failure	190	45.5	72.1	74.3	109.6	2.41 (1.54-3.77)	<0.001
Deliveries with postpartum hemorrhage, excluding hypertensive disorders of pregnancy (n=112,004)							
Acute renal failure	69	3.4	8.2	6.5	6.3	1.86 (0.82-4.22)	0.39
Deliveries without postpartum hemorrhage, excluding hypertensive disorders of pregnancy (n=1,946,931)							
Acute renal failure	117	0.64	0.60	0.57	0.60	0.94 (0.53-1.56)	0.98

CI denotes confidence interval

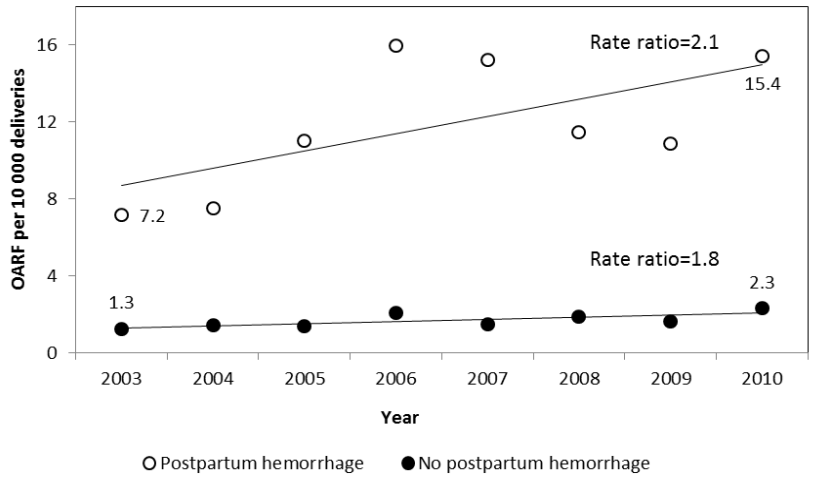
The results of logistic regression analyses based on all study women showed that several risk factors were very strongly associated with obstetric acute renal failure, including pre-existing hypertension with proteinuria, gestational hypertension with significant proteinuria, non-atonic postpartum hemorrhage, gestational edema with proteinuria, sepsis and cardiac failure (Table 6.4). However, as shown in Table 6.4, Model 1, adjustment for these risk factors did not attenuate (explain) the unadjusted 8% (95% CI 4-12%) yearly increase in obstetric acute renal failure between 2003 and 2010 (adjusted yearly increase 9%, 95% CI 5-14%). The inclusion of a product term between year of delivery and gestational hypertension with proteinuria in the regression model, however, resulted in a significant interaction (OR for interaction 1.17, 95% CI 1.08-1.28). In other words, the temporal trends in obstetric acute renal failure were different among women with and those without gestational hypertension with significant proteinuria. After inclusion of this product term, year of delivery became non-significant in the adjusted analysis (OR 1.03, 95% CI 0.98-1.08), indicating that a rise in obstetric acute renal failure only occurred among women who developed gestational hypertension with significant proteinuria (Table 6.4, Model 2). An interaction between year of delivery and all hypertensive disorders of pregnancy was also statistically significant (P=0.03), while the interaction between year of delivery and postpartum hemorrhage was not significant (P=0.18). The modification of the effect of gestational hypertension with proteinuria on obstetric acute renal failure by year of delivery, as well as the lack of such effect modification with postpartum hemorrhage, are shown in Figure 6.1.

Table 6.4. Results of logistic regression modeling showing effects of year and risk factors on acute renal failure (ARF) among all deliveries (n=2,193,425), Canada (excluding Quebec), 2003 to 2010.

	Rate of ARF per 10,000	Unadjusted odds ratio (95% confidence interval)	Model 1: odds ratio without interaction term (95% confidence interval)	Model 2: odds ratio with interaction term† (95% confidence interval)
Year of delivery	-	1.08 (1.04-1.12)	1.09 (1.05-1.14)	1.03 (0.98-1.08)
Atonic postpartum hemorrhage	8.37	4.18 (3.30-5.30)	3.56 (2.76-4.58)	3.55 (2.75-4.57)
Non-atonic postpartum hemorrhage	26.7	13.3 (10.3-17.2)	12.5 (9.4-16.8)	12.5 (9.3-16.7)
Hypertensive disorders				
Pre-existing hypertension	11.3	5.05 (2.78-9.18)	3.14 (1.67-5.89)	3.27 (1.75-6.13)
Pre-existing hypertension with proteinuria	129.8	61.4 (43.0-87.6)	29.3 (19.7-43.7)	29.9 (20.1-44.6)
Gestational hypertension no proteinuria	7.57	3.68 (2.86-4.74)	4.68 (3.56-6.17)	4.71 (3.58-6.21)
Gestational hypertension with proteinuria	76.5	53.6 (44.7-64.2)	31.6 (25.6-38.9)	14.10 (8.7-22.8)
Eclampsia	95	43.3 (26.2-71.3)	8.29 (4.70-14.6)	8.32 (4.70-14.7)
Unspecified hypertension	25.8	11.5 (6.3-21.0)	9.54 (5.04-18.1)	9.86 (5.22-18.7)
Maternal Age (in years)				
<20	1.65	1.05 (0.61-1.80)	0.89 (0.51-1.54)	0.89 (0.51-1.54)
20-24	1.57	Reference	Reference	Reference
25-29	2.09	1.33 (0.97-1.82)	1.22 (0.89-1.68)	1.22 (0.89-1.68)
30-34	2.2	1.40 (1.03-1.90)	1.20 (0.88-1.65)	1.21 (0.88-1.65)
35-39	3.36	2.14 (1.55-2.94)	1.48 (1.06-2.07)	1.50 (1.07-2.09)
≥40	4.39	2.79 (1.79-4.34)	1.19 (0.74-1.90)	1.21 (0.75-1.93)
Parity 1	1.46	Reference	Reference	Reference
Nulliparous	3.34	2.23 (1.76-2.83)	1.46 (1.14-1.88)	1.46 (1.13-1.87)
2-4	1.53	1.01 (0.71-1.44)	1.03 (0.72-1.47)	1.02 (0.71-1.46)
>5	3.67	2.43 (1.23-4.83)	2.06 (1.02-4.15)	2.07 (1.03-4.16)
Missing	1.99	1.32 (0.99-1.76)	0.87 (0.64-1.16)	0.86 (0.64-1.16)
Multi-fetal gestation	16.3	7.83 (5.84-10.49)	2.12 (1.55-2.91)	2.10 (1.53-2.88)
Diabetes	6.82	3.34 (2.62-4.26)	1.75 (1.35-2.26)	1.73 (1.34-2.25)
Gestational edema and proteinuria	32.6	14.5 (7.21-29.2)	8.40 (4.02-17.6)	8.39 (4.02-17.6)
Sepsis	101.7	47.3 (31.8-70.3)	8.82 (5.52-14.1)	9.01 (5.64-14.4)
Other puerperal infection	46.4	22.1 (16.0-30.5)	4.77 (3.28-6.93)	4.84 (3.33-7.03)
Antepartum hemorrhage/placenta previa	10.6	4.81 (3.14-7.38)	1.90 (1.21-3.01)	1.88 (1.19-2.98)
Placental abruption	21.7	10.6 (8.01-14.0)	5.29 (3.93-7.11)	5.26 (3.91-7.07)
Polyhydramnios	11	4.89 (2.76-8.67)	2.34 (1.27-4.31)	2.39 (1.30-4.41)
Induction of labour	3.35	1.68 (1.39-2.03)	0.92 (0.75-1.13)	0.92 (0.75-1.13)
Cesarean delivery	5.58	5.33 (4.43-4.81)	2.79 (2.25-3.44)	2.79 (2.25-3.44)
Uterine rupture	23.2	10.3 (4.25-24.8)	3.14 (1.16-8.47)	3.13 (1.15-8.49)
Cardiac failure	190.5	91.1 (64.4-128.9)	11.01 (7.38-16.4)	11.28 (7.55-16.8)
Gestational hypertension with proteinuria * year of study (interaction)	-	-	-	1.17 (1.08-1.28)

Models 1 and 2 were adjusted for all variables listed in table under each respective model.
†The interaction can be interpreted as showing that a rise in obstetric acute renal failure was only significant among women with gestational hypertension with significant proteinuria, and not among women without this condition. An interaction between overall hypertensive disorders and year of delivery was also significant, while the interaction between year of delivery and postpartum hemorrhage was not significant.

A)



B)

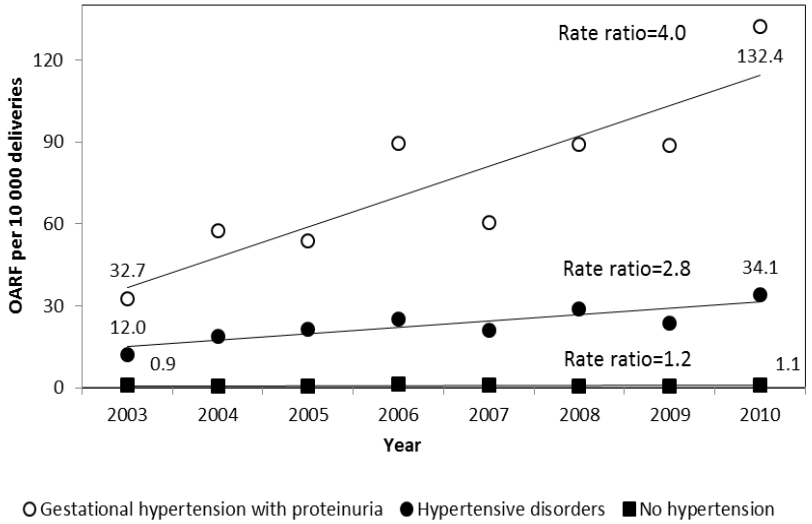


Figure 6.1. Rates of obstetric acute renal failure (OARF) among deliveries with and without postpartum hemorrhage (Panel A) and among women with gestational hypertension with significant proteinuria, hypertensive disorders of pregnancy and no hypertension (Panel B), Canada (excluding Quebec), 2003 to 2010. Rate ratios express changes between 2003 and 2010 and show that temporal patterns in OARF were different among women with and without hypertension (but not among women with and without postpartum hemorrhage).

Table 6.5 summarizes the results of logistic regression analyses that account for the interaction between calendar time and hypertensive status. Results were similar when calendar time was categorized and continuous; both models are presented in Table 6.5. The crude temporal increase in obstetric acute renal failure between 2003-04 and 2009-10 (odds ratio 2.41, 95% CI 1.54-3.77) among women with gestational hypertension and significant proteinuria was not materially changed by adjustment for risk factors (adjusted odds ratio 2.71, 95% CI 1.71-4.29). Nor did adjustment for risk factors change the non-significant increase in obstetric acute renal failure among women without hypertensive disorders between 2003-04 and 2009-10 (adjusted odds ratio 1.12, 95% CI 0.72-1.72). Full logistic regression models among women with gestational hypertension and proteinuria and among women without hypertensive disorders of pregnancy are shown in Supplementary Tables C.2 and C.3.

Table 6.5. Logistic regression model of temporal increase in obstetric acute renal failure by strata.

	Yearly increase (2003-2010)		2009-10 vs 2003-04†	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI) *	Unadjusted OR (95% CI)	Adjusted OR (95% CI) *
Among women with gestational hypertension with significant proteinuria	1.16 (1.09-1.24)	1.18 (1.10-1.26)	2.41 (1.54-3.77)	2.71 (1.71-4.29)
Among women without gestational hypertension with significant proteinuria	1.04 (0.99-1.09)	1.02 (0.97-1.07)	1.25 (0.89-1.74)	1.14 (0.81-1.60)
Among women with hypertensive disorders	1.11 (1.05-1.16)	1.11 (1.06-1.17)	1.85 (1.32-2.61)	1.95 (1.38-2.76)
Among women without hypertensive disorders	1.03 (0.97-1.10)	1.01 (0.95-1.08)	1.21 (0.79-1.86)	1.12 (0.72-1.72)

*Adjusted for atonic postpartum hemorrhage, non-atonic postpartum hemorrhage, maternal age, parity, multi-fetal gestation, diabetes, sepsis, other puerperal infection, antepartum hemorrhage/placenta previa, placental abruption, polyhydramnios, induction of labour, cesarean delivery, uterine rupture, cardiac failure.
†Additionally adjusted for years 2007-08 and 2006-05 vs. 2003-04

Table 6.6 shows temporal trends in rates of pulmonary edema among all women and among women with and without hypertensive disorders. Pulmonary edema rates declined among all women though temporal trends were not statistically significant in any category. Among women with gestational hypertension and proteinuria, pulmonary edema rates declined substantially from 77.0 per 10,000 deliveries in 2003-04 to 63.9 in 2005-06 and then increased to 74.1 per 10,000 deliveries in 2009-10.

Table 6.6. Temporal trends in rates of pulmonary edema among all deliveries and among women with and without hypertensive disorders of pregnancy, Canada (excluding Quebec), 2003 to 2010.

	All years	Pulmonary edema Rate per 10,000				Rate ratio (2009-10 vs 2003-04)	P value for trend
	cases	2003-2004	2005-2006	2007-2008	2009-2010	(95% CI)	
All deliveries (n=2,193,425)							
Pulmonary edema	515	2.7	2.5	2.0	2.3	0.86 (0.67-1.09)	0.10
Deliveries with hypertensive disorders (n=134,490)							
Pulmonary edema	306	26.3	21.9	20.3	23.0	0.87 (0.64-1.19)	0.41
Deliveries without hypertensive disorders (n=2,058,935)							
Pulmonary edema	209	1.2	1.2	0.8	0.9	0.79 (0.54-1.15)	0.06
Gestational hypertension with significant proteinuria (n=24,851)							
Pulmonary edema	174	77.0	63.9	65.6	74.1	0.96 (0.64-1.45)	0.95

CI denotes confidence interval

Additional analyses revealed that temporal changes in postpartum acute renal failure were similar to temporal changes in overall obstetric acute renal failure. Study results were unchanged when severe postpartum hemorrhage was modeled as a determinant of obstetric acute renal failure instead of postpartum hemorrhage, maternal age was modeled using restricted cubic splines, or after additional adjustment for previous cesarean delivery, chronic kidney disease, obstetric shock, and obesity.

6.5 Discussion

Rates of obstetric acute renal failure in Canada increased significantly from 1.66 in 2003-04 to 2.68 per 10,000 deliveries in 2009-10. Rates of intensive care unit admission, dialysis and maternal death among cases of obstetric acute renal failure did not change significantly across this period, suggesting no change in the severity of the renal failure. Although postpartum hemorrhage rates increased substantially over the same period and hypertensive disorders increased slightly, these rate changes did not explain the rise in obstetric acute renal failure. The rise in obstetric acute renal failure was due to increases in rates of this complication in the small (approximately 6%) subpopulation of women with hypertensive disorders of pregnancy, and was particularly striking among the smaller subset of women with gestational hypertension and significant proteinuria.

Strengths of our study included its population-based cohort design and large sample size, which allowed the study of rare outcomes. Further, we were able to adjust for sepsis, diabetes mellitus, and other important risk factors for obstetric acute renal failure, while examining the effects of postpartum hemorrhage and hypertensive disorders of pregnancy. Another strength was the demonstrated validity of our data source for postpartum hemorrhage and hypertensive disorders of pregnancy.[47] Limitations of our study include inaccuracies in the data source, such as potential inaccurate diagnosis of obstetric acute renal failure,[93] or changes in the clinical criteria for diagnosis over time. Although such inaccuracies are inherent in any large administrative database, the ICD-10-CA definitions of acute renal failure and postpartum hemorrhage remained unchanged over the study period, and the codes for acute kidney injury have been extensively validated in the non-pregnant population.[94-96]

The rate of gestational hypertension with significant proteinuria (pre-eclampsia) in our study was lower than overall rates of pre-eclampsia reported elsewhere.[97] Prior to 2012, the ICD-10 Canadian Edition indicated that women with mild pre-eclampsia were to be included under the code for gestational hypertension without significant proteinuria. Therefore, the ICD-10 code corresponding to "gestational hypertension with significant proteinuria" likely included only moderate to severe cases of pre-eclampsia. Further, gestational hypertension with proteinuria in our study did not include women with pre-existing hypertension and superimposed pre-eclampsia. Nevertheless, the rate of gestational hypertension with significant proteinuria was stable between 2003 and 2010, suggesting a constancy of coding practices during the study period. Information on pre-pregnancy body mass index and the severity of hypertensive disorders of pregnancy was not available in the database. While we included obesity (identified using ICD 10CA codes) in sensitivity analyses, this diagnosis is known to underestimate the true prevalence of obesity.[70] Finally, further study is required to assess long term renal function among women diagnosed with obstetric acute renal failure. Although a few small studies suggest good renal outcomes among women with hypertension in pregnancy and obstetric acute renal failure,[98,99] few high quality, long-term studies have addressed the long-term prognosis of pregnancy-related acute kidney injury.[100]

The marked increase in acute renal failure among women with gestational hypertension and significant proteinuria may be due to recent changes in the management of pre-eclampsia., such as changes in fluid management or anti-hypertensive treatment. Recent clinical practice guidelines have promoted the use of fluid restriction (to 80 mL/hour in the peripartum period, in order to prevent pulmonary edema and other complications of fluid overload), magnesium

sulfate use (for seizure prophylaxis), and antihypertensive pharmacotherapy (with first-line drugs such as nifedipine, labetalol, hydralazine, and methyldopa).[88,101] The management of hypertension in pregnancy, particularly in cases of pre-eclampsia, is complex. Competing priorities include lowering blood pressure and preventing maternal seizures, and preventing very preterm birth, intrauterine growth restriction, and other complications. Although the best available evidence suggests that currently recommended pre-eclampsia management is effective in reducing the frequency of eclampsia and other complications,[88] an increase in a rare, unintended side effect such as acute renal failure cannot be ruled out. Previous studies have suggested that fluid restriction protocols in pre-eclampsia may have the secondary effect of increasing rates of acute renal failure through hypovolemia and renal hypoperfusion.[88,89] On the other hand, fluid overload in pre-eclampsia treatment is associated with maternal deaths related to pulmonary edema,[102] and current guidelines emphasize the benefits of preventing pulmonary edema and other consequences of fluid overload.[89] In our study, we found no significant reduction in pulmonary edema rates among women with gestational hypertension with significant proteinuria (although the temporal pattern in rates was complex and non-linear). However, policies restricting fluids in the treatment of pre-eclampsia have been associated with significantly lower rates of pulmonary edema in previous research.[88,103] It may therefore be prudent to continue fluid restriction protocols to prevent serious maternal complications, with more careful monitoring of renal function, until further studies provide clarity regarding the risks and benefits of such management.

Other changes in the management of pre-eclampsia that may have been responsible for the increase in acute renal failure include interactions among anti-hypertensive drugs and

medications used during pregnancy and immediately post-partum. For instance, the recommended switch to nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol for postpartum pain in 2006, followed reports of codeine-related toxicity in newborn infants through breastfeeding.[104] NSAIDs are a known risk factor for acute renal failure,[105] and have been implicated in obstetric acute renal failure.[87] In a non-obstetric population, anti-hypertensives in triple-therapy combinations with NSAIDS, also appear to increase the risk of acute kidney injury.[106] In addition, higher dose (vs. low dose) statin pharmacotherapy is reported to be associated with acute kidney injury.[107] However, due to fetal safety concerns, anti-hypertensive medications used in pregnancy are different from standard pharmacotherapy. Suggested mechanisms for kidney injury due to anti-hypertensives prescribed in pregnancy may include prerenal azotemia (due to decreased blood volume) with vasodilators such as hydralazine and calcium-channel blockers, ureteral obstruction secondary to retroperintoneal fibrosis for methyldopa and hydralazine, hyperkaelemia for beta-blockers, and a "pseudo-nephrotoxicity" due to interference with laboratory determination of creatinine for methyldopa, without other clinical signs.[108] A recent study further reported that the antibiotic clarithromycin may interact with nifedipine to increase the risk of acute kidney injury through the inhibition of the CYP3A4 enzyme.[109] Further study is required to determine whether anti-hypertensive medication affects renal function in pregnancy and postpartum.

Although postpartum hemorrhage did not explain the increase in obstetric acute renal failure, it was an important risk factor for acute renal failure. The absence of an increase in acute renal failure despite the increase in postpartum hemorrhage may have been due to appropriate

and aggressive treatment of postpartum hemorrhage, which likely prevented severe hypovolaemia related to blood loss. This is evidenced by increases in postpartum hemorrhage in conjunction with blood transfusion and surgical procedures to control bleeding, including arterial embolization, uterine artery ligation, and the use of uterine compression sutures.

In conclusion, we observed a significant increase in obstetric acute renal failure in Canada that was restricted to women with hypertensive disorders of pregnancy and was particularly evident among women with gestational hypertension with significant proteinuria. Further studies are required to confirm our findings, including those related to temporal trends in pulmonary edema, and to determine the specific aspect of pre-eclampsia management (fluid restriction, anti-hypertensive therapy and other medication use) that may be increasing pregnancy-related kidney injury. In addition, the long-term impact of pregnancy-related kidney injury requires further study. Meanwhile, clinicians managing women with pre-eclampsia should carefully monitor patients for signs of impending renal failure and take appropriate steps to mitigate the risk of further kidney injury.

Chapter 7: Conclusion

7.1 Summary of findings

Rates of postpartum hemorrhage and severe postpartum hemorrhage increased in British Columbia from 2000 to 2009, and across Canada between 2003 and 2010. Chapters 2 and 3 showed that the increase occurred across key maternal, fetal and obstetric risk factors, and that none of the maternal, fetal and obstetric risk factors studied explained the increase. Factors of interest that did not explain the increase in atonic postpartum hemorrhage or severe atonic postpartum hemorrhage included increases in older maternal age, maternal obesity, previous cesarean delivery and labour induction and labour augmentation. Chapter 4 showed that the increase in postpartum hemorrhage continued to occur in Canada after 2004, and that the increase in postpartum hemorrhage and postpartum hemorrhage with blood transfusion occurred across most provinces and territories. Chapter 5 showed that the estimated population attributable fraction for postpartum hemorrhage (attributable to placenta accreta) was only 1% and that most of the postpartum hemorrhage associated with placenta accreta was third stage postpartum hemorrhage. However, the impact of placenta accreta on severe postpartum hemorrhage was substantially greater; the population attributable fraction of placenta accreta for postpartum hemorrhage with hysterectomy was 29%. Changes in the rate of placenta accreta over time could thus have had an impact on the incidence of postpartum hemorrhage with hysterectomy and other severe forms of postpartum hemorrhage. Lastly, chapter 6 showed that the rise in obstetric acute renal failure in Canada was not explained by the concurrent rise in postpartum hemorrhage. An important and unexpected finding of the final study was that the increase in obstetric acute renal failure in

Canada between 2003 and 2010 was almost entirely restricted to 6% of women with hypertensive disorders of pregnancy, and especially pronounced among the 1% of women with pre-eclampsia. Further study is required to confirm these findings and to determine whether a specific aspect of pre-eclampsia management may be responsible for the rise in obstetric acute renal failure.

7.2 Strengths and limitations

The strengths of these studies were their population-based design and large study sizes, which provided the opportunity to study rare outcomes and other associations not previously studied at the population-level. The study of the increase in postpartum hemorrhage in British Columbia examined postpartum hemorrhage in conjunction with blood transfusion and other markers of severe postpartum hemorrhage. This study permitted the examination of factors not available in previous studies, namely, pre-pregnancy body mass index, labour augmentation and a higher threshold of blood transfused to account for potential changes in practice. The study of placenta accreta allowed us to study the impact of this rare pregnancy complication on postpartum hemorrhage rates in detail, while previous research has been based on cases from a single tertiary care centre, or a select group of high-risk patients.[74-77,110] An important strength of the study on the rise in obstetric acute renal failure in Canada was the large size, which allowed the study of this rare outcome with adjustment for many potential confounders. To our knowledge this study on the rise of acute renal failure was the first study to investigate the rise in obstetric acute renal failure in North America.

Several important limitations should be noted. Differences in diagnosis and reporting are possible by provider, institution and by region. For this reason, large differences in rates of postpartum hemorrhage by province/territory should be interpreted with caution (e.g., among Canadian provinces rates of postpartum hemorrhage ranged from 3.6% (95% CI 3.3-4.0) in Prince Edward Island to 8.8% (95% CI 8.7-8.9) in Alberta). In comparison, a review of Europe reported that rates of severe postpartum hemorrhage (defined as blood loss ≥1500mL or receipt of blood transfusion) ranged from 0.7 per 1000 deliveries in Austria to 8.8 per 1000 deliveries in Finland.[111] Such large differences suggest differences in the ascertainment and recording of postpartum hemorrhage, although the possibility that part of the differences are due to maternal age and other characteristics, and the type of care provided, cannot be excluded.

Other limitations included differences in cut-offs for the diagnosis of postpartum hemorrhage by route of delivery (i.e., blood loss of ≥500 mL for vaginal delivery versus ≥1000 mL for cesarean delivery), which made the interpretation of some of the results difficult (for example cesarean delivery and certain factors associated with cesarean delivery were protective for postpartum hemorrhage). We attempted to overcome this limitation by modeling the outcome of postpartum hemorrhage in conjunction with objective markers of severity. A further limitation was that atonic postpartum hemorrhage may have included non-atonic causes, such as that due to perineal and cervical tears and lacerations, which met the definitional criteria of occurring following the third stage and within 24 hours of delivery. Unfortunately excluding women with tears and cervical lacerations would exclude women whose cause of postpartum hemorrhage was uterine atony (with associated prolonged labours, instrumental deliveries

and consequent bleeding from tears). Differentiating the original cause of the postpartum hemorrhage would be difficult in such circumstances where tears and lacerations followed uterine atony. For this reason we included all women in the analyses.

National data were not available on body mass index and labour augmentation. Both nationally and in the British Columbia data source, information was not available in the database on changes in third stage management, which is thought to be a key factor in the prevention of postpartum hemorrhage. In addition, information was not available on medications administered or their doses. Another limitation is that with multiple comparisons, Type I errors were possible. We attempted to address the multiple comparison concern by only testing risk factors reported in the literature or based on prior clinical knowledge, by reporting confidence intervals for each of our tests, and by not over-emphasizing p-values and their importance in our conclusions. Finally, large perinatal databases inevitably include some inaccuracies that arise for various reasons including coding and transcription errors.

7.3 The increase in postpartum hemorrhage – artifactual or real?

It is possible that the observed increases in postpartum hemorrhage are a consequence of changes in the diagnosis of postpartum hemorrhage, other changes in reporting, or postpartum hemorrhage management rather than a real increase in hemorrhage rates. The following sections review the arguments for and against the true increase in the incidence of postpartum hemorrhage.

7.3.1 Is the increase in postpartum hemorrhage an artifact?

In 2006, changes were made to the Canadian coding standards for hospitalization information, specifically with regard to the coding of postpartum hemorrhage. Prior to 2006, deliveries were coded as cases of postpartum hemorrhage only if the health care provider noted this diagnosis in the medical record. From 2006 onwards, a code of postpartum hemorrhage was assigned both to cases labeled as postpartum hemorrhage by a health care provider and also to where the reported blood loss was ≥500 mL for a vaginal delivery and ≥1000 mL for a cesarean delivery (even if the health care provider did not record a diagnosis of postpartum hemorrhage). This raises the possibility that from 2006 onwards the rise in postpartum hemorrhage was due to changes in coding rather than a true increase in incidence.

In addition, the diagnosis of blood loss is known to be unreliable, and blood loss is typically underestimated.[112] Some of the strategies to improve obstetrical care have focused on improved communication and training using various methods including simulation. Training courses offered by the Society of Obstetricians and Gynaecologists of Canada (www.sogc.org) include More OB (The Managing Obstetrical Risk Efficiently Program), and ALARM (Advances in Labour and Risk Management). Attendance in such courses has grown since the ALARM course premiered in 1995, and the curriculum includes education about the underestimation of blood loss.[113] In addition, the growing literature over the last decade about active management of third stage of labour may have triggered a heighted awareness about postpartum hemorrhage,[62] and may have lowered providers' threshold for diagnosing and treating postpartum hemorrhage, creating an apparent increase in incidence.

Finally, changes in the management of postpartum hemorrhage are possible and even likely. Although this would not be expected to substantially affect the invasive surgical methods of blood loss control (e.g., hysterectomy or the procedures to control bleeding studied in this dissertation), changing practice patterns may have affected the rate of postpartum hemorrhage with blood transfusion, which rose markedly in British Columbia and across Canada. The threshold for blood transfusion may have been lowered, as the safety of blood products has improved. The result may have been an increase in providers' confidence about transfusing, thereby potentially leading to higher rates of blood transfusion for postpartum hemorrhage over time. Likewise, improved estimation of blood loss may have increased providers' awareness of their patients' need for transfusion, leading to increase in both the diagnosis of postpartum hemorrhage and use of transfusion.

7.3.2 Is the increase in postpartum hemorrhage real?

Several arguments support the conclusion that the observed rise in postpartum hemorrhage represents a true occurrence. Despite the change in the Canadian coding standards about recorded blood loss in 2006, there was no difference in coding between the ICD-9 (including and prior to 2000) and ICD-10 (2001 onwards), and the increase did not occur in cases of non-atonic postpartum hemorrhage. If the increase in atonic postpartum hemorrhage was a consequence of a lowering of the threshold for a diagnosis of postpartum hemorrhage, rates of non-atonic postpartum hemorrhage should have increased as well.

In addition, postpartum hemorrhage increased based on several objective measures of severity, the most objective being hysterectomy, which increased in Canada along with other procedures to control bleeding. As described in Chapter 4, procedures to control bleeding increased dramatically in Canada with no concurrent decrease in the hysterectomy rates accompanying postpartum hemorrhage. Although it is possible that the threshold for blood transfusion may have decreased, there is no firm evidence to support such speculation. In fact a recent trial showed that reducing the threshold for blood transfusion in order to reduce symptoms of anemia and improve women's quality of life was ineffective.[20] The study also cited potential adverse events associated with blood transfusion, and warned that blood transfusion is not a benign intervention.[20]

Finally, the increase in postpartum hemorrhage has occurred internationally in several high income countries and jurisdictions which use a variety of definitions for postpartum hemorrhage.[1,3,4,7,9,10,14,33]

7.3.3 Alternative hypotheses

A further possibility remains that several distinct etiologies exist for the temporal increase in postpartum hemorrhage, including a combination of factors responsible for a real increase and also an artifactual increase due to changes in reporting. The British Columbia Perinatal Data Registry only obtained population-level data as of the year 2000, the starting year of the cohort studies in this dissertation. One possibility is that the factors underlying the increase in postpartum hemorrhage between 1991 and 2000 were different from those responsible for the increase more recently. If the situation were to occur, the possibility remains that the rise in

postpartum hemorrhage between 1991 and 2000 was real, but the rise beyond this point was an artifact of changes in diagnosis, reporting, or management. If such a situation occurred, the study design used in this dissertation would not be able to identify the causes of the increase, although factors included in the study may have been responsible for an increase.

7.4 Investigation of causes not previously addressed

As mentioned, factors such as third stage management, dose of oxytocin use, and other medication use was not available in the databases examined in this thesis.

7.4.1 Third stage management

One of the most important and widely studied factors in the prevention of postpartum hemorrhage has been the management of the third stage of labour.[114-116] The question of whether changes in the management of the third stage of labour may have been responsible for the rise in postpartum hemorrhage has remained unanswered since the increase in postpartum hemorrhage among high income countries was first identified.[1,3] An Australian study suggested that a decrease in the active management of the third stage of labour may have been responsible for rising postpartum hemorrhage rates (the management changes were attributed to an increased midwifery workload).[3] On the other hand, a reasonable assumption is that the active management of labour would have increased from the years 2000 onwards, based on the publication of several important findings, findings from several studies of adherence to third stage management guidelines, and the implementation of active management guidelines at institutions internationally (described in detail in the following

paragraphs). However the question of what components of active management are key to reducing the risk of postpartum hemorrhage remains unclear.

In 2000, an influential Cochrane review showed that active management of the third stage, consisting of the administration of a prophylactic oxytocic after delivery, early cord clamping and cutting, and controlled cord traction of the umbilical cord, was associated with a reduced risk of postpartum hemorrhage of more than 500 milliliters (odds ratio 0.34, 95% confidence interval 0.28-0.41).[62] The recommendations to use active management of the third stage were instituted at many health care institutions internationally. However what comprised active management differed by country, by institution, and by provider.[117-119] In addition to the components of active management listed in the Cochrane review,[62] some institutions included uterine massage. Uterine massage was recommended as part of active management according to the International Confederation of Midwives and International Federation of Gynecology and Obstetrics.[120] The evidence base for uterine massage is weaker than for uterotonic administration, with a recent Cochrane review concluding that it offers no benefit beyond that provided by uterotonics alone.[121] Further, in 2007, the World Health Organization excluded early cord clamping from active management, due to the benefits to the infant from delaying cord clamping.[122] Two randomized controlled trials did not show any additional effect of controlled cord traction on preventing postpartum hemorrhage, above that provided by the administration of uterotonics alone.[115,116]

What can be distilled from the literature on the implementation of (or adherence to) active management is that rates of prophylactic uterotonic administration are high, but other

components of active management vary widely in their implementation. A study of 626 women from either a teaching hospital or tertiary care centre in the Netherlands reported that prophylactic oxytocic administration occurred in 98% of deliveries, and a population-based study of 1200 births in Australia (2002) reported their use in 92% of vaginal deliveries and 97% of cesarean deliveries.[119,123] A study of policies on third stage management among 14 European countries reported wide variations in which components of third stage management were recommended, both within and between countries in 2003. The inclusion of guidelines promoting the administration of prophylactic uterotonics was high in some countries (e.g., 100% of institutions in Ireland) but not others (e.g., 55% of institutions in Austria).[118] Wide variations were also reported in the type of uterotonic recommended, as well as the timing of cutting and clamping of the cord (immediately after birth versus after the cord stops pulsating), and whether controlled cord traction was included.[118]

An interesting and unexpected hypothesis has centered around a potential *increased* risk of postpartum hemorrhage with the active management of the third stage. Two retrospective studies of midwifery care among low risk women have studied active management versus standard midwifery care.[124,125] Both studies, one from New Zealand and one from Australia, report a higher risk of postpartum hemorrhage among the low risk women who received active management of the third stage. A systematic review assessing the components of the active management of labour reported that uterine massage was associated with an increased hemorrhage risk. However this intervention was not the *a priori* study hypothesis and hence could have been the chance result of multiple comparisons.[126] Another observational study has found similar results, namely, that active management or aspects of it are associated with

higher rates of postpartum hemorrhage.[123] The findings of such studies should be interpreted with caution as the prophylaxis and treatment of postpartum hemorrhage contains similar elements, and separating out these two components may not be possible. In addition, confounding by indication is probable, as the intervention of interest may be administered more often to women with risk factors for postpartum hemorrhage.

On the other hand, few surveillance efforts have systematically evaluated the implementation of active management of the third stage or its components at the population level, and where data has been collected, the information has been incomplete.[37] Health care providers participating in the clinical trials on the active management of the third stage have been highly trained, and components of active management that require training (controlled cord traction and uterine massage) could be performed poorly in actual practice, where training expertise varies.[126] For instance controlled cord traction can lead to complications such as uterine inversion or umbilical cord avulsion (snapping and detaching from the placenta).[115] Such complications are rare in trial settings where staff are highly trained,[116] but it is unclear to what extent procedure-related complications could occur where provider skill levels vary. For example, the Confidential Inquiry into Maternal Deaths in the United Kingdom reported a death related to traction on the placenta before placental separation (where the woman in fact had a retained placenta).[79]

Finally, psychosocial theories about the third stage of childbirth have described the "holistic psychophysiological care" which comprises of having a woman feel safe and secure (said to promote uterine contractions by inhibiting the fight or flight response), immediate and

sustained skin-to-skin contact with the infant, 'self-attachment' breastfeeding, and "no fundal meddling or massage."[125] The role of skin-to-skin contact, mood of the mother, and breastfeeding have not received attention in clinical trials on third stage management and postpartum hemorrhage prevention, and are likely more complex to study. The psychosocial aspects of third stage management and the role of breastfeeding may prove to be promising areas for future research. Given that rates of breastfeeding at hospital admission for newborns in British Columbia have not changed markedly between 2003 and 2013,[127]the role of breastfeeding initiation in explaining temporal increases in atonic postpartum hemorrhage is uncertain though probably limited.

7.4.2 Oxytocin dose

Although some research has suggested that the dose of oxytocin is related to postpartum hemorrhage,[41] our data sources did not permit the examination of an oxytocin-postpartum hemorrhage dose response. However, our studies showed no evidence that oxytocin use was responsible for the rise in postpartum hemorrhage. In particular, the rise in postpartum hemorrhage was not restricted to women who received oxytocin for induction or augmentation of labour. However, more detailed study of dose-response issues was beyond the scope of this dissertation and requires more detailed information.

7.4.3 Medication use

Magnesium sulfate and tocolytics may theoretically contribute to the rise in postpartum hemorrhage, and unfortunately information on medication use in pregnancy was not available in our data sources.[5,128] Although magnesium sulfate use for pre-eclampsia appears to have

increased in recent years,[88] analyses revealed that the increase in postpartum hemorrhage was not restricted to women with pre-eclampsia. In terms of tocolytics, postpartum hemorrhage increased across gestational age, which suggests that the rise was not restricted to women who received tocolytics (which are typically used only among women with threatened preterm labour).

A rise in postpartum hemorrhage could be associated with use of Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in pregnancy, as such medications have been associated with gastrointestinal and other bleeding, potentially through their effect on platelet aggregation and the maintenance of vascular tone.[65,129] SSRIs were found to be non-significantly associated with postpartum hemorrhage in a Canadian study,[66] and significantly associated with postpartum hemorrhage in another study from the United States.[130] SSRI use in British Columbia has doubled from 1998 to 2001 when 5% of pregnant women were exposed to this drug.[64] However, analyses using data from Quebec residents on the provincial drug plan did not find that SSRI medication use or associated drug interactions could explain increases in postpartum hemorrhage.[131]

7.5 Implications of thesis research

The caveats and recommendation that arise from these studies have been divided into implication for clinical practice and implications for public health surveillance.

7.5.1 Implications for clinical practice

The implications for clinical practice extend to the management of postpartum hemorrhage in general, postpartum hemorrhage with hysterectomy for placenta accreta and obstetric acute renal failure.

7.5.1.1 Postpartum hemorrhage management

The International Postpartum Hemorrhage Collaborative Group recommended that "Clinicians should be more vigilant given the possibility that the frequency and severity of postpartum hemorrhage has in fact increased".[1] Despite doubts as to whether the increase is real, it would be prudent to adopt precautionary measures to improve quality of care and ensure that cases of severe postpartum hemorrhage are avoided. A confidential audit of severe cases of postpartum hemorrhage should be implemented, and experience from the United Kingdom demonstrates that this is feasible. The Scottish Confidential Audit of Severe Maternal Morbidity chose their threshold for audit as a blood loss of ≥2500 mL, receipt of ≥5 units of blood transfusion, or treatment for coagulopathy.[8] The purpose of having a threshold for severity would be to make an ongoing, confidential audit feasible and to facilitate the process of review and recommendation.

Quality improvement measures and protocols for diagnosing and managing postpartum hemorrhage across institutions would also be prudent. For example, blood loss estimation and postpartum hemorrhage protocol implementation can be improved through ongoing drills and education.[132-134] Postpartum hemorrhage protocols include adequate identification of risk factors for postpartum hemorrhage, the accurate estimation of blood loss, prompt diagnosis,

the recognition of abnormal vital signs (such as hypovolemia), and prompt and appropriate treatment and resuscitation.[128] Other factors essential to reducing the morbidity associated with postpartum hemorrhage include timely and adequate blood volume/product replacement, appropriate referral, consultation, and transfer of care, and an environment that facilitates and supports open communication between multi-disciplinary staff members.[128] Ongoing training and education is needed to maintain personnel competency

In addition to reducing the adverse physical effects of postpartum hemorrhage, several suggestions have been made for improving the psychological outcomes for women who have experienced a postpartum hemorrhage.[21,23,24] This is important in British Columbia, where many of the women with postpartum hemorrhage are nulliparous and may have future interactions with their maternity care teams; this makes maintaining a relationship of trust and communication particularly important. Following detailed interviews of women having experienced postpartum hemorrhage, researchers have made the following recommendations to attempt to mitigate the psychological effects of experiencing a severe postpartum hemorrhage: offering the women the services of a specially trained psychologist in the postpartum period and devising a protocol for communicating to the woman and her partner about the situation during the management of the postpartum hemorrhage with the goal of empowering the couple in their care. In addition, the researchers recommend providing information about the causes and management of postpartum hemorrhage, the risk of recurrence and the long-term consequences for future deliveries (in the case of uterine sparing procedures), and finally, having follow up discussion with the woman (and her partner) two months after the delivery to review and address residual concerns.[23,24]

7.5.1.2 Postpartum hemorrhage with hysterectomy and placenta accreta

In Chapters 3 and 4, rising rates of postpartum hemorrhage with hysterectomy were found in Canada, but not in British Columbia. This may be because rates of postpartum hemorrhage with hysterectomy were higher in British Columbia as compared with the rest of Canada between 2003 and 2007 (6.3 per 10,000 in British Columbia compared to 5.0 per 10,000 in Canada),[11] and rates in British Columbia began to stabilize. Although we suggested that other procedures to control bleeding may have been responsible for the lack of an increase in British Columbia, a similar finding was not observed across Canada. In Canada, the dramatic increase in rates of procedures to control bleeding, were accompanied by a concurrent (albeit smaller) increase in postpartum hemorrhage with hysterectomy.

The significant impact of placenta accreta on postpartum hemorrhage with hysterectomy has implications for clinical practice and surveillance. As mentioned, the rise in postpartum hemorrhage in Canada and Australia was first identified by an increase in rates of postpartum hemorrhage with hysterectomy.[1,2] In addition, postpartum hemorrhage with hysterectomy rates in Canada are reportedly higher than in other countries.[1] An important limitation of the study on placenta accreta was the inclusion of years 2009 and 2010 only, which made the study unable to provide information on trends in placenta accreta over time.

Another consideration was that 15% of placenta accreta cases had a previous cesarean delivery with no placenta previa, while 8.8% of cases had both placenta previa and a previous cesarean delivery. Such a finding supports the screening of all women with a

previous cesarean delivery for placental site location, as recommended by the Confidential Enquiry into Maternal Deaths in the United Kingdom.[79]

7.5.1.3 Obstetric acute renal failure

The most novel finding of this dissertation was that the national increase in obstetric acute renal failure was restricted to women with hypertensive disorders of pregnancy, and that the rise was particularly striking among women with moderate to severe pre-eclampsia. Information was not available in our data source about specific aspects of pre-eclampsia treatment but this finding raises important clinical questions regarding the potential trade-off between fluid restriction protocols to prevent pulmonary oedema and the risk of acute kidney injury. Additional, the role of an increased use of NSAIDs for pain relief needs to be re-examined, as these drugs are known risk factors for acute renal failure.[106] Additional considerations include potential interactions among anti-hypertensive medications and NSAIDs.

7.5.2 Implications for public health surveillance

As mentioned, the lack of information on the third stage of labour in our data source precluded us from assessing whether changes occurred in third stage management and the effect of potential changes. Lessons from the experience of other countries that routinely collect information on third stage management (e.g. Australia and New Zealand) can help implement an appropriate surveillance system in Canada.[37,124] Some of the limitations of data from elsewhere have been that the specific aspects of the third stage of labour have not been recorded, e.g., prophylactic uterotonic use (versus uterotonics used for postpartum

hemorrhage treatment).[119] In addition, the use of early cord clamping, controlled cord traction, and uterine massage, and the dose of oxytocin versus other medication used had not been recorded consistently.[119] In addition, the timing, dose and specific type of uterotonic agent needs to be documented. One significant problem with routine collection of data on third stage management arises because similar uterotonic agents are used for prophylaxis and treatment of postpartum hemorrhage, making it difficult to distinguish the effects of these two distinct interventions.

A clear definition of uterine atony, as compared to other early postpartum hemorrhage subtypes occurring in the first 24 hours, would improve postpartum hemorrhage surveillance efforts. Third stage hemorrhage is currently the only other subtype of early postpartum hemorrhage that has a distinct diagnostic code. The International Postpartum Hemorrhage Collaborative Group has already recommended that the International Classification of Diseases provide a separate code for atonic postpartum hemorrhage and other types of postpartum hemorrhage immediately following childbirth, due to other causes.[1]

Another limitation has been different definitions of postpartum hemorrhage for cesarean and vaginal deliveries, which makes modeling and the interpretation of the effect of risk factors difficult. An ideal solution would be the routine collection of estimated blood loss for every delivery,[7] which would allow a standardized diagnosis of postpartum hemorrhage regardless of mode of delivery.

7.6 Future directions

The work presented in this dissertation represents the first step in an ongoing project supported by the Canadian Institutes for Health Research (CIHR) team grant in severe maternal morbidity. A detailed chart review involving eight major hospitals with maternity services across Canada (from the approximately 19 major maternity hospitals in Canada) is currently underway and includes a study of current and past postpartum hemorrhage cases with a random selection of controls. The ongoing CIHR project addresses several gaps identified in this dissertation. For example, ongoing and proposed analyses will determine if the blood loss threshold for diagnosing postpartum hemorrhage have changed over time. Also, analyses will seek to identify potential changes in specific aspects of labour induction and augmentation, such as the dose of oxytocin and other medications used concurrently. Other analyses will examine potential changes in specific aspects of third stage management over time. It is anticipated that these and other studies will yield new insights into the enigmatic recent increases in postpartum hemorrhage and enable appropriate clinical and public health actions to help improve the health of mothers.

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Appendices

Appendix A : Postpartum hemorrhage in British Columbia (Chapters 2 and 3)

Supplementary Table A.1. International Classification of Diseases (ICD-9, ICD-10), the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP), and the Canadian Classification of Interventions (CCI) diagnosis/procedure codes used.

Diagnosis/Procedure code	ICD-9	ICD-10	CCP	CCI
Postpartum hemorrhage	6660-6663	O720-O723		
- Third stage hemorrhage	6660	O720		
- Atonic postpartum Hemorrhage	6661	O721		
- Secondary postpartum Hemorrhage	6662	O722		
- Due to coagulation defects	6663	O723		
Hysterectomy			802;803	5MD60KE; 5MD60RC; 5MD60CB; 5MD60RD; 1RM87LAGX; (1RM89LA without 1PL74;1RS80; 1RS74)
Other procedures to control bleeding				5PC91LA, 1RM13, 1KT51;5PC91HT
-Suturing of uterus (e.g. b-lynch suture)				5PC91LA
-Control of bleeding using pelvic embolization				1RM13
-Ligation of pelvic vessels				1KT51
-Uterine (and vaginal) packing				5PC91HT
Uterine rupture	6650;6651	O710;O711		
High vaginal laceration	6654	O714		
Laceration of cervix	6653	O713		
Placenta previa	6410;6411;6421	O44		
Placental abruption	6412	O45		
Polyhydramnios	657	O40		
Prolonged first stage	6620	O630		
Prolonged second stage	6622	O631		
Pre-eclampsia	6424;6425	O14		
Chorioamnionitis	6584;7627	O411		

Supplementary Table A.2. Temporal trends in atonic postpartum hemorrhage (PPH), non-atonic PPH (per 100 deliveries), and in severe PPH (by subtype) per 10,000 deliveries, British Columbia, Canada, 2001 to 2009.

	All years n	2001 n=39565	2002 n=39559	2003 n=39623	2004 n=39815	2005 n=40172	2006 n=41309	2007 n=43295	2008 n=43802	2009 n=44053	2001-2009 P for trend
PPH (rates per 100 deliveries):											
Atonic PPH	20144	4.8	4.8	5.0	4.8	5.1	5.3	6.0	6.6	6.3	<0.001
Non-atonic PPH*	5485	1.53	1.49	1.49	1.39	1.49	1.21	1.52	1.55	1.62	0.31
Third stage†	4328	1.19	1.16	1.18	1.12	1.17	0.97	1.14	1.26	1.28	0.25
Secondary PPH†	1168	0.34	0.32	0.33	0.29	0.32	0.23	0.37	0.29	0.35	0.84
Due to coagulation defects†	158	0.05	0.06	0.03	0.04	0.04	0.04	0.04	0.05	0.03	0.21
PPH + blood transfusion (rates per 10,000 deliveries):											
Atonic PPH + blood transfusion	800	16.7	16.7	19.9	19.1	23.4	20.8	22.9	28.1	25.2	<0.001
Third stage hemorrhage + blood transfusion	408	11.1	12.6	11.9	9.8	9.7	9.4	9.2	11.9	13.2	0.93
Secondary PPH + blood transfusion	132	2.8	3.3	3.3	2.8	4.5	1.7	4.6	4.3	4.5	0.09
PPH due to coagulation defects + blood transfusion	84	2.3	4.0	2.5	2.8	2.0	1.2	2.1	2.3	1.4	0.05
Severe atonic PPH (composite outcome): Atonic PPH + blood transfusion (>=3 units), hysterectomy, uterine suture, ligation or embolization, or uterine (and vaginal) packing	592	11.9	9.8	12.1	17.5	14.9	15.2	21.4	22.5	17.6	<0.001

*Excludes atonic PPH.
†May include more than one PPH subtype

Supplementary Table A.3. Proportion of deliveries with postpartum hemorrhage (PPH) receiving a blood transfusion, by subtype of PPH, British Columbia, Canada, 2001 to 2009.

	All Years		% transfused			
PPH subtype	All years n	% transfused	2001	2002	2008	2009
Third stage	408	9.4	9.3	10.9	9.4	10.3
Atonic	800	4.0	3.5	3.5	4.3	4.0
Secondary	132	11.3	12.3	9.8	6.6	7.7
Due to coagulation defects	84	53.8	47.4	69.6	47.6	50.0

Supplementary Table A.4. Odds ratios showing the temporal increase in atonic postpartum hemorrhage with blood transfusion (2009 vs 2001) adjusted for determinants of postpartum hemorrhage added incrementally to the logistic regression model.

Adjusted for	Odds ratio 2009 vs 2001	95% Confidence Interval
Crude odds ratio for period (2009 vs 2001)	1.508	1.112-2.044
Plus maternal pre-pregnancy factors: maternal age, BMI, parity, smoking status, previous cesarean delivery	1.479	1.090-2.006
Plus maternal pregnancy factors: multi-fetal gestation, pre-eclampsia, placenta previa, placental abruption, chorioamnionitis, polyhydramnios	1.445	1.064-1.963
Plus obstetric factors: labour induction and labour augmentation	1.451	1.069-1.971
Plus epidural analgesia	1.448	1.066-1.966
Plus cesarean delivery	1.448	1.066-1.966

Multiple Imputation

Multiple imputation was used as a method for dealing with missing data, specifically in terms of the missing BMI data (20% missing data for height and 23% missing data for pre-pregnancy weight). Other methods we considered were complete case analysis and regression substitution. Complete case analysis was inappropriate as there would have been a substantial loss of information. In addition, its use is only appropriate when the data are missing completely at random (MCAR), i.e. the missing values are a simple random sample of the entire set of data values, which was unlikely in this case.[1] We did not deem regression substitution, whereby a value such as a mean is substituted in the missing values, as appropriate either as it prevents us from obtaining variances around the regression estimates. This, in turn, overstates precision.[2]

Multiple imputation requires that the data are missing at random (MAR) and that the sample size is large. MAR means that missing data does not depend on unobserved data, but may depend on observed data. The first step in the multiple imputation analysis was to impute BMI using linear regression and to create multiple simulated versions of the dataset. The model we used to impute BMI included the outcome of atonic postpartum hemorrhage as well as all variables included in our final analytic model as has been recommended in the literature.[3] These multiply imputed data sets were then analyzed using generalized estimating equations. The analysis was performed separately on each imputation, and the results were pooled.

The underlying theory assumes an infinite number of imputations, M, for multiple imputation to be valid. However, the majority of literature suggests M=5, but due to the feasibility to conduct more, at least M=20 is recommended.[3] We varied the number of

imputations from M=5 to M=100 to see if this affected our results and found there was no change.

[1] Allison PD, SAS Institute. *Logistic regression using SAS : theory and application*. 2nd ed. Cary, N.C.: SAS Pub.; 2012.

[2] Rubin, Donald B., and Roderick JA Little. "Statistical analysis with missing data." *Hoboken, NJ: J Wiley & Sons* (2002).

[3] StataCorp.: STATA Multiple-Imputation Reference Manual, Release 11. 2009.

Appendix B : Postpartum hemorrhage in Canada (Chapters 4 and 5)

Supplementary Table B.1. International Statistical Classification of Diseases and Related Health Problems (ICD-10-CA), and the Canadian Classification of Interventions (CCI) diagnosis/procedure codes used in the study.

Diagnosis/Procedure code	ICD-10	CCI
Postpartum hemorrhage	O720- 0723	
Third stage hemorrhage	O720	
Atonic postpartum hemorrhage	O721	
Secondary postpartum hemorrhage	O722	
Due to coagulation defects	O723	
Blood transfusion		1LZ19HHU1; 1LZ19HHU9; 1LZ19HMU1; 1LZ19HMU9
Hysterectomy		
Cesarean hysterectomy		5MD60KE; 5MD60RC; 5MD60CB; 5MD60RD
Partial or total excision of uterus and surrounding structures, open approach		1RM87LAGX; 1RM89LA (without 1PL74;1RS80; 1RS74)
Other procedures to control bleeding		
Suturing of uterus, e.g. b-lynch suture		5PC91LA
Control of postpartum hemorrhage by ligation of pelvic vessels		1KT51
Control of postpartum hemorrhage by embolization of pelvic vessels		1RM13
Induction of labour		5AC30ALI2; 5AC30CAI2; 5AC30GUI2; 5AC30HAI2; 5AC30YAI2; 5AC30YBI2; 5AC30ZZI2, 5AC30AP, (since 2006) 5AC30
Epidural analgesia		Anesthesia code 3 or 5LD20HAP1
Forceps		5MD53KL, 5MD53KN, 5MD53KJ, 5MD53KK, 5MD53KM, 5MD53KH, 5MD55
Vacuum		5MD54
Perineal tear (3rd / 4th)	O702, O703	
Cesarean delivery	5MD60	
Placenta previa	O44	
Hypertensive disorders	O10, O11, O13, O14, O15, O16	
Diabetes	E10, E11, E13, E14, 024	
Other puerperal infection	O86	
Placental abruption	O45	
Obstetric shock	O751,T805,T886	
Uterine rupture	O710, O711	
Polyhydramnios	O40	
Chorioamnionitis	O411	
High vaginal laceration	O714	
Laceration of cervix	O713	
Morbidly adherent placenta	O432	
Antepartum Hemorrhage	O46	
Retained placenta without hemorrhage	O73	

Supplementary Table B.2. Temporal trends in postpartum hemorrhage (PPH), PPH subtypes, severe PPH and severe PPH subtypes in Canada, 2003–2010.

	All years	Rate				Rate Ratio (95% CI)	P for trend
	N	2003–2004	2005–2006	2007–2008	2009–2010		
PPH (rates per 100 deliveries)							
All PPH	122676	5.06	5.18	5.92	6.13	1.21 (1.19–1.23)	<0.001
Atonic	97920	3.90	4.14	4.78	4.96	1.27 (1.25–1.29)	<0.001
Non-atonic PPH[1]	24756	1.16	1.04	1.15	1.16	1.00 (0.97–1.04)	0.08
Third stage hemorrhage	18383	0.87	0.78	0.85	0.85	0.97 (0.93–1.01)	0.71
Secondary	6223	0.28	0.26	0.28	0.31	1.11 (1.04–1.19)	<0.001
Due to coagulation defects	1057	0.04	0.05	0.05	0.05	1.17 (0.99–1.39)	0.01
PPH with blood transfusion (rates per 10,000 deliveries)							
All PPH with blood transfusion	9575	37.4	39.8	47.3	49.2	1.32 (1.24–1.39)	<0.001
Atonic PPH with blood transfusion	6177	23.0	25.9	31.1	32.0	1.39 (1.29–1.50)	<0.001
Non-atonic PPH with blood transfusion[1]	3398	14.5	13.8	16.2	17.2	1.19 (1.08–1.31)	<0.001
Third stage hemorrhage with blood transfusion	2276	10.2	8.9	10.7	11.6	1.14 (1.02–1.28)	0.003
Secondary PPH with blood transfusion	1052	4.2	4.6	5.0	5.3	1.28 (1.08–1.53)	0.001
PPH due to coagulation defects with blood transfusion	507	2.2	2.1	2.7	2.3	1.05 (0.81–1.35)	0.21
PPH with hysterectomy (rates per 10,000 deliveries)							
All PPH with hysterectomy	1150	4.6	5.2	5.6	5.5	1.21 (1.03–1.44)	0.01
Atonic PPH with hysterectomy	623	2.4	2.9	3.0	3.0	1.26 (1.00–1.59)	0.03
Non-atonic PPH with hysterectomy[1]	527	2.2	2.3	2.6	2.5	1.16 (0.91–1.49)	0.19
Third stage hemorrhage with hysterectomy	445	1.9	2.1	2.1	2.1	1.10 (0.84–1.45)	0.63
Secondary PPH with hysterectomy	48	0.22	0.17	0.23	0.26	1.22 (0.56–2.66)	0.30
PPH due to coagulation defects with hysterectomy	194	0.78	0.87	1.02	0.86	1.10 (0.72–1.67)	0.29
PPH with other procedures to control bleeding (rates per 10,000 deliveries)							
All PPH with other procedures	1714	5.0	6.7	8.6	10.6	2.13 (1.84–2.47)	<0.001
Atonic PPH with other procedures	1357	4.0	5.1	6.9	8.4	2.11 (1.79–2.48)	<0.001
Non-atonic PPH with other procedures[1]	357	1.0	1.5	1.7	2.2	2.24 (1.61–3.11)	<0.001
Third stage hemorrhage with other procedures	272	0.88	1.2	1.2	1.7	1.89 (1.33–2.70)	<0.001
Secondary PPH with other procedures	63	0.20	0.24	0.32	0.39	1.97 (0.93–4.16)	0.03
PPH due to coagulation defects with other procedures	136	0.37	0.56	0.81	0.72	1.93 (1.12–3.33)	0.003

[1]Non-atonic PPH includes one or more of PPH due to retained placenta, secondary PPH or PPH due to coagulation defects and excludes cases with a simultaneous diagnosis of atonic PPH. The province of Quebec was not included in analyses.

Supplementary Table B.3. Maternal, fetal and obstetric characteristics by province and territory, Canada, 2003–2010.

	N.L.	P.E.I.	N.S.	N.B.	Ont.	Man.	Sask.	Alta.	B.C.	N.T.	NU	YT	Canada*
	n=37011	n=10939	n=57077	n=57077	n=106202	n=90282	n=104146	n=362547	n=329607	n=6288	n=2979	n=2765	n=2193425
Maternal Age (in years)													
<20	6.21	5.74	5.75	6.51	3.74	9.31	9.62	5.02	3.44	13.4	23.9	6.55	4.70
20–34	80.2	79.5	78.9	82.0	75.7	77.5	80.2	79.6	74.7	74.7	69.3	74.3	76.9
≥35	13.6	14.8	15.4	11.5	20.5	13.2	10.2	15.3	21.8	11.9	6.81	19.2	18.4
Previous cesarean	11.4	14.3	12.5	12.2	12.8	11.5	11.4	13.1	14.0	9.70	6.04	11.0	12.9
Multi-fetal gestation	1.41	1.06	1.46	1.02	1.39	1.26	1.18	1.54	1.46	0.52	0.23	0.90	1.40
Large fetus	0.77	1.01	1.06	0.75	1.25	2.11	6.31	3.35	2.82	1.73	1.11	3.29	2.09
Hypertensive disorders	8.92	7.37	8.65	6.75	5.70	6.61	5.94	6.61	6.00	4.91	6.08	4.27	6.13
Diabetes	4.26	2.32	4.24	3.71	4.86	5.06	4.04	4.78	7.65	2.42	1.07	3.65	5.15
Chorioamnionitis	0.44	1.54	0.69	0.45	0.90	0.84	1.37	1.35	1.72	0.49	0.37	0.36	1.09
Polyhydramnios	0.54	0.29	0.47	0.36	0.45	0.39	0.54	0.57	0.65	0.17	0.10	0.29	0.50
Placental abruption	0.90	0.72	0.92	0.81	1.05	1.06	2.06	1.50	1.17	0.83	1.34	1.19	1.18
Placenta previa	0.52	0.54	0.48	0.49	0.61	0.43	0.36	0.58	0.68	0.38	0.27	0.25	0.58
Induction of labour	26.8	27.8	26.4	26.5	21.0	21.0	21.7	24.0	18.1	13.5	10.5	15.7	21.5
Epidural	35.7	27.6	46.0	43.3	50.4	35.2	40.7	37.8	27.7	12.3	1.14	28.8	42.8
Instrumental delivery	11.5	4.43	10.1	10.00	10.3	6.80	13.2	12.5	10.5	4.93	1.51	8.07	10.6
Cesarean delivery	30.4	31.0	27.3	28.4	27.7	20.2	21.5	26.9	30.6	17.5	8.36	23.3	27.4
Uterine rupture	0.07	0.13	0.19	0.07	0.09	0.09	0.16	0.09	0.11	0.10	0.10	0.07	0.10
High vaginal laceration	0.52	0.07	0.35	0.66	0.26	0.18	0.39	0.47	0.27	0.11	0.07	0.11	0.32
Cervical laceration	0.11	0.05	0.12	0.14	0.07	0.14	0.20	0.24	0.19	0.05	0.10	0.07	0.13
Perineal tear (3rd/4th)	1.52	2.20	2.84	3.17	2.46	2.87	4.12	3.54	2.94	1.92	1.81	1.95	2.82

NL: Newfoundland and Labrador, PEI: Prince Edward Island, NS: Nova Scotia, NB: New Brunswick, Ont.: Ontario, Man.: Manitoba, Sask.: Saskatchewan, Alta.: Alberta, BC: British Columbia, NT: Northwest Territories, NU.: Nunavut, YT: Yukon

*Excludes Quebec

Appendix C : Increase in obstetric acute renal failure in Canada (Chapter 6)

Supplementary Table C.1. International Statistical Classification of Diseases and Related Health Problems (ICD-10-CA), and the Canadian Classification of Interventions (CCI) diagnosis/procedure codes used in the study.

Diagnosis/Procedure code	ICD-10	CCI
Postpartum hemorrhage	O720- O723	
Third stage hemorrhage	O720	
Atonic postpartum hemorrhage	O721	
Secondary postpartum hemorrhage	O722	
Due to coagulation defects	O723	
Blood transfusion		1LZ19HHU1; 1LZ19HHU9; 1LZ19HMU1; 1LZ19HMU9
Hysterectomy		
Cesarean hysterectomy		5MD60KE; 5MD60RC; 5MD60CB; 5MD60RD
Partial or total excision of uterus and surrounding structures, open approach		1RM87LAGX; 1RM89LA (without 1PL74; 1RS80; 1RS74)
Other procedures to control bleeding		
Suturing of uterus, e.g. b-lynch suture		5PC91LA
Control of postpartum hemorrhage by ligation of pelvic vessels		1KT51
Control of postpartum hemorrhage by embolization of pelvic vessels		1RM13
Acute Renal Failure		
Postpartum acute renal failure	O904	
Post-procedural renal failure	N990	
Acute renal failure	N17	
Unspecified kidney failure	N19	
Dialysis		Z491
Induction of labor		5AC30ALI2; 5AC30CAI2; 5AC30GUI2; 5AC30HAI2; 5AC30YAI2; 5AC30YBI2; 5AC30ZZI2, 5AC30AP, (since 2006) 5AC30
Cesarean delivery	5MD60	
Placenta previa, antepartum hemorrhage	O44, O46	
Hypertensive disorders		
Pre-existing hypertension complicating Pregnancy	O10	
Pre-existing hypertensive disorder with superimposed proteinuria	O11	
Gestational hypertension without significant Proteinuria	O13	
Gestational hypertension with significant proteinuria	O14	
Eclampsia	O15	
Unspecified maternal hypertension	O16	
Gestational edema and proteinuria	O12	
Diabetes mellitus	E10, E11, E13, E14, O24	
Sepsis	O753, O85	
Other puerperal infection	O86	
Placental abruption	O45	
Obstetric shock	O751,T805,T886	
Uterine rupture	O710, O711	
Polyhydramnios	O40	
Cardiac failure	O754,O742,O291, I50	
Obesity	E66	
Chronic kidney disease	N18	
Pulmonary edema	J81	

Supplementary Table C.2. Results of logistic regression modeling showing effects of year of delivery and risk factors on obstetric acute renal failure (ARF) among women with gestational hypertension and proteinuria (n=24,851), Canada (excluding Quebec), 2003 to 2010.

		ARF per 10,000 deliveries	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval) *
Period	2003-2004	45.5	Reference	Reference
	2005-2006	72.1	1.59 (0.98-2.59)	1.71 (1.04-2.79)
	2007-2008	74.7	1.65 (1.02-2.65)	1.81 (1.12-2.94)
	2009-2010	109.6	2.42 (1.55-3.81)	2.71 (1.71-4.29)
Atonic postpartum hemorrhage		145.3	2.07 (1.37-3.11)	2.47 (1.61-3.79)
Non-atonic postpartum hemorrhage		353.4	5.20 (3.24-8.32)	7.14 (4.29-11.87)
Maternal age (in years)				
	<20	35.8	0.65 (0.27-1.60)	0.68 (0.27-1.67)
	20-24	54.8	Reference	Reference
	25-29	74.1	1.36 (0.83-2.22)	1.26 (0.77-2.07)
	30-34	83.0	1.52 (0.94-2.46)	1.27 (0.77-2.07)
	35-39	105.3	1.93 (1.16-3.23)	1.47 (0.87-2.50)
	≥40	91.1	1.67 (0.79-3.52)	1.09 (0.51-2.35)
Parity	1	84.5	Reference	Reference
	Nulliparous	100.9	0.86 (0.59-1.26)	1.04 (0.70-1.54)
	2-4	70.3	0.86 (0.59-1.26)	0.75 (0.39-1.47)
	Missing	51.5	0.52 (0.33-0.83)	0.57 (0.35-0.92)
Multi-fetal gestation		178.0	2.57 (1.69-3.89)	1.73 (1.11-2.68)
Diabetes		102.5	1.40 (0.92-2.12)	1.19 (0.77-1.84)
Gestational edema and proteinuria		363.6	4.94 (1.20-20.4)	5.15 (1.20-22.11)
Sepsis		400.0	5.50 (2.00-15.12)	2.83 (0.95-8.44)
Other puerperal infection		445.1	6.48 (3.78-11.10)	5.10 (2.88-9.04)
Antepartum hemorrhage/placenta previa		253.2	3.45 (1.51-7.86)	1.50 (0.63-3.57)
Placental abruption		305.7	4.48 (2.83-7.09)	4.38 (2.72-7.05)
Polyhydramnios		263.2	3.58 (1.45-8.80)	3.45 (1.37-8.71)
Induction of labour		43.1	0.38 (0.27-0.51)	0.48 (0.34-0.68)
Cesarean delivery		103.8	2.46 (1.77-3.43)	1.78 (1.22-2.59)
Uterine rupture		416.7	5.67 (0.76-42.19)	2.45 (0.31-19.68)
Cardiac failure		567.4	8.11 (3.91, 16.79)	4.46 (2.08-9.58)

*Adjusted for all variables in the table.

Supplementary Table C.3. Results of logistic regression showing effects of year of delivery and risk factors on obstetric acute renal failure (ARF) among women without hypertensive disorders of pregnancy (n=2,058,935), Canada (excluding Quebec), 2003 to 2010.

		ARF per 10,000 deliveries	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)*
Period	2003-2004	0.77	Reference	Reference
	2005-2006	0.99	1.28 (0.84-1.96)	1.35 (0.88-2.07)
	2007-2008	0.91	1.19 (0.77-1.82)	1.19 (0.77-1.84)
	2009-2010	0.93	1.21 (0.79-1.86)	1.12 (0.72-1.72)
Atonic postpartum hemorrhage		4.3	5.66 (3.96-8.08)	5.23 (3.55-7.68)
Non-atonic postpartum hemorrhage		13.7	18.04 (12.27-26.53)	18.36 (11.87-28.39)
Maternal age (in years)				
	<20	0.51	0.75 (0.29-1.98)	0.61 (0.23-1.63)
	20-24	0.69	Reference	Reference
	25-29	0.76	1.11 (0.67-1.83)	1.05 (0.64-1.75)
	30-34	0.88	1.29 (0.80-2.09)	1.07 (0.65-1.75)
	35-39	1.4	2.01 (1.21-3.33)	1.46 (0.86-2.47)
	≥40	1.9	2.84 (1.41-5.71)	1.41 (0.67-2.98)
Parity	1	1.14	Reference	Reference
	Nulliparous	0.57	1.85 (1.25-2.75)	1.78 (1.18-2.69)
	2-4	0.95	1.56 (0.95-2.56)	1.47 (0.89-2.44)
	>5	2.2	3.52 (1.38-8.98)	2.29 (0.85-6.15)
	Missing	0.84	1.39 (0.88-2.19)	1.27 (0.80-2.02)
Multi-fetal gestation		5.4	6.38 (3.70-11.00)	2.70 (1.53-4.76)
Diabetes		2.6	3.13 (2.05-4.77)	2.14 (1.37-3.32)
Gestational edema and proteinuria		18.3	20.74 (7.70-55.91)	10.64 (3.75-30.23)
Sepsis		76.0	93.19 (56.50-153.71)	15.63 (8.64-28.29)
Other puerperal infection		25.7	31.63 (19.67-50.86)	6.53 (3.77-11.31)
Antepartum hemorrhage/placenta previa		7.1	8.45 (4.90-14.58)	2.14 (1.17-3.89)
Placental abruption		8.6	10.53 (6.62-16.75)	5.17 (3.14-8.52)
Polyhydramnios		6.2	7.05 (3.13-15.90)	2.97 (1.24-7.10)
Induction of labour		1.25	1.53 (1.10-2.11)	1.53 (1.09-2.15)
Cesarean delivery		1.96	3.77 (2.82-5.04)	2.94 (2.13-4.07)
Uterine rupture		14.9	16.75 (5.35-52.40)	3.50 (1.03-11.85)
Cardiac failure		137.5	172.73 (108.31-275.49)	26.92 (15.53-46.68)

*Adjusted for all variables in the table.