## IMPACT OF DELAYED CHILDBEARING IN BC, CANADA

by

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## ABSTRACT

This thesis examines the association between maternal age and adverse birth outcomes in the province of British Columbia (Canada). It explores the differential effect of plurality and parity on this association; and describes differences in obstetric interventions and birth outcomes between older mothers living in rural versus urban areas.

Data were obtained from the BC Perinatal Health Program's Database Registry, 1999-2003. The database includes all births in BC and contains information about maternal demographic characteristics, behavioural and life-style factors, and obstetric history.

Among older mothers with singleton pregnancies, we observed a higher rate of stillbirths, preterm births, small-for-gestational-age babies, and admissions to a neonatal intensive care. The risk of preterm birth and small-for-gestational-age was modified by parity. The relative risk of preterm birth associated with maternal age was higher among primiparae, compared to multiparae. Older primiparae were at elevated risk for SGA; no such association was found among multiparae.

In twin pregnancies, maternal age was not associated with perinatal death, very preterm birth, small-for-gestational-age, or prolonged neonatal intensive care unit admissions (13 days or longer), regardless of parity. However, the results suggest that the risk of these adverse outcomes is lower among older compared to younger primiparae. Chorionicity did not explain these results.

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Older mothers living in rural versus urban areas had lower rates of caesarean sections and higher rates of perinatal death; the risk of small-for-gestation-age was lower, whereas large-for-gestational-age was higher. The rates of labour induction, emergency caesarean-section, preterm birth, and NICU admission were similar in both groups. The risk of caesarean-section and perinatal death increased with the distance from the mother's residence to the nearest hospital with caesarean -section capacity.

This research adds to current knowledge by demonstrating a differential effect of parity on the association between maternal age and preterm birth and small-forgestational-age among singletons. This is the first population-based study of twins to explore the effect of parity on the association between maternal age and birth outcomes other that preterm birth. In addition, this is the first study to examine the effect of rural or remote residence on birth outcomes among older mothers.

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To my family

### **CO-AUTHORSHIP STATEMENT**

As the first author of the individual manuscripts, I formulated the research questions for this thesis. I also conceived the research design which took advantage of the existing BC Perinatal Database that contains complete and comprehensive information about all births in the province of British Columbia. I obtained the ethics approval, the approval to access the data, and performed the analyses. I interpreted the results and wrote and revised all the manuscripts.

Dr. Samuel Sheps was the thesis supervisor. He provided ongoing guidance in conducting the thesis research and interpretation of the findings. He substantially contributed to the intellectual content of the thesis, revised all the manuscripts and provided important feedback.

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## **CHAPTER 1**

## **INTRODUCTION**

#### **Overview of the dissertation**

This doctoral thesis examines the risk of adverse birth outcomes among mothers 35 years of age and older in British Columbia (BC), Canada. Adverse birth outcomes examined include stillbirth, early and late neonatal death, preterm birth, small-for-gestational-age (SGA) status, and neonatal intensive care unit (NICU) admission. The results are based on secondary analyses of the BC Perinatal Health Program ("BCPHP") Database Registry.

The dissertation is structured according to the manuscript-based format approved by the Faculty of Graduate Studies at the University of British Columbia. The introductory chapter provides the background and literature review, including an explanation of the reasoning and objectives of the thesis. Chapters 2 to 4 represent individual manuscripts that focus on a particular set of hypotheses. Chapter 2 examines the association between maternal age (20-29 versus 35-39 and 40+ years) and adverse birth outcomes of singleton pregnancies, and assesses the differential effect of parity on this association. Chapter 3 focuses on twin pregnancies and the association between maternal age (25-29 versus 35+ years of age) and adverse birth outcomes. Similar to Chapter 2, the differential effect of parity on this association is examined. Chapter 3 focuses entirely on older mothers (35+ years) and compares the rates of obstetric interventions (including labour induction and c-sections) and adverse birth outcomes

between mothers living in urban and rural areas. Chapter 5, the final chapter is a summary of studies described in Chapters 2 through 4, with an explanation of how they relate to each other, as well as recommendations for future research.

#### Background

An increasing number of women in developed countries are choosing to delay childbirth. In Canada, the proportion of live births to women aged 30-34 years rose from 18.9% in 1982 to 31.4% in 2006. The proportion of live births to women between the ages 35-39 increased from 4.7% to 14.8%, and from 0.6% to 2.8% in women 40-44 years old (1-2). Between 1980 and 2005 age-specific fertility rates rose: from 66.8 to 100.9 births per 1000 women 30-34 years old; from 19.1 to 44.9 per 1000 women 35-39 years old; and from 3.3 to approximately 7.4 per 1000 women 40-49 years of age (2-4). The average age of women giving birth rose from 23.7 in 1969 to 29.3 in 2006, when for the first time, the fertility rate of 30-34 year old women exceeded the rate for women aged 25-29 (2).

Amongst all of the Canadian provinces, BC has the highest proportion of babies born to older mothers: 18.3% of newborns have mothers aged 35-39 and 3.7% have mothers 40-44 years old. BC and Ontario have the highest average maternal age at birth (29.9 and 30 years, compared to the Canadian average of 29.3 years). In 2004, every 5<sup>th</sup> infant in BC was born to a mother aged 35 or older (2, 5).

In the United States from 1980 to 2005 the fertility rate among mothers over 30 years of age rose from 61.9 to 95.8 per 1000 women ages 30-34; from 19.8 to 46.3 for women 35-39; from 3.9 to 9.1 for women 40-44; and from 0.2 to 0.6 for women 45-49 years of age. The mean maternal age increased from 25.0 in 1980 to 27.4 years in 2005 and the mean age for first childbirth increased from 22.7 to 25.2 years during the same period (6).

In England and Wales, between 1996 and 2006, fertility rates increased from 89.9 to 104.8 live births per 1000 women aged 30-34 years; from 37.5 to 53.8 for women ages 35-39, from 6.9 to 10.8 for women ages 40-44; and from 0.3 to 0.6 for women ages 45-49. Average maternal age rose from 28.6 years old in 1996 to 29.5 in 2006. For first-time mothers the average age rose from 26.7 to 27.6 (7). Similar increases in age-specific fertility rates and average maternal age have been observed in developed countries such as Europe, Japan, Australia, and New Zealand (8-11).

The main reasons for the increased number of births in older women are: first, an increase in the absolute number of women in their later reproductive years and, secondly, a cultural shift in attitudes about the role of women. In the late 1990s and 2000, "baby boomers," born after the Second World War II (WWII) were reaching the fourth decade of their lives. In Canada, peak fertility after WWII was observed in 1959, with an echo effect in the mid-to-late 1980s (2). At the same time a change in society's perception of women and increased access to education and employment opportunities encouraged women to explore non-traditional roles and delay childbearing. The increased utilization of fertility treatments and assisted reproductive techniques (ART) enabled older women with fertility problems to conceive and give birth. As a result, women who chose to postpone childbirth were able to conceive at a later age.

Postponing childbirth in a modern society has its benefits. Women have more time to pursue higher education, career, and to reach economic and relationship stability before starting a family (12). According to a recent survey in the province of Alberta, financial security and a partner's ability to parent, ranked the highest among the factors influencing the timing of childbirth (13). Other factors include: the interest in having

children, health status, career, education and training, and becoming a homeowner. The majority of studies of delayed childbearing have shown that mothers over 35 years of age are far more likely to be educated, married and have a high socio-economic status. They are less likely to smoke or drink alcohol during pregnancy (14-17). These positive factors may lessen the risk of medical complications and poor birth outcomes for women giving birth later in life.

#### **Historical overview**

During the first half of the 20th century, maternal mortality in developed countries decreased substantially, from 37.1/100,000 live births in 1960 to 4.4 in 1997 (18). Improvements in obstetric practice, developments in antibiotic treatment and blood transfusion contributed to these changes (19).

Obstetric attention subsequently shifted more towards the newborn and the first NICU's appeared in the mid-1960s. The stillbirth rate fell from 12.0 per 1000 births in 1950, to 4.3 per 1000 in early 2000s. Early neonatal death rate declined from 11.9 to 3.6 per 1000 live births, and late neonatal death rate fell from 1.8 to 0.5 per 1000 live births during the same period (1, 5).

New advances in fertility treatments became available to women in the late 1960's. Clomiphene citrate (clomid) was approved for sale in the USA in 1967 and human menopausal gonadothropins (hMG) were introduced in Europe in 1960. Ovulation inductions have contributed to an upward trend in the incidence of twins, triplets, and higher order multiples (20).

Successful in-vitro-fertilization (IVF) was first performed in 1978. IVF and other techniques to enable reproduction have promoted the trend toward delayed childbearing

(20). In the Unites States the number of births resulting from ART increased by 120% between 1996 and 2002. In the US almost 1% of all newborns (and 18-35% of multiple births) are the product of ART and the proportion is even higher (2%-3%) in European countries (21).

ART includes any procedure in which both egg and sperm are handled in the laboratory. There are various ways of retrieving the gametes (ovarian stimulation protocols, donor oocytes and sperm) and accomplishing fertilization (intra-cytoplasmic sperm injection, assisted hatching) and variations in time of embryo transfer and use of fresh or preserved embryos (21). Ovulation induction and ART have not only contributed to an increase in fertility rates among older mothers, but also to the increase in rates of multiple births. The twinning rate increased by 70% from 18.9 babies per 1000 births in 1980 to 32.2 in the US in 2006 (35). Mothers of twins are at increased risk of perinatal complications, post-partum depression, anxiety and marital stress (20).

These technological advances and other societal influences, for example a shift in maternal characteristics, medical malpractice concerns, and an increase in multiple pregnancies, has contributed to the rising rate of Caesarean deliveries in developed countries (24). C-section rates in the US rose from 5.5% in 1970 to 29.1% in 2002 (23), partly due to the increased proportion of births to older mothers (24). C-section, as a surgical procedure, results in longer hospitalization and elevated risk of complications from the anesthesia (23).

Studies examining the association between maternal age and adverse pregnancy outcomes published before 1985 were mostly descriptive and hospital-based and included a relatively small number of women over the age of 35 (12). Limited adjustment was

made for major confounding factors. Older mothers were more likely to have many children and lower socio-economic status. A relatively small number of primiparae, among older women, had experienced fertility problems throughout their younger years, yet managed to conceive later in life (12, 25).

Gradually, the number of older primiparous women increased, bringing about changes in the demographic profile: higher socio-economic status, higher levels of education, and healthier lifestyles (26). Studies of delayed childbearing shifted from case reports and small hospital studies, to larger multi-hospital or population based studies. Advantages of these studies included increased statistical power to detect small or moderate differences in the rates of adverse birth outcomes, leading to more precise risk estimates, increased data on the birth outcomes among women of very advanced maternal age, and improved multivariate analyses of confounding factors. Moreover, monitoring the trends in adverse birth outcomes, specifically in older women, became an important part of perinatal research.

#### The effect of maternal age on birth outcomes

Despite the wide use of the term "delayed childbearing" in the scientific literature and in the media, the definition of delayed childbearing or advanced maternal age is somewhat vague. In 1958 the term "elderly primigravida" was coined by the Council of the International Federation of Gynecologists and Obstetricians to describe a mother older than 34 having her first child (27). Thus, for many people, delayed childbearing means having the first child after reaching the age of 35. Currently, some researchers regard childbirth after the age of 35 as "delayed," while others use the term "delayed childbirth" only for mothers giving birth at age 40 or later in life.

While pre-1985 studies were mostly hospital-based reports of birth outcomes of older, multiparous women, more recent literature has changed its focus to older, primiparous women. Large hospital and population-based studies (discussed below) demonstrated inconsistent results in terms of the association between maternal age and some adverse birth outcomes. In general, the studies pointed to elevated risks for older mothers. A detailed list of all studies is presented in Appendix 1.

### Population and hospital based studies of singleton births

Kiely et al. conducted a population-based study including all singleton births in New York City between 1976 and 1978 (28). The study examined the effect of maternal age and parity on different types of perinatal mortality: ante-partum stillbirth, intrapartum stillbirth, early neonatal death (within 7 days of life), and late neonatal death (between 8-28 days of life). Two groups of mothers, 30-34 years old and 35+, were compared to a group of 20-29 year olds. Race, maternal education, marital status, type of health care (private or public), and previous fetal losses were assessed as confounders. Maternal age was strongly associated with antepartum fetal mortality (death occurring before labour) but not with intrapartum (during labour) fetal death. The fetuses of older mothers had a higher risk of antepartum fetal death than fetuses of younger mothers (adjOR=3.3, CI: 2.0-3.7). The elevated risk of perinatal mortality was primarily due to higher rates of congenital anomalies. Kiely et al. found a significant effect modification by parity in the association between maternal age and neonatal death; that was reflected in a disproportionately higher relative risk among older primiparous vs. younger multiparous mothers (adjOR=2.3, CI: 1.7-3.1), as compared to relative risk among older vs. younger multiparous mothers (adjOR=1.1, CI: 0.9-1.3).

Kiely's large study represents one of the best studies of association between maternal age and perinatal mortality, because it distinguishes the various types of perinatal mortality, including antepartum and intrapartum fetal death (which have different etiologies in most cases); and examines the effect of parity on the association between maternal age and perinatal death. This study does not provide information about preterm birth, birthweight, or perinatal morbidity. The results reflect perinatal mortality in the late 70's, and, therefore, do not represent birth outcomes after the subsequent 30 years of advances in obstetric and perinatal care (such as surfactant use or extracorporeal mechanical oxygenation), nor recent changes in maternal demographics (such as higher in socio-economic status of older primiparae). These changes have contributed to overall secular decline in perinatal mortality.

Berkowitz et al. published the results of a hospital-based study comparing singleton pregnancy outcomes in two groups of primiparous women, age 35+ and 20-29 year olds (17). The study indicated that even though the risks of pregnancy complications, c-sections, and NICU admissions were significantly higher among older mothers, preterm birth, low birthweight, SGA, and perinatal mortality rates were comparable.

The Berkowitz study population was restricted to patients who received prenatal care and delivered at a private clinic in New York City, USA. This restriction potentially introduced a selection bias. Women with pregnancy complications and precipitous labour may have been transferred to hospitals and these births (more likely occurring in older mothers and more likely resulting in adverse outcomes) were not included in the study.

Moreover, the study was not powered to detect a small or moderate difference in perinatal death.

In contrast to the Berkowitz study, a Swedish population-based study, published in 1992, demonstrated that older mothers were at a higher risk than younger ones for all adverse birth outcomes (29). Sven Cnattingius and his colleagues analyzed all singleton births to Swedish primiparous women, age 20 and older, from 1983 to 1987. Birth outcomes were compared between 20-24 year old women (reference category) and three groups of older women, ages 30-34, 35-39 and 40+. Adverse outcomes examined included very preterm birth (<33 weeks of gestation), moderately preterm birth (33-36 weeks), very low birthweight (less than 1500g), moderately low birthweight (1500g-2499g), SGA, stillbirth (death in-utero after 28 weeks of gestation), and neonatal death.

In this study, smoking, a history of infertility, marital status, education, hypertensive disease, diabetes, and antepartum hemorrhage (including placenta previa and abruptio placentae) were considered potential confounders. Adjustment for pregnancy complications likely resulted in underestimation of relative risks, as these variables represent intermediate steps on the causal pathway between maternal age and birth outcomes. Risks increased significantly as maternal age increased, except for stillbirth and neonatal death; which revealed only borderline statistically significant increases (likely due to low statistical power to detect small to moderate differences). The Swedish definition of stillbirth included only late fetal deaths (28 weeks of gestation or more), which differs from the definition used in other studies (usually 20 weeks of gestation or more). Further, there was a lack of information regarding the proportion of

congenital anomalies; thus it is not clear whether the observed differences in birth outcomes were possibly due to different rates of congenital anomalies among older vs. younger mothers.

In 1993 Michael Aldous and his colleagues published a population-based study utilizing Washington State's Vital Statistics data from 1984 to 1988 (30). Singleton newborns of older primiparous women (35+ years and 40+years of age) were compared to newborns of 20-24 year old primiparae. Among white women there was an independent association between maternal age and specific adverse outcomes, namely preterm delivery (adjOR=1.6, CI: 1.4-2.0 and adjOR=1.8, CI:1.3-2.6) and low birthweight (adjOR=1.7, CI:1.4-2.2 and adjOR=2.3, CI:1.6-3.4). Very low birthweight (<1,500g) results were similar to those of preterm delivery, but did not reach statistical significance. Factors such as maternal and paternal occupations, marital status, prior fetal loss, induced abortions, smoking, pre-eclampsia, hypertension, diabetes, and c-sections were considered confounders. However, many of these factors are arguably on a causal pathway between maternal age and adverse outcomes, and, as such, should not have been controlled for because adjustment can obscure the association.

Michael Prysak et al. published the results of a hospital-based study that compared singleton pregnancy outcomes between primiparous 25-29 year olds and women age 35+ (31). Older women had higher unadjusted rates of antepartum and intrapartum complications, and neonatal morbidity. Maternal age was not a significant predictor of perinatal death after adjustment for other factors, including preterm birth, leiomyomas, and chorioamnionitis. As these complications constitute intermediate outcomes on a causal pathway between maternal age and perinatal death, adjustment for

these conditions may result in underestimation of the adjusted risk. Additionally, the study was able to detect only a 3-fold increase in risk so that small or moderate increases in the risk of perinatal mortality may have been missed.

In 1996 Bianco et al. compared pregnancy outcomes and obstetric interventions among women 40 years of age and older and women 20-29 years old in a hospital-based study (16). Among older primiparae there were more NICU admissions (adjOR=1.6; 95%CI: 1.2-2.2), Apgar scores <4 at 1 minute (adjOR=2.3; 95%CI: 1.1-4.9); older multiparae had excess risk of large-for-gestational-age infant (adjOR=1.4, 95%CI: 1.1-1.7). Findings were adjusted for race, chronic illness, infant gender, and tobacco use. The researchers did not find a higher risk of preterm birth, SGA, low birthweight, and perinatal or neonatal death among older women. Bianco concluded that, despite the excess risk of maternal morbidity, overall neonatal outcomes did not appear to be related to maternal age.

As the Bianco study population included only women with singleton deliveries who received prenatal care and delivered their babies at the same private clinic in New York City (USA) as in Berkowitz's study, the findings had the same potential for selection bias. The analysis also lacked the statistical power to detect small or moderate differences in perinatal and neonatal mortality.

In 2005 K.S. Joseph et al. published the results of a large population-based study of all singleton births (n=157,445) in the province of Nova Scotia during 1988-1995 (14). The risk of very preterm (<32 weeks) and preterm (<37weeks) births and SGA (3rd and 10<sup>th</sup> percentile) increased with advanced maternal age, showing a statistically significant excess risk for women 35 and older as compared to 20-24 year olds. The older mothers

experienced a higher risk of perinatal mortality and adverse outcomes, including perinatal mortality and morbidity (defined as Apgar score <3 at 5 minutes, severe respiratory distress syndrome, bronchopulmonary displasia, intraventricular hemorrhage grade 3-4, perivantricular leukomalacia, severe retinopathy of prematurity or necrotizing enterocolitis). Congenital anomalies were excluded from the analysis of perinatal mortality. Marital status, smoking, pre-pregnancy weight, socio-economic status, parity, prenatal class attendance, and year of birth (5 consecutive time periods) were assessed as confounders. Perinatal mortality (excluding congenital anomalies) decreased substantially from 1988-91 to 1998-2002 (adjusted OR=0.59, 95%CI: 0.44-0.79), but combined perinatal mortality and morbidity showed smaller declines (adjusted OR=0.89, 95%CI: 0.75-1.05). This discrepancy suggests that success in the reduction of stillbirth and neonatal mortality over the years was not accompanied by the same reduction of serious perinatal morbidity. Interestingly, the association between maternal age and adverse birth outcomes did not change between the earlier and later time periods, which would have reflected the changes in obstetrical practice.

This was one of the most comprehensive and well-conducted studies to examine the effect of older maternal age on birth outcomes. The risk of perinatal death was also analyzed by gestational age; the differences in gestational-age-specific perinatal mortality between younger and older mothers appeared exclusively at post-term (41 weeks and later). The effect of parity was not examined, even though the increase in rates of SGA and preterm birth showed different patterns between the total study population and a subset of primiparous women.

The association between maternal age and obstetric outcome was examined by Cleary-Goldman and her colleagues in 2005. This US study utilized prospectively collected data that included early pregnancy (14 weeks of gestation) follow-up (32). The data was originally generated as a part of a multi-centre clinical trial (First and Second Trimester Evaluation of Risk or "FASTER") to evaluate early ultrasound nuchal translucency and several serum markers as predictors of Down Syndrome.

The FASTER data on singleton pregnancies revealed a higher risk for pregnancy complications and obstetric interventions in two groups of older mothers, 35-39 and 40+ years, compared with mothers under 35 years old. Mothers 40+ years old had a higher risk of preterm delivery (<37 weeks of gestation; adjusted OR=1.4, CI: 1.1-1.7), low birthweight babies (<2,500g), and perinatal loss (adjusted OR=2.2, CI: 1.1-4.5).

The various factors that Cleary-Goldman analyzed as confounders included parity, race, education, marital status, smoking, body mass index, ART, pre-existing medical conditions, and previous adverse pregnancy outcomes. The unique strengths of the study included the ability to adjust for assisted reproduction, prospective data collection from early pregnancy, and an opportunity to measure a variety of clinical outcomes (exclusive of SGA and neonatal morbidity). As with other hospital or clinicbased cohort studies the results may have been biased by the selection of a specific study population. Further, it was not clear what proportion of eligible women refused to participate in the study, how many were lost to follow-up, or how many were excluded as a result of incomplete information. Nevertheless, the results suggest that while miscarriage and pregnancy complications are more common among mothers 35+ years

old than mothers less than 35 years old, only the oldest mothers (40+ years of age) had a higher risk of perinatal death and preterm birth.

Detailed descriptions of the above-mentioned research and related studies are provided in Appendix 1.

#### Systematic literature reviews

Two major systematic reviews that addressed the effect of older maternal age on birth outcomes were published in 2005 and 2008.

Christine Newburn-Cook and Judee Onyskiw conducted a search of studies that examined the association between maternal age and preterm birth and fetal growth restriction (an equivalent of SGA) (33). Their review included all studies between 1985 and 2002 that satisfied the following conditions: english language, preterm birth (<37 weeks) assessed by a subtype (idiopathic premature labour and premature rupture of membranes), clearly defined terminology, singleton live births, and done in a developed country. The authors found a positive association between older maternal age and preterm birth in the majority of unadjusted results, but insufficient evidence for independent association after adjustment for confounders. Studies of preterm births resulting from labour induction were excluded from the review. This exclusion can introduce a bias, since pregnancy complications that are more common amongst older mothers may lead to pre-term labour induction. Because 'iatrogenic' preterm births may be indirectly caused by older maternal age those studies should have been included in the review.

Huang et al. conducted a systematic review of the literature examining the association between maternal age and stillbirth (34). They retrieved 913 original

citations of studies published before 2007 and after exclusion of duplicates, letters, reviews, and studies with flawed design or outcome measures, 31 cohort and 6 casecontrol studies were retrieved. The authors found advanced maternal age to be an independent risk factor for stillbirth. The magnitude of risk was not clear due to the methodological heterogeneity of reviewed studies.

Huang recommended a consistent definition of stillbirth and adjustment for socioeconomic and lifestyle factors in multivariate analyses in future research and cautioned against adjustment for intermediate outcomes on the causal pathway, such as medical complications. The authors underlined the importance of evaluating the effect modification of parity on the association between maternal age and adverse birth outcomes in general.

#### Population and hospital-based studies of twin births

The vast majority of studies examining the association between maternal age and adverse birth outcomes focus on singleton births. However, the rate of twinning has significantly increased in many developed countries during the past two decades, largely due to the higher average maternal age and ART.

In Canada the rate of twin births increased from 18.9 per 1000 births in 1980 to 24.2/1000 in 1997 and to 30.8/1000 in 2005, representing a 72% increase (1,5, 37). In 2006 multiple births accounted for 3.1% of babies born in Canada (5).

In the US the twinning rate increased by 70% from 18.9 twin babies per 1000 births in 1980 to 32.2 per 1000 births in 2005 and remained stable throughout 2006 (35). Between 1980 and 2006, the twin birth rate increased by 27% for mothers <20 years of age, compared to an 80% increase for women 30-39 years old and a 190% increase for

mothers 40+ years of age. In 2006, 20% of births to women 45-54 years of age were twins, in comparison to 2% of the births to women 20-24 years of age (36). <sup>1</sup>

In European countries, the prevalence of twin births declined from mid-1960 (12/1000) to mid-1970s (9/1000), followed by a continuous rise. In 2000 there were 15.8 twin births per 1000 pregnancies in Germany, 15.0 in France and Austria, 14.2 in the United Kingdom, and 18.0 in the Netherlands (20, 39-42). The greatest increase in twin births was observed in older maternal age groups. The definition of twinning rates, however, differed by individual countries, depending on whether the statistics were based on all births or only live births; the definition of stillbirth varied as well. In Nordic countries, the twinning rate remained low, around 10 per 1000 pregnancies, until the 1990's when there was a large increase in Denmark (22.1 per 1000 pregnancies); and more moderate increases in Finland (15.1), Norway (17.6) and Sweden (15.9) (20, 39-42). Recent statistics from Sweden and Finland indicate a levelling-off, even a small decline from 2000 onwards (20, 39-42).

A similar trend has been observed in Australia, as the twinning rate gradually increased from 10 to approximately 15 per 1000 maternities from 1983 to 2000. The steepest increase was observed among mothers 30+ years old from the 1990's and onwards (42).

The proportion of twins per 1000 live births increases with maternal age in the US, most dramatically in the oldest age group: 12-18/1000 births for <20 year olds, 22/1000 births for ages 20-24, 40/1000 for ages 25-29, 48/1000 for ages 30-34, 54/1000 for ages 35-39, and 197/1000 for 40-49 year old women (36, 43, 44). Thus, one of every

<sup>&</sup>lt;sup>1</sup> The US statistics reports define the twin rate as a number of live born twins per 1000 live births.

5 infants born to women over 40 years of age was a twin, in comparison to less than 2 of every 100 infants to mothers less than 20 years of age (USA, 2005).

Despite the increase in twinning, predominantly among older mothers, there are few studies of the effect of maternal age on birth outcomes in twin pregnancies as they require large datasets with linked information regarding twins. In the early 2000's, the US National Center for Health Statistics matched the information on multiple births outcomes (live birth, fetal and infant death certificates), from the National Vital Statistics System, thereby creating a national population-wide database or "Matched Multiple Birth File" (45).

Utilizing data sets from the Matched Multiple Birth File, Zhang et al. examined the risk of very preterm birth (<33 weeks), very low birthweight (<1,500g), perinatal death, and infant death, comparing 25-29 year old mothers and 30-34, 35-39 and 40+ year old mothers (46). Singleton, twin, and triplet pregnancies were analyzed separately. The results showed significantly elevated risk for all adverse birth outcomes as maternal age increased among singletons. There was no evidence of excess risk among twins of older mothers compared to twins of younger mothers; and there was a significant decrease in risk of adverse birth outcomes among triplets as maternal age increased. Race, ethnicity, parity, maternal education, marital status, smoking, time of first prenatal visit, and concordance of fetal sexes were included in multivariate analyses. However, when the study population was restricted to twins of unmarried mothers without a college education the risk of very preterm birth, very low birthweight, and perinatal death increased with maternal age. This would suggest that socioeconomic status, or factors associated with socioeconomic status, affected the association between maternal age and

adverse birth outcomes in twins. The limitations of this study include an inability to adjust for assisted reproduction and the lack of adjustment for correlation in outcomes in multiple pregnancies.

Branum and Schoendorf focused on the differential effect of parity and very preterm birth, utilizing data from the Matched Multiple Birth File, years 1995-98 (47). When comparing primiparae 25-29 year olds with ages 30-34, 35-39, and 40+ years, the risk of very preterm birth (<33 weeks) decreased as maternal age increased, however, among multiparae, no effect of maternal age was found. The negative correlation between risk of preterm birth and maternal age was apparent only among women with >12 years of education. Once again this suggests an underlying effect of socio-economic status, or factors associated with socioeconomic status.

The variables examined by Branum and Schoendorf as possible confounders included marital status; maternal education; ethnicity, and prenatal care. Only education and parity were found to have significant interactions with maternal age. The study was restricted to pregnancies that ended in two live births with the same gestational age. The authors noted that an additional analysis including fetal deaths yielded similar results. The limitations of this study included the inability to adjust for ART, and the lack of data on rates of congenital anomalies, that could potentially explain the observed differences in outcomes.

Misra and Ananth studied trends in the rate of twinning, and the association between maternal age and infant death (48). The study population included US infants born in 1985-86, 1990-91, and 1995-96; singletons and twins were examined separately. The rate of twinning increased across time periods in each maternal age group (15-19,

20-24, 25-29, 30-34, 35-39, and 40-49 years). The biggest increase was found among the oldest mothers (66% among 40-49 year olds compared to 13.5% among 15-19 year olds).

The association between maternal age and infant death followed a "U" shaped curve for singletons and, on the contrary, a consistent downward trend for twins. Similar patterns were seen for all three birth cohorts. The risk of neonatal death among twins decreased significantly as maternal age increased. Results were adjusted for birth cohort, a number of previous pregnancies, birthweight, and gestational age. As with other twin studies, the limitations included the inability to adjust for ART and the lack of adjustment for correlation in outcomes in twin pregnancies. The study was restricted to live births, which also limited the interpretation of the results.

Perinatal outcomes of twin pregnancies among older women were described in a hospital-based Greek study by Prapas et al. (49). The study population consisted of all twin babies delivered between 1988 and 2003 in one of the Thessaloniki hospitals. Mothers <35 and 35+ years old were compared. The unadjusted results showed an association between maternal age and five adverse birth outcomes — low birthweight (<2,500g), very low birthweight (<1,500g), perinatal death, stillbirth, and neonatal death. Significantly, elevated risk was found only for very low birthweight (OR=2.0, CI: 1.1-3.3). This study had major limitations: results were poorly described, the confounding factors included in multivariate analysis were not listed, and the correlation between birth outcomes of twins was not addressed. The study lacked the power to find statistically significant differences in some birth outcomes, as only 57 older and 181 younger mothers were included. Also, the hospital-based study design may have introduced a selection bias, as both groups of mothers (younger and older) delivering at

this particular hospital might not constitute representative samples of the general population.

A recent study conducted by Delbaere et al. examined perinatal outcomes of twins among primiparous women of advanced maternal age, while adjusting for mode of conception (50). The study population included all primiparous women aged 35 years or more (N=240) and 25-29 years old (N=940) who delivered twins in the Flemish part of Belgium (2001-2004). The results revealed that even after adjustment for assisted reproduction (spontaneous conception vs. ovulation induction alone, and vs. ART), older mothers had lower risk of preterm birth (adjOR=0.75, CI: 0.44-0.79) and low birthweight (adjOR=0.75, CI: 0.58-0.98) compared to younger women. The associations between maternal age and SGA, congenital malformations, transfer to neonatal care unit, perinatal death, fetal death, and early neonatal death were not significant. The results were adjusted for confounding variables (level of education, year of birth), and intermediate variables (hypertension during pregnancy, mode of conception). The effect of zygocity and chorionicity was tested using a subset dataset (N=447), that was derived from the East Flanders Prospective Twin Study, and included multiparous women. The multivariable analysis revealed that the association between maternal age and preterm birth in twin pregnancies was not affected by chorionicity or zygocity. In this additional analysis, adjustment was made only for parity, mode of conception, and year of birth. All multivariable analyses were adjusted for inter-twin correlation. Limitations of this study include lack of adjustment for: smoking and other behavioural factors, attendance at prenatal care, previous obstetric history, and socio-economic status. Although adjustment was made for maternal education, it was defined as lower education (until the age of 18

years) versus higher education (above the age of 18 years). This dichotomy seems to be quite arbitrary; older women were found more likely to be lower-educated (49.6%) compared to younger women (44.4%). Further, ART-related policy in Flanders (introduced in 2003) includes an IVF-reimbursement law that allows for fees for six consequent IVF cycles to be refunded to the mother under the condition that only a single embryo is transferred during the first two cycles. This policy differs from ART practises in North America, where reimbursement or restrictions are not applied. Thus the results of this study might not be generalizable to North American settings.

#### Strengths and limitations of existing literature

The core evidence concerning the risk of adverse birth outcomes among older mothers is, in general, derived from population-based research. The major advantages of these studies are: a) a large study population, that allows for adequate statistical power to find small to moderate differences in rare outcomes; b) low potential for selection bias, as the study population is comprised of the entire population, c) generalizability of results to similar populations; and d) inclusion of data on maternal age and major birth outcomes, such as death, birthweight, or gestational age, that is available through national vital statistics systems.

The limitations of population-based studies include the inability to obtain detailed information about clinical, demographic, and behavioural factors that may act as significant confounders in the association between maternal age and birth outcomes. These factors include smoking, alcohol and drug use, prenatal care, income, education level, low fertility, body mass index, previous obstetric history and ART.

In contrast, hospital-based studies have the advantage of detailed clinical and demographic information on an individual level. They do, however, often lack the statistical power to detect small differences in rare outcomes, and they are prone to selection bias. Women that deliver at a particular hospital may not be representative of the overall parturient population, and the reasons for delivering at a particular hospital may differ by age and a variety of other factors (e.g. socio-economic status).

The most common study design examining maternal age and birth outcomes has been a retrospective cohort study whether hospital or population based. The exposure of

interest is maternal age, which is relatively easily ascertained. However, women are selected for a study based on the event of birth, which can lead to: a) selection bias in hospital-based studies (as mentioned above), or b) a potential problem for population-based studies in settings where some births (especially early fetal deaths) might not be registered as births for administrative, financial, or cultural reasons. Miscarriages and late pregnancy terminations (occurring before 20 weeks of gestation, but sometimes later) are typically excluded from studies of birth outcomes. This has important implications for the interpretation of results, as evidence generated by these studies pertains only to mothers who were able to conceive and sustain their pregnancies to 20 weeks of gestation or more.

In summary, studies of delayed childbearing have been limited by several factors. First, the inclusion of singleton and multiple births in one study, without separate analyses for both groups, represents a methodological flaw in several studies as these groups have different clinical risks and obstetric management. Secondly, common limitations include the inability to adjust for assisted reproduction, lack of statistical power (primarily in hospital-based studies of rare outcomes) and lack of adjustment for inter-twin correlation in twin birth outcomes (in studies where newborn/stillborn is used as a unit of analysis). Thirdly, heterogeneity in definitions of older maternal age and various birth outcomes, the extent of adjustment for confounding factors, and the availability of information about congenital anomalies, make it difficult to compare and summarize the evidence from these studies.
# **Research gaps**

While many studies have focused on associations between maternal age and adverse birth outcomes in primiparous women with singleton pregnancies, less is known about the differential effect of parity on this association. There is also a dearth of evidence concerning the effect of maternal age on birth outcomes in twin pregnancies. Existing studies have consistently found no association or even lower risk of adverse birth outcomes as maternal age increases, and the underlying reasons behind these findings remain unclear. Further, differential effects of parity on the association between maternal age and stillbirth, perinatal death, SGA, or NICU admissions in singleton and twin pregnancies have not been examined in contemporary population-based studies.

Lastly, the risks of adverse birth outcomes among older mothers with potentially limited access to advanced obstetric care (for example those living further away from a hospital) have not been adequately explored.

#### Purpose of the current thesis research

This thesis represents a first step towards addressing these limitations and gaps in the literature. It capitalizes on an opportunity to utilize the population-based data from the BCPHP Database Registry that includes all births in the province (approximately 40,000 births per year) collected for the purpose of clinical perinatal surveillance. The data is abstracted from hospital charts by trained data abstractors and includes clinical, behavioural, life-style, and demographic characteristics of women who delivered an infant in BC. Accuracy is enhanced by standardized protocols and consistency checks, including re-abstractions and comprehensive reports. In addition, the database captures home births, ensuring that all births in the province are captured.

The goal of this thesis was to examine adverse birth outcomes among older mothers in singleton and twin pregnancies, and the effect of parity and rural vs. urban residence on these outcomes.

In the first study, we examined the effect of maternal age and parity on birth outcomes among singletons (Chapter 2). Our specific primary objective was to:

 Compare birth outcomes including stillbirth, neonatal death, preterm birth < 37 weeks of gestation, SGA, and neonatal intensive care unit admission for more than 1 day between mothers 20-24 years old vs. 35-39 and 40+ year olds who delivered a singleton infant.

The secondary objectives were to:

- Examine the effect of parity on the associations between maternal age (35-39 and 40+ years versus 20-29 years) and adverse birth outcomes including stillbirth, neonatal death, preterm birth < 37 weeks of gestation, SGA, and neonatal intensive care unit admission for more than 1 day in singleton pregnancies;
- Compare the rates of perinatal death between younger and older mothers (35+ versus 20-29 years of age), and examine whether these rates differ by gestational age.

In the second study we examined the effect of maternal age and parity on birth outcomes among twins (Chapter 3). Our specific primary objectives were to:

 Examine the association between maternal age (25-29 versus 35+ years of age) and all major adverse birth outcomes in twins, including perinatal death, very preterm birth, SGA, and NICU admission for 13 days or more, while adjusting for a wide

range of demographic and lifestyle risk factors and addressing for the correlation in twin outcomes;

2) Examine the association between maternal age (25-29 versus 35+ years of age) and a combined outcome including perinatal death and/or NICU admission for 13 days or more, while adjusting for a wide range of demographic and lifestyle risk factors and addressing the correlation in twin outcomes.

The secondary objectives were to:

- Evaluate the effect of parity on the associations between maternal age and the above outlined adverse birth outcomes;
- Assess confounding by chorionicity (two placentas versus one shared placenta) by restricting the analyses to twins of opposite sex, while adjusting for demographic, lifestyle and behavioural confounders.

In the third study we examined the effect of rural vs. urban residence on obstetric interventions and birth outcomes among mothers 35 years of age or older (Chapter 3). Our specific primary objectives were to:

- Compare demographic, behavioural and lifestyle factors between older mothers (35 years of age or older) with singleton women living in rural areas versus urban areas in British Columbia;
- 2) Determine whether women with singleton pregnancy in rural areas are less likely to receive obstetric interventions (such as labour induction and c-section), and whether these women are at an elevated risk of adverse birth outcomes (including stillbirth, perinatal death, preterm birth, SGA, LGA, and NICU admission for more than 1 day).

The secondary objectives were to:

- Examine whether parity modifies the association between rural/remote residence and birth outcomes among women with singleton pregnancies who are 35 years of age or older;
- Evaluate the risks of adverse birth outcomes listed above in relation to the distance of maternal residence to the nearest hospital with c-section capacity.

The specific hypotheses for the first study of effect of maternal age and parity on the singleton birth outcomes were:

Primary hypothesis:

 The adjusted risk of perinatal death, neonatal death, prematurity, SGA, and NICU admission is significantly higher in older mothers (age groups 35-39, 40+ years) compared to younger mothers (20-29 years of age).

Secondary hypotheses were:

- The adjusted risk of adverse outcomes as in 1) is further modified by parity, with significantly higher risks in primiparous older women;
- The association between maternal age and perinatal death is modified by gestational age at birth.

The specific hypotheses for the second study of effect of maternal age on twin birth outcomes were:

Primary hypotheses:

 The adjusted risk of perinatal death, very preterm birth, and SGA is not significantly elevated among twins of older (35+ years old) compared to younger mothers (25-34 years old);

- The adjusted risk of NICU admission for 13 days or more is significantly higher among twins of older compared to younger mothers;
- The adjusted risk of the combined outcome of perinatal mortality and/or NICU admission for 13 days or more is significantly higher among twins of older compared to younger mothers.

Secondary hypotheses:

- The adjusted risk of adverse outcomes as in 1) is further modified by parity, with significantly lower risks in primiparous older women;
- The adjusted risk of adverse outcomes as in 2-3) is further modified by parity, with significantly higher risks in primiparous older women;
- The adjusted risks of adverse outcomes as in 1-3) are not significantly different when the analyses are restricted to a subset of data, including only opposite-sex twins (dichorionic).

The specific hypotheses for the third study of the effect of rural vs. urban residence on birth outcomes among mothers 35 years of age or older were:

Primary hypothesis:

- Demographic, lifestyle, and behavioural factors differ significantly between older mothers with singleton pregnancies in rural vs. urban areas;
- The adjusted risk of labour induction, c-section, and NICU admission for more than 1 day is significantly lower among rural vs. urban women;
- The adjusted risk of perinatal death, SGA, and LGA is significantly elevated among rural vs. urban women.

Secondary hypotheses:

- 1) The adjusted risk of adverse outcomes as in 2-3) is further modified by parity;
- The rates of labour induction, c-section, perinatal death, preterm birth, SGA, and LGA increase significantly as the distance to the nearest hospital with c-section capacity increases.

# References

- Health Canada. Canadian Perinatal Health Report, 2003. Cat. No. H49-142/2003E. 2003. Ottawa: Minister of Public Works and Government Services Canada, 2003.
- 2. Statistics Canada. Births 2005. [Cat. No. 84F0210XIE]. 2007. Ottawa, Ministry of Industry, 2007.
- 3. Statistics Canada. Reproductive Health: Pregnancies and Rates, Canada, 1974-1993. Ottawa: Statistics Canada. Catalogue No. 82-503-XPB.
- 4. Statistics Canada. Pregnancy outcomes, 2003. Ottawa: Statistics Canada, Catalogue No. 82-224-XIE.
- 5. Health Canada. Candian Perinatal Health Report, 2008 Edition. Ottawa, Catalogue No HP10-12/2008E.
- 6. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S. National Vital Statistics Reports (NVSS). 56[6]. 12-5-0007. CDC.
- 7. Office for National Statistics. Birth statistics: Review of the registrar general on births and patterns of family building in England and Wales, 2006. Office for National Statistics. FM1 No. 35.
- 8. Office for Official Publications of the European Communities Luxembourg. Eurostat yearbook 2002; The statistical guide to Europe, Data 1990-2000.
- 9. Office for Official Publications of the European Communities Luxembourg. Eurostat yearbook 2006-07; Europe in figures. 2007. Catalogue number: KS-CD-06-001-EN-N.
- Ageskov Ulla, Nordic Council of Ministries. Nordic statistical yearbook 2007. No.45. 2007.
- 11. Linacre Susan. Australian social trends 2007. Catalogue No. 4102.0; Australian Bureau of Statistics.
- 12. Hansen JP. Older maternal age and pregnancy outcome: a review of the literature. Obstet Gynecol Surv 1986; 41(11):726-742.
- Tough S, Benzies K, Fraser-Lee N, Newburn-Cook C. Factors influencing childbearing decisions and knowledge of perinatal risks among Canadian men and women. Matern Child Health J 2007; 11(2):189-198.

- 14. Joseph KS, Allen AC, Dodds L, Turner LA, Scott H, Liston R. The perinatal effects of delayed childbearing. Obstet Gynecol 2005; 105(6):1410-1418.
- 15. Fell DB, Joseph KS, Dodds L, Allen AC, Jangaard K, Van den HM. Changes in maternal characteristics in Nova Scotia, Canada from 1988 to 2001. Can J Public Health 2005; 96(3):234-238.
- 16. Bianco A, Stone J, Lynch L, Lapinski R, Berkowitz G, Berkowitz RL. Pregnancy outcome at age 40 and older. Obstet Gynecol 1996; 87(6):917-922.
- 17. Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL. Delayed childbearing and the outcome of pregnancy. N Engl J Med 1990; 322(10):659-664.
- 18. Chalmers B, Wen SW. Perinatal Care in Canada. BMC Womens Health 2004; 4 Suppl 1:S28.
- 19. Resnik R. The "elderly primigravida" in 1990. N Engl J Med 1990; 322(10):693-694.
- 20. Blickstein I, Keith LG. Multiple pregnancy. 2nd edition. Taylor&Francis, 2005.
- 21. Wilkins-Haug L. Assisted reproductive technology, congenital malformations, and epigenetic disease. Clin Obstet Gynecol 2008; 51(1):96-105.
- 22. Statistics Canada. Births 2006. 2008. Ottawa: Statistics Canada, Catalogue No. 84F0210X.
- 23. Resnik R. Can a 29% cesarean delivery rate possibly be justified? Obstet Gynecol 2006; 107(4):752-754.
- 24. Joseph KS, Young DC, Dodds L et al. Changes in maternal characteristics and obstetric practice and recent increases in primary cesarean delivery. Obstet Gynecol 2003; 102(4):791-800.
- 25. Carolan M, Nelson S. First mothering over 35 years: questioning the association of maternal age and pregnancy risk. Health Care Women Int 2007; 28(6):534-555.
- 26. Carolan M. Health literacy and the information needs and dilemmas of first-time mothers over 35 years. J Clin Nurs 2007; 16(6):1162-1172.
- 27. Morrison I. The elderly primigravida. Am J Obstet Gynecol 1975; 121(4):465-470.
- Kiely JL, Paneth N, Susser M. An assessment of the effects of maternal age and parity in different components of perinatal mortality. Am J Epidemiol 1986; 123(3):444-454.

- 29. Cnattingius S, Forman MR, Berendes HW, Isotalo L. Delayed childbearing and risk of adverse perinatal outcome. A population-based study. JAMA 1992; 268(7):886-890.
- Aldous MB, Edmonson MB. Maternal age at first childbirth and risk of low birth weight and preterm delivery in Washington State. JAMA 1993; 270(21):2574-2577.
- 31. Prysak M, Lorenz RP, Kisly A. Pregnancy outcome in nulliparous women 35 years and older. Obstet Gynecol 1995; 85(1):65-70.
- 32. Cleary-Goldman J, Malone FD, Vidaver J et al. Impact of maternal age on obstetric outcome. Obstet Gynecol 2005; 105(5 Pt 1):983-990.
- 33. Newburn-Cook CV, Onyskiw JE. Is older maternal age a risk factor for preterm birth and fetal growth restriction? A systematic review. Health Care Women Int 2005; 26(9):852-875.
- 34. Huang L, Sauve R, Birkett N, Fergusson D, van WC. Maternal age and risk of stillbirth: a systematic review. CMAJ 2008; 178(2):165-172.
- 35. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S. Births: final data for 2004. Natl Vital Stat Rep 2006; 55(1):1-101.
- 36. Martin JA, Hamilton BE, Sutton PD et al. Births: final data for 2005. Natl Vital Stat Rep 2007; 56(6):1-103.
- 37. Canadian Institutes for Health Information. Giving birth in Canada, a regional profile. 2004.
- 38. British Columbia Vital Statistics Agency. Selected Vital Statistics and Health Status Indicators, 135th annual report 2006. BC Vital Statistics.
- 39. Zeitlin J, Wildman K, Breart G. Perinatal health indicators for Europe: an introduction to the PERISTAT project. Eur J Obstet Gynecol Reprod Biol 2003; 111 Suppl 1:S1-S4.
- 40. Zeitlin J, Wildman K, Breart G et al. PERISTAT: indicators for monitoring and evaluating perinatal health in Europe. Eur J Public Health 2003; 13(3 Suppl):29-37.
- 41. Breart G, Barros H, Wagener Y, Prati S. Characteristics of the childbearing population in Europe. Eur J Obstet Gynecol Reprod Biol 2003; 111 Suppl 1:S45-S52.
- 42. Blondel B, Macfarlane A, Gissler M, Breart G, Zeitlin J. Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project. BJOG 2006; 113(5):528-535.

- 43. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S. National Vital Statistics Reports (NVSS). 56[6]. CDC.
- 44. Martin JA, Hamilton BE, Sutton PD et al. Births: final data for 2006. Natl Vital Stat Rep 2009; 57(7)
- 45. Mathews TJ, Menacker F, Macdorman MF. Infant mortality statistics from the 2002 period: linked birth/infant death data set. Natl Vital Stat Rep 2004; 53(10):1-29.
- 46. Zhang J, Meikle S, Grainger DA, Trumble A. Multifetal pregnancy in older women and perinatal outcomes. Fertil Steril 2002; 78(3):562-568.
- 47. Branum AM, Schoendorf KC. The influence of maternal age on very preterm birth of twins: differential effects by parity. Paediatr Perinat Epidemiol 2005; 19(5):399-404.
- 48. Misra DP, Ananth CV. Infant mortality among singletons and twins in the United States during 2 decades: effects of maternal age. Pediatrics 2002; 110(6):1163-1168.
- 49. Prapas N, Kalogiannidis I, Prapas I, Xiromeritis P, Karagiannidis A, Makedos G. Twin gestation in older women: antepartum, intrapartum complications, and perinatal outcomes. Arch Gynecol Obstet 2005;1-5.
- 50. Delbaere I et al. Perinatal outcome of twin pregnancies in women of advanced age. Hum.Reprod. 2008;23:2145-50.

# **CHAPTER 2**

# The effect of maternal age on adverse birth outcomes: Does parity matter?<sup>2</sup>

# Introduction

One of the most striking changes in the demography of developed countries around the world during the last 20 years has been the postponement of childbirth until women are in their late 30s (1). The effect of delayed childbearing on birth outcomes is an evolving issue. Maternal characteristics have changed over time, as well as prenatal, obstetric and neonatal practices (2-4). In Canada, the proportion of live births to women 30-34 years old has risen from 18.9% in 1982 to 31.4% in 2005, to 35-39 year old women from 4.7% to 14.5%, and to women over 45 years of age from 0.6% to 2.9% (5,6). Mean maternal age at birth has increased from 23.7 in 1969 to 29.2 in 2005 in Canada (6), from 25 in 1980 to 27.4 years in 2005 in the US (7) and from from 28.6 in 1996 to 29.5 in 2006 in England and Wales (8). Japan, Australia, New Zealand and developed countries in Europe have observed similar trends (9-12).

Initial studies of "advanced" maternal age focused on adverse perinatal outcomes in primiparous women alone (13-17) or in primiparous and multiparous older women combined (3, 18). Few population-based studies have examined primiparous and multiparous women separately, and have produced inconsistent findings, being limited by inadequate power (19-20), failure to adjust for socio-economic differences (14, 21-23),

<sup>&</sup>lt;sup>2</sup> A version of this chapter has been submitted for publication. Lisonkova S, Janssen PA, Sheps SB, Lee SK, Dahlgren L. Parity modifies the effect of maternal age on birth outcomes.

substance use (14, 21, 22), or visits at prenatal care (21-23). There are no contemporary large population based studies describing the risks of adverse pregnancy outcomes separately for primiparous and multiparous women, adjusting for these important variables.

Two comprehensive systematic reviews focussing on the association between advanced maternal age stillbirth (24), and preterm birth/SGA (25) explicitly state the need for evaluation of effect modification by parity, adjustment for a range of SES indicators, behavioural factors and medical history, and a population-based sampling frame. Our study addressed these methodological issues. Our specific objectives were to examine the role of parity on the associations between maternal age (35-39 and 40+ years versus 20-29 years) and adverse birth outcomes including perinatal death (stillbirth and neonatal death), preterm birth < 37 weeks of gestation, SGA, and neonatal intensive care unit admission for more than 1 day. In addition, we compared the rates of perinatal death among infants of younger and older mothers (35+ versus 20-29 years of age), and examined whether these rates differ by gestational age.

#### Methods

We conducted a retrospective population based cohort study, comparing birth outcomes of a reference cohort of younger women (20-29 years old) with two cohorts of older women (35-39 and 40+ years old) who delivered a singleton infant in British Columbia (BC), Canada, between April 1<sup>st</sup> 1999, and March 31<sup>st</sup> 2003.

The outcomes of interest were stillbirth (death in-utero after 20 weeks of gestation), neonatal death (death within the first 28 days of life), preterm birth (defined as birth before 37 weeks of gestation), SGA (10<sup>th</sup> percentile), and NICU admission for more

than 1 day. Gestational age was assessed by last menstrual period (LMP). In cases where the LMP estimate showed a discrepancy of more than 2 weeks in comparison with the first trimester ultrasound, the ultrasound estimate was used (26). SGA infants were defined as those with birthweight below 10<sup>th</sup> percentile of a standard weight distribution of Canadian male and female newborn population at a given gestational age (27). Admissions to NICU were restricted to NICUs providing level 2 and 3 care. NICU level 2/3 is characterized by high-dependency neonatal care, such as peripheral intravenous infusion administration, total parenteral nutrition, umbilical and percutaneous central lines use, mechanical ventilation, immediate access to a full range of subspecialty consultants, performance of major surgeries, extracorporeal membrane oxygenation, etc. (28). Admissions for less than 1 day were not considered relevant as they represent transitory problems in newborns or simply admissions for monitoring newborn's condition (29).

Specific demographic, behavioural and life-style factors were assessed in multivariable analyses for their role as confounders. They included marital status (yes/no), smoking during pregnancy (yes/no), alcohol and drug use during pregnancy (yes/no), low attendance at prenatal care visits (less than 4 visits versus more), infant's sex (male versus female), as well as low income residential area, rural residence, and aboriginal status. A woman without a partner during the pregnancy was considered a single mother. Drug use represented any drug (illicit, prescription or other drug potentially harmful to baby) used during pregnancy. Primipara refers to a woman who is experiencing her first pregnancy and has completed at least 19 weeks of gestation; multiparae are women who have had at least one prior pregnancy lasting to at least 19

weeks of gestation. History of abortions includes previous induced (yes/no) and spontaneous abortions (yes/no). We obtained additional information about previous obstetric history including prior stillbirth, and/or prior neonatal death (yes/no). Women with previous low birthweight (<2,500g) or very premature newborn (<32 weeks of gestational age) were also identified. Newborns with congenital anomalies were those identified by ICD9 code 740.0 to 759.9 noted on discharge hospital abstracts.

Information about maternal age, birth outcomes, and potential confounders were retrieved from the BC Perinatal Health Program (BCPHP) birth registry. This registry captures all births in the province of BC, Canada (about 40,000 births per year). These data are abstracted from hospital charts after discharge by trained health records staff using to standardized protocols (30). Vital Statistics data including neonatal deaths are linked to the BCPHP registry. A low income neighbourhood was defined as an area with a residential postal code with a median income within the lowest quintile of the BC income distribution. Rural residence was defined by postal codes corresponding to cities with < 10, 000 inhabitants (31). Aboriginal women were identified as those registered in the Indian registry as having aboriginal ancestry as defined by the Indian Act (32).

#### Data analysis

Birth outcomes in each cohort were compared using frequency distributions and relative risks (RRs) and their 95% confidence intervals (CI). The RRs (with CIs) of adverse outcomes were calculated for primiparous and multiparous women separately. A chi-square p-value was used to describe statistically significant differences in the distribution of risk factors among the cohorts (p<0.05), but did not influence the choice of variables used in the multivariable analyses.

Logistic regression was performed to adjust for confounding factors (described above). A stepwise backward process was used to eliminate non-significant variables, however, if a variable elimination changed the estimated OR of the exposure (maternal age) by 10% or more, the variable was retained in the model regardless of the statistical significance of its explanatory value to the model (33). Parity and maternal age (primiparae x 35-39 year old, primiparae x 40+ year old) were tested as interaction terms in the regression models. A separate model was constructed for each of the outcomes (stillbirth, neonatal death, SGA, preterm birth, NICU admission). The overall goodness-of-fit of the model was assessed by Hosmer-Lemeshow test (33).

We also compared perinatal mortality (number of stillbirths and deaths within the first week of life per 1000 births) between 20-29 year old mothers and 35+ year old mothers and by parity. In both groups, gestational-age-specific perinatal mortality and 95% CIs were calculated for each 2-week interval, defined by the number of deaths (inutero or within the first weeks of life) per 1000 fetuses-at-risk, as described by Yudkin et al. (34). Fetuses-at-risk represent all live fetuses among pregnant women (i.e. all ongoing pregnancies) at the beginning of a given gestational age interval. This approach was also used and described by Joseph (35-38) and others (39-41). All data analyses were performed using SAS statistical package, version 9.1.3.

# Results

Our two study cohorts included 25,058 women aged 35-39 years, and 4,816 women aged 40 years and over, and a comparison cohort of 69,023 women aged 20-29 years. Demographic, socioeconomic, and other characteristics of study cohorts are presented in Table 1.1. NICU admissions were available only for years 2002-2003,

including 34,537 women 20-29 years old, 12,838 women 35-39 years old, and 2,604 women in 40+ year group.

The rates of stillbirths among mothers aged 35-39 years and 40+ years were significantly elevated (55/10,000 and 62/10,000 total births) compared to the reference cohort (43/10,000 total births). Intra-partum stillbirth occurred in 8.1%, 7.9%, and 13.3% of all stillbirths in age groups 20-29, 35-39 and, 40+ years, however, the time of stillbirth was not known in about 17% (data not shown). Neonatal mortality was not significantly different across all age groups. (Table 2.2) However, the rates of premature birth and SGA differed significantly by age groups, and by parity. NICU admissions were similar for newborns of 20-29 and 35-39 year old mothers (around 4.65 % in both cohorts), but significantly elevated for newborns of 40+ year old mothers (5.6%). Parity did not significantly affect the RR of NICU admission. (Table 2.2) Among those newborns who were admitted to NICU for more than 1 day the median length of stay was 7 days (quartile range 12) for the 20-29 year old group, 6 days (quartile range 11) for the 35-39 year old group, and 8 days (quartile range 12) for 40+ year old group; the difference was not statistically significant using Wilcoxon non-parametric test (data not shown).

In a multivariable analysis the odds of stillbirth, adjusted for parity, suboptimal prenatal care, and prior stillbirths/newborn deaths, was 1.52 (95%CI: 1.21-192) for 35-39 year old mothers, and 1.55 (95%CI: 1.01-2.37) for 40+ year old mothers compared to 20-29 year old women. Older maternal age was not significantly associated with neonatal death. A significant effect modification by parity was found in the association between maternal age and two adverse birth outcomes: preterm birth and SGA. The risk of preterm birth for older mothers, compared to their younger counterparts, was higher

among primiparae than among multiparae. With regards to SGA, only primiparous women faced significantly elevated odds, the adjusted OR was 1.25 (95%CI: 1.14-1.36) for 35-39 year old women, and 1.37 (CI: 1.13-1.66) for 40+ year old women after adjustment for other confounders. Regardless of parity, older maternal age was independently associated with NICU admissions for more than 1 day; for mothers 35-39 years adjOR = 1.17 (CI: 1.04-1.31), and for mothers 40+ years old adjOR = 1.38 (CI: 1.12-1.69). (Table 2.3)

Overall, the perinatal mortality rate was elevated among women 35+ years old (7.47 deaths per 1000 total births compared to 6.26 deaths per 1000 total births in women 20-29 years old, p-value = 0.033). The perinatal mortality rate did not differ by parity. The gestational age-specific perinatal mortality per 1000 fetuses-at-risk, examined by 2-gestational-weeks intervals, followed a broad "J" shaped curve. All four groups of women, 20-29 year old primiparae, 20-29 year old multiparae, 35+ year old primiparate and 35+ year old multiparae followed the same curve from 20 to 41 gestational weeks, with mortality below 20 per 10,000 fetuses-at-risk. The gestational-specific mortality above 41 weeks of gestation further increased to 40 per 10,000 fetuses-at-risk among younger multiparous women, to 75 per 10,000 fetuses-at-risk among older multiparous women. The perinatal mortality after 41 weeks of gestation was based on small number of deaths, thus the differences between maternal age and parity groups were not statistically significant at the 0.05 level (Figure 2.1).

#### Discussion

This is the first population based study to describe effect modification by parity on the relationship between older maternal age and preterm birth and SGA, while controlling for important confounders such as socioeconomic status, race, low attendance at prenatal care, previous abortions, and smoking and substance use during pregnancy. Gestational-age-specific perinatal mortality rates were similar in younger and older mothers of both parity groups between 20-41 weeks of gestation.

Only a few previous studies have examined the risks of older maternal age on birth outcomes by parity (21-23, 42). Like our results, Kiely et al. reported no differential effect of parity on the risk of stillbirth in older mothers. Kiely found a positive relationship between neonatal death rate and maternal age among primiparae that was not observed among multiparous women. The reported neonatal death rates of 10.6-17.3 per 1000 births among primiparous women (20-29 and  $\geq 30$  years of age) reflect the study period between 1976 and 1978 (22). We might not have observed similar results due to a low statistical power, since our neonatal death rates were considerably smaller (2.6-3.6 per 1000 births; see the limitations below). Using the US population data, Schempf et al. described an excess risk of preterm birth among older primiparous women, and to a lesser extent also among older multiparous women, which is consistent with our findings (21). This study, however, was limited by lack of adjustment for socioeconomic status, prenatal care, and lifestyle factors. Although the categorization and adjustment for potential confounders was different in Schempf's study compared to ours, the results are compatible. In contrast, Astolfi et al. found no differential effect of parity on risk of preterm birth among older mothers in Italy

(1990-1994) (23). The study, however, was limited to the first and second born infants of married mothers, and the multivariable analysis was restricted only to mothers over 30 years of age, which might have introduced a selection bias. Using population data from Nova Scotia, Canada, Joseph et al. described a gradual increase in risk of preterm birth and SGA (<10<sup>th</sup> percentile) as maternal age increased among primiparae (3). This relationship was less apparent in all women combined, suggesting an effect modification by parity similar to our results. In contrast to our results, Bianco et al. did not find an elevated risk of preterm delivery, SGA, perinatal death, and neonatal deaths in primiparous nor in multiparous older women (>39 years versus 20-29 years of age) (20). The study was hospital based and limited to private patients, which might have introduced a selection bias.

Our study has several potential limitations that could explain or mitigate our findings. First, we were not able to adjust for maternal education, body mass index (BMI), assisted reproduction therapy (ART), and other potential confounders such as, ethnicity (other than Aboriginal status), short interval between births (in multiparae), stress, lack of family support, nutrition, and environmental factors. We assessed a potential impact of BMI (approximated by pre-pregnancy weight) on our findings for about 80% of women in our study, for whom data were available. Our results were not affected by pre-pregnancy weight; except for the association between maternal age and stillbirth among 40+ year old women, that was weaker after adjustment for pre-pregnancy weight: adjOR=1.5 (95%CI: 1.0-2.4) changed to adjOR=1.3 (95%CI: 0.7-2.4). It is, therefore, possible, that the elevated risk of stillbirth among 40+ year old women could be, at least partly, explained by overweight/obesity of 40+ year old women.

Second, inadequate power can contribute to our findings of a non-significant association between maternal age and neonatal death. Our study was powered (80% or more) to detect at least 50% difference in the risk of neonatal death among 35-39 year old women, and 100% or larger differences among 40+ year old women. We observed no differences in absolute neonatal mortality rates between 20-29 and 35-39 year old women (approximately 0.26% of live births in both groups), and approximately 40% difference in neonatal mortality rates between 20-29 and 40+ year old women. Similarly, lack of power might have contributed to our findings of no significant effect modification by parity on maternal age and stillbirth or neonatal mortality. The calculation of power to detect a statistically significant effect modification in multivariable analysis is unclear. It has been shown, based on data simulations, that the dataset needed to detect the effect modification has to be at least 4-times larger compared to a dataset needed to detect the main effect (43, 44). A larger dataset than ours is needed to ascertain the differential effect of parity on stillbirth and neonatal mortality. However, the RRs of stillbirth (comparing 20-29 and 35+ year old women with singleton deliveries) were similar between primiparae and multiparae, suggesting that effect modification by parity is unlikely. The relative risk of stillbirth among 35+ year old compared to 20-29 year old primiparae was 1.2 (CI: 1.0-1.6); relative risk of stillbirth among 35+ year old compared to 20-29 year old multiparae was 1.2 (CI: 1.0-1.4). However, the RRs of neonatal death were different between primiparae and multiparae, indicating a possible effect modification by parity. The relative risk of neonatal death among 35+ year old compared to 20-29 year old primiparae was 1.3 (CI: 1.0-1.8); and the relative risk of neonatal death among 35+ year old compared to 20-29 year old multiparae was 0.9 (CI: 0.7-1.1).

The reasons for an excess risk of adverse birth outcomes among older women are several. Higher prevalence of chronic diseases can contribute to higher rates of adverse outcomes in older mothers. In our study, the prevalence of any chronic disease (including any of the following conditions: asthma, cardiac disease, diabetes mellitus, diabetes insipidus, hypertension) increased from 9.3% to 13.3%, and to 17.7%, respectively, among 20-29, 35-39 and 40+ year old primiparous women; and from 4.7% to 8.0%, and to 11.7% among multiparae, respectively. This increase was statistically significant in each of the parity groups (p-values for trend were <0.001). Among multiparae, however, the increase was significantly steeper, as compared to the increase among primiparae (i.e. the difference between the slopes of these two trends was statistically significant, p=0.003). We did not include chronic diseases in our multivariable analyses as they are on a causal pathway in the association between maternal age and adverse birth outcomes. However, the parity and age related differences in chronic conditions may be, at least partly, responsible for the differential effect of parity on this association.

Further, congenital anomalies are also more common in older mothers, which might explain the excess risk of mortality and morbidity. A separate set of additional analyses indicated that our results were not affected by adjustment for congenital anomalies.

Preterm birth has been included among adverse birth outcomes in our study. From a clinical point of view, preterm birth can be spontaneous (due to idiopathic preterm labour), or iatrogenic (as a result of labour induction or c-section due to a

maternal or fetal condition). We have not made a distinction between these two; since the causes of both, spontaneous or iatrogenic preterm labour, can be considered as intermediate factors (on a causal pathway) in the association between maternal age and preterm birth. However, early delivery can prevent imminent fetal death or other detrimental conditions in-utero (45). In these cases, preterm delivery would not be considered an adverse outcome from a clinical point of view. Additional analysis of our data revealed that 45.1%, 57.3% and 59.3% of preterm births were iatrogenic (either labour induction, including the induction after preterm rupture of membranes-PROM; or a caesarean section) among mothers 20-29, 35-39 and 40+ year old, respectively (p<0.0001). These proportions were similar in both parity groups. Even though some of these iatrogenic preterm births may have prevented even worse perinatal outcomes, the consequences of preterm birth, such as a need for advanced newborn care, still need to be considered.

In the context of changing maternal demography, it is important to study birth outcomes and their association with age and parity. Our results have analytical implication for studies of birth outcomes such as preterm birth and SGA. Maternal age and parity should be treated not only as confounders, but also as effect modifiers, in order to obtain not only valid estimates of risk, but also an understanding of the dynamic effects of parity and age. The elevated risk of SGA warrants more vigilant monitoring of intrauterine growth among older primiparae. Even though the absolute risks of adverse birth outcomes remain low, our results have implications for health services planning; since the need for advanced obstetric and neonatal care among older mothers is likely to increase as the trend towards delayed childbearing continues in the future.

Maternal age (years)	20-29	35-39	40+		
Total	N=69023	N=25058	p-value	N=4816	p-value
Parity: Para 1(Primipara)	35790 (51.87)	7549 (30.14)	<0.001	1267 (26.32)	< 0.001
Para 2	23560 (34.14)	10367 (41.39)	< 0.001	1743 (36.21)	< 0.001
Para 3+	9652 (13.99)	7133 (28.48)	< 0.001	1803 (37.46)	< 0.001
Single parent	4835 (7.39)	767 (3.17)	< 0.001	204 (4.41)	< 0.001
Low attendance at prenatal care (<4 visits)	2061 (3.17)	576 (2.43)	<0.001	159 (3.52)	0.186
Smoking during pregnancy	10940 (15.85)	1859 (7.42)	< 0.001	343 (7.12)	< 0.001
Alcohol use during pregnancy	936 (1.36)	219 (0.87)	< 0.001	50 (1.04)	0.063
Drug use during pregnancy	1674 (2.43)	266 (1.06)	< 0.001	60 (1.25)	< 0.001
Prior stillbirth or neonatal death	712 (1.03)	440 (1.76)	< 0.001	168 (3.49)	< 0.001
Prior low birthweight or premature birth	2910 (4.22)	1690 (6.74)	< 0.001	437 (9.07)	<0.001
Prior induced abortions (any)	10820 (15.77)	4784 (19.23)	< 0.001	1069 (22.44)	< 0.001
Prior spontaneous abortion (any) Rural residence (<10 000	11891 (17.33)	7309 (29.37)	< 0.001	1923 (40.37)	< 0.001
residents)	10104 (14.75)	2814 (11.29)	< 0.001	590 (12.35)	< 0.001
Low SES neighbourhood area*	13401 (19.52)	3682 (14.74)	< 0.001	710 (14.82)	< 0.001
Aboriginal status	5100 (7.39)	660 (2.64)	< 0.001	131 (2.72)	< 0.001
Any congenital anomaly (ICD9 740-759)	3307 (4.79)	1422 (5.67)	<0.001	315 (6.54)	<0.001
Newborn's male gender	35426 (51.33)	12885 (51.42)	0.8	2511 (52.16)	0.266

Table 2.1: Mother and newborn characteristics by maternal age; singleton pregnancies, BC, 1999-2003; N (%)

\*lowest quintile of BC median income per postal code

Maternal age (years)/parity		20-29	35-39	RR (CI)	40+	RR (CI)
Stillbirth	all women	295 (0.43)	139 (0.55)	1.20 (1.05 -1.38)	30 (0.62)	1.42 (1.01-2.00)
Neonatal death	all women	179 (0.26)	66 (0.26)	1.01 (0.82 -1.24)	17 (0.36)	1.33 (0.85-2.10)
Preterm birth <37 weeks	all women	4640 (6.75)	1953 (7.84)	1.12 (1.08 -1.17)	442 (9.24)	1.37 (1.25-1.50)
	primiparae	2386 (6.07)	719 (9.58)	1.37 (1.28-1.46)	131 (10.36)	1.57 (1.31-1.87)
	multiparae	2249 (6.80)	1232 (7.08)	1.03 (0.98-1.08)	311 (8.84)	1.29 (1.16-1.44)
SGA 10th percentile	all women	4976 (7.26)	1633 (6.57)	0.92 (0.88 -0.96)	317 (6.63)	0.91 (0.82-1.02)
	primiparae	3167 (8.90)	767 (10.24)	1.14 (1.06-1.21)	139 (11.00)	1.26 (1.06-1.49)
	multiparae	1806 (5.48)	863 (4.97)	0.93 (0.88-0.99)	178 (5.07)	0.93 (0.8-1.07)
NICU admission > 1 day <sup>a</sup>	all women	1605 (4.67)	593 (4.64)	1.00 (0.93 -1.07)	145 (5.60)	1.19 (1.02-1.40)

Table 2.2: Newborn outcomes by maternal age, parity; singletons, BC, 1999-2003; N (%); Relative Risk (RR) and 95% confidence intervals (CI)

<sup>a</sup> based on years 2001-03

Maternal age (years)/parity		35-39	40+
		AdjOR (CI)	AdjOR (CI)
Stillbirth	all women	1.52 (1.21-1.92)	1.55 (1.01-2.37)
Neonatal death	all women	1.18 (0.85-1.63)	1.33 (0.74-2.37)
Preterm birth <37 weeks	primiparae	1.54 (1.39-1.69)	1.60 (1.30-1.97)
	multiparae	1.14 (1.05-1.24)	1.28 (1.11-1.48)
SGA 10th percentile	primiparae	1.25 (1.14-1.36)	1.37 (1.13-1.66)
	multiparae	0.96 (0.88-1.05)	0.96 (0.81-1.14)
NICU admission > 1 day <sup>c</sup>	all women	1.17 (1.04-1.31)	1.38 (1.12-1.69)

Table 2.3: Infant outcomes by maternal age; singletons, BC, 1999-2003; adjusted odds ratio <sup>ab</sup> (adjOR), 95% confidence intervals (CI)

<sup>a</sup> 20-29 years old is a reference category

<sup>b</sup> adjusted for parity (if not an effect modifier), marital status, low-income neighbourhood, rural residence, smoking, alcohol and drug use during pregnancy, suboptimal prenatal care, infant's sex, aboriginal status, previous induced abortions, previous spontaneous abortions

<sup>c</sup> based on years 2001-03

Figure 2.1: Perinatal mortality per 10,000 fetuses-at-risk by maternal age and parity, BC, 1999-2003.



# References

- 1. Tough SC, Newburn-Cook C, Johnston DW, Svenson LW, Rose S, Belik J. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. *Pediatrics* 2002; 109:399-403.
- 2. Fell DB, Joseph KS, Dodds L, Allen AC, Jangaard K, Van den HM. Changes in maternal characteristics in Nova Scotia, Canada from 1988 to 2001. *Can.J.Public Health* 2005; 96:234-238.
- 3. Joseph KS, Allen AC, Dodds L, Turner LA, Scott H, Liston R. The perinatal effects of delayed childbearing. *Obstet.Gynecol.* 2005; 105:1410-1418.
- 4. Bell JS, Campbell DM, Graham WJ, Penney GC, Ryan M, Hall MH. Can obstetric complications explain the high levels of obstetric interventions and maternity service use among older women? A retrospective analysis of routinely collected data. *BJOG*. 2001; 108:910-918.
- Health Canada. Canadian Perinatal Health Report, 2003. Cat. No. H49-142/2003E. 2003. Ottawa: Minister of Public Works and Government Services Canada, 2003.
- 6. Statistics Canada. Births 2005. (Cat. No. 84F0210XIE). 2007. Ottawa, Ministry of Industry, 2007.
- 7. Martin, J. A., Hamilton, B. E., Sutton, P. D., Ventura, S. J., Menacker, F., and Kirmeyer, S. National Vital Statistics Reports (NVSS). 56(6). 12-5-0007. CDC.
- 8. Office for National Statistics. Birth statistics: Review of the registrar general on births and patterns of family building in England and Wales, 2006. 2007. Office for National Sataistics. FM1 No. 35.
- 9. Office for Official Publications of the European Communities Luxembourg. Eurostat yearbook 2002; The statistical guide to Europe, Data 1990-2000. 2008.
- Office for Official Publications of the European Communities Luxembourg. Eurostat yearbook 2006-07; Europe in figures. 2007. Catalogue number: KS-CD-06-001-EN-N.
- Ageskov Ulla and Nordic Council of Ministries. Nordic statistical yearbook 2007. No.45. 2007.
- 12. Linacre Susan. Australian social trends 2007. 2008. Catalogue No. 4102.0; Australian Bureau of Statistics.

- 13. Barkan SE, Bracken MB. Delayed childbearing: no evidence for increased risk of low birth weight and preterm delivery. *Am.J.Epidemiol.* 1987; 125:101-109.
- 14. Cnattingius S, Forman MR, Berendes HW, Isotalo L. Delayed childbearing and risk of adverse perinatal outcome. A population-based study. *JAMA* 1992; 268:886-890.
- 15. Prysak M, Lorenz RP, Kisly A. Pregnancy outcome in nulliparous women 35 years and older. *Obstet.Gynecol.* 1995; 85:65-70.
- 16. Roberts CL, Algert CS, March LM. Delayed childbearing--are there any risks? *Med.J.Aust.* 1994; 160:539-544.
- 17. Aldous MB, Edmonson MB. Maternal age at first childbirth and risk of low birth weight and preterm delivery in Washington State. *JAMA* 1993; 270:2574-2577.
- 18. Jolly M, Sebire N, Harris J, Robinson S, Regan L. The risks associated with pregnancy in women aged 35 years or older. *Hum.Reprod.* 2000; 15:2433-2437.
- 19. Chan BC, Lao TT. Influence of parity on the obstetric performance of mothers aged 40 years and above. *Hum.Reprod.* 1999; 14:833-837.
- 20. Bianco A, Stone J, Lynch L, Lapinski R, Berkowitz G, Berkowitz RL. Pregnancy outcome at age 40 and older. *Obstet. Gynecol.* 1996; 87:917-922.
- 21. Schempf AH, Branum AM, Lukacs SL, Schoendorf KC. Maternal age and parityassociated risks of preterm birth: differences by race/ethnicity. *Paediatr.Perinat.Epidemiol.* 2007; 21:34-43.
- 22. Kiely JL, Paneth N, Susser M. An assessment of the effects of maternal age and parity in different components of perinatal mortality. *Am.J.Epidemiol.* 1986; 123:444-454.
- 23. Astolfi P, Zonta LA. Risks of preterm delivery and association with maternal age, birth order, and fetal gender. *Hum.Reprod.* 1999; 14:2891-2894.
- 24. Huang L, Sauve R, Birkett N, Fergusson D, et al. Maternal age and risk of stillbirth: a systematic review. *CMAJ*. 2008; 178:165-172.
- 25. Newburn-Cook CV, Onyskiw JE. Is older maternal age a risk factor for preterm birth and fetal growth restriction? A systematic review. *Health Care Women Int.* 2005; 26:852-875.
- 26. Synnes AR, Ling EW, Whitfield MF, Mackinnon M, Lopes L, Wong G *et al.* Perinatal outcomes of a large cohort of extremely low gestational age infants (twenty-three to twenty-eight completed weeks of gestation). *J.Pediatr.* 1994; 125:952-960.

- 27. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M *et al.* A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics* 2001; 108:E35.
- 28. Lee Shoo K. Levels of neonatal care. Paediatrics & Child Care 11(5), 303-306. 2006.
- 29. Zupancic JA, Richardson DK. Characterization of the triage process in neonatal intensive care. *Pediatrics* 1998; 102:1432-1436.
- British Columbia Reproductive Care Program. British Columbia Perinatal Database Registry - Overview. 2003. Ref Type: Report
- 31. Statistics Canada. Postal code conversion file (PDDF), reference guide. 2004. Catalogue no. 92F0153GIE.
- Indian and Northern Affairs Canada, aboriginal people and communities. http://www.ainc-inac.gc.ca/ap/tln-eng.asp . 2008. 7-10-0009. Ref Type: Electronic Citation
- Hosmer DH and Lemeshow S. Applied logistic regression. 2nd. 2000. John Wiley & Sons, Inc.
- 34. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet* 1987; 1:1192-1194.
- 35. Joseph KS. Theory of obstetrics: the fetuses-at-risk approach as a causal paradigm. *J.Obstet.Gynaecol.Can.* 2004; 26:953-960.
- 36. Joseph KS. The fetuses-at-risk approach: clarification of semantic and conceptual misapprehension. *BMC.Pregnancy.Childbirth*. 2008; 8:11.
- 37. Joseph KS. Theory of obstetrics: an epidemiologic framework for justifying medically indicated early delivery. *BMC.Pregnancy.Childbirth.* 2007; 7:4.
- 38. Joseph KS. Incidence-based measures of birth, growth restriction, and death can free perinatal epidemiology from erroneous concepts of risk. *J.Clin.Epidemiol.* 2004; 57:889-897.
- 39. Kramer MS, Liu S, Luo Z, Yuan H, Platt RW, Joseph KS. Analysis of perinatal mortality and its components: time for a change? *Am.J.Epidemiol.* 2002; 156:493-497.
- 40. Kramer MS, Ananth CV, Platt RW, Joseph KS. US Black vs White disparities in foetal growth: physiological or pathological? *Int.J.Epidemiol.* 2006; 35:1187-1195.

- 41. Cnattingius S, Stephansson O. The epidemiology of stillbirth. *Semin.Perinatol.* 2002; 26:25-30.
- 42. Chan BC, Lao TT. Influence of parity on the obstetric performance of mothers aged 40 years and above. *Hum.Reprod.* 1999; 14:833-837.
- 43. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. *Methods in observational epidemiolgy. 2nd edition.* Oxford University Press, Inc., 2006.
- 44. Smith PG, Day NE. The design of case-control studies: the influence of confounding and interaction effects. *Int.J.Epidemiol.* 1984; 13:356-365.
- 45. Joseph KS, Demissie K, Kramer MS. Obstetric intervention, stillbirth, and preterm birth. *Semin.Perinatol.* 2002; 26:250-259.

# **CHAPTER 3**

# Effect of older maternal age on birth outcomes in twin pregnancies: a population based study<sup>3</sup>

### Introduction

Delayed childbearing, increasingly observed in developed countries over the past two decades, has been paralleled by an increased rate of twin births, predominantly due to the growing use of fertility treatments (1, 2). In the US, the twinning rate has increased by 93% since 1980, reaching 32.2 twins per 1000 births in 2005 (3, 4). In Canada, twin births have increased from 17.9 per 1000 total births in 1974 to 30.8 per 1000 births in 2005 (2, 5), an increase of 72% (5, 6). Similar trends have been observed in other developed countries, such as the United Kingdom (7), Denmark (8), and other European countries (9, 10). Older mothers experience the greatest relative increase in twinning. During the period between 1995 and 2005, among 40-44 year old US women, the twin fertility rate increased from 5.5 to 9.1 per 1000 women, among 35-39 year olds from 31.7 to 46.5 per 1000 women, and among women 30-34 years of age from 80.8 to 95.9 per 1000 women, compared to a decrease among 25-29 and 20-24 year old women (from 120.2 to 115.8, and from 88.6 to 70 per 1000 women, respectively) (11). Although the rate of twin births has increased predominantly among older women, the association between older maternal age and adverse birth outcomes in twin pregnancies has received little attention.

<sup>&</sup>lt;sup>3</sup> A version of this chapter will be submitted for publication. Lisonkova S, ,Sheps SB, Janssen PA, Lee SK, Dahlgren L. Effect of older maternal age on birth outcomes in twin pregnancies: a population based study.

Previous studies of twins have not indicated that older mothers have an elevated risk of major adverse birth outcomes, including perinatal death (12-14), stillbirth (12), neonatal death (12, 14), infant death (13-16), very preterm birth (12-14, 17), preterm birth (12, 14), low birthweight (12, 14), very low birthweight (13, 14), or SGA (14). Only one study examined the differential effect of parity on the association between maternal age and very preterm birth (17). Among primiparae, the risk decreased with maternal age, whereas among multiparae, a decrease was not apparent. Some previous studies have been limited by lack of adjustment for smoking (12, 14, 16, 17), alcohol and drug use (12, 14-17), socio-economic status (12, 13, 16), prenatal care (16), or obstetric history (12, 14-17). One study was limited by a small sample size (12). Some studies of twins, where an infant was the unit of statistical analysis, have not corrected for correlation between twins (12, 13, 16).

Only two studies examined the risk of short-term newborn outcomes (12, 14), including low Apgar score (12), intubation (14), or transfer to a neonatal intensive care unit (NICU); these outcomes were not significantly elevated among twins of older mothers. Little is known about neonatal morbidity that requires a high-acuity NICU care longer than a few days. This outcome is important, as lack of significantly elevated risk of perinatal death among twins of older mothers may be offset by serious neonatal morbidity.

The primary objectives of this study were to examine the association between maternal age and adverse birth outcomes in twins, including perinatal death, very preterm birth, small-for-gestational age (SGA), prolonged NICU admission (13 days or more), and a combined outcome of perinatal death and/or prolonged NICU admission; in a

population-based approach, adjusting for demographic and lifestyle risk factors and correlation among twin outcomes. Secondary objectives were to describe the effect of parity on these associations. Lastly, to address potential confounding by chorionicity (two placentas versus one shared placenta) we restricted our analyses to twins of opposite sex, as these are always dichorionic twins.

#### Methods

We conducted a population-based retrospective cohort study comparing birth outcomes between twins born to mothers 35+ year old and twins born to mothers 25-34 years of age. We included all twins born at 20 weeks of gestation or later in British Columbia (BC), Canada, from April 1<sup>st</sup>, 1999 to March 31, 2003.

The outcomes of interest were perinatal death (death in-utero after 20 weeks of gestation or within first 28 days of life), very preterm birth (<33 weeks), SGA (<10<sup>th</sup> percentile), NICU admission for 13 days or more, and a combined outcome including perinatal death and/or NICU admission for 13 days or more. Our data include all NICU transfers between hospitals or readmissions during the first year of infant's life. NICU admissions were restricted to NICUs level 2 or 3, characterized by a high-dependency neonatal care, such as total parenteral nutrition, mechanical ventilation, performance of major surgeries, or extracorporeal membrane oxygenation (18). NICU admissions for a few days were not considered relevant as they may represent transitory problems in newborns or simply admissions for monitoring newborns' condition. Although some studies indicate that the majority of triage patients or those with minor conditions are admitted for less than 1 day (19), we chose a more conservative cut-off (13 days or more). Reports describing newborns admitted to Canadian NICUs in 1996-97 and

1998-99 (Canadian Neonatal Network Report Volume I and II) indicate a median 13 days of hospitalization; excluding newborns who were admitted for less than 1 day (20). Thus the 13 days cut-off identifies approximately one half of newborns that are hospitalized for the longest period of time.

Gestational age was defined initially by date of the last menstrual period (LMP). In cases where was a discrepancy of more than two weeks between the LMP and first trimester ultrasound, the ultrasound estimate was used (21). SGA (<10<sup>th</sup> percentile) was defined using a US twin male and female newborn population (22). Primipara refers to a woman who is experiencing her first pregnancy lasting 20 weeks of gestation or longer; multiparae are women who have had at least one prior birth (at 20 weeks of gestation or later).

Factors examined in multivariable analyses for their role as confounders included smoking during pregnancy (yes/no), alcohol (yes/no) and drug use during pregnancy (yes/no), single parent (a woman without partner during the pregnancy, yes/no), low attendance at prenatal care (<4 visits during pregnancy versus more), prior spontaneous abortions (yes/no) and prior induced abortions (yes/no), infant's gender, low-income neighbourhood residence (yes/no), rural residence (yes/no), and ethnicity indicated by Aboriginal status (yes/no). Drug use represented any drug (illicit, prescription or other drug potentially harmful to baby) used during pregnancy. Low income area was defined as a residential area (by postal code) with median income within the lower quintile of BC income distribution. Neighbourhood level income is considered an adequate approximation of a household income in studies of health outcomes in Canada (23). Rural residence was defined by postal codes corresponding to areas with < 10,000

inhabitants, according to Statistics Canada (24). Aboriginal women were identified as those registered in the Indian registry as having aboriginal ancestry as defined by the Indian Act (25).

We also obtained information about previous obstetric history: stillbirth or neonatal death (yes/no); previous low birthweight or preterm birth (yes/no); prepregnancy weight (>70kg versus <=70kg); congenital anomalies (ICD9 code 740.0 to 759.9 noted on discharge hospital abstracts); as well as hospital readmissions and transfers during the first year).

Maternal age, birth and newborn information as well as information about potential confounders were extracted from the British Columbia Perinatal Health Program (BCPHP) birth registry, which captures all births in the province of BC (about 40,000 births per year). These data are abstracted from hospital charts after discharge by trained health records staff according to standardized protocols. Validity checks include data re-abstractions, and quarterly reports examining data consistency. Vital Statistics data including neonatal deaths are linked to the BCPHP registry. The information about aboriginal status was obtained from the Ministry of Health. Ethics approval was obtained from Behavioral Research Ethics Board of the University of British Columbia.

#### Data analysis

Differences in demographic, behavioural, and life-style characteristics were compared. In a univariate analysis, relative risks (RRs) and their 95% confidence intervals (CIs) were calculated for the entire study population and then for subgroups stratified by parity. In addition we compared the distribution of gestational age at birth between twins of younger and older mothers, and by parity. The unit of analysis for

outcome measures was an infant. In the analyses of perinatal mortality, stillbirths were also included.

Generalized estimating equation (GEE) models for binary outcomes were used to adjust for confounding factors, and account for correlation in twin birth outcomes. Potential confounders were excluded one-by-one, ordered by the smallest contribution to the model. If a confounder's removal changed the estimated OR of the exposure (maternal age) by 10% or more, the confounder was kept in the model regardless of the statistical significance of its explanatory value to the model (26). The interaction term of parity and maternal age (primiparity x older maternal age) was tested as well. The same set of analyses was performed using a dataset restricted to opposite-sex twins, in order to eliminate confounding by chorionicity. The models were fit using Genmod procedure in SAS statistical package (SAS, version 6.1.3.).

#### Results

During our 4-year study period (1999-2003), 1088 twin infants were born to mothers 35+ years old (446 to primiparae and 642 to multiparae); and 2550 twin infants were born to mothers 25-34 years old (1158 to primiparae and 1392 to multiparae). Since NICU admission information was available only for the last two years of the study (2001-03), the analysis of NICU admissions included only 1310 twins born to mothers 25-34 years old and 626 twins born to mothers 35+ years old. Compared to younger mothers, older mothers were significantly less likely to smoke during pregnancy, and less likely to weigh >70 kg before pregnancy (information about pre-pregnancy weight was available for approximately 80% of mothers). Older mothers were more likely to have had a prior spontaneous abortion, and a prior stillbirth or neonatal death. Twin infants in
both cohorts were similar with respect to congenital anomalies and infant's sex. (Table 3.1).

Unadjusted results showed that twin infants of older mothers were significantly less likely to be SGA compared to twins of younger mothers. The rates of perinatal death, very preterm birth, and NICU admissions were not significantly different between the cohorts. Among multiparae, the associations between maternal age and very preterm birth and SGA were closer to the null, compared to primiparae. Statistically significant differences according to parity were observed in the association between maternal age and NICU admission (13 days or more), and a combined outcome including perinatal death and/or NICU admission (13 days or more): higher risks among twins of older multiparae, and no elevated risk among twins of older primiparae, compared to twins born to younger mothers. (Table 3.2) The adjusted analyses yielded similar results. Twins of older mothers had no excess risk of perinatal death, very preterm birth, or SGA (adjOR=0.99, CI: 0.65, 1.53; adjOR=0.84, CI: 0.65, 1.08; and adjOR=0.76, CI: 0.51, 1.13; respectively). Twins born to older primiparae had no elevated risk of NICU admissions for 13 or more days (adjOR=0.99, CI: 0.66, 1.50), as compared to twins born to younger primiparae. Among multiparae, this association was positive (adjOR=1.58, CI: 1.09, 2.30). (Table 2.2) However, the effect modification by parity was not statistically significant (p=0.09); the overall adjOR (including both parity groups) was 1.28 (CI: 0.97-1.68). Similarly, the risk of perinatal death and/or NICU admissions for 13 days or more was adjOR=0.92 (CI: 0.62-1.34) among primiparae; and adjOR=1.70 (CI: 1.18-2.44) among multiparae; yielding marginally significant effect modification; the overall adjOR (for both parity groups combined) was 1.27 (CI: 0.98-1.65).

The distribution of gestational age at birth for each cohort and parity is shown in Figure 3.1. Among multiparae, twins followed a similar gestational age distribution curve that peaked at 37-38 weeks and included a relatively large proportion of births between 35-36 weeks. Among primiparae, the gestational age distribution curves also peaked at 37-38 weeks. Twins of older primiparae had a relatively large proportion of births at 35-36 weeks (similarly to twins of multiparae); however, twins of younger multiparae had a relatively smaller proportion of births at 35-36 weeks. The differences were not statistically significant (P>0.05).

## Birth outcomes of opposite sex twins

Analyses restricted to opposite sex twins showed that older mothers had significantly lower risk of perinatal death and preterm birth < 33 weeks. (Table 2.3) The RRs did not differ significantly by parity for perinatal death, very preterm birth, and SGA, but were modified by parity for NICU admission for 13 days or more and for the combined outcome (perinatal mortality and/or NICU admission for 13 days or more), similarly to our entire sample. The results did not change substantially after adjustment for other confounding factors. The associations between maternal age and adverse birth outcomes were stronger among opposite-sex twins, compared to results of unrestricted analysis of all twins.

# Discussion

As multifetal pregnancies among older women have become an increasingly important issue, our results help to address important gaps in the literature. This study describes an independent association between older maternal age and major adverse birth outcomes, while adjusting for a wide range of demographic, behavioural and life-style

factors. To our knowledge, this is the first study to describe the association between maternal age and a prolonged NICU stay; and the first study to explore the effect of parity on birth outcomes other than very preterm birth. Our results suggest that a relatively lower risk of perinatal mortality among older mothers is not likely offset by an increase in serious neonatal morbidity among primiparae.

Previous studies describing the association between maternal age and adverse birth outcomes in twins are scarce, however, the results are in agreement with ours. Zhang et al. found no excess risk of perinatal death, and very preterm birth among older mothers in a US population (13). Misra et al. reported no significant increase in neonatal mortality among twins of women aged 30-35, 35-39 and 40+ years compared to twins of 25-29 year old mothers; these results being adjusted for gravidity, birthweight, birth cohort (1985-86, 1990-91, versus 1995-96), and gestational age (16). Prapas et al. found no significant excess risk for NICU admission and perinatal death among older mothers, however, the results were based on a small number of women (57 women  $\geq 35$  years of age and 181 women < 35 years of age) and no adjustment was made for potential confounders (12). The results of a population-based study, including twins born in Flanders (Belgium) in 2001-2004, indicated that risk of adverse birth outcomes (perinatal death, SGA, very preterm birth, and any NICU admission) was not elevated among older vs. younger primiparous women (14). The risk of preterm birth was significantly lower among older primiparae; adjusted for mode of conception (spontaneous vs. ART, and ovulation induction), education, hypertension, year of birth, and intra-twin correlation.

Branum et al found differential effects of parity on the relationship between maternal age and very preterm birth in twin pregnancies, comparable with our findings

(17). Among primiparae, very preterm birth rates decreased with increasing maternal age, and older women had a significantly lower risk of very preterm birth after adjusting for ethnicity, prenatal care and marital status. Multiparae showed no apparent trend. However, Branum et al's study did not examine stillbirths, and no adjustment was made for factors such as smoking, alcohol and drug use, rural residence, and obstetric history. In fact, the authors recommended that future analyses should account for these measures as has been done in our study.

Our findings of no association or a negative association between maternal age and adverse birth outcomes among twins are in contrast with positive associations observed among singletons (an elevated risk among older mothers) (1, 27, 28). This paradox has been noted in the previous literature (29), however, the reasons behind the discrepancy have not been identified to date. A possible confounding effect of ART and chorionicity has been mentioned (13, 14). A study from Flanders indicated that the mode of conception (spontaneous, IVF, and ovulation induction) or chorionicity did not account for a relatively favourable birth outcomes among older primiparae with twins (14). This is in agreement with our study. When we restricted the analysis to a subset of oppositesex twins, always dichorionic, the results revealed even lower risk of adverse birth outcomes among older compared to younger mothers, demonstrating that chorionicity is not likely to explain the lack of elevated risks of adverse birth outcomes among twins born to older mothers. However, policies related the number of embryos transferred during IVF differ between Belgium and North America; thus the effect of ART on twins among older mothers deserves further evaluation.

A number of other hypothesis regarding possible explanations emerge. First, the differential clinical management of twin pregnancy between older and younger mothers can contribute to the differences in birth outcomes. It has been shown that medically indicated early delivery (labour induction or c-section), followed by an adequate neonatal care, can prevent stillbirth or perinatal death (30-32). Children of older mothers, especially primiparae, are sometimes viewed as "premium" babies. Thus these pregnancies may be monitored with a heightened vigilance and lower threshold for obstetric interventions and NICU admission, possibly preventing some of the adverse birth outcomes. However, all multiple pregnancies, in general, are considered high-risk from a clinical point of view, and monitored accordingly. Further research is needed to elucidate whether any potential differences in obstetric management exist and what their influences are on twin pregnancy outcomes.

Secondly, older mothers, who were able to conceive twins and remain pregnant after 20 weeks of gestation, may represent a select cohort of healthy women. Some authors point out that these women may have a biologic advantage of high quality eggs (except those who use donor eggs), and healthy reproductive systems, contributing to better birth outcomes (14). However, findings of Luke et al. indicate that the risk of maternal morbidity increases with maternal age in a similar manner in both, twin and singleton pregnancies (15), which does not support this hypothesis.

Thirdly, changes in the uterus due to aging might be, to some extent, advantageous to older women pregnant with twins. In general, a higher rate of uterine distention in twin compared to singleton pregnancy may contribute to a lower average gestational age at birth among twins (33). There may be several mechanisms involved,

including the increased level of oxytocin that stimulates contractions and initiates the delivery. It is possible that low oxytocin receptivity and altered uterine contractility (34) can make twin uterus less susceptible to preterm delivery among older, compared to younger women with twins. This hypothesis is supported by findings of Luke et al. indicating that the need for tocolysis declines significantly with maternal age in twin pregnancies (15). This hypothesis needs further evaluation.

Fourthly, adverse medical events before 20 weeks of gestation may result in a shift of riskier pregnancies from twin to singleton, predominantly among older mothers. The incidence of spontaneous abortion or pregnancy termination due to congenital anomalies increases as maternal age increases (35). Miscarriage results in a pregnancy loss in singleton pregnancies; however, in twin pregnancies, a loss of only one fetus may occur resulting in a 'vanishing twin' phenomenon or a one-twin fetal demise (when both fetuses remains in-utero). The reported rates of vanishing twin vary widely, as this phenomenon is difficult to detect. Based on several small studies, Landy & Keith estimated a one-twin loss rate range between 7.3 and 38%, depending on the mode of conception (natural vs. ART) and gestational age (36). Worse outcomes for a survivor twin are plausible, as placental pathology occurs more often in the context of a vanishing twin, in the form of irregular plaques, hemorrhages into decidua, and other complications (36). The surviving twin is at elevated risk of mortality, low birthweight, preterm birth, and NICU admissions (37, 38).

More serious repercussions for a surviving twin may occur after a selective onetwin termination, compared to a vanishing twin scenario, as the terminations occur later in pregnancy. Selective termination refers to the deliberate termination of an anomalous

twin in a multiple gestation, usually in the second trimester, to improve the outcome of the other normal twin and to prevent delivery of an abnormal fetus. The population rate of selective one-twin terminations (for any reason) is not known; one hospital-based study reports that out of 1000 consecutive multifetal IVF pregnancy reductions, 14% were twins to singletons (39).

Iatrogenic multifetal pregnancies in older women arise not only from IVF, but also from the use of fertility drugs (without IVF). In fact, some authors suggest that an increase in twinning among older women is largely due to fertility drug treatment (5). Studies of a commonly used fertility drug such as clomiphene citrate suggest a 30% multifetal pregnancy loss (40, 41), however, little is known about its potentially detrimental effect on the fetus itself (40, 42) and twin-to-singleton pregnancy reduction.

A potential limitation of our study is our inability to adjust for maternal education, mode of conception, body mass index (BMI), fertility problems, and other potential confounders such as, ethnicity (other than aboriginal status), short interval between births (in multiparae), stress, nutrition, and environmental factors. Additional analyses adjusting for pre-pregnancy weight, and congenital anomalies yielded similar results to our original analyses.

We used NICU admission for 13 days or more to identify infants with potentially serious neonatal morbidity. The median length of stay at NICU was 13 days in our data after excluding admissions for 1 day or less, similarly to other Canadian NICUs (20). There is not any defined threshold for a number of NICU days that would identify serious neonatal morbidity. However, the longer the NICU stay, the less likely that it is due to a transitory medical condition or for an observation. The unadjusted analyses did not

account for inter-twin correlation; thus the calculated confidence intervals around the relative risks are narrower than the true 95% confidence intervals would be if the newborns were singletons. This limitation was addressed by multivariable analyses.

Our dataset had statistical power to detect approximately 100% differences in perinatal mortality. These differences were not unrealistic, since we observed 90% difference in perinatal mortality (among primiparae). However, we lack the power to detect a statistically significant effect modification by parity on the association between maternal age and adverse birth outcomes. The results suggest that parity does modify the effect of age on perinatal death and prolonged NICU stay; however, large studies are needed to test this hypothesis. Lack of power does not influence the interpretation of our findings that indicate no increased risk of perinatal death, preterm birth, SGA among twins born to older primiparae. These associations were negative (showing a decline in risk among older mothers) with borderline statistical significance (at p=0.05).

In conclusion, this study shows that twins of older women overall are not at excess risk of adverse birth outcomes compared to twins born to younger women, with the single exception of admissions to NICU (13 days or more) among older multiparous women. Primiparae, in general, were at decreased risk of adverse birth outcomes among older compared to younger women; this association was not apparent among multiparae. Our results suggest that this lack of elevated risk among primiparae was not likely offset by an increase in neonatal morbidity. However, it is important to note that twins, regardless of maternal age, have higher rates of all adverse birth outcomes compared to singletons.

Maternal age (years)	25-34	35+	
	N=1275	N=544	P-value
Parity			0.203
Para 1 (primipara)	579 (45.41)	223 (40.99)	
Para 2	460 (36.08)	208 (38.24)	
Para 3+	236 (18.51)	113 (20.77)	
Single parent	38 (3.09)	20 (3.86)	0.411
Suboptimal prenatal care (<4 visits)	49 (4.33)	18 (3.57)	0.475
Smoking during pregnancy	137 (10.75)	41 (7.54)	0.035
Alcohol use during pregnancy	10 (0.78)	5 (0.92)	0.771
Drug use during pregnancy	16 (1.25)	8 (1.47)	0.712
Prior stillbirth or neonatal death	15 (1.18)	17 (3.13)	0.004
Prior low birthweight or premature birth	65 (5.10)	37 (6.80)	0.148
Prior induced abortions (any)	191 (15.05)	82 (15.24)	0.918
Prior spontaneous abortion (any)	289 (22.77)	156 (29.00)	0.005
Rural residence (<10,000 residents)	157 (12.38)	66 (12.15)	0.893
Low SES neighborhood area <sup>a</sup>	197 (15.46)	73 (13.42)	0.262
Aboriginal status	42 (3.30)	12 (2.21)	0.212
Pre-pregnancy weight > 70 kg	271/1022 (26.52)	89/434 (20.51)	0.015
Any congenital anomaly (ICD9 740-759)	205/2550 (8.04)	83/1088 (7.63)	0.675
Newborn's male gender	1253/2550 (50.82)	568/568 (52.21)	0.445

Table 3.1: Mother and Newborn Characteristics by Maternal Age; Twin Pregnancies, BC, 1999-2003; N (%)

<sup>a</sup> defined as the lowest quintile of BC median income per postal code

Maternal age (years)	parity	25-34	35+	RR	Confidence intervals		AdjOR <sup>b</sup>	Confidence intervals	
		N=2550	N=1088						
Perinatal death	all	100 (3.94)	36 (3.31)	0.88	0.66	1.17	0.99	0.65	1.53
	primiparae	59 (5.09)	12 (2.69)	0.60	0.35	1.01			
	multiparae	41 (2.95)	24 (3.74)	1.18	0.85	1.63			
Preterm birth <33 weeks	all	334 (13.11)	124 (11.40)	0.89	0.76	1.05	0.84	0.65	1.08
	primiparae	174 (15.34)	57 (12.84)	0.86	0.68	1.09			
	multiparae	134 (9.77)	54 (8.64)	0.91	0.72	1.15			
SGA 10th percentile	all	130 (5.13)	38 (3.50)	0.74	0.56	0.99	0.76	0.51	1.13
	primiparae	78 (6.88)	19 (4.28)	0.68	0.45	1.03			
	multiparae	44 (3.21)	16 (2.56)	0.85	0.55	1.30			
NICU admission (13+ days) <sup>a</sup>	all	205/1310 (15.65)	102/626 (16.29)	1.03	0.87	1.23	1.28	0.97	1.68
	primiparae	118/594 (19.87)	40/255 (15.69)	0.81	0.61	1.09	0.99	0.66	1.50
	multiparae	87/716 (12.15)	62/317 (16.71)	1.26	1.02	1.56	1.58	1.09	2.30
Perintal death and/or NICU admission (13+ days) <sup>a</sup>	all	354/1332 (19.07)	117/634 (18.45)	0.97	0.82	1.15	1.27	0.98	1.65
	primiparae	149/608 (24.51)	45/256 (17.58)	0.74	0.56	0.97	0.92	0.62	1.34
	multiparae	105/724 (14.50)	72/378 (19.05)	1.23	1.01	1.50	1.70	1.18	2.44

Table 3.2: Infant Outcomes by Maternal Age and Parity; Twins, BC, 1999-2003; N(%); Relative Risk (RR), Adjusted Odds Ratio (AdjOR), 95% Confidence Intervals

<sup>a</sup> based on years 2001-03

<sup>b</sup> adjusted for low-income residence, single parent, smoking during pregnancy, drug use, alcohol use during pregnancy, suboptimal prenatal care, aboriginal status, rural residence, prior induced abortion, prior spontaneous abortion, male gender, parity

Table 3.3: Newborn Outcomes by Maternal Age; Twins of Opposite Sex, BC, 1999-2003; N(%), Relative Risk (RR), Adjusted Odds Ratio (AdjOR), 95% Confidence Intervals

Maternal age (years)	parity	25-34	35+	RR	Confidence intervals		AdjOR <sup>b</sup>	Confidence intervals	
		N=810	N=404	1					
Perinatal death	all	24 (2.96)	2 (0.50)	0.23	0.06	0.86	0.19	0.04	0.83
Preterm birth <33 weeks	all	88 (11.03)	18 (4.46)	0.48	0.31	0.74	0.4	0.22	0.73
SGA 10th percentile	all	32 (4.02)	11 (2.72)	0.75	0.45	1.26	0.73	0.36	1.48
NICU admission (13+ days) <sup>a</sup>	primiparae	48/229 (20.96)	5/124 (4.04)	0.24	0.10	0.55	0.21	0.08	0.55
	multiparae	10/186 (5.38)	19/132 (14.39)	1.68	1.24	2.26	2.41	1.04	5.56
admission (13+ days) <sup>a</sup>	primiparae	58/236 (24.58)	7/124 (5.65)	0.27	0.13	0.55	0.23	0.11	0.57
	multiparae	12/186 (6.45)	19/132 (14.39)	1.56	1.14	2.13	2.40	1.04	5.53

<sup>a</sup> based on years 2001-03

<sup>b</sup> adjusted for low-income residence, single parent, smoking during pregnancy, drug use, alcohol use during pregnancy, suboptimal prenatal care, aboriginal status, rural residence, prior induced abortion, prior spontaneous abortion, male gender, parity





# References

- 1. Tough SC et al. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. Pediatrics 2002;109:399-403.
- 2. Tough SC et al. Effects of in vitro fertilization on low birth weight, preterm delivery, and multiple birth. J.Pediatr. 2000;136:618-22.
- 3. Martin JA et al. Births: final data for 2004. Natl.Vital Stat.Rep. 2006;55:1-101.
- 4. Martin JA et al. National Vital Statistics Reports (NVSS). 56[6]. 12-5-0007. CDC.
- 5. Bissonnette F et al. Incidence and complications of multiple gestation in Canada: proceedings of an expert meeting. Reprod.Biomed.Online. 2007;14:773-90.
- 6. Statistics Canada. Births 2005. [Cat. No. 84F0210XIE]. 2007. Ottawa, Ministry of Industry, 2007.
- 7. The multiple birth foundation, media inquiries, general information. <u>http://www.multiplebirths.org.uk/media.asp; accessed Dec 2008</u>.
- 8. Westergaard T et al. Population based study of rates of multiple pregnancies in Denmark, 1980-94. BMJ 314, 775-786. 2008. accessed Dec 2008
- 9. Steegers-Theunissen RP et al. Multiple birth prevalence in The Netherlands. Impact of maternal age and assisted reproductive techniques. J.Reprod.Med. 1998;43:173-9.
- 10. Blondel B, Kaminski M. Trends in the occurrence, determinants, and consequences of multiple births. Semin.Perinatol. 2002;26:239-49.
- 11. Martin JA et al. Births: final data for 2005. Natl.Vital Stat.Rep. 2007;56:1-103.
- 12. Prapas N et al. Twin gestation in older women: antepartum, intrapartum complications, and perinatal outcomes. Arch.Gynecol.Obstet. 2005;1-5.
- 13. Zhang J et al. Multifetal pregnancy in older women and perinatal outcomes. Fertil.Steril. 2002;78:562-8.
- 14. Delbaere I et al. Perinatal outcome of twin pregnancies in women of advanced age. Hum.Reprod. 2008;23:2145-50.

- Luke B, Brown MB. Contemporary risks of maternal morbidity and adverse outcomes with increasing maternal age and plurality. Fertil.Steril. 2007;88:283-93.
- 16. Misra DP, Ananth CV. Infant mortality among singletons and twins in the United States during 2 decades: effects of maternal age. Pediatrics 2002;110:1163-8.
- 17. Branum AM, Schoendorf KC. The influence of maternal age on very preterm birth of twins: differential effects by parity. Paediatr.Perinat.Epidemiol. 2005;19:399-404.
- Lee Shoo K. Levels of neonatal care. Paediatrics & Child Care 11[5], 303-306. 2006.
- 19. Zupancic JA, Richardson DK. Characterization of the triage process in neonatal intensive care. Pediatrics 1998;102:1432-6.
- 20. McMillan, Lee KS, Chan HWP. Canadian NICU Network, 1996-1997; Volume I. 1999.
- 21. Synnes AR et al. Perinatal outcomes of a large cohort of extremely low gestational age infants (twenty-three to twenty-eight completed weeks of gestation). J.Pediatr. 1994;125:952-60.
- 22. Alexander GR et al. What are the fetal growth patterns of singletons, twins, and triplets in the United States? Clin.Obstet.Gynecol. 1998;41:114-25.
- 23. Mustard CA et al. Assessing ecologic proxies for household income: a comparison of household and neighbourhood level income measures in the study of population health status. Health Place. 1999;5:157-71.
- 24. Statistics Canada. Postal code conversion file (PDDF), reference guide. 2004. Catalogue no. 92F0153GIE.
- 25. Indian and Northern Affairs Canada, aboriginal people and communities. http://www.ainc-inac.gc.ca/ap/tln-eng.asp. accessed Dec 2008
- 26. Hosmer DH, Lemeshow S. Applied logistic regression. 2nd. 2000. John Wiley & Sons, Inc.
- 27. Joseph KS et al. The perinatal effects of delayed childbearing. Obstet.Gynecol. 2005;105:1410-8.
- 28. Cnattingius S et al. Delayed childbearing and risk of adverse perinatal outcome. A population-based study. JAMA 1992;268:886-90.
- 29. Oleszczuk JJ, Keith LG, Oleszczuk AK. The paradox of old maternal age in multiple pregnancies. Obstet.Gynecol.Clin.North Am. 2005;32:69-80, ix.

- 30. Joseph KS. Theory of obstetrics: an epidemiologic framework for justifying medically indicated early delivery. BMC.Pregnancy.Childbirth. 2007;7:4.
- 31. Joseph KS, Demissie K, Kramer MS. Obstetric intervention, stillbirth, and preterm birth. Semin.Perinatol. 2002;26:250-9.
- 32. Joseph KS et al. Causes and consequences of recent increases in preterm birth among twins. Obstet.Gynecol. 2001;98:57-64.
- 33. Baldwin VJ. Pathology of multiple pregnancy. Springer, 1994.
- 34. Adashek JA et al. Factors contributing to the increased cesarean birth rate in older parturient women. Am.J.Obstet.Gynecol. 1993;169:936-40.
- 35. Nybo Andersen AM et al. Maternal age and fetal loss: population based register linkage study. BMJ 2000;320:1708-12.
- 36. Landy HJ, Keith LG. The vanishing twin: a review. Hum.Reprod.Update. 1998;4:177-83.
- 37. Pinborg A, Lidegaard O, Andersen AN. The vanishing twin: a major determinant of infant outcome in IVF singleton births. Br.J.Hosp.Med.(Lond) 2006;67:417-20.
- 38. Pinborg A et al. Vanishing twins: a predictor of small-for-gestational age in IVF singletons. Hum.Reprod. 2007;22:2707-14.
- 39. Stone J et al. Contemporary outcomes with the latest 1000 cases of multifetal pregnancy reduction (MPR). Am.J.Obstet.Gynecol. 2008;199:406-4.
- 40. Oktay K et al. The re-incarnation of an old question--clomid effect on oocyte and embryo? Fertil.Steril. 2000;74:422-3.
- 41. Wu CH. Less miscarriage in pregnancy following Tamoxifen treatment of infertile patients with luteal phase dysfunction as compared to clomiphene treatment. Early Pregnancy. 1997;3:301-5.
- 42. London SN et al. Clomiphene citrate-induced perturbations during meiotic maturation and cytogenetic abnormalities in mouse oocytes in vivo and in vitro. Fertil.Steril. 2000;73:620-6.

# **CHAPTER 4**

# Birth outcomes among older mothers in rural versus urban areas: a residence-based approach<sup>4</sup>

## Introduction

Delayed childbearing has become an increasingly common phenomenon in the developed world. Advanced maternal age (35+ years) is associated with higher rates of pregnancy complications, obstetric interventions, and an elevated risk of adverse birth outcomes (1-4). Thus, adequate access to appropriate obstetric care is particularly important for older parturients. It is not known whether older women with potential geographic barriers to advanced obstetric care, such as those living in rural areas, have different birth outcomes than urban women.

Previous research on rural maternity services has concluded that with appropriate regionalization of obstetric and perinatal care, mothers delivering in rural hospitals may not be at greater risk of adverse perinatal outcomes compared to mothers delivering in urban hospitals (5). Most studies, however, compared rural and urban place of childbirth, rather than maternal residence. Thus, little is known about the relation between adverse birth outcomes and maternal residence (5-7). We suggest that the residence-based approach employed in this study is a better approach to compare the actual risks to rural mothers, as it reflects not only the performance of rural hospitals (delivering

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predominantly low-risk women), but also transport plans for women with moderate/high risk pregnancies before or during labour.

In addition, several studies have shown that the risk of obstetric interventions and birth outcomes among older women depends on parity (8, 9). However, no previous research has examined the differential effect of parity between rural and urban older women. Finally, little is known about how distance to the nearest hospital with caesarean section capacity influences birth outcomes among older mothers.

The objectives of our study were to describe demographic, behavioural and lifestyle factors among older mothers (35+ years) in rural and urban areas in BC; and to examine the association between rural/remote residence, and risk of obstetric interventions and adverse birth outcomes among older mothers. Further, we assess the effects of parity on these associations. We also evaluate the risk of these outcomes in relation to distance to the nearest hospital with c-section capacity.

### Methods

We conducted a retrospective population-based cohort study of all mothers age 35 or older who delivered a singleton infant in British Columbia (BC), Canada, between April 1, 1999 and March 31, 2003 to compare the rate of obstetric interventions and adverse birth outcomes between women residing in rural areas versus urban residents.

The two exposures of interest were: 1) rural residence, defined as communities with less than 10,000 inhabitants, based on the 2001 Canadian Census population (21); and 2) distance to the nearest hospital with c-section capacity (<50km, 50-150km, and >150km). We used Geographic Information System (ArcGIS version 9.0) to calculate the distance from residence to hospital. The GIS software enabled us to map the shortest

'crow-fly' (straight line) distance between postal codes of maternal residences and postal codes of hospitals with c-section capacity. Postal codes were localized on maps by their central points' latitude and longitude (10). The distances between residences and hospitals were then manually measured using highway maps. Where applicable, the distances were recalculated to represent longer actual road distances, resulting from geographical barriers, such as mountains, inlets, rivers, etc.

The outcomes of interest included labour induction, c-section, and adverse birth outcomes. Labour induction was defined as use of medical (oxytocin or prostaglandin) or surgical means to induce labour prior to the spontaneous onset of labour. C-section rates were reported as: a) primary c-section rate; b) repeat c-section rate; and c) the proportion of emergency c-sections (those not scheduled or otherwise planned) among all caesarean births. Adverse birth outcomes included stillbirth (death in-utero at 20 weeks of gestation or later), perinatal death (stillbirth or death within the first 28 days of life), preterm birth (<37 weeks), small-for-gestational-age (SGA, <10<sup>th</sup> percentile), large-forgestational-age (LGA, >90<sup>th</sup> percentile), and neonatal intensive care unit (NICU) admission for more than 1 day. Gestational age was assessed by last menstrual period (LMP). In cases where the LMP estimate showed a discrepancy of more than 2 weeks in comparison with the first trimester ultrasound, the ultrasound estimate was used (11). SGA and LGA infants were those with birthweight  $<10^{th}$  and  $>90^{th}$  percentile of a standard Canadian male and female birthweight distribution (12). NICU admission was defined as any admission to NICU providing high-dependency neonatal care, such as infusion administration, total parenteral nutrition, or mechanical ventilation (13).

Admissions for less than 1 day were not considered since they represent transitory problems or newborn monitoring.

Specific demographic, behavioural and life-style factors were assessed for their role as confounders. They included parity (primiparae versus multiparae), single mother (yes/no), smoking during pregnancy (yes/no), alcohol and drug use during pregnancy (yes/no), suboptimal prenatal care (<4 visits versus 4+), prior induced abortions (yes/no), prior spontaneous abortions (yes/no), any congenital anomaly (ICD9 codes 740-759, yes/ no), infant's sex, low-income neighborhood (postal code area with median income within the lowest quintile in BC) (10), and Aboriginal status (Registered Indian Status as defined by the Indian Act) (14).

Information about maternal age, birth outcomes, and potential confounders were retrieved from the BC Perinatal Health Program (BCPHP) birth registry. This registry captures all births in the province of BC (about 40,000 births per year). These data are abstracted from hospital charts after discharge by trained health records staff according to standardized protocols. The database includes information about the mode of delivery, type of c-section, prenatal care, prior obstetric history (such as prior spontaneous and induced abortions) and behavioural factors such as smoking, alcohol and drug use. Vital statistics data, including neonatal deaths, are linked to the BCPHP registry.

#### Data analysis

Demographic and lifestyle factors were compared between the cohorts of mothers (rural versus urban areas) using the chi-square test. Relative risks (RR) and 95% confidence intervals (CI) were calculated for each outcome.

We undertook a multivariate analysis using logistic regression to further evaluate associations for which significant differences were found in univariate analysis. A stepwise backward process was used to eliminate non-significant confounders, however, if a confounder's removal changed the estimated OR of the exposure by 10% or more, the confounder was kept in the model (15). Parity and rural residence were tested as interaction terms in regression models.

Rates of all birth outcomes were calculated for each distance category (<50, 50-150, and >150km) that was analyzed as a scale variable. Statistical significance was assessed by the Cochran-Armitage test for trend. Adjusted P-values for trend were obtained using logistic regression.

The overall goodness-of-fit of all models was assessed by the Hosmer-Lemeshow test (15). All analyses were carried using the SAS statistical package, version 9.1.3. Ethics approval was obtained form the University of British Columbia Behavioral Research Ethics Board.

### Results

The study population included 29,698 women 35 years of age or older who delivered a singleton stillborn or live infant in BC during 1999-2003 (after exclusion of 492 women due to missing postal codes). Of these, 11.5% (3,404 mothers) lived in rural areas. (Table 4.1) Rural mothers were more likely to be multiparae, to smoke and drink alcohol during pregnancy, to have had a prior low birthweight or premature birth, a prior spontaneous abortion, to live in low-income neighbourhoods, and to be Aboriginal.. As expected, rural mothers were also more likely to live more than 50km from the nearest hospital with c-section capacity, and more likely to have a mode of transportation to the

nearest hospital other than car (such as ferry or air transport). In addition, older rural mothers were more likely to have suboptimal prenatal care (<4 visits), and they were less likely to have had prior induced abortions, compared to urban mothers. The median age of older mothers in both urban and rural settings was 37 years.

## Analysis by rural residence

Rates of labour induction were similar between rural and urban mothers, however, among multiparae, the rates of labour induction were slightly higher. (Table 4.2) The rates of c-section (overall, primary, and repeat c-section) were significantly lower among rural versus urban women. These lower rates were found among multiparae, no association was seen among primiparae. The adjusted odds ratio of csection in rural compared to urban women was 0.85 (CI: 0.79-0.91). Effect modification by parity was not statistically significant. The proportion of emergency c-sections was similar in both groups, regardless of parity.

Older women in rural areas were at higher risk of stillbirth and perinatal death compared to urban women. However, this association was only seen in multiparae. (Table 4.3) The overall adjusted ORs were marginally statistically significant (stillbirth adjOR 1.50, CI: 0.97-2.30; perinatal death adjOR 1.47, CI: 1.01-2.14). Rural newborns were significantly less likely to be SGA, and more likely to be LGA, which was again apparent only among multiparae. No differences in preterm birth and NICU admissions were found; the length of stay at NICU was not significantly different (median 8 versus 6 days). The interaction term for parity and residence was not statistically significant in multivariate analysis of any of the above mentioned associations.

Analysis by distance to the nearest hospital with c-section capacity

Among all older mothers in BC, 27,836 (93.7%) lived <50km from the nearest hospital with c-section capacity, 1534 mothers (5.2%) lived in areas 50-150km from the hospital, and 328 (1.1%) lived >150km. (Table 4.4) The overall odds of having a csection decreased as distance increased (borderline statistically significant trend p=0.06). The rates of stillbirth were higher among mothers living 50-150km and >150km versus those living <50km from the hospital, however no significant trend was found after adjustment for confounding. As the distance increased, the risk of perinatal death increased (adjOR=1.53; CI: 1.10-2.12 per distance category). Rates of labour induction, primary and repeat c-section, emergency c-section, preterm birth, SGA, LGA, and NICU admission did not show significant differences by distance.

#### Discussion

The results of this population-based retrospective cohort study of older mothers revealed that women living in rural areas had a higher risk of perinatal death, which increased significantly as the distance from the hospital with c-section capacity increased. Further, rural older multiparae were less likely to give birth by c-section. Among women with prior caesarean birth, rural mothers were more likely to deliver vaginally.

To date, obstetric interventions or birth outcomes in older mothers in rural versus urban areas have not been studied. Previous research has focussed on comparing birth outcomes between rural and urban hospitals, evaluating hospital size, delivery volume, csection capacity, and physician's specialty (6, 7, 16-18). Studies evaluating the relationship between rural residence and adverse birth outcomes regardless of a final place of delivery are scarce. Black and Fyfe showed that with appropriate management and referral of high-risk women, the birth outcomes in a small rural community in

Ontario, Canada in 1984 did not differ from urban births (16). Similarly, Larson et al. found that rural residence was not independently associated with adverse birth outcomes including neonatal death and low birthweight. Adjustment for pregnancy complications, however, might have obscured the association, as complications can arise as a result of delayed access to care (5). Further, both studies examined rural mothers in general, which might not have revealed elevated risks among different age groups. Moreover, both studies were conducted in mid-late 1980s, thus do not reflect current advances in obstetric and neonatal care, as well as organization of care, that potentially increase the disparity between high-risk parturients with immediate versus delayed access to advanced care.

Our findings address several aspects of rural obstetric care. The unadjusted rates of labour induction were higher among rural than urban multiparae. It is possible that in the settings where women have to leave their communities to give birth, elective labour inductions may be done in order to reduce women's waiting time away from home (19). This is particularly relevant to multiparae, who are concerned about making childcare arrangements (20). In our study, inductions for logistical reasons, such as these, were more common among rural compared to urban multiparae (2.5% vs. 1%, p-value<0.001, data not shown).

In BC, about 11% of older mothers live in rural areas. Births to older mothers represent approximately 17% of all rural singleton deliveries (data not shown). Our findings of higher risk of stillbirth and perinatal death, accompanied by lower rates of csection among rural older women (particularly multiparae), could indicate geographical barriers to appropriate obstetric care. Recent findings of a qualitative study conducted

among rural mothers in BC have described concerns about relocating to await birth, including possible travel disruptions due to weather conditions, and additional financial burden. In this regard, multiparae expressed more concerns (20, 21). These issues may delay travel to receive referral obstetric care in the event of pregnancy complications, potential or actual.

The observed differences in perinatal mortality in our study, however, were not accompanied by higher rates of preterm birth (which increases the risk of death due to prematurity), suggesting a different pattern of causes of perinatal death between rural and urban mothers. The risk of SGA was lower, whereas the risk of LGA was significantly higher among rural newborns, indicating different rural/urban birthweight distributions. This is in agreement with a similar observation from US, showing approximately 30% of rural newborns to be LGA (versus 10% of US newborn population) (22). In BC, infants of Chinese and South Asian descent were found to have significantly lower birthweight compared to infants of European descent (23), thus a different ethnicity mix in rural and urban areas might have contributed to our findings regarding SGA and LGA, as the majority of Chinese/South Asian immigrants live in urban areas (24). In addition, rural areas had a larger proportion of Aboriginal women, who tend to have heavier newborns (25). Elevated risk of perinatal death among rural newborns was not mirrored by an elevated risk of NICU admission, possibly suggesting limited access to advanced neonatal care.

Timely medically indicated obstetric interventions (labour induction or c-section) have been a cornerstone of modern obstetrics and contributed to a downward temporal trend in stillbirth and perinatal mortality (26, 27). However, our research suggests that

rural older mothers might not have experienced the same benefit as their counterparts in urban settings.

Limitations of our study include the inability to adjust for confounders such as maternal education, body mass index, assisted reproduction therapy, short interval between births (in multiparae), stress, presence or lack of family support, nutrition, and environmental factors. However, most of these confounders are known to be correlated with socioeconomic status and lifestyle factors that we did adjust for, thus the impact on our findings is likely small.

In summary, our study suggests that older mothers in rural or distant areas may be at elevated risk of perinatal mortality. Further research is urgently needed to explore how rural residence influences birth outcomes in older mothers. As older mothers are at elevated risk for pregnancy complications and obstetric intervention, it is important assure adequate access to appropriate obstetric care.

Residence		rural	urban	
Total		N=3404	N=26294	p-value
Parity Para 1 (primipara)		847 (24.93)	7926 (30.15)	< 0.0001
Para 2-3		1792 (52.75)	15668 (59.60)	
Para 4+		758 (22.31)	2704 (10.29)	
Single parent		121 (3.78)	836 (3.29)	0.149
Suboptimal prenatal care (<4 visits)		123 (3.86)	600 (2.41)	< 0.0001
Smoking during pregnancy		399 (11.72)	1790 (6.81)	< 0.0001
Alcohol use during pregnancy		50 (1.47)	217 (0.83)	< 0.0001
Drug use during pregnancy		43 (1.26)	279 (1.06)	0.284
Prior stillbirth or neonatal death		78 (2.29)	524 (1.99)	0.245
Prior low birthweight or premature birth		276 (8.11)	1835 (6.98)	0.016
Prior induced abortions (any)		603 (17.89)	5215 (19.98)	0.004
Prior spontaneous abortion (any)		1244 (36.90)	7938 (30.41)	< 0.0001
Distance to the nearest hospital >5	0km	2482 (72.91)	25354 (96.43)	< 0.0001
50	-150km	736 (21.62)	798 (3.03)	
15	0+km	186 (5.46)	0 (0.00)	
Predominant mode of transport other	r than car	480 (14.10)	0 (0.00)	< 0.0001
Low SES neighbourhood area *		770 (22.62)	3615 (13.75)	< 0.0001
Aboriginal status		254 (7.47)	527 (2.01)	< 0.0001
Any congenital anomaly (ICD9 740-	-759)	196 (5.76)	1530 (5.82)	0.886
Newborn's male gender		1751 (51.47)	13548 (51.53)	0.948

Table 4.1: Older mothers (35+ years) and singleton newborn characteristics by rural/urban residence; BC, 1999-2003; N (%)

\* lowest quintile of BC median income per postal code

Dosidonoo		rural	urban	DD (CI)	
Residence		rurai	urban		
Labour induction	all women	759 (22.30)	5531 (21.04)	1.07 (0.99-1.15)	
	primiparae	249 (29.40)	2343 (29.56)	0.99 (0.86-1.14)	
	multiparae	509 (19.96)	3188 (17.36)	1.16 (1.06-1.27)	
C-section	all women	991 (29.11)	8666 (32.96)	0.85 (0.79-0.91)	0.84 (0.78-0.91)
	primiparae	356 (42.03)	3333 (42.05)	1.00 (0.88-1.14)	
	multiparae	633 (24.82)	5333 (29.04)	0.83 (0.76-0.90)	
Primary c-section	all women	528/2756 (19.16)	4709/21190 (22.22)	0.85 (0.77-0.93)	0.89 (0.80-1.00)
	primiparae	356/847 (42.03)	3333/7926 (42.05)	1.00 (0.88-1.14)	
	multiparae	172/1909 (9.01)	1376/13264 (10.37)	0.87 (0.75-1.01)	
Repeat c-section	multiparae (prior c-section)	382/638 (59.87)	3402/5075 (67.03)	0.76 (0.66-0.88)	0.75 (0.63-0.88)
Emergency c-section	all women with c-section	559/991 (56.41)	5129/8666 (59.19)	0.90 (0.80-1.02)	
	primiparae with c-section	298/356 (83.71)	2795/3333 (83.86)	0.99 (0.76-1.29)	
	multiparae with c-section	259/633 (40.92)	2334/5333 (43.77)	0.90 (0.78-1.05)	

Table 4.2: Obstetric interventions among older mothers (35+ years) with singletons, by residence and parity; BC, 1999-2003

\* adjusted for parity, single parent, low-income neighbourhood, aboriginal status, smoking, alcohol, drug use during pregnancy, congenital anomalies, previous spontaneous abortions, induced abortions, male gender, suboptimal prenatal care

Residence/parity		rural	urban	RR (CI)	AdjOR* (CI)
Stillbirth	all women	27 (0.79)	141 (0.45)	1.48 (1.02-2.22)	1.51 (0.97-2.35)
	primiparae	5 (0.59)	49 (0.62)	0.96 (0.41-2.21)	
	multiparae	21 (0.82)	92 (0.52)	1.53 (1.04-2.25)	
Perinatal death	all women	40 (1.18)	208 (0.79)	1.48 (1.06-2.08)	1.47 (1.01-2.14)
	primiparae	7 (0.83)	76 (0.96)	0.87 (0.43-1.78)	
	multiparae	32 (1.25)	132 (0.72)	1.61 (1.18-2.20)	
Preterm birth < 38 weeks	all women	573 (17.00)	4619 (17.68)	0.96 (0.88-1.04)	
	primiparae	157 (18.67)	1424 (18.11)	1.03 (0.88-1.22)	
	multiparae	415 (16.45)	3194 (17.50)	0.94 (0.85-1.03)	
SGA (<10th percentile)	all women	194 (5.76)	1748 (6.69)	0.87 (0.76-0.99)	0.83 (0.71-0.98)
	primiparae	85 (10.11)	815 (10.37)	0.97 (0.79-1.21)	
	multiparae	108 (4.28)	932 (5.11)	0.85 (0.71-1.02)	
LGA (>90th percentile)	all women	568 (16.86)	3900 (14.93)	1.14 (1.04-1.24)	1.13 (1.02-1.25)
	primiparae	74 (8.80)	735 (9.35)	0.94 (0.75-1.18)	
	multiparae	494 (19.60)	3165 (17.34)	1.14 (1.03-1.25)	
NICU admissions > 1 day**	all women	82/1769 (4.64)	646/13472 (4.80)	0.97 (0.78-1.19)	
	primiparae	26/447 (5.82)	252/4048 (6.23)	0.94 (0.64-1.37)	
	multiparae	55/1320 (4.17)	394/9421 (4.18)	1.00 (0.77-1.28)	

Table 4.3: Adverse singleton birth outcomes among older mothers (35+years) by residence and parity; BC, 1999-2003; N (%); relative risk (RR); adjusted odds-ratio (AdjOR); 95% confidence intervals (CI)

\* adjusted for parity, single parent, low-income neighbourhood, aboriginal status, smoking, alcohol, drug use during pregnancy, congenital anomalies, previous spontaneous abortions, induced abortions, male gender, suboptimal prenatal care \*\* based on years 2001-2003

Distance	<50km	50-150km	150+km	p-value (trend)	adjusted p-value*
	N=27,836	N=1,534	N=328		
Labour induction	5908 (21.22)	313 (10.40)	69 (21.04)	0.7446	
C-section	9099 (32.69)	464 (30.25)	94 (28.66)	0.0132	0.0634
Primary c-section	4931/22433 (21.98)	253/1238 (20.44)	53/275 (19.27)	0.0988	0.8552
Repeat c-section	3574/5395 (66.25)	183/464 (62.24)	36/52 (69.23)	0.4406	
Emergency c-section	5378/9099 (59.11)	258/464 (55.60)	52/94 (55.32)	0.1125	
Stillbirth	150 (0.54)	15 (0.98)	3 (0.91)	0.0267	0.1048
Perinatal death	221 (0.79)	19 (1.24)	8 (2.44)	0.0004	0.0106
Preterm birth < 38 weeks	4984 (17.93)	261 (17.09)	59 (18.10)	0.5871	
SGA (<10th percentile)	1861 (6.70)	106 (6.96)	20 (6.13)	0.9894	
LGA (>90th percentile)	4202 (15.13)	218 (14.32)	66 (20.25)	0.2619	
NICU admissions > 1 day**	648/14333 (4.77)	32/815 (3.93)	12/177 (6.78)	0.9537	

Table 4.4: Adverse singleton birth outcomes among older mothers (35+ years) by distance to the nearest hospital with c-section capacity; BC, 1999-2003; N (%); P-value for trend

\* adjusted for parity, single parent, low-income neighbourhood, aboriginal status, smoking, alcohol, drug use during pregnancy,

congenital anomalies, previous spontaneous abortions, induced abortions, male gender, suboptimal prenatal care

\*\* based on years 2001-2003

# References

- 1. Indian and Northern Affairs Canada, aboriginal people and communities. http://www.ainc-inac.gc.ca/ap/tln-eng.asp accessed December 2008.
- 2. The Characteristics of the Migration Flow for B.C.'s Census Metropolitan Area. 2007. Migration Special Feature Article, BC Statistics, 2007.
- 3. Astolfi P, Zonta LA. Risks of preterm delivery and association with maternal age, birth order, and fetal gender. Hum.Reprod. 1999;14:2891-4.
- 4. Black DP, Fyfe IM. The safety of obstetric services in small communities in northern Ontario. Can.Med.Assoc.J. 1984;130:571-6.
- 5. Chaska BW et al. Influence of site of obstetric care and delivery on pregnancy management and outcome. J.Am.Board Fam.Pract. 1988;1:152-63.
- 6. Cnattingius S et al. Delayed childbearing and risk of adverse perinatal outcome. A population-based study. JAMA 1992;268:886-90.
- 7. Grzybowski SC, Cadesky AS, Hogg WE. Rural obstetrics: a 5-year prospective study of the outcomes of all pregnancies in a remote northern community. CMAJ. 1991;144:987-94.
- 8. Hosmer DH, Lemeshow S. Applied logistic regression. 2nd. 2000. John Wiley & Sons, Inc.
- 9. Janssen PA et al. Standards for the measurement of birth weight, length and head cisrcumference at term in neonates of European, chinese and South Asian ancestry. Open Medicine [1(2)], e74-e88. 2007.
- 10. Jolly M et al. The risks associated with pregnancy in women aged 35 years or older. Hum.Reprod. 2000;15:2433-7.
- 11. Joseph KS et al. The perinatal effects of delayed childbearing. Obstet.Gynecol. 2005;105:1410-8.
- 12. Kireans W et al. Charting birth outcome in British Columbia: determinants of optimal health and ultimate risk an expansion and update. 2003. BC Ministry of Health, Division of Vital Statistics.
- 13. Klein MC et al. Does delivery volume of family physicians predict maternal and newborn outcome? CMAJ. 2002;166:1257-63.
- 14. Kornelsen J, Grzybowski S. The reality of resistance: the experiences of rural parturient women. J.Midwifery Womens Health 2006;51:260-5.

- 15. Kornelsen J, Moola S, Grzybowski S. Geographic induction of rural parturient women: is it time for a protocol? J.Obstet.Gynaecol.Can. 2007;29:583-5.
- 16. Kramer MS et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 2001;108:E35.
- 17. Larson EH, Hart LG, Rosenblatt RA. Rural residence and poor birth outcome in Washington state. J.Rural.Health 1992;8:162-70.
- Lee Shoo K. Levels of neonatal care. Paediatrics & Child Care 11[5], 303-306. 2006.
- Rosenthal TC, Holden DM, Woodward W. Primary care obstetrics in rural western New York. A multi-center case review. N.Y.State J.Med. 1990;90:537-40.
- 20. Schempf AH et al. Maternal age and parity-associated risks of preterm birth: differences by race/ethnicity. Paediatr.Perinat.Epidemiol. 2007;21:34-43.
- 21. Statistics Canada. Postal code conversion file (PDDF), reference guide. 2004. Catalogue no. 92F0153GIE.
- 22. Storms MR, Van Howe RS. Birthweight by gestational age and sex at a rural referral center. J.Perinatol. 2004;24:236-40.
- 23. Synnes AR et al. Perinatal outcomes of a large cohort of extremely low gestational age infants (twenty-three to twenty-eight completed weeks of gestation). J.Pediatr. 1994;125:952-60.
- 24. Tough SC et al. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. Pediatrics 2002;109:399-403.
- 25. Joseph KS, Demissie K, Kramer MS. Obstetric intervention, stillbirth, and preterm birth. Semin Perinatol 2002; 26(4):250-259.

# **CHAPTER 5**

# CONCLUSION

This chapter summarizes findings from Chapters 2 to 4, explains how they relate to each other, discusses the results and limitations, and describes the implications of the results in the context of current literature.

## **Overview of the findings**

This thesis consists of three separate population-based studies of birth outcomes among older mothers. Data from the BC Perinatal Database Registry was used to examine the risk of stillbirth, neonatal death, perinatal death, preterm birth, small-forgestational-age (SGA) status, large-for-gestational-age (LGA) status, and neonatal intensive care unit (NICU) admission among older mothers.

Chapters 2 and 3 compare adverse birth outcomes in younger and older mothers with singleton (Chapter 2) and twin pregnancies (Chapter 3).

Chapter 4 focuses exclusively on older mothers and examines the risk of adverse birth outcomes for older mothers living in rural settings in comparison to urban settings.

The results presented in Chapter 2 indicate that older mothers (35-39 and 40+ years of age) with singleton pregnancies were at an elevated risk of stillbirth, preterm birth, SGA, and NICU admission for more than 1 day, as compared to younger mothers (20-29 years of age). There were significant differences in the risk of preterm birth and SGA between primiparae and multiparae. Older primiparae (35-39 and 40+ year olds) had a higher rate of preterm births (adjOR=1.5, CI: 1.4-1.7; adjOR=1.6, CI: 1.3-2.0)

compared to younger primiparae; but the effect of maternal age was weaker among multiparae (adjOR=1.1, CI: 1.1-1.4; adjOR=1.3, CI: 1.1-1.7). The association between maternal age and SGA was apparent only among primiparae, ages 35-39 and 40+ compared to 20-29 year olds (adjOR=1.2, CI: 1.1-1.4; and adjOR=1.4, CI: 1.1-17). These results were adjusted for marital status, low-income neighbourhood, low attendance at prenatal care, smoking during pregnancy, alcohol and drug use during pregnancy, prior spontaneous and induced abortions, and infant's gender. Additional analyses adjusting for congenital anomalies in the current pregnancy, pre-pregnancy weight, and prior perinatal death or preterm birth yielded similar results to our original analyses.

Our analysis of gestational-age-specific perinatal mortality, based on the fetusesat-risk method of risk assessment, confirmed that the incidence-density or risk-ratio of perinatal mortality (approximated by a short-interval cumulative incidence) changes during the course of pregnancy. The immediate risk of delivering a baby that dies (either *in utero* or within 7 days of life) remained low (less than 20 per 10,000 ongoing singleton pregnancies) until term, and then, at post-term (>41 weeks), gradually increased to 120/10,000 among older primiparae (35+ years), 57/10,000 among older multiparae, and 40/10,000 for younger multiparae (25-29 years).

Our study is the first to identify the parity differences in the post-term gestationalage-specific perinatal mortality rates. This study also contributes to the literature by pointing out the differential effect of parity in the association between maternal age and preterm birth or SGA.

Although we found a higher incidence of adverse birth outcomes among older mothers with singleton pregnancies, the results of our twin study showed no association between maternal age and perinatal death, very preterm birth, or SGA, regardless of parity. We observed a significant differential effect of parity on the association between maternal age and NICU admission (13 days or more) and a combined outcome including perinatal death and /or prolonged NICU hospitalization (13 days or more): twins of older vs. younger primiparae had no elevated risk, whereas twins of older vs. younger multiparae had an elevated risk of these outcomes.

The most commonly cited reason for a lack of the association between maternal age and birth outcomes among twins is the effect of assisted reproductive techniques (ART). Older women, especially nulliparae, are more likely to use ART compared to younger women. The confounding effect of ART may be due to the differences in chorionicity between ART-conceived twins (predominantly dichorionic) and spontaneously conceived twins (mono- or dichorionic) (1). The differences in chorionicity may result in more favourable birth outcomes in ART-conceived twins, as dichorionic twins are less likely to experience serious complications, such as twin-to-twin transfusion syndrome. However, when the analysis was restricted to opposite-sex twins, that are always dichorionic, the results revealed even lower risk of adverse birth outcomes among older compared to younger mothers, demonstrating that chorionicity is not likely to explain the lack of elevated risks of adverse birth outcomes among twins born to older mothers.

The study presented in Chapter 4 compared older mothers (35+ years) residing in rural and urban areas. Place of residence has not been previously studied as a

determinant of pregnancy outcomes among older mothers. The results revealed that older mothers living in rural areas had lower rates of primary and repeat c-sections, but higher rates of perinatal death and LGA, compared to mothers living in urban areas. These differences were evident primarily among multiparae. In addition, the rates of c-section declined, while the rates of perinatal death increased, as the distance from the maternal residence to the nearest hospital with c-section capacity increased. These findings may suggest a potential geographical barrier to advanced obstetric care among rural mothers.

#### **Discussion of results**

### Chapter 2 and 3

The strengths of the studies presented in Chapter 2 and 3 include the cohort design and population-based data source. The advantage of a cohort study is that the incidence rates of outcomes of interest can be directly calculated. These incidence rates represent an average probability of a given outcome (absolute risk). Both studies were population-based and included all singletons or twins in the province of British Columbia (1999-2003), who were delivered by a physician or a certified midwife in a hospital or at home (2). Births attended by lay midwives were not captured in our study (estimated less than 0.1% of all births) (3). The quality of data collected in the BC Perinatal Database Registry is maintained by use of standardized reporting forms, data entry software programs with built-in error warnings, abstraction verification, and periodic reports that include consistency checks (4).

There were several limitations to the singleton and twin studies, besides those already mentioned in Chapter 2 and 3.

Our ability to adjust for a correlation between repeated births (when a woman had two or more births during the study period) was limited. Additional analyses, revealed that adjustment for previous adverse birth outcomes yielded similar results, as compared to our original analyses. In these additional analyses, we treated variables 'previous low birthweight or preterm birth' and 'previous stillbirth or neonatal death' as confounders, since they were associated with both, maternal age and a subsequent adverse birth outcome. However, clustering caused by repeated pregnancy is a complicated statistical issue (7). There is no guarantee that this approach accounted for all the correlation between repeated pregnancy outcomes in our study.

Behavioral, lifestyle, and demographic factors that were adjusted for in multivariable analyses were subject to a measurement error. Misclassification of a confounder can result in a bias in logistic coefficient estimate of the effect of exposure (29). The degree of this bias depends on a magnitude of correlation between the confounder and the exposure as well as the imprecision of the confounder and exposure variable measurements (29). Unfortunately, given the dataset we had to work with (the BCPHP perinatal data) we cannot determine the precision (or imprecision) of the variables it contains. Thus it was not possible to correct for any potential misclassification of confounders.

Further, preterm birth has been included among adverse birth outcomes. From a clinical point of view, preterm birth can be spontaneous (due to idiopathic preterm labour), or iatrogenic (as a result of labour induction or c-section due to a maternal or fetal condition). We have not made a distinction between these two, as both can be considered as intermediate factors (on a causal pathway) in the association between
maternal age and preterm birth. However, early delivery can prevent imminent fetal death or fetal hypoxia (6). In these cases, preterm delivery (especially near term at 35-36 weeks) would not be considered as an adverse outcome from a clinical point of view.

## Singleton and Twin Study Comparisons

Singleton and twin pregnancies need to be studied separately (Chapter 2 vs. Chapter 3), because the risk of complications and the clinical management of pregnancy and labour differ widely between multiple and singleton pregnancies. The mean gestational age at birth is lower among twins compared to singletons (35.6 versus 39.0 weeks). Consequently, the rates of preterm birth, very preterm birth, and low birthweight are higher among twins compared to singletons (54.3% vs. 9.7%, 14.7 vs. 1.8%, and 53.7% vs. 6.1%, respectively. Approximately 35% of twins are small-for-gestational-age at birth, according to singleton standards (singleton standard birthweight distribution) (1). Not surprisingly, the differences in neonatal and infant mortality are also larger (25.6 vs. 4.0 per 1000 live births, and 31.1 vs. 2.6 per 1000 live births, respectively) (1;8). Similarly, pregnancy complications (including preeclampsia, eclampsia, gestational diabetes, and premature rupture of membranes) and obstetric interventions (including Csection, labour induction, tocolysis, excessive bleeding during labour and delivery) are more common in twins compared to singletons (8).

To accommodate these differences in our twin study (Chapter 3), we modified the definition of adverse birth outcomes from our previous study of singletons (Chapter 2). These choices aimed to identify a relatively small percentage of twins who were at the

highest risk of immediate complications, such as bronchopulmonary dysplasia, retinopathy of prematurity, or intraventricular hemorrhage, and long-term health sequelae, such as cerebral palsy. We used very preterm birth (< 33 weeks) in twins, as opposed to preterm birth (<37 weeks) in singletons, to identify very premature twins. SGA was defined using standard twin birthweights to identify twin babies that are small relative to the twin, rather than singleton, population.

Currently, no consensus exists regarding which standard should be used to assess SGA among newborn twins. In our opinion, the use of singleton standards to identify SGA twins in epidemiological studies is flawed and likely introduces a bias. The twin and singleton standard birthweights are similar and increase in a similar manner as gestational age increases until approximately 33 weeks of gestation, at which point the singleton weights begin to increase at a higher rate compared to twins (9). Thus the frequency of SGA twins increases gradually after 33 weeks when singleton standard weights are applied. Due to this gradual increase, a cohort of twins that have on average lower gestational age would have more favourable outcomes in terms of SGA, as compared to a cohort of twins born at later gestational ages. The differences in gestational age thus bias the SGA results, when singleton birthweight standards are applied to twins, and the SGA is compared between two groups of infants. However, the use of singleton birthweight standard in twins may be useful, from a clinical point of view, to identify compromised newborns.

The reference maternal age group (25-34 years of age) differed from the study concerning singletons (20-29 years of age), as mothers aged less than 25 years are known to have suboptimal twin pregnancy outcomes, compared to 25-34 year old mothers (8).

Further, we used "NICU admission for more than 1 day" to identify newborns with medical problems in our singleton study (Chapter 2). However, NICU admissions lasting a few days may still include newborns with minor or transitory medical conditions. In the twin study (Chapter 3), we used a prolonged NICU stay (13 days or more) to better differentiate between newborns with transitory and serious medical conditions. The 13 days cut-off point corresponds to the median NICU stay based on our data (after exclusion of newborns admitted for < 1 day), and based on statistics from other Canadian NICUs (10).

The results indicated that relative risk of NICU hospitalization for 13 days or more was RR=0.81 (CI: 0.61-1.09) among primiparae; and RR=1.26 (CI: 1.02-1.56) among multiparae. Similarly, the risk of perinatal death and/or NICU stay for 13 or more days was lower among twins born to older vs. younger primiparae (RR=0.74, CI: 0.55-0.97); and higher among twins of older multiparae (RR=1.23, CI: 1.01-1.50). The reasons for this discrepancy are not clear. Some studies have implied that the highest probability of survival among twins is at 37-38 weeks of gestational age at birth (11). Among younger primiparae in our study, a significantly higher proportion of birth (27.3%) was outside the range 35-38 weeks, as compared to older primiparae (21.4%), pvalue=0.01. This higher dispersion of gestational ages at birth among younger primiparae may be responsible for the observed suboptimal outcomes; and indirectly result in relatively better outcomes among older primiparae.

# Discussion – Chapter 4

Our findings of an elevated risk of perinatal mortality among older mothers in rural vs. urban areas deserve further discussion. Two issues related to access to obstetric

care emerge: a) the availability and performance of BC rural hospitals without c-section capacity; and b) the availability and logistics of transport of pregnant women to a hospital with a higher level of acuity prior to the development of complications (of pregnancy or delivery). Maternal chronic morbidity and other obstetric risk factors (for example obesity) are likely to be more prevalent among older mothers in rural vs. urban areas. However, if maternal morbidity and other clinical risk factors were more prevalent among rural mothers, higher rates of obstetric interventions, including c-sections, would have been expected among these mothers, providing that adequate access was in place. In contrast, we observed lower rates among rural vs. urban mothers in our study.

Timely medically indicated obstetric interventions (as mentioned earlier) have contributed to a downward temporal trend in stillbirth rate and perinatal mortality (12). The decision and timing of a medically indicated c-section depends on the availability of advanced neonatal care that can manage the newborn's prematurity and its sequelae. It is possible that rural mothers have not benefited from this trend in obstetric practice to the same degree as urban mothers due to the rural vs. urban differences in the availability of such care.

### Implications of thesis findings

This thesis adds to our knowledge of adverse birth outcomes among older mothers. These findings are related to several public health issues. These need to be interpreted within a context of current medical literature related to reproduction at older maternal age.

# Individual level risk

Women and their partners need to weigh advantages and disadvantages of delayed childbearing when planning a family. While they should be aware of the risks of adverse birth outcomes associated with advanced maternal age, our study and other research show that the absolute risks are small in magnitude and that overall rates of adverse birth outcomes are low. For example, stillbirth is a very rare event (0.43% of total births among 20-29 year olds) and even though the relative risk is significantly higher among older women (RR=1.2), the probability of experiencing fetal death is still very low (0.55% of total births among women 30-35 and 0.62% for women 40+ years of age).

Our study indicates that the absolute risk of a preterm birth increases only moderately as maternal age advances. Women 20-29 years old, regardless of parity, have about a 6% risk of delivering a baby preterm and there is a 6-9% risk of preterm birth among both groups of older multiparae (ages 35-39 and 40+). However, for older primiparous women the risk of preterm birth is 10.5%.

In this thesis, we examined an *average* risk of adverse birth outcomes in the BC population of pregnant women of different age groups. However, to advise women about their *individual* risk, the effect of maternal age should be assessed in the context of other risk factors contributing to adverse birth outcomes.

Joseph et al. developed a scoring system for singleton pregnancies that translates the effect of all major risk factors for perinatal death (excluding congenital anomalies) into the absolute rates of perinatal mortality/morbidity (per 1000 total births) (13). The scoring system includes maternal age, parity, pre-pregnancy weight, smoking status, prior perinatal death, and prior low birthweight baby. As the overall score increases, the perinatal mortality rate increases exponentially. Thus, the effect of maternal age is

relatively small when none of the other risk factors are present but relatively large when there are concurrent risk factors. This scoring system better reflects the individual chance of perinatal death (and/or major perinatal morbidity).

The absolute risk of adverse birth outcomes in twins is much higher compared to singleton pregnancies. For older mothers the average risk of perinatal death for one twin is 40 per 1000 twin babies and the average risk of very preterm birth is 110 per 1000 twins compared to 7.5 and 1.3 per 1000 singletons, respectively (reported in Chapters 2 and 3). This represents approximately a fourfold higher risk of perinatal death among twins compared to singletons of older mothers (35+ years). Women planning to delay pregnancy cannot predict whether they will conceive a singleton or twins, unless ART is involved. A single embryo transfer and resulting singleton pregnancy represents lower obstetrical risks, as compared to multiple embryo transfer that more likely leads to a multiple pregnancy, when using assisted reproduction.

# Summary (individual level risk)

In summary, this thesis and other research indicate that, based on the maternal age alone, pregnancy after the age of 35 is safe for women who had no option of earlier childbearing. However, we cannot assess the risks of childbearing after the age of 45 due to a small number of these women in our study (75 women with singletons, 8 with twins) and the limited evidence available in medical literature.

In general, the "biological" disadvantage of older maternal age is, at least partially, offset by modern advances in obstetric, perinatal and neonatal care, as well as the higher socioeconomic status and education of older women (particularly primiparae).

However, women should bear in mind that the ability to conceive decreases exponentially after the age of 35 years. A singleton pregnancy should be a goal when ART is involved.

Older women living in rural or remote areas and their maternity care providers should evaluate the risk of pregnancy complications and estimate the impact of geographic barriers to advanced obstetric care that might become necessary. An appropriate delivery plan (including a choice of delivery hospital, transport options, etc.) should be in place in order to minimize potential adverse pregnancy outcomes.

# **Public health issues**

# Perinatal mortality

Even though the individual risks of adverse birth outcomes among older mothers are relatively small, the population-attributable risks (etiologic fractions) increase as the prevalence of older mothers in the parturient population increases. For example, between 1988 and 2002, perinatal mortality/morbidity attributable to maternal age groups 35-39 and 40+ years increased from 2.6 to 4.7%, and from 0.7 to 1.5%, respectively (data from Nova Scotia)<sup>5</sup> (13). This is important from a population health perspective, as rates of perinatal morbidity and mortality (as well as other adverse birth outcomes) attributable to advanced maternal age are likely to increase.

US data indicate that 5% of all live births to women 35-39 years old and 20% percent of births to women 40+ are twins, compared to 2% of births among younger women (20-25 years) (14;15). Our data revealed lower proportions of twins (3.4 and 4.1% compared to 2.4% for younger women), potentially due to different practices related to embryo transfer.

<sup>&</sup>lt;sup>5</sup> We could not calculate the population-attributable fraction to maternal age groups 35-39 and 40+ years from our data, since we did not examine the whole maternal age spectrum.

In our population of older mothers (35+ years), the perinatal mortality populationattributable risk of twins was 9.1%. In populations with a higher percentage of twins, the attributable risk (fraction) will be larger.

# NICU admissions

Our analyses of twin and singleton data for the period 1999-2003, together with other literature, indicate that newborns of older mothers are more likely to be admitted to NICU's than infants of younger mothers. The relative risk of NICU admission (>1 day) among singletons of older mothers was small (RR=1.2 for 35-39 year olds; RR=1.4 for 40+ year old women). The proportion of newborns to women 35 years of age or older has risen during the study period (1999-2003) from 22.8% to 26.1% of total births. Given the constant relative risks, the population-attributable risk will increase as the proportion of 'exposed' (i.e. older mothers) in the population increases.

Further, our data shows that approximately 30% of twins of older mothers were admitted to NICU for more than 1day and approximately 15% of twins stayed for 13 days or longer, contributing to high-acuity level health services resource utilization.

The costs associated with NICU admissions are noteworthy. The cost of NICU hospitalization can range from 854 to 2443 US\$ per day (USA, 1994) (16), and it is on average 10 times higher than care for a healthy newborn (17). The cost of a c-section delivery is CAD\$7,700 compared to CAD\$ 1,340-2,700 for a routine vaginal delivery (Canada, 2004) (17). Similarly, the demand for prenatal care, including screening for congenital anomalies, and related cost are higher among older mothers.

Healthcare costs for multiple pregnancies are several-fold higher. A US hospitalbased study of 13,206 pregnant women, 1986-91, indicated that hospital charges for twin births compared to singletons were approximately four times higher (18). The same study suggested that if all multiple gestations resulting from ART had been singleton pregnancies, savings to the health care system would have been over 3 million US dollars per year in the study hospital alone (18).

Health care planners should acknowledge that aging of the parturient population and the increased rate of twinning among older mothers represent a financial burden to the healthcare system. This cost will likely continue to rise. However, the increased rate of twinning among older mothers is largely due to ART and ovulation induction (1), and is, thus, modifiable by regulation of the number of implanted embryos.

#### Assisted reproduction

For the reasons noted above, a steep increase in rate of multiple births in developed countries is becoming a public health concern. It is estimated that 12-35% of multiples are conceived by ART (1, 18).

Reduction in the number of implanted embryos has been shown to improve birth outcomes, decrease health services utilization, and lower the cost of delivery and postpartum care (19). In Canada, an average 2.7 embryos are transferred per IVF cycle (20). Examples from Sweden and Finland suggest that a lower multiple birth rate is achievable through public health regulation limiting the number of embryos transferred during ART to a maximum of 2. However, the success of ART clinics in a competitive private-sector environment is measured by the pregnancy rate per treatment cycle. Thus, it is potentially difficult for ART clinics to address what is, in effect, a conflict of interest, between the short-term advantages of multiple-embryo transfer (higher chance of pregnancy, lower direct cost, and fewer treatment episodes) and long-term societal disadvantages (reflected in birth outcomes such as prematurity, high cost of hospitalization, and elevated mortality and morbidity). Current proposals to regulate the number of implanted embryos need to address the impact of policy changes, including adverse birth outcomes as well as pregnancy rates.

Awareness of the risks associated with twin birth is generally low among older women contemplating pregnancy (21). Since women are central to the decision-making process regarding ART regulation, educating the public, in general, and women, in particular, about these risks is important from a policy perspective.

# Public health issues relevant to rural obstetric care

The results presented in Chapter 4 should be interpreted in the context of BC rural maternity care. During our study period (1999-2003), approximately 17 small rural maternity care facilities were closed or placed under *moratoria*, due to funding cuts or lack of physicians available to deliver babies (22, 23). Between 2004 and 2005, a total of 2,806 women from rural BC gave birth in the referral centres, which represent 7.1% of all BC deliveries (24).

Regionalization of maternity care raises many clinical decision-making questions (23): "Is it safe to deliver low-risk rural mothers in their home communities with no c-section capacity?" "Assuming low-risk pregnancies, what are the minimum requirements for optimal care in these rural settings?" "What is the appropriate risk scoring and

decision algorithm for transfer to higher level of healthcare facility?" Some of these questions were addressed at a conference in Vancouver in 2000 (Consensus Conference on Obstetrical Services in Rural or Remote Communities) (23). For example, the conference supported continuation of essential services to childbearing women in BC, providing that: 1) proper disclosure is provided and informed consent is obtained to ensure that women delivering in rural hospitals are aware of services available; 2) system planning and co-ordination are in place to deal with transportation (including multidisciplinary teams involving referring physicians/midwives, higher level hospital physicians, and local transport advisors); 3) there is continued development and dissemination of clear clinical management guidelines; and 4) suitable facilities and equipment for the given level of care are ensured. Identification of healthcare providers' competencies, availability of consultation via phone and electronic links, and a continuing education program, are important to help rural physicians to provide adequate maternity care.

If indeed geographic barriers contribute to excess perinatal mortality in BC, it is not likely that a one-size-fits-all approach would solve the problem. Provision of maternity care has to be tailored to specific needs of individual geographic regions. For example, in regions that have a relatively large number of parturient women with difficult access to obstetric services, a healthcare facility providing these services should be considered. It has been shown that capacity for c-sections to be performed in rural settings is associated with a greater proportion of local deliveries and a lower rate of preterm deliveries (25). The cost-effectiveness of such a facility, however, also needs to be considered. A low volume of deliveries requiring high-level obstetric care may not

justify the expense to sustain year-round provision of such services. In many cases, however, the difficulty lies in the recruitment and retention of physicians and nurses competent to provide maternity services, including c-sections, in rural health care facilities and the challenge of maintaining the requisite skills and confidence levels in a low-volume obstetric practice (22). In regions where providing higher level maternity care is not sustainable, travel for intra-partum service will remain the only option, and thus planning for such transport becomes critical.

Previous qualitative research undertaken in BC has indicated that relocation from a resident community in preparation to giving birth is especially complicated for multiparae who have responsibilities for other children and who have previously delivered a baby and feel confident and familiar with the birthing process (26). These multiparae may be also at a higher risk of precipitous labour or experience an urgent need for obstetric services in case of complications. Families of these expectant mothers and newborns need extra support. It may be possible to alleviate the difficulties related to temporary relocation for childbirth or neonatal hospitalization, by helping to accommodate the needs of the family for housing, meals, or childcare. This strategy needs further evaluation.

Researchers specializing in rural maternity care suggest that resource constraints and policies requiring centralized service delivery are the major reasons for the diminishing access to maternity care among rural women (27). To improve this situation, all stakeholders need to be involved in rural maternity care policy decisions in order to balance the issues of access, quality, and cost control.

# **Further research**

This thesis has quantified the effect of older maternal age on adverse pregnancy outcomes, identified the differential effect of parity on some birth outcomes, and revealed the disparity in birth outcomes between rural and urban mothers, 35 years of age or older. However, a number of unanswered research questions remain.

Future research is needed to assess how delayed childbearing affects health services utilization and associated cost. Initially, this topic was to be included in this thesis, however, the acquisition of relevant data from the BC Ministry of Health was delayed. Nevertheless, we have recently obtained the data including maternal and infant hospitalizations and physician visits (during the time period before and after birth), which will allow us to examine the differences in health care utilization between younger and older mothers and their infants, to quantify the health care costs attributable to older maternal age and identify temporal trends. Further, we will have the opportunity to examine the patterns of health services utilization among older mothers in rural and urban areas, which can further elucidate the reasons behind the discrepant rates of perinatal mortality between rural and urban mothers. A validation study, currently planned by BCPHP, will quantify the accuracy of variables collected in the BCPHP database. The study will enhance the confidence in the data and improve future analyses, helping to eliminate (or quantify) some of the bias introduced by measurement imprecision.

It will be interesting to further examine costs associated with NICU admissions among newborns of older mothers. Zupancic et al. estimated that 16% of the newborns in the hospital studied underwent a NICU admission solely for a triage process or for minor medical conditions. The cost of such admissions accounted for 9.5% of the total NICU

cost (5). If infants of older mothers are more likely to be admitted to NICU for triage or minor conditions, these costs can be modified by changes in NICU structure or admission policy that would distinguish between low-risk patients and infants with serious medical conditions.

Further, more research is needed to examine the impact of ART on the rates of adverse birth outcomes, multiple pregnancy, and health services utilization. Reasons behind the differential effects of ART on singleton and multiple pregnancies have not been explained to date. Many unanswered questions exist about ovulation induction protocols, proper embryo handling, selection of the most viable embryos, the potential for congenital anomalies monozygotic splitting, and other aspects of ART.

Multiple births may be due to ovulation induction (OI) by fertility drugs such as clomiphene citrate or human menopausal gonadothropin, as described in Chapter I. In the USA (2000), it is estimated that 21% of twins and 40% of triplets were conceived by ovulation induction alone (1). According to the experts in the field of human reproduction, the contribution of OI to the multiple birth rate is increasing (1). However, little is known about the temporal changes in fertility drug use and the current impact of OI on pregnancy outcomes among older mothers.

In future research we propose to evaluate the trend in fertility drug use and its association with pregnancy outcomes such as multiple pregnancy, miscarriage, induced abortion, congenital anomalies, and preterm birth.

The contribution of IVF to multiple pregnancy rates may decline in the future, as regulations regarding the number of embryos transferred during IVF will likely be imposed in developed countries. Thus, OI alone has the potential to become a major

contributor to multiple pregnancies among older mothers in the future. Therefore, it is crucial to examine the prevalence of fertility drug use in the population and associated adverse birth outcomes.

Further, we plan to examine the relationship between rural residence and adverse birth outcomes among all parturient women in BC. Our research will also examine rural and urban differences in other perinatal health indicators, such as the underlying cause of death, gestational age distribution, and gestational-age-specific mortality. In addition, geographic-information-system analysis of perinatal mortality may reveal particular geographic clusters with excess mortality. Potential barriers to obstetric care services among rural older women need to be examined within a conceptual framework that includes a wide range of determinants that influence health service use (28).

In general, current research is limited in its ability to assess many complex aspects of reproduction simultaneously. Previous studies have focused on isolated solitary outcomes (such as conception, pregnancy complications, birth, or infant mortality). However, these events exist as points on a continuous reproductive trajectory, starting with the period prior to conception. Modern statistical methods of longitudinal data analyses can provide useful tools to model temporal sequences of these multiple events, as well as their determinants and consequences.

## Summary

This thesis quantifies the risk of adverse birth outcomes among older mothers with singleton and twin pregnancies. It contributes to current knowledge by the findings of the differential effect of parity on the association between maternal age and preterm

birth and SGA among singletons, and by examining these effects of parity on twin birth outcomes.

This is the first residence-based study comparing the obstetric interventions and adverse birth outcomes among older mothers living in rural and urban areas. Our findings of a lower c-section rate and a higher rate of perinatal mortality among older mothers in rural areas have not been reported to date.

# References

- 1. Blickstein I, Keith LG. Multiple pregnancy. 2nd edition. Taylor&Francis, 2005.
- Dale S, Miyazaki L, Pacheco T, Kilthei J. Midwifery in British Columbia. British Columbia Reproductive Care Program, editor. 2008. Ref Type: Report
- BC Vital Statistics Agency, BC Perinatal Health Program, BC Public Health Nursing Leaders Council. British Columbia Perinatal Data Set. 2007. Ref Type: Report
- 4. British Columbia Reproductive Care Program. British Columbia Perinatal Database Registry Overview. 2003
- 5. Zupancic JA, Richardson DK. Characterization of the triage process in neonatal intensive care. Pediatrics 1998; 102(6):1432-1436.
- 6. Joseph KS, Demissie K, Kramer MS. Obstetric intervention, stillbirth, and preterm birth. Semin Perinatol 2002; 26(4):250-259.
- 7. Louis GB, Dukic V, Heagerty PJ et al. Analysis of repeated pregnancy outcomes. Stat Methods Med Res 2006; 15(2):103-126.
- 8. Luke B, Brown MB. Contemporary risks of maternal morbidity and adverse outcomes with increasing maternal age and plurality. Fertil Steril 2007; 88(2):283-293.
- 9. Min SJ, Luke B, Gillespie B et al. Birthweight references for twins. Am J Obstet Gynecol 2000; 182(5):1250-1257.
- 10. McMillan, Lee KS, Chan HWP. Canadian NICU Network, 1996-1997; Volume I. 1999.
- 11. Blickstein I, Keith LG. Multiple pregnancy. 2nd edition. Taylor&Francis, 2005.
- 12. Joseph KS. Theory of obstetrics: an epidemiologic framework for justifying medically indicated early delivery. BMC Pregnancy Childbirth 2007; 7:4.
- 13. Joseph KS, Allen AC, Dodds L, Turner LA, Scott H, Liston R. The perinatal effects of delayed childbearing. Obstet Gynecol 2005; 105(6):1410-1418.
- 14. Martin JA, Hamilton BE, Sutton PD et al. Births: final data for 2005. Natl Vital Stat Rep 2007; 56(6):1-103.

- 15. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S. National Vital Statistics Reports (NVSS). 56[6]. 2007. CDC.
- 16. Rogowski J. Measuring the cost of neonatal and perinatal care. Pediatrics 1999; 103(1 Suppl E):329-335.
- 17. Canadian Institutes for Health Information. Giving birth in Canada. The Costs. 2006.
- Callahan TL, Hall JE, Ettner SL, Christiansen CL, Greene MF, Crowley WF, Jr. The economic impact of multiple-gestation pregnancies and the contribution of assisted-reproduction techniques to their incidence. N Engl J Med 1994; 331(4):244-249.
- 19. Bissonnette F, Cohen J, Collins J et al. Incidence and complications of multiple gestation in Canada: proceedings of an expert meeting. Reprod Biomed Online 2007; 14(6):773-790.
- 20. Gunby J, Bissonnette F, Librach C, Cowan L. Assisted reproductive technologies in Canada: 2005 results from the Canadian Assisted Reproductive Technologies Register. Fertil Steril 2008.
- 21. Grobman WA, Milad MP, Stout J, Klock SC. Patient perceptions of multiple gestations: an assessment of knowledge and risk aversion. Am J Obstet Gynecol 2001; 185(4):920-924.
- 22. Grzybowski S, Kornelsen J, Cooper E. Rural maternity care services under stress: the experiences of providers. Can J Rural Med 2007; 12(2):89-94.
- 23. British Columbia Reproductive Care Program. Report on the findings of a consensus conference on obstetrical services n rural or remote communities. 2000.
- 24. Kornelsen J, Moola S, Grzybowski S. Geographic induction of rural parturient women: is it time for a protocol? J Obstet Gynaecol Can 2007; 29(7):583-585.
- 25. Lynch N, Thommasen H, Anderson N, Grzybowski S. Does having cesarean section capability make a difference to a small rural maternity service? Can Fam Physician 2005; 51:1238-1239.
- 26. Kornelsen J, Grzybowski S. The reality of resistance: the experiences of rural parturient women. J Midwifery Womens Health 2006; 51(4):260-265.
- 27. Kornelsen J, Grzybowski S. Safety and community: the maternity care needs of rural parturient women. J Obstet Gynaecol Can 2005; 27(6):554-561.
- 28. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Soc Behav 1995; 36(1):1-10.

29. Phillips AN, Smith GD. Bias of relative odds estimation owing to imprecise measurement of correlated exposures. Statistics in medicine 1992; 11; 953-961.

# APPENDICES

# **Appendix 1: Literature review**

Author	Type of study/study population	Age groups	Results	Adjustment
Spellacy WN (1986)	retrospective 13-hospitals- based cohort, (1982-1984) N=41,335	40+ years (N=511); 20-30 years (reference)	significantly higher rates of fetal death, macrosomia (>4,500g); no significant differences in prematurity and neonatal death	stratified by pre-pregnancy weight (<67kg) and parity
Kiely JL (1986)	prospective population-based cohort, singletons >24 weeks, N=320,726 (1976-1978)	35+years, 20-29 years (reference)	late antepartum fetal death (AOR=2.3, CI:2-2.7); intrapartum fetal death (AOR=1, CI:0.7-1.6); neonatal death nulliparae (AOR=2.3, CI:1.7-3.1), multiparae (AOR=1.1, CI:0.9-1.3)	parity, mat. education, prior fetal loss, race, type of service (private or not), marital status; parity examined as effect modifier
Barkan S (1987)	prospective hospital-based cohort, white primiparous women (first prenatal visit) 15% refused, singletons, N=6219	30+ years, <30 years (reference)	No association with preterm delivery	stratified by spontaneous abortions, infertility; marital status, infant sex, education, smoking, gestational age, any chronic diseases
Berkowitz GS (1990)	retrospective hospital-based cohort study, singletons, primiparae (N=3917)	35+years, 20-29 years (reference)	preterm birth (AOR=1, CI:0.7-1.5), SGA (AOR=1, CI:0.7-1.5), NICU admission (AOR=1.4, CI:1.1-1.8), perinatal death >500g (AOR=0.7, CI:0.3-1.6)	race, marital status, level of education, prior infertility, prior spontaneous abortion, smoking, chronic medical condition, sex of infants

Author	Type of study/study population	Age groups	Results	Adjustment
Cnattingius S (1992)	retrospective population-based cohort, singletons >28 weeks, primiparae, N=173,715 (1983-1987)	35-39, 40+years, 20-24 years (reference)	late fetal death (>28 weeks of gestation) (AOR=1.4, CI:1.1-1.8; AOR=1.4,1-2); early neo deaths (AOR=0.9, CI:0.7-1.2, 1.3, CI=0.9-2), very preterm birth (AOR=1.7, CI=1.4-2.1; AOR=1.9, CI:1.2-2.9), SGA (AOR=1.7, CI:1.5-2; AOR=1.4, CI:1-2)	education, marital smoking, smoking, infertility, maternal disease, complications of pregnancy
Aldous MB (1993)	retrospective population based cohort (1984-1988), live born singletons, primiparae (N=4429)	35-39, 40+ years, 20-24 years (reference)	preterm birth (AOR=1.6, CI:1.4-2; AOR=1.8, 1.3-2.6)	paternal and maternal occupation, marital status, smoking, prenatal care, prior fetal loss, hypertension, c-section
Cnattingius S (1993)	retrospective population based cohort, first and second births (>28 weeks) to one women between 1979-1989 (N=210,735)	35+years, 20-24 years (reference)	first births late fetal death (AOR=2, CI:1.5-2.8); early neonatal death (AOR=2.6, CI:1.9-3.6), preterm birth (AOR=1.3, CI: 1.2-1.6); SGA (AOR=1.2, CI:1-1.4); second births: late fetal death (AOR=1, CI:0.5-1.8), early neonatal death (AOR=1.7, CI:1.1-2.8), preterm birth (AOR=1.6, CI:1.4-1.8), SGA (AOR=1, CI:0.8-1.2)	maternal disease (hypertension, diabetes, antepartum hemorrhage), for second births also previous birth outcomes

Author	Type of study/study population	Age groups	Results	Adjustment
Roberts CL (1994)	retrospective population-based study; singletons >19 weeks, primiparae, (1990-1991) N=7422	30-34, 35+years (N=679), 20-29 years (reference)	preterm birth (33-36weeks) (AOR=1.3, CI:1-1.7; AOR=2, CI:1.5-2.8); SGA (AOR=1.1,CI:0.9-1.3; AOR=1.3, CI:1-1.6); NICU (AOR=1.3, CI:1.1-1.6, AOR=1.5, CI:1.2-2); perinatal death (AOR=2, 1.2-3.4, AOR=1.1, CI:0.4-3)	Asian ethnicity, socioeconomic status, marital status, private insurance; for NICU outcome also SGA, hypertension, breech delivery, preterm birth, antepartum hemorrhage
Ezra Y (1995)	retrospective hospital-based cohort study, singletons and multiples >500g, parity < 6, (1985-1992) N=1217	>40 years (N=405), 35-40 years (reference)	preterm labour (OR=1.4, Cl; 0.9-2.3); NICU admission (OR=1.2, Cl:0.7-2.2); no significant differences in perinatal mortality	stratified by parity, no other adjustment
Prysak M (1995)	retrospective hospital based cohort, singleton, primiparae (1986-1990), N=1944	35+ years (N=890), 25-29 years (reference)	significantly elevated rates of preterm delivery, SGA, NICU admissions; but nor perinatal death	maternal age was not a significant predictor of perinatal mortality (adjusted for leiomyomas, preterm birth, chorioamnionitis
Fretts RC (1995)	retrospective hospital-based cohort, singletons and multiples >500g, (1961-1993), N=94,346)	35-39, 40+years, <30 years (reference)	1961-1974: fetal death (AOR=1.9 Cl:1.5-2.4; AOR=1.9, Cl:1.1-3.1): 1978-1993: fetal death (AOR=1.9, Cl:1.3-2.7; AOR=2.4, Cl:1.3-4.5)	stratified by year of delivery; marital status, parity, previous abortions, previous fetal death, multiple gestation, diabetes, hypertension, placenta previa, placental abruption
Bobrowski RA (1995)	retrospective hospital-based cohort, singleton, N=9556	35+ years, 20-29 years (reference)	no association with preterm birth, SGA, NICU admissions	no adjustment; stratified by parity

Author	Type of study/study population	Age groups	Results	Adjustment
Dollberg S (1996)	retrospective hospital-based cohort, matched, N=324	35+ years, 20-29 years (reference)	Preterm birth (OR=5.5, p=0.02)	matched for maternal and paternal ethnicity, chronic diseases, marital status, smoking; no multivariate analysis
Yuksel B (1996)	retrospective hospital-based cohor, singleton, prenatal care, (1992) N=3,518	35+years (N=477), <35 years (reference)	admission to NICU (p<0.05)	stratified by smoking, no other adjustment (not clear)
Lagrew DC (1996)	reterospective hospital-based cohort study, singletons with prenatal care, matched, (1988-1993) N=492	40 + years, 20-29 years (reference)	preterm birth (OR=1.3, CI:0.7-2.3), SGA (OR=0.3, CI:0.1-1)	matched 1:2 for choice of physician (physician factors); gravidity, parity, smoking, alcohol
Bianco A (1996)	retrospective hospital-based cohort; singletons, N=8,382	40+ year, 20-29 years (reference)	NICU admission, nulliparae (AOR=1.6, CI:1.2-2.2); LGA, multiparae (AOR+1.4, CI:1.1-1.7); no association: SGA, preterm birth, neonatal death, perinatal death	race, chronic illness, smoking; analyses separately by parity
MacNab YC (1997)	retrospective population based cohort, singleton and multiples, (1987-1994) N=342,219	35+ years, 20-29 years (reference)	primiparae: preterm birth (AOR=1.3, CI:1.3-1.5); stillbirth (AOR=1, CI: 0.8-1.3); multiparae: preterm birth (AOR=1.1, CI:1-1.2); stillbirth (AOR=1.2, CI:1-1.4)	maternal and infant complications, chromosomal anomalies; stratified by parity

Author	Type of study/study population	Age groups	Results	Adjustment
Dulitzki M (1998)	retrospective cohort hospital- based, singleton, 1988-1995, N=418	44+years, 20-29 years (reference)	maternal age was not an independent risk factor for preterm birth	parity, infertility, previous uterine surgery (c-section), any chronic diseases
Chan BCP (1999)	retrospective hospital-based cohort, singletons/multiples mixed, N=15,337 (1994-1996)	40+ (n=206) ; compared to <40	no association with preterm birth, NICU admissions, perinatal mortality	stratified by parity, no adjustment
Astolfi P (1999)	retrospective popualtion based cohort, legitimate first (N=1344195) or second born (955932), 1990-1994	35-39, 40+ years, 30-34 years (reference)	preterm birth (AOR=1.4, CI:1.4-1.4)	education, birth order, baby gender
Jolly M (2000)	retrospective 18-hospital-based cohort study, singleton, (1988-1997) N=385120	35-40, 40+years (N=7331), 18-34 years (reference)	preterm birth (AOR=1.2, CI:1.1-1.2; AOR=1.4, CI:1.2-1.6); stillbirth (AOR=1.4, CI:1.2-1.7; AOR=1.8, CI:1.3-2.66); special care unit admission >1day (AOR=1, CI:1-1.1; AOR=0.9, CI:0.8-1.1); SGA5th (AOR=1.3, CI:1.2-1.4, AOR=1.5 CI:1.3-1.7)	gestational diabetes, smoking, pre- existing diabetes, pre-eclampsia; abruptio placentae, c-section <37weeks (for NICU admission), induction
Bell J S (2001)	retrospective cohort, hospital- based (1988-1997), N=28,484	20-29 (reference); 30-31, 32-33, 34-35, 36-37, 38-39, 40+	no association with NICU admission	birthweight, gestation, congenital anomaly, newborn resuscitation, mode of delivery, neonatal jaundice, preeclampsia, hypertension, ante- partum hemorrhage; separate analysis by parity

Author	Type of study/study population	Age groups	Results	Adjustment
Misra DP (2002)	retrospective population-based cohort, live births, twins (N=535544), 1985-1991	35-39, 40+ years, 25-29 years (reference)	neonatal mortality (RR=0.9, CI:0.8-1; RR=0.9, CI:0.8-1.1)	no adjustment
Zhang J (2002)	retrospective population-based cohort, >23 weeks of gestation, singletons N=3775974, twins N=155777 pregnancies, 1995=1997	35-39, 40+years, 25-29 years (reference)	significanly elevated risk of very preterm birth an dperinatal death among singletons; no association among twins	race, parity, education, marital, first prenatal visit, smoking during pregnancy, fetal sex
Seoud MAF (2002)	retrospecive hospital-based cohort, singleton > 20 weeks, N=319 (1992-1996)	40+ years, 20-30 years (reference)	preterm birtth (AOR=1.8, CI:1-3.1)	parity, obstetric complications (not clear if other)
Salihu HM (2003)	retrospective population-based cohort, singleton and multiples, (1997-1999), N=10,556,985	30-39, 40-49, 50+years (N=539), 20-29 years (reference)	singletons: preterm birth (AOR=1.2, CI:1.1-1.2; AOR=1.6, CI:1.6-1.7; AOR=3, CI:2.1-3.8); SGA (AOR=1, CI:0.9-1; AOR=1.2, CI:1.1-1.3; AOR=1.7, CI:1.2-2.4); fetal death (AOR=1.1, CI: 1-1.3; AOR=1.9, CI:1.7-2.3; AOR=2.2, CI:1-4.7); multiples: preterm birth (AOR=0.9, CI:0.8-1.1; AOR=1, CI:0.8-1.1; AOR=1.2, CI:0.8-1.7); SGA (AOR=1, CI:0.9-1.2; AOR=1, CI:0.9-1.2; AOR=1.6, CI:1.1-2.2); fetal death (AOR=0.7, CI:0.4-1.1; AOR=0.7, CI:0.4-1.2; AOR=1.1, CI:0.4-3)	parity, marital status, education, smoking, drinking alcohol during pregnancy, prenatal care, year of birth; stratified by singleton/multiples

Author	Type of study/study population	Age groups	Results	Adjustment
Temmerman M	retrospective	20-29 ref, 30-34, 35-39, >40	RR=7 for 35+, 30 for 40+	not clear, c-section, ethniciry, education
Porreco RP	cohort (prospective)	45+ women ART conception or not	preeclampsia (significantly higher), hospital days, NICU days and composite) ;same risk in the same high-risk maternal fetal practice	plurality
Jacobsson B (2004)	retrospective population based cohort, singleton and multiples, (1987-2001) N=1,566,313	40-44, 45+ years (N=1205); 20-29 years (reference)	preterm birth (AOR=1.5, CI:1.5-1.6; AOR= 1.6 CI:1.3-2); SGA (AOR=1.9, CI:1.8-2.1; AOR=2.7, CI:2-3.5); perinatal mortality (AOR=1.7, CI:1.5-1.9; AOR=2.6, CI:1.6-4); stillbirth (AOR=2.1, CI:1.8-2.4; AOR=3.8, CI;2.2-6.4); neonatal death (AOR=1.3, CI: 1.1-1.5; AOR=1.4, CI:0.6-3.2)	parity, marital, malformations, smoking, maternal disease, multiple pregnancy
Joseph KS (2005)	population-based cohort, singletons, N=157,455	35-39, 40+ years, 20-24 years (reference)	preterm birth (ARR=1.6, Cl: 1.4-1.8; ARR=1.8, Cl:1.4-2.4); SGA (ARR=1.3, Cl: 1.2-1.4; ARR=1.7, Cl:1.3-2); perinatal mortality (ARR=1.6, Cl:1-2.6; ARR=2.8, 1.3-6.3), perinatal mortality/morbidity (ARR=1.5, Cl:1.1-1.9; ARR=1.9, Cl:1.1-3.3)	marital status, smoking, pre- pregnancy weight, prenatal class attendance, parity, period, (congenital anomalies excluded from perinatal mortality)

Author	Type of study/study population	Age groups	Results	Adjustment
Cleary- Goldman J (2005)	FASTER trial, retrospective analysis of a prospectively collected data	<35 (reference), 35-39, 40+	preterm birth (AOR=1.0, CI:0.9-1.1; AOR=1.4, CI:1.1-1.7);perinatal mortality (AOR=1.1, CI=1.6-1.9; AOR=2.2, CI: 1.1-4.5)	race, parity, BMI, education, marital, smoking, medical history, ART, study site
Branum AM (2005)	retrospective population-based cohort, live birth twin pregnancies, same gestational age, 1995-1998, N=177075 pregnancies	35-39, 40+ years, 25-29 years (reference)	very preterm birth primiparae (OR=0.8, CI:08-0.9; OR=0.7, CI:0.7-0.8), multiparae (OR=0.9, CI:0.9-1; OR=1, CI:0.9-1.1)	race, prenatal care, marital status; strata by parity, education (<12 years or more)
Reddy UM (2006)	retrospective population based cohort, singletons >20 weeks, no congenital anomalies, (2001-2002), N=5,458,735	35-39, 40+years, <35 years (reference)	stillbirth: 35-39years: 20-27 weeks (RR=1.23, Cl:1.1-1.36); 28-33 weeks, non-significant; 37-41 weeks: RR increases gradually from 1.3 to 1.7(all Cls:1.2-2.2) ; 40+ years: all RRs significantly elevated 1.7-3.3 (Cls:1.5-4.9)	stratified by gestational age (foetuses at risk analysis), medical disease, race, parity
Delbarae I (2006)	retrospective population-based cohort study, singletons >500g, primiparae, N=26,891	35+, 25-29 years (reference)	preterm birth (AOR=1.1, CI:1-1.3); SGA (AOR=1.5, CI:1.4-1.8); perinatal death (1.7, CI:1.1-2.6)	ART, hypertension, diabetes, level of education

Author	Type of study/study population	Age groups	Results	Adjustment
Prapas N (2006)	retrospective hospital-based cohort study, twins >24 weeks, >500g, N=476 (1988-2003)	35+ years, <35 years (reference)	no association with perinatal death, stillbirth, neonatal death, NICU admissions; or preterm birth (by pregnancy)	no adjustment
Luke B (2007)	retrospective population based cohort, singletons and twins >19weeks; (1995-2000, N=22,991	35-39, 40+ years, 25-29 years (reference)	singletons: preterm birth<29 weeks (AOR=1.3, CI:1.3-1.4; AOR=1.6, CI:1.6-1.7); fetal death (AOR=1.1, CI: 1.1-1.1; AOR=1.4, CI:1.4-1.5); twins: preterm birth<29 weeks (AOR=0.8, CI:0.8-0.9; AOR=0.7, CI:0.6-0.8); at least one fetal death (AOR=0.8, CI: 0.7-0.9; AOR=0.7, CI:0.6-0.8)	ethnicity, parity, smoking; singletons and twins analyzed separately
Schempf AH (2007)	retrospective population based cohort, singleton, (2000-2002) N=10,740,852	35-39, 40-49 years, 25-29 years (reference)	primiparare: extremely preterm (<28weeks) (OR=1.5, CI:1.3-2.2; OR=1.5 CI:1.2-3), very preterm birth (OR=1.7, CI:1.6-2, OR=2, CI:1.7-3.1), moderately preterm (OR=1.4, CI:1.3-1.5; OR=1.5, CI 1.4-1.9); Multiparae: not clear increase	stratified by ethnicity, parity; adjusted for education

AOR adjusted odds ratio

OR odds ratio

RR relative risk

CI 95%Cinfidence intervals

Preterm birth <37 weeks of gestation

Very preterm birth < 32 weeks of gestation

SGA 10th percentile unless otherwise stated

NICU neonatal intensive care unit

# **Appendix 2: Definition of congenital anomalies**

ICD9 codes:	Congenital anomaly
740	Anencephalus and similar anomalies
741	Spina bifida
742	Other congenital anomalies of nervous system
743	Congenital anomalies of eye
744	Congenital anomalies of ear, face and neck
745	Bulbus cordis anomalies and anomalies of cardiac septal closure
746	Other congenital anomalies of heart
747	Other congenital anomalies of circulatory system
748	Other congenital anomalies of respiratory system
749	Cleft palate and cleft lip
750	Other congenital anomalies of upper alimentary tract
751	Other congenital anomalies of digestive system
752	Congenital anomalies of genital organs
753	Congenital anomalies of urinary system
754	Certain musculoskeletel deformitites
755	Other congenital anomalies of limb
756	Other congenital musculoskeletel deformitites
757	Congenital anomalies of integument
758	Chromosomal anomalies
759	Other unspecified congenital anomalies

ICD International Classification of Diseases