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Impact of Advanced Maternal Age on the Risk of Stillbirth

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Impact of advanced maternal age on the risk of stillbirth

by

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ABSTRACT

Since more women are having pregnancies at an older age, there are growing concerns about their pregnancy outcomes. Previous studies reveal an uncertain relationship between maternal age and stillbirth risk. This retrospective cohort study aimed to test the hypothesis that stillbirth risk increases with increasing maternal age. We analyzed data on 3,549,993 births from the birth cohorts of 1985 to 2000 in Canada and used logistic regression to evaluate the relative risk of stillbirth.

A total of 15,905 stillbirths were reported during the study period, giving an overall stillbirth rate of 4.5 per 1,000 births. Stillbirth risk was increased for mothers with advanced age after accounting for the confounders and effect modifiers. The older age effect on stillbirth risk was especially pronounced among nulliparous women. We suggest that careful prenatal surveillance and appropriate obstetrical advice and interventions be provided to women with advanced maternal age at their first delivery.

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LIST OF ACRONYMS

ART	assisted reproductive technology
BID-LF	Birth and Infant Death Linked File
BMI	body mass index
BW	birth weight
CBDB	Canadian Birth Data Base
CI	confidence interval
CMDB	Canadian Mortality Data Base
FIGO	International Federation of Gynaecology & Obstetrics
GA	gestational age
HELLP	hemolysis, elevated liver enzymes, low platelets
IUGR	intrauterine growth restriction
OR	odds ratio
PIH	pregnancy induced hypertention
PROM	premature rupture of membranes
RR	risk ratio
SAS	Stati*stical Analysis Systems*
SES	socioeconomic status
SGA	small for gestational age
WHO	World Health Organization

CHAPTER 1 INTRODUCTION

Stillbirth, or late fetal death, is a tragic adverse pregnancy outcome. It currently accounts for more than 50% of all perinatal deaths (late fetal deaths plus neonatal deaths within 7 days of birth) and one third of all feto-infant deaths in developed world.[1] The overall stillbirth rate in developed countries varied under 10 per 1,000 total births.[2-5] Between 1960 and 1980, the absolute risk of stillbirth decreased more than 50%, but the proportion of perinatal deaths made up by stillbirths has increased.[6] This could be due to advances in obstetric care that have improved delivery outcomes and decreased early neonatal deaths.

Besides the loss of a current pregnancy, stillbirth also increases the risk of recurrent stillbirth.[7-11] It has a significant psychological impact on parents during a subsequent pregnancy and beyond.[9,12-14] In addition, more than 25 percent of stillbirths are due to unknown causes,[15,16] which further increases the anxiety of parents in future pregnancies. Stillbirth is also an important public health problem in developing countries where its frequency is higher.

While the overall stillbirth rate is low, it can vary extensively by several maternal and fetal factors. Smulian et al.[17] found that the stillbirth rates for women with placental abruption, small for gestational age fetuses (SGA), or gestational hypertension were 61.4, 9.6, 3.5 per 1,000 total births, respectively, compared to 1.6 for low risk pregnancies. Potential risk factors for stillbirth include hypertensive disorders, diabetes mellitus, placental complications, multiple births (twins or the higher), nulliparity or grand multiparity, SGA and advanced maternal age.[17-19]

Among these risk factors for stillbirth, the independent association of maternal age has recently become very relevant to physicians and women who intend to conceive. This is due to profound increases in the number of women who have delayed childbirth to their late 30s because of economic, technologic, and social changes in the developed world. In Italy, the proportion of nulliparous woman aged greater than or equal to 35 years increased from about 4% in 1984 to 7.5% in 1994.[2] An even larger jump has been seen in America where the proportion of first-time mothers aged 30 or older has increased from 4% in 1969 to 21% in 1994.[1]

The relationship between advanced maternal age and the risk of stillbirth is complex. Although the mechanism is still unclear, a direct effect of older maternal age on stillbirth may exist, especially for early fetal deaths.[20] These fetal deaths may result from failed uterine vasculature dynamics and reduced placental blood flow caused by older age.[21] Older maternal age may also increase stillbirth risk through the higher prevalence of pregnancy-related complications including gestational diabetes,[22,23] placenta previa[22-24] and placental abruption[24] among older women. However, some studies showed the age-related increase in stillbirth can not be explained solely by the increased incidence of pregnancy-related disorders or complications such as gestational diabetes, hypertension, or placental complications.[25,26]

Although maternal age has been extensively studied as a potential risk factor for stillbirth, the influence of older maternal age on stillbirth remains unclear. Published data on the association between high maternal age and the risk of stillbirth has been inconsistent. Some studies have reported that older mothers have an elevated risk of stillbirth.[22,25-28] In contrast, other studies have showed no association.[18,29-31] These inconsistent results could be due to different study populations (e.g. singletons versus singletons plus multiple births), varing study power, inconsistent cut off points for high maternal age or reference age groups, inappropriate statistical modelling strategies, poor control for potential confounding factors, or no consideration of effect modifiers or interactions.

Since maternal age is related to many medical and demographic factors, a careful consideration of confounders and effect modifiers is essential when quantifying the effect of maternal age on stillbirth. This population-based retrospective cohort study aims to clarify the association between maternal age and stillbirth. It will test the hypothesis that advanced maternal age is associated with increased risk of stillbirth after effectively taking into account the potential confounders and effect modifiers including paternal age, fetal sex, parity, history of stillbirth, mother's residential area, and year of birth using a large population-based database.

CHAPTER 2 LITERATURE REVIEW

2.1 Stillbirth

2.1.1 Definition and registry criteria

Fetal death is 'a death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles'.[32] Stillbirth is a fetal death that occurs in late pregnancy.[32] The gestational age at which a fetal death is considered as a stillbirth depends on a country's law on registration criteria of live births and fetal deaths.

Due to the different criteria for the legal registration of live birth or stillbirth between countries or even within countries, there is no official definition of stillbirth for registration proposed by the World Health Organization (WHO). However, in order to conduct international or other comparisons, WHO recommended that all fetuses weighing at least 500g at birth, whether alive or dead, should be included in the statistics of live birth or stillbirth, and that when information on birth weight is unavailable, the corresponding criteria for gestational age of 22 completed weeks should be used.[32]

In Canada, the definition of stillbirth for registration varies across the provinces and territories. In most Canadian provinces and territories (Nova Scotia, Manitoba, Alberta, British Columbia, Yukon and the North West Territories; Saskatchewan before 1994), stillbirth is defined as a fetal death with birth weight of $\geq$ 500g or gestational age of $\geq$ 20 weeks. Several provinces (Newfoundland, New Brunswick and Quebec; Saskatchewan since 1994) have a single birth weight criterion of $\geq$ 500g, while Prince Edward Island has an exclusive gestational age criterion of ≥ 20 weeks.[33] The discrepancy in the definition of stillbirth has also been observed between countries. For example, in South Australia a stillbirth is defined as a fetal death with birth weight of at least 400g or a gestational age of at least 20 weeks,[5] but in the USA the standard used is a fetal death with birth weight of ≥ 350g or, if weight is unknown, of ≥ 20 completed weeks(www.cdc.gov/nchs/vital, 2004).[34]

2.1.2 Stillbirth rate

Stillbirth rate is usually expressed as the number of stillbirth per 1,000 total births (live births plus stillbirths). Every year there are approximately 3.3 million officially reported stillbirths worldwide. The actual number is likely to be higher because of underreporting.[35] Stillbirth rates vary widely between countries and regions. Nearly 97 percent of stillbirths occur in developing countries. The highest stillbirth rates occur in sub-Saharan Africa, with rates as high as 100 per 1000 births reported in some areas.[35,36] Stillbirth rates are usually between 10 and 50 per 1,000 total births in developing countries. For example, in Latin America, the overall stillbirth rate is 20 per 1,000 total births, ranging between 9 and 44.[37] The reported stillbirth rate in India ranges between 10.4 and 41.9 per 1,000 total births in different areas of the country.[38] However, stillbirth rates in most developed countries are less than 10 per 1,000 total births. Dodd[5] found that the average stillbirth rate in South Australia in the 1990's was 6.6 per 1,000 total births. In 2000, the rate in the USA was 7 per 1,000.[3] In the same year, Canada reported a stillbirth rate of 5.8 per 1,000 total births.[4]

Due to improved obstetrical care, stillbirth rates greatly decreased over the past several decades. For example, stillbirth rate dropped from 14.0 per 1,000 total births in 1970 to 6.7 in 1998 in the USA.[36] Similarly, a Montreal study[26] reported that between 1960 and 1993, the fetal death rate fell significantly from 11.5 to 3.2 per 1,000 total births ($p<0.01$). Reduced stillbirth rates have also been seen in northern England (from 5.2 during the 1980s to 4.2 per 1,000 total births in the 1990s for singletons) and in Sweden (from 7.5 in 1983 to 6.1 per 1,000 total births in 1994).[39]

Variations between countries in stillbirth rates do not necessarily represent differences in population health. This is because stillbirth definitions vary between countries especially regarding cut off points of gestational age. Countries with lower age cut off points would be expected to have higher stillbirth rates. Therefore, one needs to be cautious when comparing stillbirth rates from different countries and studies.

2.1.3 Risk factors for stillbirth

A large number of studies have investigated factors associated with stillbirth. These potential risk factors for stillbirth include advanced maternal age, previous fetal loss, parity, advanced paternal age, socioeconomic factors (SES), maternal medical conditions including hypertension, diabetes, obesity and thrombophilia, multiple births and use of assisted reproductive technology (ART). The association between these factors (except advanced maternal age) and stillbirth will be presented separately in this section. The relationship between advanced maternal age and stillbirth will be discussed in greater detail with a systematic review in Section 2.2.

2.1.3.1 Previous fetal death

Previous fetal death refers to a spontaneous abortion (miscarriage) or a late fetal death (stillbirth) in any pregnancy prior to the current delivery. Spontaneous abortion or miscarriage is usually defined as pregnancy termination prior to 20 week's gestation or less than 500g birth weight without medical or mechanical means to empty the uterus.[40]

Previous fetal death increases the incidence of adverse outcomes including stillbirth,[7-11] low birth weight,[9,41,42] preterm birth[9,41-43] and SGA[9] in subsequent pregnancies.

Three studies have shown that previous fetal death has a strong and consistent association with stillbirth risk in subsequent pregnancies after adjusting for important covariates including maternal age, parity, race, maternal education, type of service (delivery on a public ward service vs. a private physician) or quality of prenatal care:

- Keily and colleagues[7] found that prior fetal death increased the risk of antepartum stillbirths (fetal deaths that occur before labor) by 35% and intrapartum stillbirths (fetal deaths that occur during labor) by 59%. A greater stillbirth risk was seen in women with more than one prior fetal loss. The relative risks were 2.83 (95% CI 2.40, 3.34) for antepartum and 3.24 (95% CI 2.22, 4.75) for intrapartum stillbirths respectively compared with women who had no prior fetal loss.
- A UK study[10] showed a similar effect of previous fetal loss in 6993 pregnancies of 3053 women. It found that the effect of previous fetal loss on subsequent fetal death(s) was cumulative and possibly multiplicative with a threefold increase in the risk of a third fetal loss following two previous losses (OR 3.19; 95% CI 1.60, 6.35). To prevent history of fetal death from being over-represented, they ran separate analyses for each of pregnancy orders 1, 2 and 3. For pregnancy orders 2 and 3, additional terms were included to assess the impact of previous pregnancy outcomes. The authors concluded that previous pregnancy loss might be the strongest determinants of fetal loss in subsequent pregnancies.

- Ferraz and associates[8] found an association between history of fetal loss and subsequent stillbirth risk in a case control study. They found that there was a significant higher percentage of past fetal loss if the present pregnancy ended in a stillbirth (OR 1.8; 95% CI 1.2, 2.8).

However, not all studies have found a significant association between previous fetal loss and stillbirth. Two studies on unexplained antepartum stillbirth failed to find a significant association between prior spontaneous abortion or stillbirth and an increase in unexplained fetal death in a subsequent pregnancy.[15,16] Huang and associates[16] hypothesized that any inherent risk associated with previous fetal death could be nullified by better surveillance that those women would have received.

There are physiological reasons to expect an association between previous fetal loss and stillbirth risk. They include impaired placental development and function caused by a compromised vascular support system. This mechanism is similar to that in women with previous stillbirth who have an increase in placental abruption.[41] In addition, studies have found that repeated stillbirth or fetal loss is associated with amniotic infection syndrome diagnosed by the findings of chorioamnionitis, placentitis and congenital pneumonia caused by the aspiration of infected amniotic fluid[43] and a higher incidence of diabetes and hypertension in pregnancy.[9,12]

2.1.3.2 Parity

Parity refers to the total number of previous pregnancies that survived past 20 weeks gestation. It is usually categorized in three levels: nulliparity, low multiparity and grand multiparity. Nulliparity refers to women without a previous pregnancy of more than

20 weeks gestation. The cut off point for grand multiparity varies in literatures from 4 to 7. It is usually higher in older literature.[44]

Parity is a measure of both women's fertility status and pregnancy success. It is one of the most commonly studied factors in researches on adverse pregnancy outcomes. Studies have demonstrated an increased risk of stillbirth for both nulliparaous[25,45] and grand multiparaous mothers.[7,16] Raymond and colleagues[25] conducted a population-based cohort study on 638,242 singleton births among Nordic women in Sweden and found that nulliparous women had a 1.3 times higher risk of stillbirth (95% CI 1.2,1.4) compared to women with a parity of one or more. This association remained even after adjusting for maternal age and smoking . Keily et al.[7] found that high parity (≥ 4) was strongly related to intrapartum fetal death (adjusted OR 1.90; 95%CI 1.28, 2.82) compared to parity of 1-3.

However, several studies did not find a significant effect of high parity on stillbirth after adjusting for the confounding factors.[8,46] A case control study done in Brazil showed that multiparity (parity>2) was significantly associated with stillbirth in univariate analyses, but ceased to be significant after controlling for other risk factors.[8] Another study done in Israel did not find a statistically significant higher stillbirth rate in grand multiparas (parity ≥ 5).[46]

Currently, grand multiparous women account for only 3-4% of all births in developed countries.[47] Compared to low multiparas, grand multiparous women had a higher risk of many maternal pregnancy complications including placenta previa,[48,49] abruptio placentae,[48,50] malpresentation,[51] diabetes mellitus[46,47] and hypertension.[44,52] Each of these pregnancy complications has been associated with an increased risk of stillbirth.[17] For example, Smulian and associates[17] found that women with gestational hypertension, chronic hypertension, or diabetes are 1.4, 2.7, and 2.5 times, respectively, more likely to have a stillbirth than low risk women.

Since women of great parity tend to be older as well, the effect of advanced parity on pregnancy complications may be confounded or modified by maternal age. Both Babinszki[53] and Toohey[54] studies showed that the difference in incidence of diabetes between grand multiparas and low multiparas disappeared after the adjustment of maternal age. Ananth and associates[49] observed an interaction of older maternal age with parity on risk of placenta previa and abruptio placentae. They found an increased risk of placenta previa and abruptio placentae only in younger women (20-25 years) with high parity, suggesting that other factors may be responsible.

High parity is associated with socioeconomic disadvantage. Women with high parity are less likely to have received higher education or adequate prenatal care.[44] In the USA, the coverage rate of private health insurance is lower in women with high parity.[47] This socioeconomic disadvantage may be on one of the pathways for the relationship between high parity and the increased risk of fetal deaths.

It is commonly assumed that both older nulliparas and younger multiparas have an increased risk of adverse pregnancy outcomes. Only limited studies have considered an interaction of parity and maternal age on stillbirth with fitting of a multivariate regression model.[25,45,55] They stated that they did not observe the notable interaction effect of maternal age with parity on stillbirth risk, but the statistical estimates and p-values of interaction terms were not shown in any of these studies.

2.1.3.3 Paternal age

The effect of paternal age on fetal death has not been studied as much as maternal age. Moreover, the bulk of the studies that have been done focused on early fetal death (abortion) rather than stillbirth. The association between paternal age and stillbirth risk was initially proposed in 1939 by Yerushalmy who observed a U-shaped association between paternal age and stillbirth rate across each maternal age group.[56] Recently, a large Danish cohort study including 23,821 pregnancies found that pregnancies in which the fathers aged 50 or older had an increased risk of late fetal death (≥20 weeks of gestation) compared to fathers of 25-29 years old (hazard ratio 3.94, 95% CI 1.12,13.80) after adjusting for maternal age, parity, number of previous abortions, maternal lifestyle during pregnancy including smoking, alcohol or coffee consumption, paternal smoking, and maternal and paternal occupation status.[57] However, a study done by Resseguie and associates[58] in a homogeneous population (i.e. white, with no prior stillbirth) did not find that stillbirth rates increase with father's ageing independently of maternal variables. In addition, Kinzler et al.[59] found that parental age difference in stillbirth risk varies by race. For example, stillbirth rates were higher for white mothers of all ages when they were older than their male partners with the effect being stronger for younger mothers (<20 years). In contrast, for black women, the rate was higher for younger mothers when they were older than their male partners, and the rate decreased for older mothers (>35 years) older than the male partners.

Several other epidemiological studies have focused on the effect of paternal age on early fetal death. They concluded that increasing paternal age increased the risk of spontaneous abortion.[60-62] However, the effect of paternal age on this association is not consistent. Slama et al.[62] reported that the effect of paternal aging on the risk of spontaneous abortion was only seen among those whose female partner was less than 30 years old. However, de la Rochebrochard[61] demonstrated that increased paternal age increased the risk of miscarriage when mother's age is >=35 years or in the combination of mother's age being 30-34 and father's age 40-64.

The biological mechanism behind paternal aging associated with late fetal death is uncertain. An increased genetic damage on germ cells accumulated with male age could be a reason to explain higher rate of fetal loss with older fathers.[63]

2.1.3.4 Socioeconomic Factors

A number of socioeconomic (SES) measures (i.e. social class, family income, ethnicity, maternal education, marital status, or socio-economic deprivation) have commonly been used as indicators of socioeconomic factors. These socioeconomic measures have been known to be important predictors of human health. This relationship seems true for stillbirth as well.

Lower SES has been reported to be associated with an increased risk of stillbirth.[45,55,64,65] A Swedish study adopted household SES that is the equivalent of the highest SES in the household as a measure of SES for stillbirth. The study demonstrated that births to unskilled blue-collar workers had an elevated risk of stillbirth compared to those with intermediate level white-collar workers after controlling for maternal age, parity and mother's smoking (OR 1.8; 95% CI 1.4, 2.4). It also found that lower maternal educational level increased the risk of stillbirth (OR 1.6; 95% CI 1.1, 2.1).[55] Another study in England and Wales which linked perinatal deaths to a deprivation index in enumeration districts presented that some cause-specific stillbirth rates were associated with social deprivation. For example, the rate of antepartum stillbirth with unexplained cause increased by 46% (95% CI 21%, 74%) across the range of deprivation[64]. Race was demonstrated to influence stillbirth risk as well. Black women were found to experience a greater risk of stillbirth compared to women with other race groups.[45,66]

However, two studies[55,67] failed to find an association between socioeconomic status and stillbirth risk. In these studies, all socioeconomic factors including mother's education, mother's occupation, marital status and medical insurance were significantly related to the risk of perinatal deaths and stillbirths in univariate analyses. However, the significance disappeared after adjustment for the effects of maternal age, parity, and smoking in multivariate model.

Reasons for the possible association between lower SES and increased stillbirth risk are unknown but could be explained by confounders. Women in lower SES categories have a greater prevalence of factors associated with stillbirth including pre-pregnancy obesity, smoking, and high coffee consumption during pregnancy.[68] Several studies have shown an adverse effect of these exposures on pregnancy outcomes.[16,45,69] However, women in lower SES were younger and had lower consumption of alcohol,[68] both of which are associated with better perinatal outcomes. Health service could be another major confounder to the association between low SES and stillbirth risk. Women with low SES are less likely to access to antenatal care or high quality obstetric care. A case control study in Brazil found that women with inadequate antenatal care (prenatal care <5 visits) had 1.9 times higher risk of stillbirth (95% CI 1.4, 2.7) compared to women with ≥ 5 prenatal care visits.[8] Quality of care may also affect the risk of stillbirth. A study in Sweden where pregnant women have equal opportunities to receive free antenatal care and other obstetric services found that the increased risk of stillbirth in women of lower SES was more likely to occur in term or near-term fetuses. This suggests that the quality of care may differ with social classes.[65]

2.1.3.5 Maternal medical conditions

The risk of stillbirth is increased in pregnancies complicated by various kinds of maternal medical conditions including hypertensive disorders, diabetes, obesity, lupus, and chronic renal disease.[17,28,70-78] Overall, about 10% of all fetal deaths at 20 weeks or greater are associated with maternal medical illnesses.[79] Table 2.1 shows the estimated stillbirth rates by maternal diseases.

Table 2.1 Maternal medical disease: Current stillbirths rates --- Adapted from Simpson 2002[79]

Condition	Estimated stillbirth rate (per 1,000)
All pregnancies	6-7
Hypertensive disorders	
Chronic hypertension	5-25
Superimposed pre-eclampsia	52
Mild pre-eclampsia	9
Severe pre-eclampsia	21
Eclampsia	18-48
HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)	51
Diabetes mellitus	
Gestational diabetes	5-10
Type 1 diabetes	6-10
Type 2 diabetes	35
Obesity	15-20
Systemic lupus erythematosus	40-150
Chronic renal diseases	
Mild renal insufficiency	15
Moderate and severe renal insufficiency	32-200
Thyroid disorders	
Stable treated hyperthyroidism	0-36
Uncontrolled thyrotoxicosis	100-156
Subclinical hyperthyroidism	0-15
Overt hyperthyroidism	15-125
Cholestasis of pregnancy	12-30

Hypertensive disorders

Hypertensive disorders are the most frequent medical complication of pregnancy, affecting 6% to 12% of all pregnancies.[79,80] Many studies have suggested an increased risk of stillbirth in pregnancies complicated by various types of hypertensive disorders. The relative risks or odds ratios of stillbirth for women with hypertensive disorders range between 1.3 and 3.8 depending on the types of hypertensive disorders, and the covariates included in the multivariate model.[17,25,26,28,80-82] For example, a retrospective cohort study found that the stillbirth risk was 1.4 (95% CI 1.3, 1.5) times higher in women with gestational hypertensive disorders and 2.7 (95% CI 2.4, 3.0) times higher in women with chronic hypertension as compared with low-risk women who were in the absence of vaginal bleeding, placenta previa, placental abruption, hypertensive disorders, diabetes and small for gestational age after adjusting for confounders.[17] Another retrospective cohort study found that the relative risks of stillbirth for women with chronic hypertension, eclampsia, and pregnancy induced hypertension (PIH) was 3.29 (95% CI 2.43, 4.43), 2.23 (95% CI 1.51, 3.30) and 1.42 (95% CI 1.15, 1.79) respectively.[82] In a study on HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, Martin et al.[73] reported a stillbirth rate of over 50 per 1,000 births in patients with HELLP syndrome while the rate in severe preeclampsia without HELLP syndrome was only 21 per 1,000 births.

Placental abruption could be the most plausible pathway between hypertensive disorders and stillbirths. Studies demonstrated that women with hypertensive disorders had a higher risk of placental abruption.[49,83,84] Other pathways speculated include utero-placental insufficiency, placental infarction, or fetal-maternal hemorrhage.[36,79]

In addition, hypertensive disorders in pregnancy are distributed unevenly among some demographic factors. Studies showed that primiparas[85,86] or older mothers[24,83] had a higher risk of having PIH.

Due to great improvements in medical and obstetric care, the ratio of fetal deaths associated with hypertensive disorders to total fetal deaths has decreased dramatically from 20% to 40% in the past[87,88] to less than 10% in 1990s.[5,15,89] Most authors agree that the increased risk of stillbirth associated with hypertension is primarily found in women with severe PIH and preeclampsia superimposed on chronic hypertension. Stillbirth risk in women with mild chronic hypertension or mild gestational hypertension (gestational hypertension without protenuria) is not higher than that for normotensive women.[80,90]

Diabetes Mellitus

Diabetes mellitus is another common medical complication of pregnancy. There are two major types of diabetes mellitus, namely, type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes. Pregnant women with diabetes mellitus can be separated into those who have been diagnosed prior to the onset of pregnancy (pregestational diabetes) and those whose glucose intolerance evolves and is first recognized during pregnancy (gestational diabetes). In America, gestational diabetes accounts for about 90% of diabetes in pregnancy.[40]

Diabetes mellitus affects 2% to 5% of all pregnancies and such pregnancies account for 3% of all stillbirths.[79] Studies found that mothers with diabetes mellitus (combined with subgroups of diabetes) have a 2 to 8 fold higher risk of stillbirth than non-diabetic mothers.[17,25,26,28,75,91] Women with type 2 diabetes have much poorer pregnancy outcomes than women with type 1 diabetes. A recent study found a 4 to 9 times increase of perinatal mortality rate in women with type 2 diabetes compared with women with type 1 diabetes and non-diabetics.[92] Cundy et al.[75] also found a 7-fold increase in stillbirth rate among patients with type 2 (35 of 1,000 births) vs. type 1 (6 of 1,000 births) diabetes. The probability of stillbirth in women with type 1 diabetes is low in the absence of associated vascular or hypertensive disease.[79]

Analogous to hypertension, the risk of having diabetes in pregnancy is associated with increased maternal age. Joseph et al. found mothers aged 40 or older were 3.4 times more likely to have gestational diabetes than those 20-24 years.[24] A similar association was seen in a recent multi-centre study finding that women of ≥ 40 were 2.4 times more likely to have gestational diabetes (95% CI 1.9, 3.1) than women <35.[23]

Several studies demonstrated a relationship between gestational diabetes and previous stillbirth or prior abortion.[12,93,94] For example, Samueloff et al.[12] studied 403 stillbirths and found that the recurrent–stillbirth group (34 cases) had a two times higher incidence of diabetes than did those women experiencing their first stillbirth. Robson et al.[93] reported that women with a previous unexplained stillbirth had a 4-fold increase in glucose intolerance or gestational diabetes in subsequent pregnancies.

The exact mechanism of how diabetes in pregnant women increases stillbirth risk is not fully understood. Perhaps two pathways are worth being mentioned. One is Changes in fetal carbohydrate metabolism and the other is a utero-placental insufficiency secondary to vascular diseases.[79]

The effect of diabetes on stillbirth risk may be underestimated because of undiagnosed diabetes and glucose intolerance in stillbirths of unknown causes. Lau et al.[95] found that 18% of patients with unexplained stillbirth had abnormal glucose tolerance testing but did not meet the criteria for gestational diabetes. They speculated that some of these unexplained stillbirths might be due to undetected maternal diabetes.

Maternal obesity

The increased prevalence of obesity makes it a major public health problem in developed counties. Maternal obesity, which is defined as maternal pre-pregnancy body mass index (BMI) of 30.0 kg/m^2 or more, was found to be independently associated with an increased risk of stillbirth after controlling for factors such as maternal smoking and drinking, maternal age, parity, maternal height, hypertensive disorders, diabetes mellitus and SES. The risk of stillbirth was more than doubled compared to women with normal pre-pregnancy BMI (18.5 - 24.9 kg/m^2). The reported adjusted odds ratio ranged between 2 and 2.8.[96-99] The reported OR was even higher for women in some subgroups, i.e. 4.3 (95% CI 2.0, 9.3) for nulliparous obese women.[98] Compared with stillbirth in non-obese women, stillbirth in obese women often occurred at term or post term.[96,97] Hyperlipidaemia commonly seen in the obese is probably an important factor associated with a higher risk of stillbirth among obese women. A postulated pathway is that hyperlipidaemia decreases placental perfusion through reducing prostacycline secretion, elevating thromboxane production and thus increasing the risk of placental thrombosis.[96]

Maternal thrombophilia

Thrombophilia, classified as inherited and acquired, refers to disorders which are associated with a persistent hypercoagulable state and a tendency towards thrombosis. The estimated prevalence of maternal thrombophilia is 1% - 5%.[100] Some studies have demonstrated a relationship between thrombophilia and an increased risk of stillbirth.[101-104] The odds ratio ranged from as low as 2.8 to as high as 12 due to the heterogeneity in diagnostic criteria of thrombophilia and types of stillbirth included or perhaps small sample size. However, a few studies did not reach a consistent conclusion .[105,106] Failing to find a positive relationship could be due to lack of study power. Previous studies also showed that women with obstetric complication or adverse pregnancy outcome are more likely to have a positive thromboplilia screen.[107,108] For example, Kupferminc et al. [107] found that 65% of women experiencing pregnancy complications such as pre-eclampsia, intrauterine growth restriction (IUGR) and placental abruption and women having unexplained stillbirth had some form of thrombophilia with odds ratio of 5.2 (95% CI 2.8, 9.6) for thrombophilia mutations including factor V Leiden, MTHFR C677T mutation and G20210 A prothrombin gene.

Other diseases

Studies found that Systemic Lupus Erythematosus (SLE), chronic renal disease and thyroid disorders were also related to an increased risk of stillbirth. The reported odds ratios are 6-20 for SLE, 2.2-30 for renal disease and 2.2-3.0 for thyroid disorders respectively.[100]

2.1.3.6 Other factors

Multiple births

The incidence of multiple births has increased dramatically over last two decades in developed countries due to delayed childbearing and the increasing use of assisted reproductive technology (ART). In 2003, approximately 1% of U.S infants were conceived through ART and these infants accounted for 18% of multiple births.[109] Multiple births had a higher mortality rate than singletons.[110,111] A national study in Demark[111] found that stillbirth rate ($\geq$ 28 gestational weeks) increased exponentially from singletons to triplets births, being 4.3 per 1,000 total births among singletons, 20.0 among twins and 50.4 among triplets during 1989 to 1993. Higher risk of being born preterm or being of low birth weight was also observed among multiple births, which may contribute to the increased infant mortality rate.[112]

Multiple births have been reported to occur more frequently for older women.[113] However, the increased incidence of multiple pregnancies among older women is strongly associated with the higher exposure to assisted reproductive interventions. Lynch et al.[114] found that there is no association between advanced maternal age and multiple births after adjusting for the use of assisted conception and other covariates.

Previous studies on twins found that some factors differentiated the influence of maternal age on certain adverse pregnancy outcomes.[115,116] For example, Zhang et al.[115] reported that socioeconomic status modified the effect of advanced maternal age on poor perinatal outcomes in twin pregnancy. They found that in twin pregnancy older women with lower socioeconomic status had a higher risk of poor perinatal outcomes. However older women with higher socioeconomic status did not have an increased risk . Similarly, Branum's study[116] found that the effect of maternal age on very preterm birth of twins differed according to parity. Among primiparas, women at 40 or older had a significantly lower risk of very preterm birth than women at 25-29, but the risk was not different for multiparas.

In Vitro Fertilization (IVF)

IVF is one of the major assisted reproductive technologies (ART). A national survey in the UK found that IVF accounted for more than 80% of assisted conception technologies.[117] Delayed childbearing and increased access to infertility treatment have resulted in a dramatic increase in use of IVF. Between 1996 and 2002, the number of IVF procedures in the USA linearly increased by 92% from 49,680 to 95,563 transfer procedures.[118]

Women undergo IVF procedures had a much higher risk of having multiple pregnancies. It is estimated that in England and Wales, more than 1% of all infants are born through IVF, and the multiple birth risk with IVF is about 45%.[119] An US national ART surveillance data showed that of 48,756 infants born through ART, as high as 51% infants were born in multiple-birth deliveries in five states where the highest number of ART was reported.[109] Among women exposed to ART, the attributable risk of multiple pregnancies was 48%.[114]

The increase in risk of perinatal mortality among women conceived with ART is thought to be largely attributable to multiple births. Multiple pregnancies carry significantly elevated risk to the fetus. For example, multiple pregnancies constitute about 3% of all births, but about 10% of all stillbirths.[36] Compared to the estimated stillbirth rate of 0.5% for singletons, the stillbirth rate is 1.8% for twins, 2.4% for triplet, 3.7% for quadruplet and 5.6% for quintuplet.[120]

Studies have demonstrated that women experienced IVF and had singleton gestation also had a significantly increased risk of perinatal mortality,[121,122] preterm delivery,[122-124] low birth weight [121,122] and SGA[125,126] compared to women with spontaneously conceived singletons. The overall odds ratios were 2.2 (95% CI 1.6, 3.0), 2.0 (95% CI 1.7, 2.2), 1.8 (95% CI 1.4, 2.2) and 1.6 (95% CI 1.3, 2.0) based on a systematic review including 15 individual studies.[127] This review also showed a higher risk of stillbirth in IVF group versus spontaneous conception group (OR 2.6; 95% CI 1.8, 3.6) estimated on 7 studies where stillbirth data were available.[127] All those individual studies controlled for maternal age and parity when estimating the odds ratios of each of the adverse pregnancy outcomes for women with IVF versus spontaneous conception.

2.2 Advanced maternal age and the risk of stillbirth

In this section I reported on a systematic review that I conducted to examine the impact of maternal age on stillbirth risk.

Shifts in maternal age over the past decades have been dramatic. Economic, technologic and social changes in the developed world have had a large impact on the age that women have children. An increasing number of women have delayed childbirth to their late 30s. Between 1980 and 1993, the mean maternal age at birth rose by 1.5 years (from 27.1 to 28.6) in the European Union.[128] In the USA, the proportion of first births for women aged 35-39 and 40-44 increased by 36 percent and 70 percent, respectively, between 1991 and 2001.[1,129] Since advanced maternal age is reported to account for an increase in maternal morbidity, obstetrical interventions and adverse pregnancy outcomes, concerns for the pregnancy outcomes of women with advanced maternal age are increasing. Indeed it has become an important public health issue that involves in health professionals, women intend to conceive, their families and even the communities.

However, studies on the relationship between increased maternal age and stillbirth risk have reached inconsistent conclusions. Poor evidence for the association of advanced maternal age with increased stillbirth risk has made it difficult for patients and doctors to make informed decisions. To help women make informed choices about childbirth, we conducted a systematic review of observational studies to help elucidate the association between advanced maternal age and the risk of stillbirth.

2.2.1 Methods

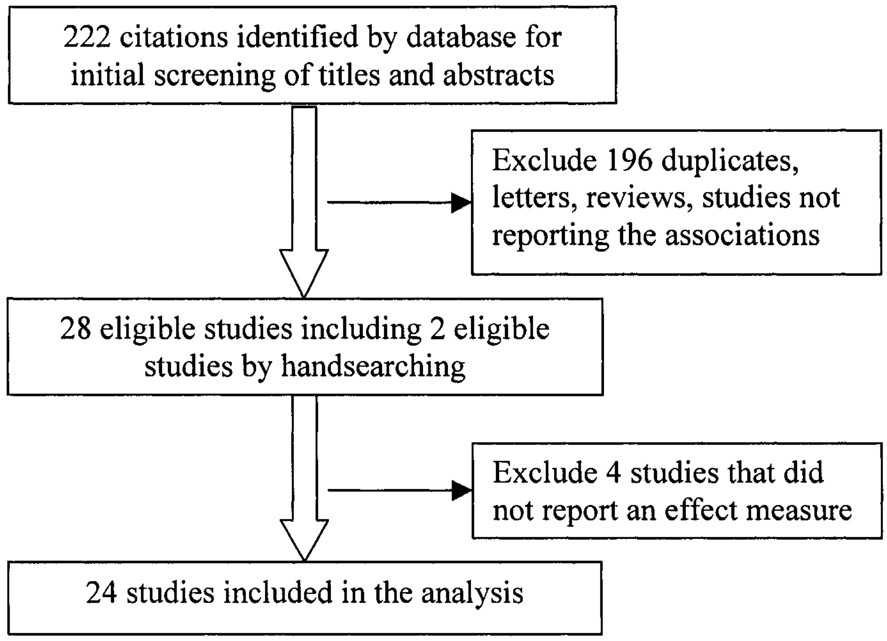
2.2.1.1 Selection criteria

Randomized trials cannot address this question due to the nature of the research topic. Therefore, we included all cohort studies (prospective or retrospective) or case control studies that examined the association between advanced maternal age and stillbirth risk. To be included in the systematic review, studies had to cite the odds ratio or relative risk of stillbirth by maternal age or provide sufficient data to construct contingency tables for maternal age and stillbirth.

2.2.1.2 Data sources

We undertook the search strategy shown in Appendix A. The search included the following databases: Medline (1966 to 2004), EMBASE (1980 to 2004.2) and Healthstar (1975 to 2004). The key words used were: "stillbirth", "fetal death", "perinatal death", "advanced maternal age", "increased maternal age", 'older mothers". Search strategies for observational studies were used to identify potentially eligible studies. We also hand searched the bibliographies of retrieved articles to further identify related studies. No language restriction was used. We did not attempt to identify articles from the grey literature. Figure 2.1 shows the result of our search strategy.

Figure 2.1 Flowchart of the included studies



2.2.1.3 Data extraction

Two reviewers independently extracted data from all included studies. The information abstracted from each study included: study design; database used for analysis (population-based or hospital-based); the characteristics of study subjects, including plurality (singletons, multiple birth, or both), parity (nullipara, multipara or both), and cut off points of gestational week and birth weight for stillbirth; types of included stillbirths; potential confounders or effect modifiers considered in the analyses; numbers of live births and stillbirths by maternal age group; or risk ratio/odds ratio for stillbirth (Appendix B). The inter-observer agreement for data abstraction was assessed using Kappa statistics[130] and found to be 0.96 for the overall agreement in this study. This Kappa score corresponds to very good agreement between the reviewers.[131]

2.2.1.4 Statistical analyses

Both the crude and (if available) adjusted risk ratio/odds ratio of stillbirth risk for maternal age was recorded. We did not quantitatively combine the effect measure of each study because of heterogeneity that we observed between studies regarding methodological design, outcome measures, adjusted covariates, cut off points for maternal age, and modeling strategy used (Table 2.2-2.3).

2.2.2 Results

The systematic literature search identified 222 citations. Twenty-eight were deemed potentially eligible and after further review, 24 studies (21 retrospective cohort and 3 case control studies) met the study inclusion criteria.[2,6,8,19,21,22,25-27,29,31,37,38,45,55,65,132-139] Among them, 10 were from Europe, 8 were from North America, 3 were from Asia and 3 were from Latin America. Twenty one studies were published in English and the remaining 3 were published in Spanish, German and Italy.

A brief description of the characteristics of these studies is presented in table 2.2-2.3. The cut off points used to define increased maternal age and the age group used as the reference varied extensively between studies. Studies also differed with regards to the gestational age and birth weight used to define stillbirth, in the plurality, and parity of study subjects. Due to important clinical and methodological heterogeneities, meta-analytic combination of the results from these studies was not conducted.

Table 2.2 Individual studies included in the systematic review: Study characteristics

First author (Published year)	Study year	Country	Database (Pop vs. Hosp)	Sample sizes	Study subjects	*Definition of Stillbirth
Retrospective cohort studies (21):						
Astolfi (2002)	1990-1994	Italy	Pop-based	2,305,879	Singletons Primi & secondiparous	GA ≥ 26w BW ≥ 500g
Bianco (1996)	1988-1994	USA	Hosp-based	8,382	Singletons Women ≥ 20y	All GA BW ≥ 500g
Cnattingius (1992)	1983-1987	Sweden	Pop-based	173,715	Singltons Women ≥ 20y Nulliparous	GA ≥ 28w All BW
Donoso (2003)	1999	Chile	Pop-based	182,322	Singletons & Multiple Women ≥ 20y	All GA All BW
Feldman (1992)	1987-1989	USA	Pop-based	370,051	Singletons & Multiple	GA ≥ 26w All BW
Fretts (1995)	1961-1974 &1978-1993	Canada	Hosp-based	94,346	Singletons & Multiple	All GA BW ≥ 500g
Fretts (1997)	1961-1974 &1978-1995	Canada	Hosp-based	101,640	Singletons & Multiple	All GA BW ≥ 500g
Gadow (1991)	1982-1986	Latin America	Hosp-based	869,750	Singletons & Multiple	All GA BW ≥ 500g
Haglund (1993)	1985-1986	Sweden	Pop-based	185,156	Singletons Women 15-44y	GA ≥ 28w All BW
Heimann (1993)	1975-1985	German	Hosp-based	1,175	Women 20-29& ≥ 40y	All GA All BW
Jolly (2000)	1988-1997	UK	Hosp-based	385,120	Singletons Women ≥ 18y	All GA All BW
Khandait (2000)	1993-1997	India	Hosp-based	46,443	Singletons & Multiple	GA ≥ 28w BW ≥ 1000g
Lammer (1989)	1982	USA	Pop-based	76,323	Singletons & Multiple	All GA All BW
Naeye (1983)	1959-1966	USA	Hosp-based	44,386	Singletons Women: ≥ 17y	All GA All BW
Nybo-Andersen (2000)	1978-1992	Denmark	Popo-based	634,272	Singletons & Multiple	GA: ≥ 28w All BW

Abbreviations:
Pop: Population; Hosp: Hospital; SB: Stillbirth; LB; Live birth; BW: birth weight; GA: gestational age
* Unless otherwise specified, studies included all stillbirth types

Table 2.2 Continued

First author (Published year)	Study year	Country	Database (Pop vs. Hosp)	Sample sizes	Study subjects	*Definition of Stillbirth
Pugliese (1997)	1983-1993	Italy	Hosp-based	6,997	Women	All GA All BW
Rasmussen (2003)	1967-1998	Norway	Pop-based	1,676,160	Singletons	GA ≥ 28w All BW Unexplained SB
Raymond (1994)	1983-1989	Sweden	Pop-based	638,242	Singletons women	GA ≥ 28w All BW
Sheiner (2000)	1990-1997	Israel	Hosp-based	78,453	Singletons	All GA BW ≥ 500g Intrapartum SB
Tough (2002)	1990-1996	Canada	Pop-based	283,956	Singletons & Multiple	All GA All BW
Viegas (1994)	1986-1991	Singapore	Hosp-based	21,442	Singletons & Multiple women	GA ≥ 28w All BW
Case control studies (3):						
Ferraz (1991)	1984-1986	Brazil	Hosp-based	Case: 234 Control: 2,555	Singletons	All GA BW ≥ 500g
Little (1993)	1980	USA	Pop-based	Case: 1,104 Control: 2,565	Singletons Nulliparous	GA ≥ 28w BW ≥ 500g
Stephansson (2001)	1987-1996	Sweden	Pop-based	Case: 702 Control: 702	Singletons Primiparous	GA ≥ 28w All BW

Abbreviations:
Pop: Population; Hosp: Hospital; SB: Stillbirth; LB; Live birth; BW: birth weight; GA: gestational age
* Unless otherwise specified, studies included all stillbirth types

Table 2.3 Individual studies included in the systematic review: Study analysis and results

First author (Published year)	Maternal age modeled (Continuous vs. categorized)	Confounders adjusted for	Effect modification considered	*Calculated RR or OR and 95% CI	Reported adjusted RR or OR and 95% CI
Retrospective Cohort studies (21):					
Astolfi (2002)	Categorized	Stratified by parity and education	No	**1.44 (1.35-1.53) (≥ 35y vs. <35y)	---
Bianco (1996)	Categorized	Chronic conditions, race, tobacco use	No	0.34 (0.08,1.43) (≥ 40y vs. 20-29y)	0.5 (0.1,2.0) (≥ 40y vs. 20-29y)
Cnattingius (1992)	Categorized	Chronic conditions, antepartum hemorrhage, infertility, education, smoking	No	1.37 (1.00,1.88) (≥ 35y vs. 20-24y)	1.4 (1.0,2.0) (≥ 35y vs. 20-24y)
Donoso (2003)	Categorized	None	No	2.18 (1.69,2.82) (≥ 40y vs. 20-34y)	---
Feldman (1992)	Categorized	None	No	1.53 (1.38,1.69) (≥ 35y vs. <35y)	---
Fretts (1995)	Categorized	Medical conditions, placenta previa and placental abruption, year of delivery, multiple gestation, marital status,prior abortion or fetal death	No	1.57 (1.29,1.90) (≥ 35y vs. <35y)	Did not report the corresponding adjusted OR
Fretts (1997)	Categorized	None	No	1.53 (1.27,1.85) (≥ 35y vs. <35y)	---
Gadow (1991)	Categorized (RxC table)	None	No	1.94(1.86,2.02) (≥ 35y vs. <35y)	---
Haglund (1993)	Categorized	SES, parity, smoking	Age*parity Age*smoking Prity*smoking	1.31 (1.05,1.63) (35-44y vs. <35y)	Did not report for maternal age
Heimann (1993)	Categorized (RxC table)	None	No	0.70 (0.27, 1.81) (≥ 40y vs. 20-29y)	---
Jolly (2000)	Categorized	Parity,race,BMI, hypertension,diabetes pre-eclampsia smoking	No	1.37 (1.21,1.54) (35-40y vs.18-34y)	1.41 (1.17,1.70) (35-40y vs.18-34y)
Khandait (2000)	Categorized (RxC table)	None	No	2.81(2.36,3.34) (≥ 30y vs. 20-29y)	---
Lammer (1989)	Categorized	None	No	1.69 (1.29,2.22) (≥ 35y vs. 20-34y)	---
Naeye (1983)	Categorized	None	No	2.13 (1.73,2.62) (≥ 35y vs. <35y)	---
Nybo-Andersen (2000)	Categorized	None	No	1.27(1.12,1.44) (≥ 35y vs. <20-34y)	---

* by RevMan 4.2; ** by Excel

Abbreviations:

SB: Stillbirth; LB; Live birth; OR: odds ratio; RR: risk ratio; CI: confidence interval; BW: birth weight; GA: gestational age; BMI: Body Mass Index

Table 2.3 Continued

First author (Published year)	Maternal age modeled (Continuous vs. categorized)	Confounders adjusted for	Effect modification considered	*Calculated RR or OR and 95% CI	Reported adjusted RR or OR and 95% CI
Pugliese (1997)	Categorized (RxC table)	None	No	0.35 (0.05,2.55) (≥ 40y vs. 20-29y)	---
Rasmussen (2003)	Categorized	Birth order	No	**1.57(1.42, 1.74) (≥ 35y vs. 20-34y)	Reference: <20y 1.2 (1.2, 1.5) 20-24y 1.2 (1.2, 1.5) 25-29y 1.4 (1.0, 1.6) 30-34y 1.7 (1.4, 2.1) 35-39y 2.0 (1.5, 2.6) 40-44y 3.9 (2.2, 7.0) ≥ 45y
Raymond (1994))	Categorized	Parity,smoking	Age*GA	1.45 (1.29,1.62) (≥ 35y vs. 20-34y)	1.5 (1.4, 1.7) (≥ 35y vs. 20-34y)
Sheiner (2000)	Categorized	Abruption placenta, cord problem, race, BW, polyhydramnios, malpresentation, congenital malformation	No	1.48 (0.74, 2.96) (>35y vs. 20-35y)	2.1(1.1, 3.8) (>35y vs. 20-35y)
Tough (2002))	Categorized	None	No	1.44 (1.26, 1.63) (≥ 35y vs. <35y)	---
Viegas (1994)	Continuous	Race, parity	No	0.78 (0.41-1.50) (≥ 35y vs. <35y)	Did not report adjusted OR for maternal age; Did not report estimate of age
Case control studies (3):					
Ferraz (1991)	Categorized	Medical condition, vaginal bleeding, previous pregnancy loss, maternal weight, prenatal care, I antrapartum complication, congenital anomalies	Age*smoking	2.0 (1.33, 3.01) of ≥ 35y (≥ 35y vs. <35y)	Did not report
Little (1993)	Categorized	Education , races, drinking, smoking , maternal height, BMI region of birth, sex of infant, first delivery, maternal weight	# No	1.61 (1.21, 2.16) of ≥ 35y (≥ 35y vs. <35y)	1.67 (1.27, 2.20) of ≥ 35y (≥ 35y vs. <35y)
Stephansson (2001)	Categorized	SES, BMI, maternal height mother's country of birth	No	2.00 (1.32, 3.04) of ≥ 35y (≥ 35y vs. 20-24y)	Did not report

* by RevMan 4.2; ** by Excel

\# Did not mention in the method part, but stated in the result part 'No notable interactions among variables were detected'.

Abbreviations:

SB: Stillbirth; LB; Live birth; OR: odds ratio; RR: risk ratio; CI: confidence interval;
BW: birth weight; GA: gestational age; BMI: Body Mass Index

Among 21 retrospective cohort studies, 15 found a statistically significant association between increased maternal age and stillbirth (Figure 2.2). The reported crude relative risk of stillbirth ranged from 1.27 to 2.81 for older women versus their younger counterparts. The criteria for older maternal age and reference age varied among these studies. The most commonly used criterion (7/15 studies) was ≥ 35 years old for older women versus <35 years old for the reference age group. These 7 studies reported about 1.44 to 2.13 times higher risk of stillbirth among older women compared to women of the reference age. The risk ratios (RRs) of the other 8 studies did not show any trend that studies with higher cut off point of older maternal age or lower cut off point of reference age had a bigger RR for stillbirth (Table 2.3). The remaining 6 of 21 studies failed to find a statistically significant relationship between older maternal age and stillbirth risk (Figure 2.2). All 3 case control studies showed a significant relationship between advanced maternal age and stillbirth, giving crude odds ratios (ORs) of older maternal age ranging from 1.61 to 2.00 in stillbirth versus live birth group (Table 2.3).

Twelve studies (9 retrospective cohort and 3 case control) controlled for potential confounders when measuring the association between maternal age and stillbirth risk. Of these, 7 studies reported both crude and adjusted RRs/ORs (Figure 2.3). The confounders adjusted for in each study varied. The factors most frequently adjusted were smoking and parity, followed by race, chronic medical problems, and body mass index (BMI). The RRs/ORs did not change extensively in either direction or magnitude after adjustment for confounders. One exception was the study by Sheiner et. al [138] in which the crude RR of 1.48 (95% CI 0.74, 2.96) for women of more than 35 years old increased to 2.1 (95% CI 1.1, 3.8) after adjustment.

Figure 2.2 Crude risk ratio/odds ratio of stillbirth in older versus younger women

Study name	Events / Total: Older women	Events / Total: Younger women	Odds ratio	Lower limit	Upper limit
Population-based					
Lammer EJ	59 / 5086	435 / 63044	1.689	1.285	2.220
Cnattingius S	41 / 7880	629 / 165644	1.372	1.000	1.883
Feldman GB	441 / 46596	2013 / 323455	1.526	1.376	1.692
Haglund B	95 / 21467	536 / 158006	1.306	1.049	1.625
Raymond EG	349 / 75062	1811 / 563180	1.448	1.291	1.624
Nybo Anderson AM	261 / 48950	3015 / 718514	1.272	1.121	1.444
Astolfi P	1174 / 202054	8455 / 2089070	1.438	1.353	1.529
Tough SC	270 / 29233	1643 / 254723	1.436	1.262	1.634
Donoso SE	65 / 7066	742 / 175256	2.184	1.693	2.817
Rasmussen S	457 / 163782	2539 / 1428378	1.571	1.422	1.736
Hospital-based					
Naeye RL	110 / 3346	513 / 32639	2.129	1.727	2.624
Gadow EC	3000 / 91416	10503 / 611844	1.943	1.864	2.024
Heimann F	7 / 560	11 / 615	0.695	0.268	1.806
Viegas OAC	10 / 2410	101 / 19032	0.781	0.407	1.498
Fretts RC (1995)	127 / 11942	561 / 82376	1.568	1.292	1.902
Bianco A	2 / 1404	29 / 6978	0.342	0.081	1.434
Fretts RC (1997)	133 / 13222	582 / 88390	1.533	1.269	1.852
Pugliese A	1 / 314	60 / 6683	0.353	0.049	2.553
Jolly M	312 / 48658	1581 / 336462	1.367	1.210	1.544
Khandait DW	160 / 2700	920 / 41913	2.807	2.362	3.336
Sheiner E	10 / 10114	41 / 61422	1.482	0.742	2.959
Population-based					
Little RE	81 / 1104	120 / 2565	1.613	1.206	2.158
Stephansson O	67 / 702	37 / 702	2.002	1.319	3.039
Hospital-based					
Ferraz EM	31 / 234	181 / 2555	2.003	1.333	3.009

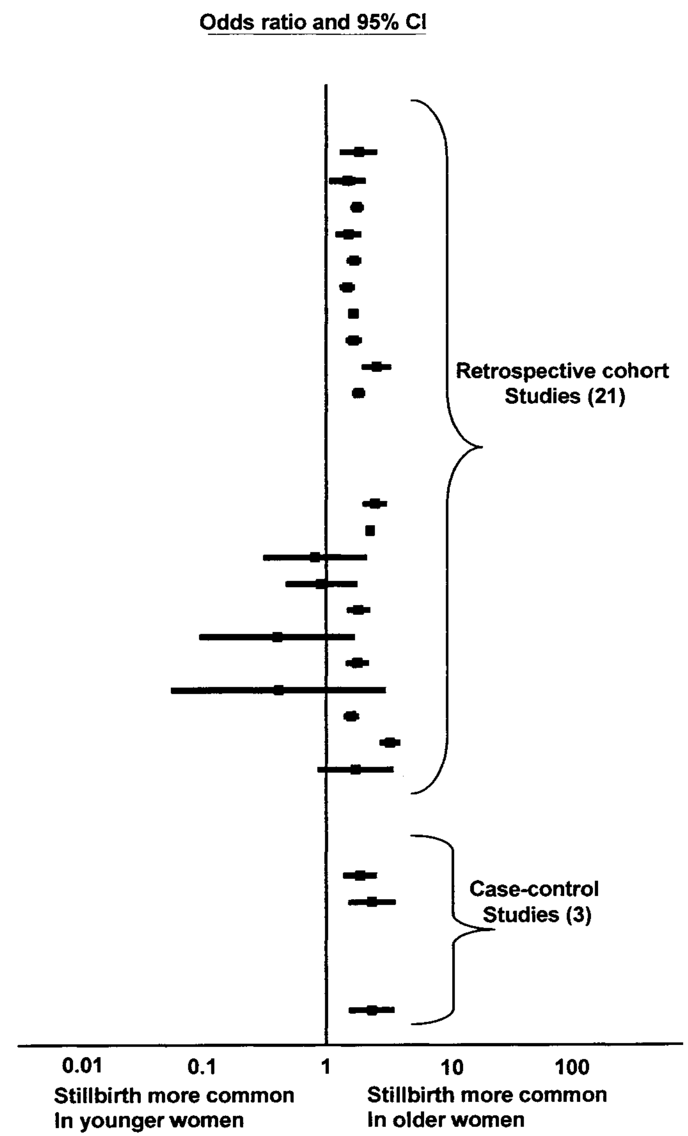
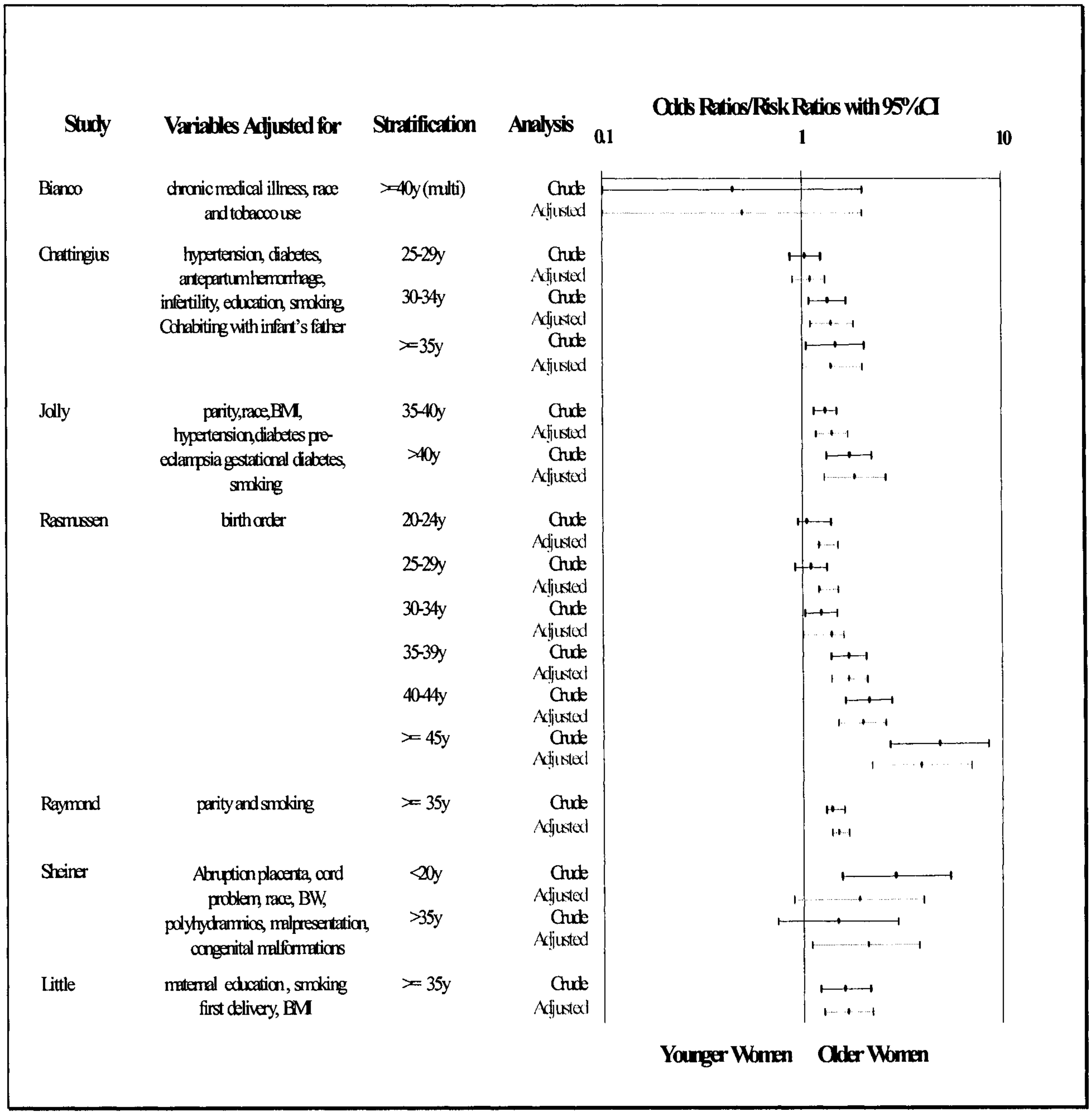


Figure 2.3 Risk ratio/odds ratio of stillbirth in older versus younger women: Adjusted vs. crude analyses



2.2.3 Comments

2.2.3.1 Principal findings

This systematic review included 24 studies that examined the association between advanced maternal age and the risk of stillbirth. Eighteen studies (75%) demonstrated a statistically significant increased risk of stillbirth in women with advanced maternal age. The crude odds ratio ranged from 1.27 to 2.81 for older mothers, showing a weak to moderate positive association. Among the 7 studies presenting both adjusted and crude RRs/ORs, most studies (5/7 studies) found less than a 10% difference between crude and adjusted RRs/ORs. This suggests that the association of increased maternal age and stillbirth risk is likely independent of these other factors that could increase with age.

Six studies reported a non-significant association between increased maternal age and stillbirth risk. Among them 5 (83%) used hospital-based data and 4 (67%) of them were university-based. Three factors could explain this lack of association. First, the majority of the studies had a small sample size. Half of the studies had fewer than 1500 older women and the smallest was only 314, suggesting a lack of study power as responsible for the absence of increased stillbirth risk among women with older maternal age. Second, lower threshold for obstetrical interventions in certain study settings including teaching centres might be another important reason for the lack of the association. All of the 5 hospital based studies were conducted in a single large hospital, such as tertiary care centre, private service medical centre and university-affiliated hospital. Older women in large hospitals may have a lower threshold for interventions such as induction of labor and elective Caesarean Section.[22] Earlier obstetrical intervention may decrease the risk of fetal complications and deaths. Wen and associates[140] showed that elective and emergency Caesarean Section can result in an 88%

reduction of intrapartum fetal death. These interventions could balance the risk caused by increased incidence of antepartum and intrapartum complications with aging and lead to favorable outcomes for fetuses. Finally, women pursuing obstetric care in large hospitals may receive better medical care for their chronic diseases or pregnancy complications which would decrease the risk of stillbirth. This influence on stillbirth risk would be stronger in older women since incidence/prevalence of these conditions increases with ageing.

Meta-analysis could not be conducted to get an overall effect measure because of heterogeneity in study design, measurement, and definition of stillbirth across the studies. Variation between studies in the magnitude of the association between maternal age and stillbirth risk could be due to many study factors. First, the cut off point of older age varied between the studies with values of ≥ 35, > 35, 35-44, and ≥ 40. This variation reflects the uncertainty of the maternal age at which stillbirth risk increases. In 1958 the International federation of Gynecology and Obstetrics (FIGO) defined pregnant women aged 35 years or more as "elderly primigravidae". In obstetrical practice, pregnant women over the age of 35 years have been regarded as higher risk and are considered for routine genetic screening. However, some studies found that the 35 year old threshold is not applicable in healthy women with good health behavior because neonatal outcomes in such women do not change at 35.[30] Other researchers have even suggested that pregnancy at ages 45 to 50 is safe in the absence of pre-existing medical disorders.[141] This could explain why several studies used a higher cut point for older maternal age such as an age of ≥ 40. Variation between studies in the maternal age cut-point will make comparison between them difficult.

Another source of study heterogeneity involves plurality. Some studies included all deliveries while others only included singletons. Multiple births are more likely to experience complications during pregnancy and in labor.[142,143] They also have a higher risk of adverse pregnancy outcomes including preterm labor, low birth weight, and stillbirth.[112,141,143,144] Because of their greater use of assisted reproductive technology (ART), older women experienced a dramatic increase of multiple birth rate compared to their younger counterparts.[113,115,145] Older women were 1.5 to 2 times more likely to have a multiple birth than younger women.[113,138] Consequently, a careful examination of potential confounding and effect modification of multiple pregnancy is essential in studies that include both singletons and multiple births. This is especially true when comparing with studies that only include singletons. About half of the studies in this systematic review included both singletons and multiple births and none of them mentioned a consideration of confounding or effect modification of multiple births on stillbirth risk, which makes their conclusions questionable. Also, none of them conducted a separate analysis for multiple births.

In addition, among the 24 included studies, less than a third of them (7/24) controlled for confounders and only three studies examined for interactions between maternal age and other factors on stillbirth risk. Variation in confounder adjustment or lack of the consideration of effect modification might in a certain degree contribute to differences between studies in the association between maternal age and stillbirth risk.

The possibility of publication bias was assessed using a funnel plot of these 24 studies The plot shows an asymmetry with the lack of published small studies showing a positive association between older maternal age and increased risk of stillbirth. This funnel plot asymmetry may be due to publication bias, but it may also result from clinical and methodological heterogeneity such as hospital verses population-based among studies.

2.2.3.2 Strengths and weaknesses of this review

This study has several strengths. A systematic review of the association between advanced maternal age and the risk of stillbirth has never been published before. Half of the studies included in this systematic review were population-based studies with large sample sizes. Such studies presented consistent results regarding the association between the advanced maternal age and the increased risk of stillbirth.

The limitations of our systematic review are primarily due to the studies themselves. First, we could not conduct a meta-analysis to estimate the overall odds ratio for the included studies due to the clinical and methodological heterogeneity between the studies. Such heterogeneity also prevented us from conducting subgroup analysis or using meta-regression techniques to investigate the effect of the covariates on stillbirth rates. Second, less than one third of the included studies adjusted for important confounders. The confounders that these studies controlled for also varied among the studies, which could affect the relationship between maternal age and the outcome. Third, birth registry databases on which most population-based studies relied usually lack information on medical conditions, pregnancy complications, life style factors and socioeconomic status. Therefore, most studies could not adjust for these factors when associating maternal age and stillbirth risk. The possibility of linkage of birth data to hospital discharge database or other relevant databases such as census or survey databases will help to control for the important confounders for the association between advanced maternal age and risk of stillbirth.

2.2.3.3 Suggestions

Based on the findings of this systematic review, we make three suggestions for future studies of stillbirth and maternal age. First, although most individual studies in this systematic review presented an association between advanced maternal age and increased risk of stillbirth, the huge heterogeneity in the definition of stillbirth and study methodology prevent us from quantifying the overall estimated risk of stillbirth for older mothers. Therefore, we suggest that researchers adopt the WHO recommended cut off points of

gestational age and birth weight for stillbirth definitions in their future studies. This will make inter-study comparison possible as well as combination of the risk estimates from different studies. Second, we recommended that maternal age be modeled carefully in regression models. The cut-points of maternal age should be based on dose-response effects from the publish studies when categorizing maternal age and linearity check between maternal age and outcomes should be done when maternal age is modeled as a continuous variable so that the relationship between maternal age and outcome can be examined more accurately. Finally, assessment of effect modification for maternal age on outcomes should be considered as important as control for confounders.

The extent of the association between maternal age and stillbirth is still uncertain because of the limitations of the previous studies found in our systematic review. The limitations include variations in definition of stillbirth, cut off points of older or reference maternal age, combination of singletons and multiple births in the same model, and lack of consideration of interactions. Therefore, we conducted the present study to test the hypothesis that advanced maternal age is associated with an increased risk of stillbirth and to quantify the association through an appropriate modeling method for maternal age and a careful consideration of potential confounding and interaction for maternal age in regression model. This large population-based study adopted the WHO recommended definition of stillbirth.

CHAPTER 3 STUDY DESIGN

3.1 Study type

Population-based retrospective cohort study

3.2 Research objectives

Primary objective:

To examine the association between maternal age and the risk of stillbirth.

Secondary objectives:

1. To determine if the effect of maternal age is confounded by paternal age, fetal sex, parity, history of stillbirth, mother's residential area, or year of birth.
2. To determine if the effects of paternal age, fetal sex, parity, history of stillbirth, mother's residential area and year of birth interact with the influence of maternal age on stillbirth risk.

3.3 Materials and methods

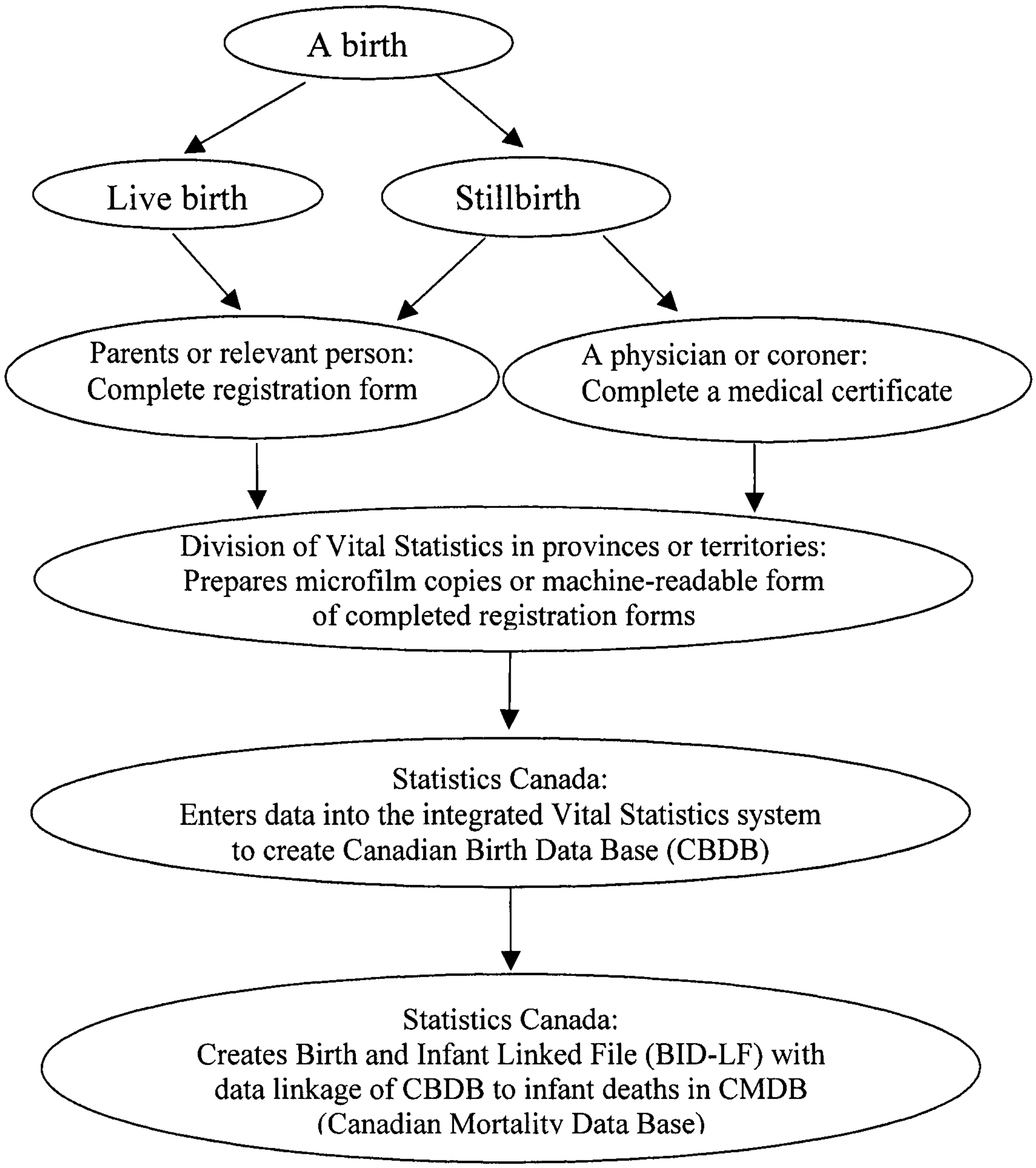
3.3.1 Database

3.3.1.1 Birth and stillbirth registry in Canada

The registration of all births (both live births and stillbirths) is mandatory under provincial and territorial Vital Statistics Acts in Canada. Although the acts are not identical, and the registration of birth information varies somewhat from province to province, key elements on birth certificates are uniform. The items recorded for each birth by all provinces and territories include: date and place of birth; sex, birth weight and gestational age of fetus; parents' age; marital status and birth place; mother's place of residence; type of birth (singleton or multiple births); parity; and underlying cause of death (if stillbirth). Appendix C shows an example of a live birth and a stillbirth certificate from Alberta.

All births and stillbirths are registered in the Canadian Vital Statistics System. Figure 3.1 summarizes how birth data gets into the Canadian Vital Statistics System. Every live birth must be registered with the Division of Vital Statistics in the provincial Ministry of Health, usually within 30 days from birth. Births are registered by parents or their representatives. If a stillbirth occurs, parents complete a stillbirth certificate and a medical practitioner or coroner completes a medical certificate, both of which are delivered to a funeral director. The funeral director submits these forms to the Division of Vital Statistics in the Ministry of Health. The provincial or territorial registrar of Vital Statistics produces a microfilm of source documents which is submitted along with machine-readable records to Statistics Canada. The data are reformatted, edited, verified, and stored in Statistics Canada's Integrated Vital Statistics files from which the Canadian Birth Data Base (CBDB) is created.

Figure 3.1 Flowchart of birth data



3.3.1.2 Birth and infant death linked dataset

This study used Statistics Canada's Birth and Infant Death Linked File (BID-LF) for the years 1985-2000. Statistics Canada creates the BID-LF by linking infant deaths in Canadian Mortality Data Base (CMDB) to CBDB using a probabilistic linkage (or maximum likelihood linkage) that was performed using the Generalized Record Linkage System developed by Statistics Canada. This linkage system compares fields common to the two files, assigns weights to the resulting links and calculates a total weight. Corresponding strategies are adopted to confirm a linked record according to the value of the total weight. Details regarding data linkage are available in the literature.[146] Information for each birth record (both live births and stillbirths) in the BID-LF includes the mother's name and address, maternal and paternal age, sex of fetus or infant, year of birth, gestational age, birth weight, the number of previous live birth and stillbirth, birth type and the one year survival status for live births.

Since birth registration is compulsory in each Canadian province and territory, reporting is virtually complete. Regular processing operations exist to identify duplicate registrations and missing registrations. A standard data dictionary and correlation edits for data entry which showing the standard record layout for inputting data including description of variables and their valid values are recommended by Statistics Canada to provincial and territorial registrars to improve the quality of data input. Statistics Canada also applies more extensive edit routines to the data to determine the completeness and quality of the data. The response rates for most of the demographic variables on CBDB are very high. For example, Statistics Canada found a response rate for last name of mother and date of birth was both 100% on the stillbirth database of 1997-2000.[147]

There is extensive agreement between important variables in the BID-LF and provincial records that are collected independently by the provincial perinatal surveillance programs. For example, the agreement rate for birth weight categories was as high as 97%. In addition, the quality of coding for some variables in BID-LF has improved by identifying and correcting coding errors in the CBDB and CMDB during the live birth and infant death linkage process.[146]

3.3.2 Inclusion/Exclusion criteria

In this study, all live births and stillbirths from 1985 to 2000 from all Canadian provinces except Ontario and Newfoundland were extracted from the BID-LF (n= 3,638,994). We excluded births to mothers residing in Ontario because of documented data quality concerns.[148] We also excluded births in Newfoundland because of incomplete data before 1991.[4] We restricted our analysis to singleton births due to the inherent higher risk nature of multiple births (n= 80,814). We also excluded births with unknown maternal age (n=790) since this was the key exposure variable of this study. Because of the WHO recommended registry criterion for live births and stillbirths, we excluded births that had a birth weight less than 500 grams or a gestational age less than 22 weeks with a missing value for birth weight (n=7,397).

In the final study sample of 3,549,993, we assumed that clinically implausible values of gestational age more than 44 weeks (n=17) and birth weight heavier than 7000 grams (n=13) were potential coding errors and changed their values to missing. We also treated gestational age less than 20 weeks (n=53) as a missing value because of the WHO recommended registration criterion for births and the biases on mortality statistics introduced by its inclusion.[149]

3.3.3 Variables considered in the study

3.3.3.1 Stillbirth

This is the outcome for the analysis. In our study, stillbirth was defined by WHO recommended criterion of registration as a fetal death with a birth weight of at least 500 grams or a gestational age of at least 22 weeks when birth weight is unknown.

3.3.3.2 Maternal age

Maternal age is the age of mother at delivery. It was rounded down to the nearest year and was modeled as a continuous and categorized variable separately in the regression analysis. For categorical analyses, maternal age was divided into 7 groups: <20, 20-24, 25-29, 30-34, 35-39, 40-44 and ≥ 45.

3.3.3.3 Paternal age

Paternal age is the age of father at delivery. It was rounded down to the nearest age and was also modeled as a continuous and categorized variable separately in the regression analysis. For categorical analyses, paternal age was divided into 7 groups: <20, 20-24, 25-29, 30-34, 35-39, 40-44 and ≥ 45.

3.3.3.4 Parity

In our study, parity is the number of previous live births of greater than 20 weeks born to the mother. This definition is commonly used in studies.[7,16,44] Parity is usually grouped into three levels: nulliparity; low multiparity; and grand multiparity. However, there is no universally accepted cut off point used to categorize low and grand multiparity. In our analysis, parity took the value of 0 for nulliparas who had no previous live births, 1 for multiparas who had one to three previous live births and 2 for grand multiparas who had four or more previous live births. The choice of parity 4 as the cut off point for grand multiparity was based on the suggestion of a recent large study (n=512,733) in Australia which found a sharply increased risk for obstetric complications, neonatal morbidity, and perinatal mortality starting from parity 4.[47]

3.3.3.5 Previous stillbirth

This variable was dichotomized based on whether a woman has had one or more previous stillbirths.

3.3.3.6 Others

Other covariates examined in the model included fetal sex, mother's residential area (provinces/territories) and the year of birth. The definitions and the codes in analyses of these factors are listed in table 3.1.

Table 3.1 Variables in the analyses

Variables	Values in database	Codes in analyses
Maternal age	Years	Continuous or categorized as: <20, 20-24, 25-29, 30-34,35-39, 40-44 and ≥45
Paternal age	Years	Continuous or categorized as: <20, 20-24, 25-29, 30-34, 35-39, 40-44 and ≥45
Gestational age: Complete weeks from the first day of last menstrual period to the time of delivery	Weeks	Categorized as: 20-21,22-23,24-25,26-27,28-31, 32-33,34-36,37-41 and ≥42
Fetal sex	1-male, 2-female	0-female, 1-male
Birth weight	Grams	Categorized as: <1500, 1500-2499, 2500-3999 and ≥ 4000
Parity: Total number of previous live birth and stillbirth	Times	Categorized as: 0, 1-3 and >3
Multiple births: Twins or the higher	New variable created from variable birth kind 1-singleton, ≥2-multiple	Categorized as: 0-singleton, 1-multiple
History of stillbirth	New variable created from number of previous stillbirth 0-No, ≥1-Yes	Categorized as: 0-No, 1-Yes
Year of birth	Calendar year	Categorized as: 1-1985, 2-1986, 3-1987, 4-1988 5-1989, 6-1990, 7-1991, 8-1992 9-1993, 10-1994, 11-1995 12-1996, 13-1997, 14-1998 15-1999, 16-2000
Mother's residential area	910-Nfld, 911-PEI, 912-NS, 913-NB,924-QC,946-MA, 947-Sask,948-AB,959-BC, 960-Yukon,961-NWT, 962-Nunavut (from 1999)	1-PEI, 2-NS, 3-NB, 4-QC, 6-MA 7-Sask, 8-AB, 9-BC, 10-Yukon 11-NWT(including Nunavut)

3.3.4 Data imputation

The preliminary exploration of the database provided the percentages of missing values for the variable in table 3.2.

Table 3.2 Percentages of missing values for the covariates in the study dataset

Variables	Percentages (%) Total births (n=3,549,993)	 Live births (n=3,534,088)	 Stillbirths (n=15,905)
Paternal age (years)	8.35	8.27	24.11
Parity	1.40	1.39	3.34
History of previous stillbirth	1.39	1.38	1.87
Birth weight	0.26	0.23	5.32
Gestational age	0.47	0.47	1.53
Fetal sex	0.01	0.01	0.43
Birth year	0.00	0.00	0.00
Mother's residential area	0.00	0.00	0.00
Any above variables	10.23	10.14	30.98

Data imputation was used to account for missing values because the proportion of observations having at least one missing value exceeded 5%.[150] Data imputation was also considered important because the distribution of key variable (maternal age) varied significantly between the original data set and the data set that only included observations with any missing values. As we observed from table 3.3, mothers with younger age were more likely to have missing data. Since paternal age had a significantly higher missing percentage (close to 10%), we adopted a multiple imputation method done by the proc MI in SAS to impute the missing values for the variables with missing data.

Table 3.3 Distribution of maternal age in three different data sets

Maternal age (years)	Percentages (%) Data set A (n=3,549,993)	Data set B (n=363,240)	Data set C (n=3,186,753)
< 20	6.5	23.5	4.6
20-24	22.3	32.3	21.1
25-29	35.9	23.9	37.3
30-34	25.6	14.0	26.9
35-39	8.5	5.3	8.9
40-44	1.2	0.9	1.2
≥ 45	0.0	0.0	0.0
Median (years)	28	23	28

A --- Original data set
B --- Data set of observations with any missing values
C --- Complete data set (excluding those with any missing values)

Multiple imputation replaces each missing value with one from a set of plausible values. Therefore, multiple imputation encompasses the uncertainty about the correct imputation value. It prevents the estimated variance of the parameter estimates from being biased toward zero.[151] Multiple imputation assumes that the missing data are missing at random (MAR). This means the probability of missing data on a variable Y is unrelated to the true value of Y, but may depend on values of other variables. For example, consider a data set with variables Y1, Y2 and Y3, among which Y1 and Y2 are fully observed, and Y3 has missing values. MAR assumes that the probability that Y3 is missing for an individual may be associated with the individual's values of Y1 and Y2, but not with its value of Y3.[152]

Multiple imputation inference involves three distinct phases:

- The missing data are imputed m times to generate m complete data sets.

- The m complete data sets are analyzed by using standard procedures.
- The results from the m analyses are combined for the final results.

Because of the arbitrary missing data pattern examined, which means that when a variable Xj is missing for the individual i, not all subsequent variables Xk (where k>j) are necessarily missing for that individual, the Markov Chain Monte Carlo (MCMC) method was chosen as the imputation mechanism in the procedure MI. MCMC method creates multiple imputations by using simulations from a Bayesian prediction distribution for normal data. [152] The variables included in the model of the procedure MI contain stillbirth, maternal age, paternal age, parity, previous stillbirth, fetal sex, birth year and provinces/territories. The imputation time of 2 (m=2) was chosen because the large sample size prohibited a greater number of imputations.

Distributions of maternal age and the covariates in imputed data sets were compared with those in original data set and the complete data set which excluded observations with any missing value (Table 3.4). There were no differences in distributions of maternal age and the covariates between the four data sets except paternal age in two imputed data sets and maternal age in complete data set. The lower percentage for younger maternal age in complete data set indicated that missing values of paternal age are more likely to be found among younger subjects, which leading to the fact that higher percentages for younger paternal age were observed in the imputed data sets compared to those in the original and complete data set. There were no differences in distributions of all variables between two imputed data sets.

Table 3.4 Distributions of the variables in four different data sets

Characteristics	Original dataset (n=3,549,993)	#Complete dataset (n=3,186,753)	Imputed dataset1 (n=3,549,993)	Imputed dataset2 (n=3,549,993)
Maternal age (years)				
< 20	6.52	4.58	6.52	6.52
20-24	22.56	21.11	22.56	22.56
25-29	35.89	37.26	35.89	35.89
30-34	25.62	26.94	25.62	25.62
35-39	8.51	8.87	8.51	8.51
40-44	1.16	1.19	1.16	1.16
≥ 45	0.04	0.04	0.04	0.04
Median (years)	28	28	28	28
Paternal age (years)				
<20	1.45*	1.45	2.27	2.28
20-24	11.77*	11.76	13.03	13.03
25-29	31.65*	31.62	31.58	31.56
30-34	32.59*	32.60	31.50	31.50
35-39	15.80*	15.81	15.19	15.20
40-44	4.94*	4.94	4.73	4.73
≥ 45	1.81*	1.81	1.70	1.70
Missing (%)	8.35	-	-	-
Median (years)	30	30	30	30
Fetal sex				
Male	51.32	51.37	51.33	51.33
Female	48.67	48.63	48.67	48.67
Missing	0.01	-	-	-
Parity				
0	43.97	42.92	43.98	43.98
1-3	53.59	54.77	53.61	53.61
≥ 4	2.41	2.31	2.41	2.41
Missing	0.02	-	-	-
Previous stillbirth:				
No	96.09	97.44	97.47	97.47
Yes	2.53	2.56	2.53	2.53
Missing	1.39	-	-	-

Note: * --- denominator excluding those with missing paternal age (n=296,267)
--- data set excluding observations with any missing value

3.3.5 Statistical analyses

3.3.5.1 Descriptive analyses

Different kinds of descriptive analyses were performed for maternal age and each covariate. Frequency distributions were obtained for categorical variables and continuous variables after grouping. We compared the frequency distributions of characteristics among stillbirths versus live births. We also obtained the distributions of the covariates in each maternal age group. Proportions of maternal age groups by year were presented as well to examine the temporal trend of maternal age.

The stillbirth rate was calculated as the number of stillbirths (see definition in section 3.3.3.1) divided by the total number of births (sum of live births and stillbirths). Rates were calculated for each year. Temporal trends of overall and maternal age specific stillbirth rate were assessed using the Chi square test for linear trend. A geographic variation in overall stillbirth rate was obtained by mother's residential province or territory and examined by using the Chi square test. We also calculated stillbirth rates for other covariates stratified by 7 maternal age groups (<20, 20-24, 25-29, 30-34, 35-39, 40-44 and ≥ 45) to explore the possibility of effect modification on the association between maternal age and the risk of stillbirth.

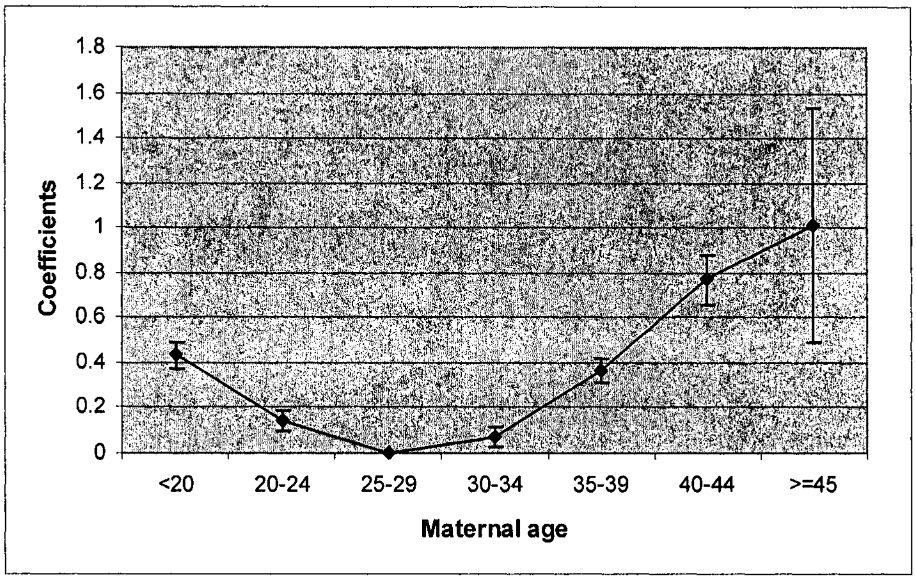
3.3.5.2 Modeling strategies

Since stillbirth risk is a dichotomous outcome, we used unconditional logistic regression to examine the association between this outcome and maternal age while controlling for the covariates. Model parameters were estimated using the maximum likelihood method. The logistic models were also used to predict stillbirth risk for maternal age after adjusting for confounder values. Maternal and paternal age was treated as continuous or categorized variables separately in different regression models. Age was divided into seven groups: <20, 20-24, 25-29, 30-34, 35-39, 40-44 and ≥ 45 years.

Assessment of linearity

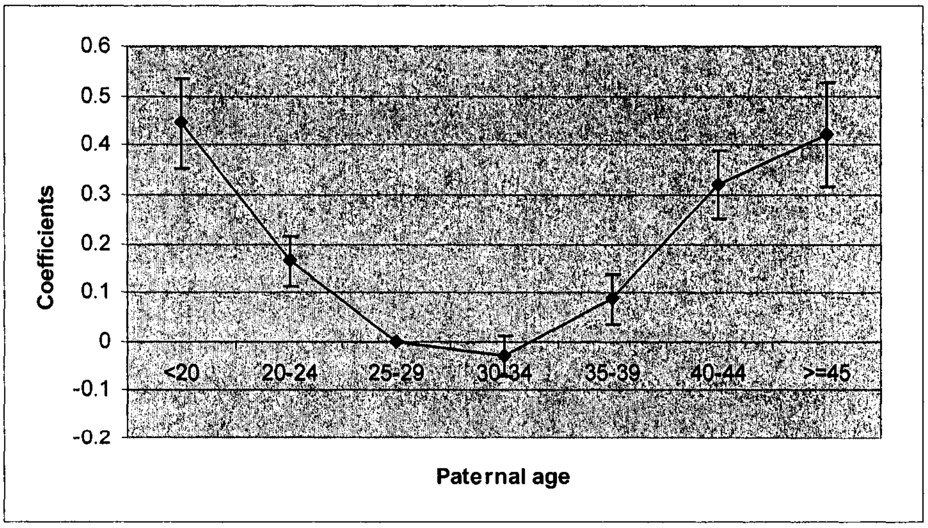
Linearity between stillbirth and maternal or paternal age was examined when age was modeled as a continuous variable. We plotted the parameter estimates from a univariate logistic regression model verses mid-points of 7 age groups with age of 25 to 29 as the reference group. The same process was used for paternal age. The curves showed a quadratic relationship between stillbirth risk and both maternal and paternal age (Figure 3.2 and 3.3). We also assessed the linearity of age using the log likelihood ratio test by comparing the model with age as a continuous variable and that with age as a categorized variable. The test statistic was calculated as –2 times the difference of log-likelihood statistics between two models. The p-value of the test was determined by comparing the test statistics to a chi-square distribution with degrees of freedom which calculated as the difference of the numbers of parameters between the two models. This test also supported the non-linearity relationship between stillbirth and maternal age ($G=419.93$; $df=5$; $p<0.0001$) or stillbirth and paternal age ($G=268.38$; $df=5$; $p<0.0001$) observed through the curves.

Figure 3.2 Parameter estimates of stillbirth by maternal age in a univariate logistic regression model



Note: Age group of 25-29 was the reference group

Figure 3.3 Parameter estimates of stillbirth by paternal age in a univariate logistic regression model



Note: Age group of 25-29 was the reference group

Selection of type of logistic regression

In terms of the non-linear relationship between maternal or paternal age and stillbirth risk, different regression models that deal with non-linearity issue were tested. These include regression models with introducing polynomial terms of age such as age square and age cube. We determined the terms kept in the final model by checking the statistical significance of the terms and the contribution to the model by adding an interest term. To minimize the possible colinearity when introducing terms for a continuous variable, we modeled maternal age with its centered value (age – age median) in regression models and compared the models with those using non-centered age.

Establishment of multivariate regression model

Univariate logistic regression was applied to maternal age and each of the covariates in the BID-LF with the exception of birth weight and gestational age. These two variables were not included in the model because they would be reduced if stillbirth occurs. In other words, their value may be the result of, rather than the cause of, stillbirth. Therefore, they should not play a role in estimating the risk of stillbirth in a predictive model.

Variables having p-value of less than 0.05 for Wald Chi-Square test in the univariate model were selected for potential inclusion in the multivariate regression model. We entered these candidate variables sequentially (i.e. one by one) into the model. We determined the significance of added variables with the log-likelihood ratio test by calculating the log-likelihood statistics of the models with and without the variable of interest. The added variable was deemed significant and kept in the model if the log-likelihood test was significant.

Descriptive analysis of the distributions of stillbirth rates among each maternal age group for the covariates revealed that parity and paternal age could be potential effect modifiers for the association of maternal age and stillbirth risk. We therefore examined interaction terms for these two variables with maternal age in the multivariate model. We compared models with and without the interaction terms. The interaction terms were considered statistically significant if the log-likelihood ratio test was significant, and the estimates for the terms in the model were statistically significant as well ($p<0.05$ for Wald Chi-Square test).

In terms of the potential problems of small numbers at the extremes of maternal age, parity and paternal age, we excluded subjects with unusual combinations between the three variables including 1) maternal age of < 15 and parity of ≥1; 2) maternal age of < 18 and parity of ≥ 3; 3) paternal age of < 20 and maternal age of ≥ 35 and 4) maternal age of < 20 and paternal age of ≥ 50. These models were compared with the corresponding models from the complete data set.

The adjusted predicted probabilities of stillbirth by maternal and paternal age from the final regression model were displayed using 3 dimensional curves. These estimates adjusted for all other covariates in the model and were presented for distinct strata of the important covariates.

The same process of establishing the main effect model and checking the interaction was conducted for the model with maternal and paternal age being categorized into 7 groups. We formed a composite variable that categorized by both maternal age and parity in the final model and presented the adjusted ORs by these new categories stratified by maternal age and parity.

All analyses were performed by Statistical Analysis Systems (SAS, version 8.2)

CHAPTER 4 RESULTS

4.1 Descriptive analysis

4.1.1 Distributions of maternal age and the covariates

4.1.1.1 Proportions of maternal age

There were 3,549,993 total births in Canada excluding Newfoundland and Ontario during the study period of 1985-2000. In 2000, the proportions of births to women across specific maternal age groups were 6.1% (< 20y), 20.3% (20-24y), 31.8% (25-29y), 27.3% (30-34y), 12.4% (35-39y) and 2.1% (≥40y). Compared to the year 1985, the proportion of older maternal age more than doubled at the age group of 35-39 (5.3% vs. 12.4%) and more than tripled at the age group of 40 or greater (0.6% vs. 2.1%) (Table 4.1).

A strong increasing linear trend in the percentages of births to women of age 35 years or older is also shown in figure 4.1. The percentage increased significantly from 5.9% in 1985 to 14.5% in 2000 (x^2=29893.45; df=15; p<0.0001).

Figure 4.1 Percentage of births to women 35 and older in Canada excluding Newfoundland and Ontario, 1985 to 2000

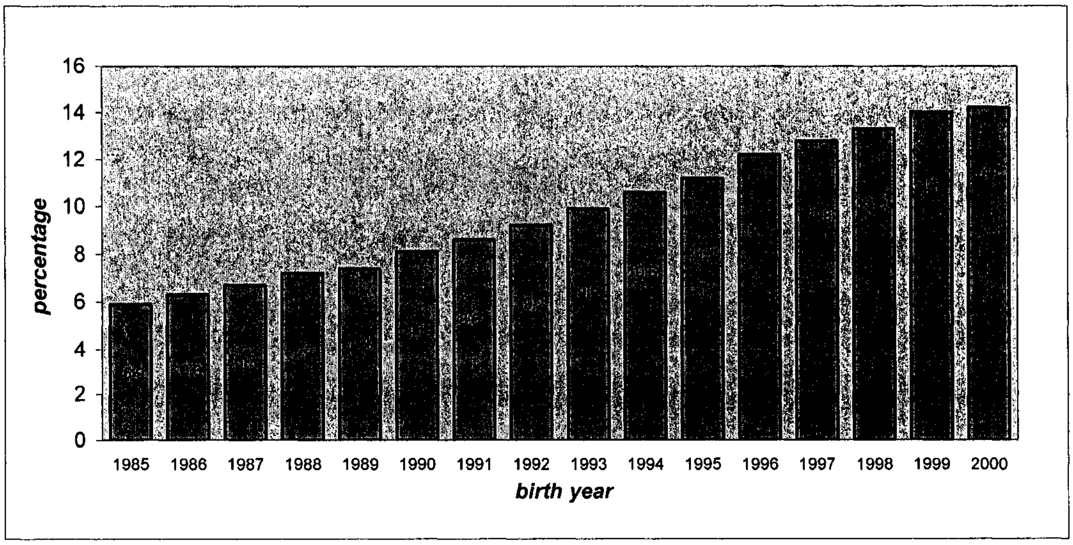


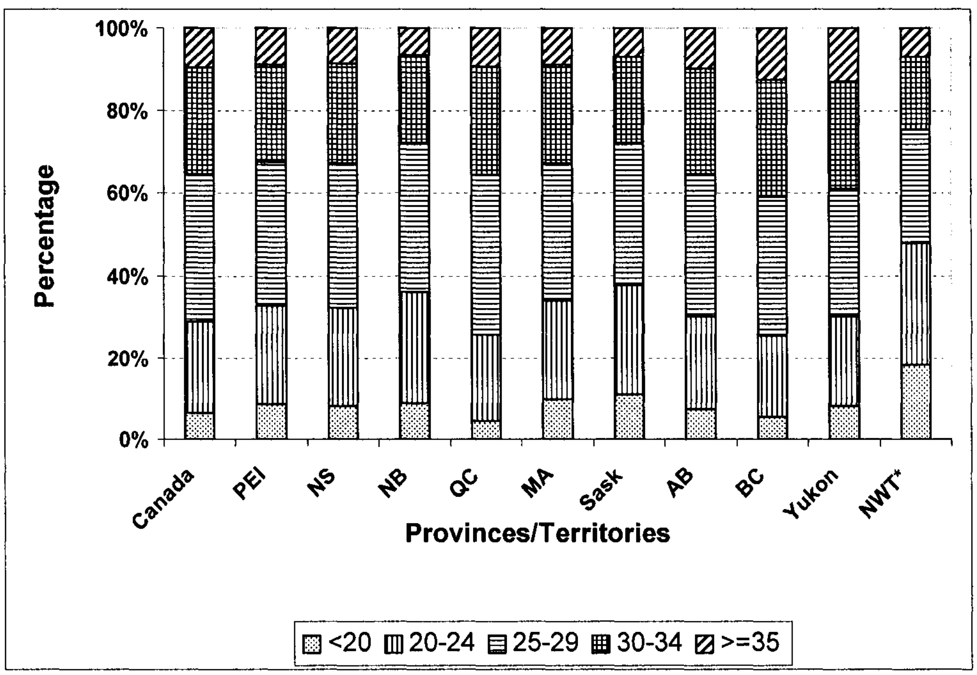
Table 4.1 Maternal age distribution in Canada excluding Newfoundland and Ontario, 1985-2000

Birth year	Maternal age (year)					
	<20	20-24	25-29	30-34	35-39	≥ 40
1985	6.5	27.9	39.4	20.4	5.3	0.6
1986	6.4	26.5	39.5	21.2	5.6	0.7
1987	6.4	25.1	39.5	22.4	5.9	0.8
1988	6.4	23.9	39.5	23.1	6.4	0.9
1989	6.5	23.0	39.1	24.0	6.6	0.8
1990	6.5	21.9	38.6	24.9	7.2	0.9
1991	6.6	21.6	37.5	25.7	7.6	1.0
1992	6.6	20.9	36.6	26.8	8.1	1.1
1993	6.6	20.9	35.1	27.4	8.8	1.2
1994	6.8	20.7	33.9	28.0	9.3	1.3
1995	6.9	20.7	32.7	28.6	9.8	1.4
1996	6.6	20.4	32.4	28.4	10.6	1.6
1997	6.4	20.4	32.3	28.1	11.1	1.7
1998	6.6	20.6	32.0	27.6	11.5	1.8
1999	6.4	20.5	31.8	27.3	12.1	1.9
2000	6.1	20.3	31.8	27.3	12.4	2.1

4.1.1.2 Distributions of covariates by maternal age

The distributions of maternal age and the covariates (paternal age, fetal sex, parity and previous stillbirth) within each maternal age group are presented in table 4.2. Except for fetal sex, for which distribution was similar across all maternal age groups, changes in the distribution of all other covariates between maternal age groups were observed. Older women were more likely to be multiparous and were more likely to have experienced previous stillbirth. As expected, women usually have a male partner whose age was similar or a few years older. In addition, we compared the distribution of maternal age geographically (Figure 4.2). Maternal age was relatively younger in the Atlantic provinces and Saskatchwan and older in British Columbia. In the Northwest Territories, a much higher than average percentage was observed in the extremely young age group (< 20y).

Figure 4.2 Distribution of maternal age in each province/territory,1985-2000



Note: * including Nunavut

4.1.1.3 Distribution of characteristics between live births and stillbirths

We compared the characteristics of maternal age and other covariates between stillbirths and live births (Table 4.3). Compared to live births, women having a stillbirth were younger (< 20 years) or older (>=35 years). This age pattern was similar for the age of their male partners (<25 or >=40 years). Women having stillbirth were more likely to be nulliparous or grand multiparous (parity>3) and were more likely to have had a prior stillbirth. In addition, the stillbirth was more likely to be male.

Table 4.2 Distribution of characteristics by maternal age among 3,549,993 births in Canada excluding Newfoundland and Ontario, 1985-2000

Characteristics	Total		Maternal age (%)						
	No.	%	<20 (N=231,528)	20-24 (N=790,102)	25-29 (N=1,274,252)	30-34 (N=909,430)	35-39 (N=302,042)	40-44 (N=41,327)	≥ 45 (N=1,312)
Paternal age (years)									
<20	80,958	2.3	26.2	2.3	0.1	0.0	0.0	0.0	0.1
20-24	462,156	13.0	50.1	34.7	4.8	1.0	0.4	0.3	0.2
25-29	1,121,017	31.6	18.6	45.5	46.9	11.8	4.2	2.2	1.7
30-34	1,118,302	31.5	3.9	13.4	36.9	51.3	20.6	9.8	6.6
35-39	539,383	15.2	0.8	3.0	8.6	27.7	46.7	25.2	14.6
40-44	167,977	4.7	0.2	0.7	1.9	6.3	21.1	39.4	23.1
45-49	43,466	1.2	0.1	0.2	0.5	1.4	5.1	16.7	33.5
≥ 50	16,734	0.5	0.0	0.1	0.2	0.5	1.9	6.3	20.3
Fetal sex									
Male	1,727,718	48.7	48.7	48.7	48.6	48.7	48.8	48.6	47.8
Female	1,822,275	51.3	51.3	51.3	51.4	51.3	51.2	51.4	52.2
Parity									
0	1,561,491	44.0	82.8	57.7	43.3	30.4	25.2	23.3	20.3
1-3	1,902,841	53.6	17.2	41.8	55.1	66.1	67.4	61.7	50.7
≥ 4	85,661	2.4	0.0	0.6	1.6	3.4	7.5	15.0	29.0
Previous stillbirth:									
No	3,460,303	97.5	98.9	98.1	97.6	97.0	96.0	94.6	93.7
Yes	89,690	2.5	1.1	1.9	2.4	3.0	4.0	5.4	6.3

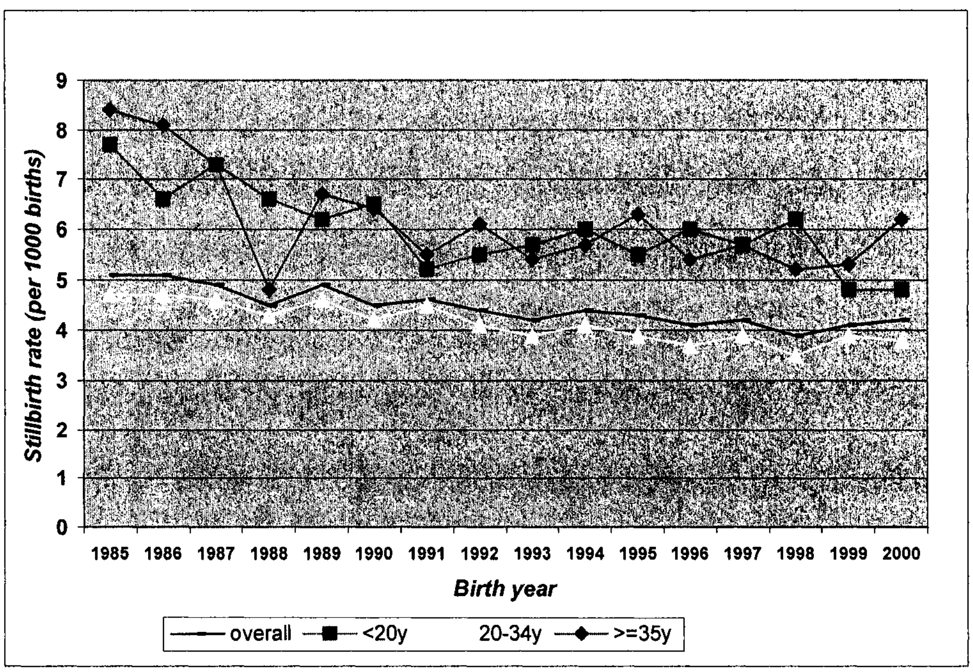
Table 4.3 Maternal age and other characteristics between live births and stillbirths in Canada excluding Newfoundland and Ontario, 1985-2000

Characteristics	Live births (n=3,534,088)		Stillbirths (n=15,905)		P-value
	No.	%	No.	%	
Maternal age (years)					
<0.0001					
< 20	230,130	6.5	1,398	8.8	
20-24	786,522	22.3	3,580	22.5	
25-29	1,269,237	35.9	5,015	31.5	
30-34	905,586	25.6	3,844	24.2	
35-39	300,337	8.5	1,705	10.7	
40-44	40,978	1.2	349	2.2	
≥ 45	1,298	0.0	14	0.1	
Paternal age (years)					
<0.0001					
<20	80,317	2.3	543	3.4	
20-24	460,208	13.0	2,308	14.5	
25-29	1,116,096	31.6	4,687	29.5	
30-34	1,113,758	31.5	4,539	28.5	
35-39	536,886	15.2	2,486	15.6	
40-44	166,996	4.7	960	6.0	
≥ 45	59,827	1.7	382	2.4	
Fetal sex					<0.0001
Male	1,813,731	51.3	8,426	53.0	
Female	1,720,357	48.7	7,479	47.0	
Parity					<0.0001
0	1,553,182	43.9	8,024	50.5	
1-3	1,895,896	53.7	7,225	45.4	
≥ 4	85,010	2.4	656	4.1	
Previous stillbirth					<0.0001
No	3,444,903	97.5	15,259	95.9	
Yes	89,185	2.5	646	4.1	

4.1.2 Stillbirth rate

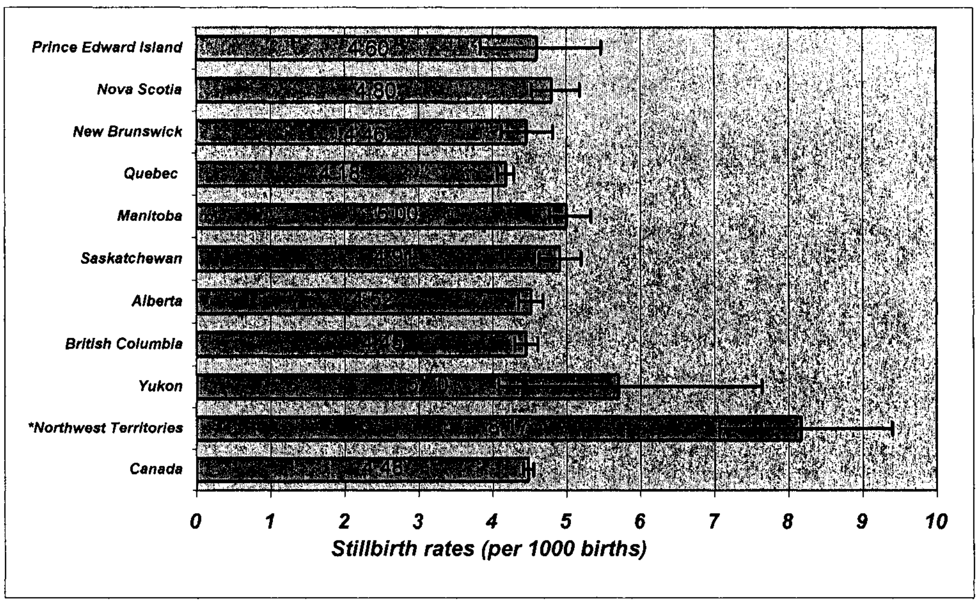
There were 15,905 stillbirths reported between 1985 and 2000, giving an overall stillbirth rate of 4.5 per 1,000 total births. The highest rate was 5.1 in 1985 and the lowest was 3.9 per 1,000 total births in 1998. The overall stillbirth rate decreased significantly from 5.1 per 1,000 total births in 1985 to 4.2 per 1,000 total births in 2000 (x^2=81.26; df=15; p<0.0001 for linear trend test). Each age-specific stillbirth rate also showed a significant decrease, which the Chi squares were 13.55, 81.05 and 15.25 for maternal age group of <20, 20-34 and ≥ 35 separately and all the p-values were <0.001 for the linear trend test. A greater decrease in rate occurred in younger mothers (<20 years) during study period (Figure 4.3).

Figure 4.3 Temporal trends of stillbirth rate by maternal age in Canada excluding Newfoundland and Ontario, 1985-2000



There were significant geographic variations in stillbirth rates (x^2=136.85; df=9; p<0.0001). The lowest stillbirth rate was found in Quebec with a rate of 4.18 per 1,000 total births. British Columbia and provinces on the east coast (except Nova Scotia) had lower stillbirth rates than the prairie provinces (except Alberta) and territories. The Northwest Territories had the highest stillbirth rate which was 8.17 per 1,000 total births (Figure 4.3).

Figure 4.4 Stillbirth rate and 95% Confidence Interval by provinces/territories in Canada excluding Newfoundland and Ontario, 1985-2000



* Included Nunavut

Table 4.4 shows stillbirth rates at different levels of the covariates stratified by maternal age. There appeared to be no interaction between maternal age and fetal sex or maternal age and previous stillbirth for stillbirth rates. However, patterns of stillbirth rates by maternal age group appeared to vary for paternal age and parity. This suggests paternal age and parity may be potential effect modifiers for the impact of maternal age on stillbirth.

Table 4.4 Stillbirth rates (per 1,000 total births) among the covariates stratified by maternal age among 3,549,993 births in Canada Excluding Newfoundland and Ontario, 1985-2000

	Stillbirths		Maternal age (years)						
Covariates	No.	Rate	<20 (N=231,528)	20-24 (N=790,102)	25-29 (N=1,274,252)	30-34 (N=909,430)	35-39 (N=302,042)	40-44 (N=41,327)	≥ 45 (N=1,312)
Overall	15,905	4.5	6.0 (1,398)*	4.5 (3,580)	3.9 (5,015)	4.2 (3,844)	5.6 (1,705)	8.4 (349)	10.7 (14)
Paternal age (years)									
<20	543	6.7	6.4 (391)	7.1 (130)	11.9 (19)	--- (2)	--- (1)	--- (0)	--- (0)
20-24	2,308	5.0	5.4 (629)	4.6 (1,263)	5.4 (331)	8.6 (76)	6.1 (8)	--- (1)	--- (0)
25-29	4,687	4.2	7.0 (303)	4.4 (1570)	3.7 (2234)	4.7 (503)	5.5 (70)	6.5 (6)	--- (0)
30-34	4,539	4.1	6.4 (58)	4.4 (469)	3.8 (1801)	3.9 (1807)	6.1 (380)	5.4 (22)	--- (2)
35-39	2,486	4.6	4.5 (8)	4.6 (110)	4.5 (495)	4.2 (1064)	5.1 (725)	8.1 (84)	--- (0)
40-44	960	5.7	16.6 (8)	4.5 (26)	4.1 (100)	5.1 (294)	6.1(385)	8.8 (143)	--- (4)
≥ 45	382	6.3	---(1)	4.9 (12)	4.2 (35)	5.5 (98)	6.4 (135)	9.8 (93)	11.2 (8)
Fetal sex									
Male	8,426	4.6	6.3 (748)	4.7 (1921)	4.0 (2641)	4.3 (2005)	5.9 (910)	9.2 (194)	10.2 (7)
Female	7,479	4.3	5.7 (650)	4.3 (1659)	3.8 (2374)	4.2 (1839)	5.4 (795)	7.7 (155)	11.2 (7)
Parity									
0	8,024	5.2	6.0 (1,144)	4.8 (2174)	4.5 (2487)	5.6 (1534)	7.9 (597)	8.8 (84)	--- (4)
1-3	7,225	3.8	6.3 (253)	4.1 (1368)	3.4 (2353)	3.5 (2090)	4.7 (964)	7.5 (192)	7.5 (5)
≥ 4	656	7.7	--- (1)	8.5 (38)	8.4 (175)	7.1 (220)	6.4 (144)	11.7 (73)	13.1(5)
Previous stillbirth:									
No	15,259	4.4	6.0 (1374)	4.4 (3447)	3.9 (4835)	4.2 (3665)	5.6 (1610)	8.1 (315)	10.6 (13)
Yes	646	7.2	9.6 (24)	8.7 (133)	5.9 (180)	6.5 (179)	7.9 (95)	15.2 (34)	--- (1)

*: numbers in parentheses are numbers of stillbirth; --- : stillbirth number less than 5

4.2 Regression Analyses

Based on the modeling strategy described in Section 3.3.5.2 of Chapter 3, we compared the models having different higher orders of maternal age and found that the model with age and age square had the best fit since adding the cubic term did not improve the model. Models with centered maternal age produced a very similar modeling effect as that with non-centered age. The relevant information was summarized in table 4.5. Similar results were found for paternal age.

Table 4.5 Comparison of the models with different terms of maternal age

	Log likelihood test			
Models	G	D_df	P-value	P-values for terms
Non-centered age:				
$SB=\alpha+\beta X$	4.15	1	<0.05	0.0415 for X
$SB= \alpha+\beta_1 X + \beta_2 X^2$	505.57	1	<0.001	<0.0001 for X and X^2
$SB= \alpha+\beta_1 X+\beta_2 X^2+\beta_3 X^3$	0.04	1	>0.05	<0.001 for X, 0.0149 for X^2, 0.8547 for X^3
Centered age:				
$SB=\alpha+\beta X$	4.15	1	<0.05	0.0415 for X
$SB= \alpha+\beta_1 X + \beta_2 X^2$	505.57	1	<0.001	0.0281 for X, <0.0001 for X^2
$SB= \alpha+\beta_1 X+\beta_2 X^2+\beta_3 X^3$	0.04	1	>0.05	0.1639 for X, <0.0001 for X^2, 0.8547 for X^3

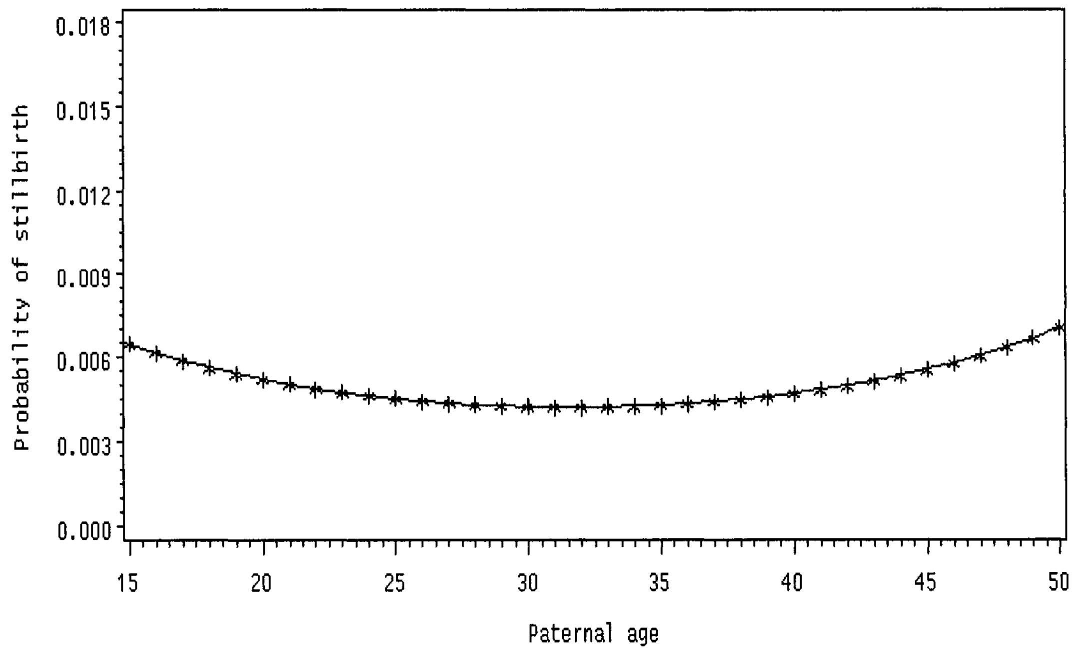
Note: SB---stillbirth; X---maternal age; G---difference of –2logL between two models; D_df---difference of degree of freedom between two models

The crude odds ratio and 95% CI were calculated by univariate logistic regression. Parity, previous stillbirth, fetal sex, year of birth, and mother's residential area all had a statistically significant relationship with stillbirth risk (Table 4.6). Paternal age was also significantly associated with risk of stillbirth and demonstrated a non-linear relationship (Figure 4.5). Additional models confirmed that the paternal age effect could be modelled using a quadratic form ($p<0.0001$ for the estimates of both age and age square). This suggests that these variables are the candidates for the multivariate logistic regression model.

Table 4.6 Crude odds ratio and 95% Confidence Intervals (95% CI) of stillbirths, Canada excluding Newfoundland and Ontario, 1985-2000

Variables	Crude odds ratio	95% CI
Fetal sex		
Male	1.164	1.038 - 1.082
Female	Reference	
Parity		
0	1.355	1.310 - 1.404
1-3	Reference	
≥ 4	2.026	1.870 - 2.197
Previous stillbirth:		
No	Reference	
Yes	1.633	1.510 - 1.768
Birth year		
1985	Reference	
1986	0.997	0.919 - 1.081
1987	0.969	0.892 - 1.052
1988	0.881	0.810 - 0.958
1989	0.962	0.886 - 1.043
1990	0.889	0.818 - 0.965
1991	0.907	0.836 - 0.985
1992	0.863	0.794 - 0.938
1993	0.825	0.758 - 0.899
1994	0.856	0.786 - 0.931
1995	0.837	0.768 - 0.912
1996	0.802	0.735 - 0.875
1997	0.826	0.757 - 0.902
1998	0.766	0.700 - 0.839
1999	0.808	0.739 - 0.884
2000	0.827	0.756 - 0.905
Provinces/Territories		
Prince Edward Island	1.102	0.926 - 1.313
Nova Scotia	1.161	1.081 - 1.248
New Brunswick	1.068	0.983 - 1.160
Quebec	Reference	
Manitoba	1.209	1.138 - 1.285
Saskatchewan	1.176	1.104 - 1.253
Alberta	1.082	1.034 - 1.132
British Columbia	1.067	1.021 - 1.115
Yukon	1.356	1.000 - 1.839
Northwest Territories	1.965	1.703 - 2.268

Figure 4.5 Unadjusted paternal age effect on risk of stillbirth



To establish the best fitted multivariate regression model, a series of regression models were created to examine the effect of confounding or effect modification of these covariates with maternal age for stillbirth risk following the modeling strategy in Chapter 3. Table 4.7 summarizes the modeling process for establishing the main effects regression model. We left the variable of fetal sex out because of the very small confounding effect with maternal age on stillbirth risk. We kept the variable of prior stillbirth in the model due to clinical consideration although a minor confounding effect was found as well. The results summarized in table 4.7 show that the final main effects model includes maternal age (plus age square), paternal age (plus age square), parity, previous stillbirth, year of birth and mother's residential area.

Table 4.7 Modeling process of forming the main effects regression model

Models	Log likelihood test G	D_df	P-value	Change (%) of estimates of maternal age
1. $SB=X+X^2$	509.7	2	<0.0001	
2. $SB=X+X^2$+ Parity	425.3	2	<0.0001	15.5
3. $SB=X+X^2$+ Parity+PreSB	127.9	1	<0.0001	0.2
4. $SB=X+X^2$+ Parity+PreSB+Sex	18.2	1	<0.001	0.1
5. $SB=X+X^2$+ Parity+PreSB+Bthyr	135.0	15	<0.001	2.8
6. $SB=X+X^2$+ Parity+PreSB+Bthyr +Province	104.6	9	<0.001	4.6
7. $SB=X+X^2$+ Parity+PreSB+Bthyr +Province+ $Y+Y^2$	38.7	2	<0.001	10.9

Note: SB---stillbirth; X---maternal age; Y---paternal age; PreSB---prior stillbirth; Bthyr---birth year
G---difference of –2logL between two models;
D_df---difference of degree of freedom between two models

Potential effect modifiers for maternal age were tested. We found that introducing interaction terms of maternal age and parity to the main effect model had statistical significance and the estimates of the terms with maternal age were statistically significant, suggesting parity modifies the effect of maternal age on stillbirth risk. We could not find an effect of modification of paternal age on the relationship between maternal age and stillbirth in our analyses. To deal with the small number issue between higher parity and younger maternal age, we also used the same modeling method to model the variables for the data set which excluded subjects with the unusual combinations between maternal age, paternal age and parity described in 3.3.5.2. Modeling with this data set did not significantly change either magnitude or direction of the estimates in the regression models (Table 4.8).

Table 4.9 shows the estimates of the final model which was used to calculate adjusted predicted stillbirth risks for all combinations of maternal and paternal ages in the three dimensional curves. The corresponding odds ratios (95% CI) for the variables were also presented in table 4.9 except maternal age and parity because of their significant interaction and paternal age because of the age square term included in the model. The predicted risks of stillbirth were presented for distinct strata of parity. The curves were further stratified by previous stillbirth because of its significantly clinical influence. We used the average estimates of birth year (the year of 1994) and provinces/territories (Nova Scotia) for plotting the 3 dimensional curves (Figure 4.6-1 and Figure 4.6-2).

Table 4.8 Comparison of the estimates between models with and without excluding unusual combinations of maternal, paternal age and parity

Variables	Without exclusion		With exclusion	
	Estimates	P-values	Estimates	P-values
* Maternal age	-0.288	<0.000	-0.288	<0.000
Maternal age square	0.005	<0.000	0.005	<0.000
* Paternal age	-0.040	0.022	-0.040	<0.000
Paternal age square	0.001	0.003	0.001	<0.000
Parity				
0	-1.557	<0.000	-1.553	<0.000
1-3	Reference		Reference	
≥ 4	1.398	0.249	1.408	0.256
Previous stillbirth:				
No	Reference		Reference	
Yes	0.492	<0.000	0.492	<0.000
Birth year				
1985	Reference		Reference	
1986	-0.004	0.906	-0.004	0.920
1987	-0.035	0.410	-0.036	0.385
1988	-0.134	0.002	-0.134	0.002
1989	-0.046	0.264	-0.046	0.261
1990	-0.127	0.003	-0.127	0.003
1991	-0.110	0.009	-0.110	0.009
1992	-0.163	0.000	-0.163	0.000
1993	-0.214	<0.000	-0.214	<0.000
1994	-0.183	<0.000	-0.183	<0.000
1995	-0.212	<0.000	-0.212	<0.000
1996	-0.260	<0.000	-0.260	<0.000
1997	-0.232	<0.000	-0.232	<0.000
1998	-0.313	<0.000	-0.313	<0.000
1999	-0.265	<0.000	-0.265	<0.000
2000	-0.244	<0.000	-0.244	<0.000
Provinces/Territories				
Prince Edward Island	0.107	0.233	0.107	0.228
Nova Scotia	0.149	<0.000	0.149	<0.000
New Brunswick	0.079	0.063	0.079	0.059
Quebec	Reference		Reference	
Manitoba	0.161	<0.000	0.160	<0.000
Saskatchewan	0.147	<0.000	0.148	<0.000
Alberta	0.078	0.001	0.078	0.001
British Columbia	0.055	0.014	0.055	0.014
Yukon	0.266	0.087	0.266	0.088
Northwest Territories	0.585	<0.000	0.585	<0.000
Maternal age *parity				
Maternal age*parity 0	0.109	<0.000	0.109	<0.000
Maternal age*parity ≥ 4	-0.007	0.921	-0.008	0.936
Maternal age square*parity				
Maternal age square*parity 0	-0.001	0.000	-0.001	0.000
Maternal age square*parity ≥ 4	-0.001	0.633	-0.001	0.620

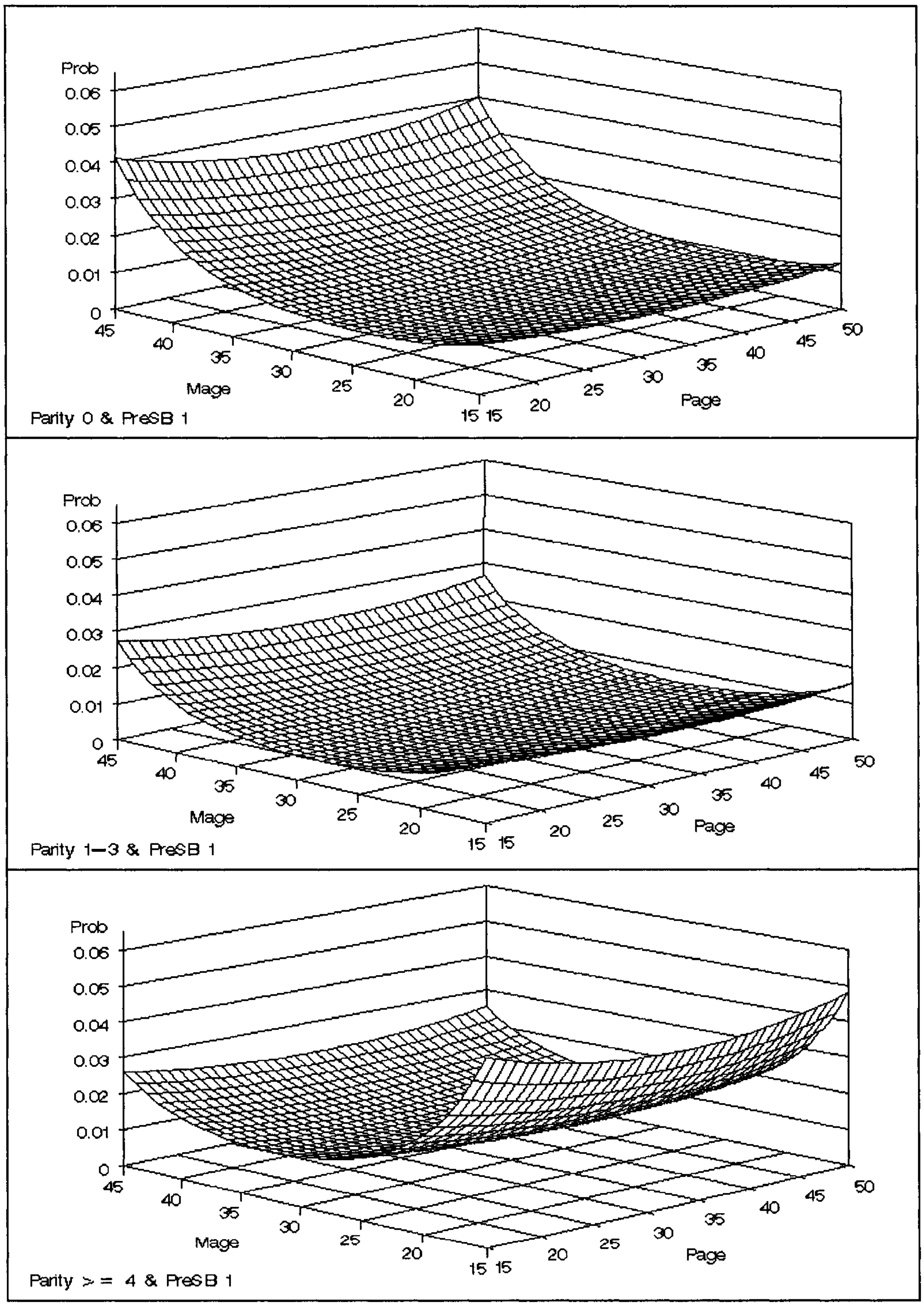
* Unit of maternal and paternal age in the model was expressed as a year

Table 4.9 Adjusted estimates and odd ratios (95% CI) in the model with age as a continuous variable

Variables	Estimates	P-values	ORs	95% CI
* Maternal age	-0.288	<0.000	---	---
Maternal age square	0.005	<0.000	---	---
* Paternal age	-0.040	0.022	---	---
Paternal age square	0.001	0.003	---	---
Parity				
0	-1.557	<0.000	---	---
1-3	Reference			
≥ 4	1.398	0.249	---	---
Previous stillbirth:				
No	Reference			
Yes	0.492	<0.000	1.636	1.510-1.772
Birth year				
1985	Reference			
1986	-0.004	0.906	0.998	0.920-1.082
1987	-0.035	0.410	0.966	0.890-1.049
1988	-0.134	0.002	0.875	0.804-0.951
1989	-0.046	0.264	0.955	0.880-1.036
1990	-0.127	0.003	0.881	0.811-0.956
1991	-0.110	0.009	0.896	0.825-0.972
1992	-0.163	0.000	0.850	0.781-0.923
1993	-0.214	<0.000	0.807	0.741-0.879
1994	-0.183	<0.000	0.833	0.765-0.907
1995	-0.212	<0.000	0.809	0.742-0.882
1996	-0.260	<0.000	0.771	0.707-0.842
1997	-0.232	<0.000	0.793	0.726-0.866
1998	-0.313	<0.000	0.731	0.668-0.810
1999	-0.265	<0.000	0.767	0.701-0.839
2000	-0.244	<0.000	0.783	0.716-0.857
Provinces/Territories				
Prince Edward Island	0.107	0.233	1.112	0.933-1.326
Nova Scotia	0.149	<0.000	1.161	1.080-1.247
New Brunswick	0.079	0.063	1.082	0.996-1.176
Quebec	Reference			
Manitoba	0.161	<0.000	1.175	1.104-1.249
Saskatchewan	0.147	<0.000	1.158	1.087-1.236
Alberta	0.078	0.001	1.081	1.034-1.131
British Columbia	0.055	0.014	1.057	1.011-1.104
Yukon	0.266	0.087	1.305	0.962-1.768
Northwest Territories	0.585	<0.000	1.795	1.553-2.073
Maternal age *parity				
Maternal age*parity 0	0.109	<0.000	---	---
Maternal age*parity ≥ 4	-0.007	0.921	---	---
Maternal age square*parity				
Maternal age square*parity 0	-0.001	0.000	---	---
Maternal age square*parity ≥ 4	-0.001	0.633	---	---

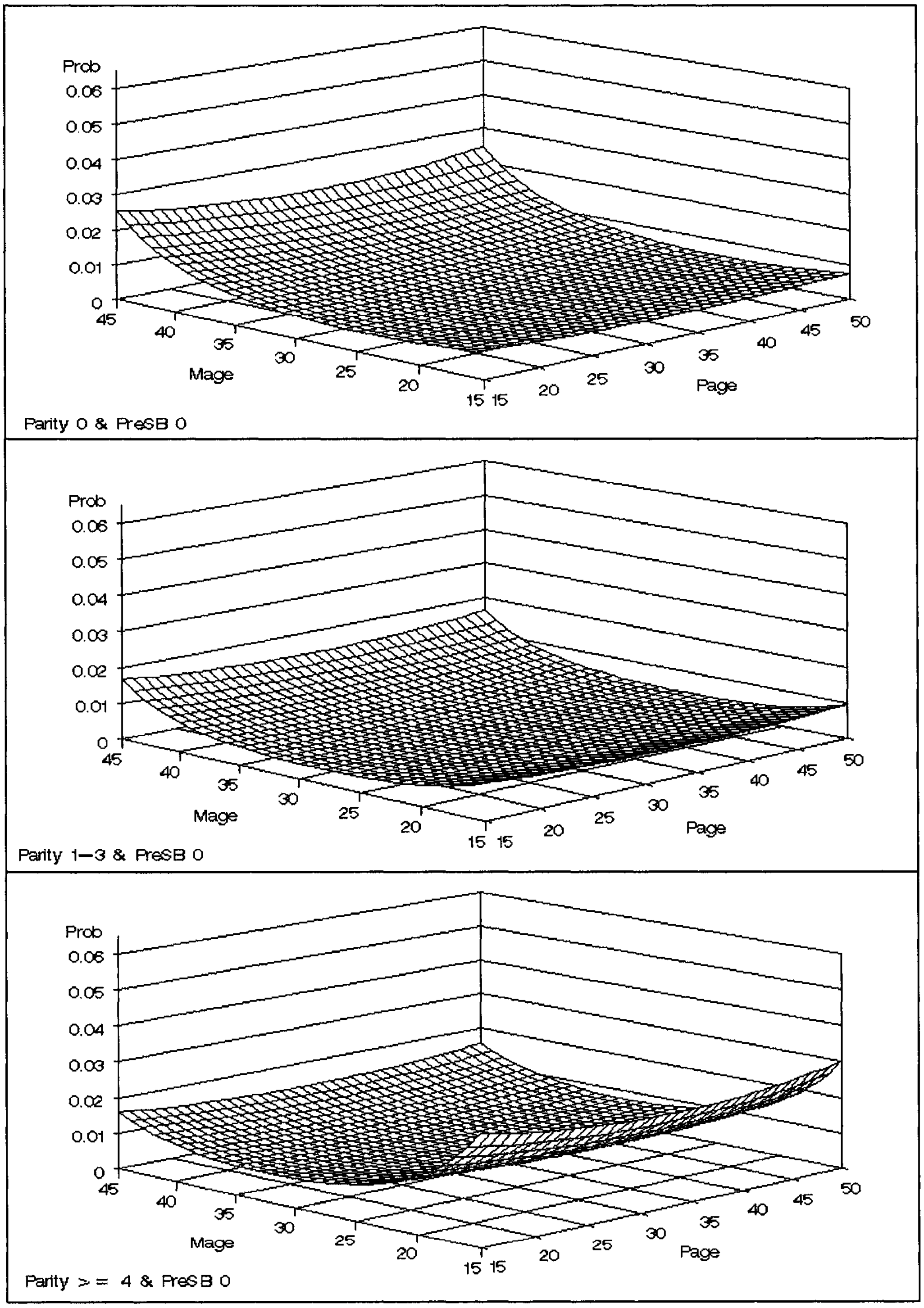
* Unit of maternal and paternal age in the model was expressed as a year

Figure 4.6-1 Predicted probabilities of stillbirth by 3 parity groups among women with prior stillbirth from multivariate logistic regression model



Note: Prob---predicted probability of stillbirth; Mage---maternal age; Page---paternal age; PreSB 1---with previous stillbirth

Figure 4.6-2 Predicted probabilities of stillbirth by 3 parity groups among women without prior stillbirth from multivariate logistic regression model



Note: Prob---predicted probability of stillbirth; Mage---maternal age; Page---paternal age; PreSB 0---without previous stillbirth

In most of the plots, curves of stillbirth risk by maternal age had an asymmetrical "U" shape. The risks were higher at both high and low maternal ages. The lowest stillbirth risk was observed at age 25-30 for nulliparas (parity=0) and low multiparas (parity=1-3) and at age 30-35 for grand multiparas (parity $\geq$ 4). While stillbirth risk was higher in women at both extreme ages, risk increased faster at older age among nulliparas and low multiparas and at younger age among grand multiparous women.

The effect of paternal age on stillbirth risk was notably smaller than that for maternal age with only very slightly increases for both extremes of paternal age. In addition, women with previous stillbirth had a higher stillbirth risk compared to those without prior stillbirth.

These plots also highlight the striking interaction of maternal age with parity. A similar pattern of the curves was found for nulliparas and low multiparas which showing a stronger older age effect on stillbirth. Nulliparas had a higher risk of stillbirth than low multiparas except at the younger extreme age. However, a different picture was found for grand multiparas. In this parity group, maternal age effect on stillbirth was stronger for younger age than older age. Women at the younger extreme age had a much higher risk of stillbirth than other age groups. The stronger effect for younger mothers in this high parity group may be influenced by small numbers of younger mothers. However, as we stated in the previous section, the exclusion of subjects with very young age and high parity did not significantly change the estimates in the model (Table 4.8).

Modeling maternal and paternal age as categorized variables in the model produced a similar effect of maternal age, parity and paternal age on stillbirth risk and very close estimates for other covariates including previous stillbirth, year of birth and provinces/territories. Table 4.10 shows the adjusted odd ratios and 95% CI of stillbirth for maternal age stratified by parity and for paternal age.

Table 4.10 Adjusted odd ratios (95% CI) in the model with age as a categorized variable

Parity	Maternal age (years)	Paternal age (years)	Odds ratio	95% CI
0	<20		1.633	1.500-1.778
0	20-24		1.418	1.332-1.510
0	25-29		1.379	1.303-1.460
0	30-34		1.702	1.593-1.818
0	35-39		2.339	2.127-2.571
0	40-44		2.451	1.958-3.067
0	≥45		4.263	1.584-11.473
1-3	<20		1.757	1.534-2.012
1-3	20-24		1.196	1.116-1.283
1-3	25-29*		1	
1-3	30-34		1.036	0.974-1.101
1-3	35-39		1.366	1.259-1.482
1-3	40-44		2.086	1.788-2.434
1-3	≥45		2.004	0.829-4.848
≥4	<20		7.573	1.054-54.412
≥4	20-24		2.362	1.711-3.262
≥4	25-29		2.341	2.005-2.734
≥4	30-34		1.969	1.711-2.266
≥4	35-39		1.715	1.443-2.039
≥4	40-44		2.979	2.342-3.789
≥4	≥45		3.146	1.295-7.644
		<20	1.254	1.129-1.392
		20-24	1.064	1.006-1.125
		25-29*	1	
		30-34	0.998	0.954-1.043
		35-39	1.046	0.988-1.108
		40-44	1.193	1.102-1.292
		≥45	1.228	1.096-1.376

* reference group

CHAPTER 5 DISCUSSION

5.1 Summary of findings

Delivering at an advanced age is becoming increasingly common for Canadian women. We found that the proportion of births to women at age of 35 years or older increased steadily by almost 150% between 1985 and 2000 ($p<0.0001$). Both overall and maternal age-specific stillbirth rates decreased significantly during the study period ($p<0.0001$). Geographic variations in stillbirth rate were observed in this study with the lowest being 4.18 in Quebec and the highest rate being 8.17 per 1,000 total births in the Northwest Territories.

This study demonstrated that the risk of stillbirth increased for women with advanced age even after accounting for the effects of paternal age, previous stillbirth, year of birth, residential area, and parity. The effect of paternal age on stillbirth risk was not as marked as that of maternal age with only a slight increase in risk at very low and very high paternal age. This study also found that stillbirth risk was higher in women with previous stillbirth. In addition, male fetuses had a slightly higher risk of stillbirth than female fetuses.

Parity significantly modified the effect of maternal age on stillbirth risk. Although women at extremely low and high maternal ages had a higher predicted risk for stillbirth for all three parity groups, the age effect was stronger for older women in nulliparas and low multiparas groups and for younger women in grand multiparas group. Low multiparas had a lower predicted stillbirth risk than women in other two parity groups except the similar risk as nulliparas at extremely young age. Therefore older nulliparas and younger grand multiparas bore the highest risk of stillbirth.

5.2 Biological interpretation of the effect of increased maternal age on stillbirth

The biological mechanism of the increased stillbirth risk in advanced maternal age is unclear. One possible explanation considers low utero-placental perfusion caused by poor uterine vasculature in older women resulting in an inability to meet the increased hemodynamic demands of pregnancy. Naeye[21] reported that disorders associated with utero-placental under-perfusion, including abruptio placenta, large placental infarcts and placental growth retardation, accounted for about a half of the increase in stillbirth among women older than 39 years. The study also found a higher proportion of sclerotic lesions in myometrial arteries in women older than 39 (83%) than women aged 17 to 19 (11%), suggesting these lesions in arteries were perhaps a cause of under-perfusion in older maternal age.

Increased stillbirth risk in older women could be also due to an increased prevalence of chronic diseases or medical complications of pregnancy including pregnancy induced hypertension and diabetes with aging. Studies found that about 50-70% of mothers of stillborn infants have medical or obstetrical complications during their pregnancy.[36] A higher risk of these medical or pregnancy complications in older women and an increase in stillbirth risk for women with these complications have been demonstrated in previous studies.[17,22-25,73,75,79,82,83] Placental abruption could be the most important pathway leading to stillbirths in pregnant women with hypertensive disorders. Hypertensive disorders, especially chronic hypertension is significantly associated with an increased risk of placental abruption.[49,83,84] A meta-analysis on placental abruption reported the overall ORs of 1.73 and 3.13 for women with pre-eclampsia or chronic hypertension, respectively, when compared to nomotensive women.[49]

Other pathways hypothesized as related to an increased risk of stillbirth include utero-placental insufficiency, placental infarction or fetal-maternal hemorrhage.[36,79] Diabetes (mainly type 2) is another common factor associated with aging. The exact mechanism of stillbirth in diabetic women is not completely understood. Changes in fetal carbohydrate metabolism could be a possible explanation.[79] Utero-placental insufficiency secondary to vascular disease and the increase in lethal congenital anomalies in diabetic mothers could be other reasons. However, increases in chronic diseases or pregnancy complications with maternal aging does not explain all of the increased risk of stillbirth with increased age since several studies have shown that advanced maternal age increased the risk of stillbirth even after the adjustment for these diseases or complications such as hypertension, gestational diabetes, placenta previa and placental abruption.[25,26]

Finally, the risks of aneuploidy (defined as the occurrence of one or more extra or missing chromosomes leading to an unbalanced chromosome complement) and lethal congenital anomalies increase with maternal age. This is likely to be a contributing factor in increased rate of stillbirth in older women.[22]

5.3 Comparison of present with previous findings

5.3.1 Overall effect of advanced maternal age on stillbirth risk

This large population-based study found that the risk of stillbirth increased in older women after adjustment for important confounders. The finding is consistent with those of several previous studies.[2,22,25,26,45,137] A large population based study[2] on 2,305,879 Italian newborns showed that older women (≥ 35) found a 1.5 to 2 fold higher risk of stillbirth compared with their younger counterparts when the effects of parity and education were taken into account. This study also demonstrated that older mothers had an increase in the risk of other adverse pregnancy outcomes including preterm birth and low birth weight. Another large study[22] using data from a maternity information system database found a similar increase in stillbirth among older mothers. Women aged 35-40 or older than 40 had a 1.41 (95%CI 1.17, 1.70) or 1.83 (95%CI 1.29, 2.61) times higher risk for stillbirth than younger mothers aged 18-34 after controlling for parity, ethnicity, BMI, gestational diabetes, preeclampsia and smoking.

In contrast, several hospital-based studies reported no increase in stillbirth observed among women with advanced maternal age, although these studies consistently demonstrated that older women had an increased risk for various antipartum and intrapartum complications.[29,31,134,136,153] As we stated in the systematic review (Section 2.2.3.1), selection bias and poor statistical power may explain the lack of association between advanced maternal age and increased risk of stillbirth among these small hospital based studies.

5.3.2 Confounders or modifiers for the association of maternal age and stillbirth

5.3.2.1 Parity

Parity is strongly related to maternal age. Our data show that parity significantly interacted with the association of maternal age on stillbirth risk. We found that both older nulliparas (parity=0) and younger grand multiparas (parity≥3) had a higher risk of stillbirth.

Previous studies have reported an increased risk of stillbirth among nulliparous women with adjusted odds ratios ranging between 1.2 and 1.3 compared to women with parity of ≥ 1.[25,45] Huang and associates[16] found that nulliparous women had a higher risk of unexplained fetal death even after controlling for deleterious factors associated with nulliparity, including preeclampsia. Nulliparity also had the highest etiologic fraction (24%)

to unexplained fetal death in their study. As a distinct obstetric entity, primigravidas have a higher risk of certain complications during pregnancy and labor such as pregnancy induced hypertension (PIH) and premature rupture of membranes (PROM).[47,85] Reviewing existing literature revealed that about 85% of PIH occurs in nulliparous women, who have a four to five fold higher risk of having PIH than multiparous women.[85] A population-based study in Australia[47] demonstrated a much higher risk of PIH and PROM among primigravida women after the adjustment for maternal age, maternal smoking, and other socio-demographic factors. Raymond et al.[25] reported a higher risk of hypertensive diseases and intrauterine growth restriction (IUGR) in nulliparous vs. non-nulliparous women. Immunological factors may play a role in a higher risk of PIH in nulliparous women. Some authors have postulated that the increased risk could be related to the first exposure to the fetal originated trophoblast for the nulliparous women.[154] However, Linn and associates[155] did not observe the protective effect of previous pregnancy. They failed to find a reduction in preeclampsia or eclampsia among women who had one or two previous induced abortions consistently.

Our study found that older nulliparous women had the highest risk of stillbirth. First delivery at an older age has been considered to be a special obstetric event because of a striking increase of difficult and prolonged labour in older nulliparous women.[7] In 1958 the International Federation of Gynaecology & Obstetrics (FIGO) defined the term 'elderly primigravidas' to identify women giving her first birth at 35 years or more. Early studies demonstrated that these elderly primigravidas had an increased risk of antepartum and intrapartum complications and a higher risk of perinatal mortality.[156-158] However, some later studies failed to confirm these earlier findings.[159,160] For example, Prysak et al.[160] found that

older nulliparous women had a higher risk of antepartum, intrapartum, and newborn complications but no increased risk of perinatal mortality. This suggests that improved antenatal and intrapartum surveillance, early labour intervention, and better neonatal care could ameliorate the increased risk due to frequency of complications among older nulliparas. The higher risk of perinatal mortality observed in older nulliparas in early studies could be related to medical conditions. Stein[161] found no increase in perinatal mortality in older nulliparous women after excluding women with hypertension, obesity, diabetes and thrombophlebitis. Our data could not provide information on medical conditions. As a result, we were unable to examine a potential effect of these factors on the relationship between stillbirth risk and older nulliparity. Nevertheless, regardless of the inconsistent findings on perinatal outcome, older nulliparas should be managed carefully in terms of the consensus presented that these women are prone to pregnancy complications.

Our analysis showed a higher risk of stillbirth among grand multiparas compared to low multiparas. This finding has been supported by some investigators.[7,16,162,163] In a population-based study[163] in New York, Kiely and associates[7] found a nearly two times risk of intrapartum fetal deaths among women with parity of 4 or more compared parity of 1-3 independent of maternal age, fetal loss, and socio-economic status. A recent hospital-based study also demonstrated that parity of 5 or more was an independent determinant of unexplained intrauterine fetal deaths. In contrast, other studies showed similar stillbirth risk for grand multiparas and low multiparas pregnancies.[46,48,51] Improvements in obstetric practice and neonatal intensive care may explain the changes in stillbirth risk for grand multiparaous pregnancies.[46] However, bias from low statistical power and failure to control for confounders could be another reason of failing to find the difference in stillbirth risk

between the two parity groups in these studies.

The higher risk of stillbirth among grand multiparas has been attributed to pregnancy complications. Despite the inconsistency in the association between high parity and stillbirth risk, there is some consensus amongst investigators that maternal complications such as placenta previa,[48,49] abruptio placenta[48-50] and abnormal presentations[51] are more common in grand multiparas than in low multiparas. Although the mechanism by which high parity increases the risk of these complications is unknown, some biological mechanisms have been postulated. For example, some authors assumed a pathway of an underlying atrophy of endometrium due to some changes in vessels at sites of prior placental attachment among women with high parity. This change in endometrium may lead to a tendency for the placenta to spread over a larger area than usual to maintain adequate blood flow, thus increasing the risk of placenta previa.[49,51] The elevated risk of abruptio placenta was attributed to the higher prevalence of hypertension in women with high parity.[49]

Women with high parity tend to be older and they often have associated disadvantageous socio-economic factors. They are less likely to have higher education, have private health insurance, or pursue adequate prenatal care.[44,47,54] Seidman and associates[164] conducted a study of socio-economically stable and homogenous Jewish women and concluded that the obstetric and neonatal risk of the grand multiparae is a consequence of environment and poor prenatal care and not a function of inherent biological characteristics.

Our study also found that the increased stillbirth risk was especially pronounced among younger women with grand multiparity. Literature reviews found that the mean maternal age of grand multiparity ranged from 31 to 33, suggesting that younger (i.e. <25 years) grand multiparas are an infrequent phenomenon and represent an exceptional maternal group.[54,165,166] Several groups have studied the association between obstetric complications or perinatal deaths and young grand multiparas with mixed results. A population-based study[49] on uteroplacental bleeding disorders in pregnancy found an elevated risk of placenta previa and abruptio placentae with higher parity among younger women after controlling for hospital type, year of birth, previous abortions, hypertensive disorders and other factors. The analysis of joint effects of maternal age and parity showed that strong parity effects on placenta previa, abruptio placenta and uterine bleeding of unknown etiology were observed for women under 30, up to 35 and under 25 years separately. The authors attributed the higher risk of uteroplacental bleeding disorders in young grand multiparous to their short birth intervals or confounding by unmeasured factors that characterize women who have many pregnancies (parity 3+) at a relatively young age (i.e., 20-24 years). In contrast, a recent population-based study[166] from Utah, USA found that young grand multiparas (aged 18-34 years, parity 5+) did not have a higher risk for most intrapartum or newborn complications compared with young nulliparous, young lower grand multiparas and older women with high parity (aged >= 35 years, parity 5+) after adjusted for confounders.

Women who have several births while very young comprise a special obstetric entity since they might be unique in many aspects. It is difficult to interpret biologically how high parity may influence the risk of these complications among these young women. Biological immaturity including low gynecologic age (years since menarche) or incomplete body growth such as low prepregnancy weight or body mass could explain the higher risk of complications among some of very young.[167] However, SES may play an important role in their pregnancy outcomes. As mentioned in the previous paragraph, high parity group is associated with SES disadvantage. The SES situation is worse for young grand multiparity. Simonsen et al.[166] presented that young women with high parity were less likely to be married and receive adequate prenatal care whereas they are more likely to be minority status, to have lower educational level and to use tobacco during pregnancy.

We found that three individual studies[25,45,55] in our systematic review considered a possible interaction between maternal age and parity on stillbirth risk in the regression models and none of these studies found a significant interaction. Failing to find the interaction could be related to small numbers of younger grand multiparas and the differences in criteria of high parity and inclusion of study subjects from the present study. For example, two of these studies[25,45] grouped parity into two types: nulliparity (parity=0) and multiparity (parity $\geq$1) (the third study did not state or show how parity was categorized in the multivariate regression model). They didn't separate grand multiparity from low multiparity which had different risk patterns across maternal age. Second, two Swedish studies[25,55] restricted their subjects to Nordic citizens to increase the homogeneity of the population. This could dilute in a certain degree the effect of socioeconomic factors due to the lack of the effect of race and thus influence the actual risk for younger multiparous women who were demonstrated to have socioeconomic disadvantages.

5.3.2.2 Previous stillbirth/ fetal loss

Our study demonstrated that women with prior stillbirth(s) had increased risk of stillbirth in subsequent pregnancies. A history of stillbirth is a well-established risk factor for poor pregnancy-related outcomes. Reports in the literature have demonstrated that women with prior fetal loss (spontaneous abortion or stillbirth) have an increased risk of stillbirth.[7-11, 45] Cnattingius et al.[9] observed a substantial tendency to repeat an adverse pregnancy outcome from the first to the second birth including late fetal death, early neonatal death, low

birth weight, preterm birth, and small for gestational age. The adjusted odds ratio for having the same outcome in the second birth was 2.7 for late fetal death, 5.2 for preterm birth, 7.9 for low birth weight, 8.2 for SGA and 8.7 for early neonatal death (results controlled for maternal age at first birth, diabetes, hypertensive disorders and antepartum hemorrhage). Kiely and associates[7] found that women with a single prior fetal loss (stillbirth or spontaneous abortion) had 1.35 times higher risk for antepartum stillbirth (95% CI 1.17, 1.56) and 1.59 times higher risk for intrapartum stillbirth (95% CI 1.15, 2.20) compared to women without prior fetal loss. The adjusted OR among women with two or more prior fetal loss increased to 2.83 (95% CI 2.40, 3.34) and 3.24 (95% CI 2.22, 4.75) for antepartum and intrapartum stillbirth respectively, suggesting a cumulative effect of prior spontaneous abortion or stillbirth on the risk of fetal death in subsequent pregnancies.

Other studies also demonstrated a similar cumulative effect of previous fetal loss on an increased risk of stillbirth in future pregnancies.[10]

The literature has demonstrated that a history of stillbirth or abortion is associated with other pregnancy complications such as placental abruption and gestational diabetes. These complications could explain the increased risk of stillbirth in current pregnancy. A nested case control study[168] in the United States found a 3.5 fold higher risk of placental abruption (95%CI: 1.8-7.0) among women with a history of prior stillbirth than those without prior stillbirth. This association was independent of chronic hypertension, pregnancy induced hypertension, gestational diabetes, low BMI, smoking, alcohol use, race, medical payment status, maternal age, parity and other factors. Similarly, Heinonen et al.[41] found that placental abruption was significantly more common in women with stillbirth in an earlier pregnancy (5.4% vs. 0.7%). The increased risk of placental abruption in current pregnancy
may be related to impaired placental development or function that is a result of a comprised vascular support system.[41] Prior stillbirth is also related to a higher risk of gestational diabetes in subsequent pregnancies.[12,93] For example, the population-based study of Robson and associates[93] found a 4-fold increase in glucose intolerance or gestational diabetes among women with a prior unexplained stillbirth. In addition, autopsies on 783 stillborn infants and neonatal deaths of less than 72 hours found that amniotic fluid infection syndrome, which is diagnosed by the finding of chorioamnionitis, placentitis and congenital pneumonia due to the aspiration of infected amniotic fluid was significantly more common with a maternal history of fetal loss. The result suggests that this syndrome might be responsible for repeated unsuccessful pregnancies.[43]

5.3.2.3 Paternal age

Our study found a very weak independent association of older paternal age on stillbirth risk in the multivariate regression model. Stillbirth risk only increased slightly for fathers at the two extreme age ranges although these changes were statistically significant in the model. In addition, we found no evidence that paternal age modified the effect of maternal age on stillbirth risk.

Five studies were found that focused on the effect of paternal age on stillbirth risk, of which three studies were conducted in 1960s and 1970s and the other two were published in the 2000s.[57,58,169-171]

Inconsistent results were obtained from these studies. Two recent population-based studies demonstrated a relationship between advanced paternal age and the increased risk of stillbirth. One conducted by Astolfi and associates[171] in Italy observed that stillbirth risk increased with increased paternal age in mothers of 30 years old or greater. The effect was also modified by family education. The other study[57] was a prospective cohort study that found a higher stillbirth risk among fathers of 50 years or older (hazard ratio 3.94; 95% CI 1.12, 13.8) compared to fathers aged 25-29 years old. However, this result should be interpreted cautiously due to the small number of fetal deaths (3 cases) in the paternal age group of ≥ 50 years old. This study did not find an interaction between paternal age and maternal age on stillbirth risk. However, an earlier population-based study[58] failed to find the association between stillbirth risk with paternal age. The study minimized confounding by restricting the subjects to white women who had a white husband, delivered a singleton, and had no prior stillbirth or infant deaths and stratifying the data by maternal education and birth order. The authors found that stillbirth rates did not increase with paternal aging independently of maternal factors.

The explanations behind the conflicting results of these studies are uncertain. Increased mutations on germ cells accumulated with male age are perhaps one of the main pathways leading to fetal death for older paternal age. As early as 1955, Penrose suggested that continued spermatogonial divisions would provide opportunity for mutations to accumulate in the male germ line with increased age.[172] The number of mitotic divisions for the cells creating sperm increases with male age, i.e. the cells experience 380 mitotic divisions for man aged 30, and at age of 50, the number reaches 840. More divisions create higher possibilities of introducing a genetic error into the germ line.[63] However, the increased mutations caused by male ageing influenced early fetal death rather than stillbirth. Two cytogenetic showed a higher proportion of abortuses with chromosomal anomalies in the first trimester than in second trimester.[173,174] This was also supported by a recent prospective study[60] which demonstrated that the effect of male aging was stronger for first

trimester fetal losses (6-12 weeks) than for those occurring later (13-20weeks). In addition, Tarin and associates[175] presented that the mutational effect on nuclear DNA of paternal aging is clinically relevant only at very advanced ages, i.e. in the fifties and above.

5.4 Methodological issues

Several methodological issues concerning the analyses of maternal age and stillbirth warrant further discussion.

5.4.1 Criteria of stillbirth

As mentioned in a previous section, the definition of stillbirth varies among countries and regions. The difference was reflected in various cut off points of birth weight and/or gestational age. The discrepancy was even greater in published studies on stillbirth. For example, cut off points of $\geq$ 350g, $\geq$ 500g, $\geq$ 1000g, or no lower limit for birth weight were used by 24 studies included in our systematic review. Similarly, cut off points for gestational weeks used included $\geq$ 20, $\geq$26, $\geq$ 28 or no lower limit.

In order to conduct international or other comparisons, WHO recommended that all fetuses and infants weighting at least 500g at birth, whether alive or dead, should be included in birth statistics. WHO also recommend that a gestational age of 22 completed weeks should be used for stillbirth criteria when birth weight information is unavailable. However, this cut off point of $\geq$ 500g of birth weight for stillbirth is not widely applied in studies. We found only 5 of 24 studies mentioned (20.8%) used this recommended definition. Discrepancies in stillbirth definition will affect the comparison of study results and may bias stillbirth risk estimation when potential risk factors (predictors) are closely related to birth weight or gestational age. For our study, we used the WHO recommended definition of stillbirth and we strongly suggest that this recommended standard be used in future studies from different countries or regions so that cross-country comparisons are simplified.

5.4.2 Plurality of birth

A higher risk of pregnancy complications and adverse pregnancy outcomes for multiple births has been extensively demonstrated.[111,112,142-144,176] Moreover, older women have an increased incidence of multiple births compared to younger counterparts because of the increased use of assisted reproductive technology.[113] Compared to women with naturally conceived pregnancies, women exposed to assisted reproductive treatments had 25 fold higher likelihood of having multiple births (95% CI 18, 35). A report from a U.S assisted reproductive technology surveillance showed that 51% of infants through ART were born as multiple births in 2003.[109] In addition, as we described in Section 2.1.3.6, factors such as SES and parity modified the effect of maternal age on certain pregnancy outcomes including very preterms birth, very low birth weight and perinatal mortality in twin pregnancies.

In terms of the inherent high-risk nature of multiple pregnancies and the effect modification observed among multiple pregnacies, it is recommended that perinatal outcome analyses should be stratified by plurality to provide more meaningful information. A careful consideration of potential confounding and effect modification of multiple pregnancies is important for studies that include both singletons and multiple births. Unfortunately, twelve individual studies in our systematic review included both singletons and multiple births, but none of them either considered confounding or effect modification of multiple births or conducted a separate analysis for singletons and multiple births when studying the association of maternal age and stillbirth risk.

5.4.3 Consideration of Non-linearity

Generally, including continuous variables in models involves a stronger model assumption than if categorized variables are used. Parameter estimates in conventional logistic regression models are obtained with the assumption that each unit change in a continuous variable produces the same change of the logit of outcome (i.e. the predictor variable is linearly predictive of the logit). Departures from the linear logit relationship can invalidate analyses usiong the continuous variable. Therefore, possible non-linearity should be taken into account when a continuous variable is included in conventional logistic regression models. Biased parameter estimates can result from a simple linear regression model when a non-linearity exists between a continuous exposure variable and the outcome. Fortunately, various alternatives for regression models exist to deal with non-linearity issues. These methods include linear polynomial regression as was used in the current study, fractional polynomial regression and nonparametric regression including LOESS, GAM modeling and spline regression methods. The distinguishing feature of nonparametric regression is that it traces the independence of a response variable on one or several predictors without a priori knowledge about the form of the true function which is being estimated. The function is modeled by typically using many free parameters which have no physical meaning in relation to the problem. Details in these methods can be found in relevant statistical textbooks and the published literature.[177,178]

There is no gold standard in selecting an appropriate regression method since these methods dealing with non-linearity each have their own advantages and disadvantages and the choice depends on, in a great degree, how well the method fits the data set. In addition, we should always keep in mind that parsimony and the biologic meanings of functional terms

of exposure variables are two of basic principles in selecting a simplest adequate model. Irrelevant terms should be avoided in models since keeping too many terms in a model would decrease the precision of parameter estimates.

In our study maternal age was modeled including a quadratic term since we saw evidence of a non-linear relationship between maternal age and stillbirth risk. The results of our multivariate regression model show a clear curve in the association between maternal age and stillbirth risk

5.4.4 Interaction

Although assessing the interaction between independent variables is an important factor for evaluating the validity of multivariate regression analysis, it is rarely done. A review on 193 articles published in four generic Obstetrics and Gynecology journals in 1985, 1990 and 1995 found that 86.4% of articles reported multivariate logistic regression analysis without considering interactions.[179] A slightly lower percentage (73%) failed to consider interactions for papers in *Lancet* and *New England Journal of Medicine* published between 1985 and 1989.[180] In our systematic review, twenty one out of twenty four individual studies (87.5%) did not test for an interaction between maternal age and some covariates.

Since conducting a test for interaction needs a large sample size to keep an effective study power, it is not suggested to conduct a general screening for all possible interactions for a data set. However it doesn't mean that testing interaction should be avoided. Usually candidate variables for interaction test are selected based on the clinical meaning of the interaction and the results of previous studies.

Studies have demonstrated a differential effect of parity on maternal age with certain study outcomes including neonatal death,[7] placenta previa and abruptio placentae.[49] Our

preliminary stratified analysis also suggested a potential interaction between maternal age and parity for stillbirth. We then introduced the interaction terms in our main effect regression model and found that parity significantly interacted with maternal age to influence stillbirth risk.

Maternal age and parity are two closely related demographic factors. They are commonly included in obstetric care records because of their influences on pregnancy complications and outcomes. Our finding of an interaction between maternal age and parity for stillbirth could help obstetricians determine stillbirth risk for patients. More importantly, our findings can guide obstetricians in applying appropriate obstetrical management to women with different obstetric risk. For example, based on our study, women with advanced maternal age have an increased risk of having a stillbirth compared to women with medium age. However, the older maternal age effect is much stronger in a woman who is having her first delivery. The risk can be much lower for their subsequent deliveries when they are healthy and have no other risk factors.

5.5 Study advantages

One of the main advantages of this study is that it used a large population-based dataset that produced stable estimates of effects even for the extreme age groups that had a relatively small numbers of events. In fact, this is the second largest study to date examining the effect of older maternal age on stillbirth risk. Also, the population-based nature of the study essentially eliminated selection biases. This should increase the generalizability of our results to other populations.

Another study strength is how maternal age was modeled in our analyses. Besides categorizing maternal age in regression model, which is the most common way used in studies on maternal age and perinatal outcomes, our study also fitted maternal age as a continuous variable to avoid the information loss. Linear quadratic regression was applied to model maternal age in terms of its non-linearity with stillbirth risk. In addition, the potential interactions related to maternal age were also tested.

It is also notable that we adopted a multiple imputation method to deal with the missing data in our study in terms of a relatively high percentage of missing values for paternal age, a common problem in birth registry data set.[63] Multiple imputation methods estimate each missing value with a set of plausible values that represent the uncertainty about the right value to impute. This allowed us to minimize the bias from missing values and avoid a decrease in study power resulted from the exclusion of the subjects with missing values.

5.6 Study limitations

A number of limitations of this study should be recognized. Although several common confounding characteristics such as parity, paternal age, and prior stillbirth, were reasonably controlled for in our study, our data lacked detailed medical information such as diabetes mellitus and hypertension, socio-economic status, and life style factors such as smoking and drinking that have important effects on the association of maternal age and stillbirth risk. As previous studies demonstrated, socio-economic status, life style factors, medical diseases and pregnancy complications are associated with stillbirth. Our inability to control for these potential confounders will weaken the internal validity of our study. However, other studies that have controlled for these factors found a persistent association between increased maternal age and stillbirth risk. Therefore, we do not believe that the absence of these data seriously biased our results.

A second limitation is that we could not distinguish antepartum stillbirths that occur prior to labor from intrapartum stillbirths that happen during labor. Antepartum stillbirths account for more than 80% of total stillbirths in developed world.[45,181] These two types of stillbirth have widely different etiologic determinants. Researchers agree that antepartum stillbirths usually occur with severe maternal and placental complications or fetal abnormalities, whereas intraparum stillbirths are often the result of obstructed labor or fetal distress that is related to poor quality or delayed obstetrical care. Merging these two types of stillbirth might cloud determination of risk factors for them, especially for intrapartum stillbirths that are much less common. Findings based on analyses of total stillbirths will predominantly reflect risk factors for antepartum stillbirths.

Unfortunately, the timing of stillbirths in stillbirth registry documents is incomplete. We explored the stillbirth database of 1985 to 2000 from Statistics Canada and found that the timing of stillbirth was indicated on less than one third of stillbirths. Literature demonstrated that the distribution of unknown timing of fetal deaths was also unbalanced in terms of some socioeconomic status factors such as race and maternal education. For example, a U.S study[45] found that women who were black or had the lowest educational level were much more likely to have no information recoded to indicate the timing of fetal death. Excluding subjects without information on the timing of the fetal death could introduce selection bias when studying the potential risk factors for antepartum and intrapartum stillbirths separately.

Third, we were unable to assess the association between older maternal age and stillbirth risk among multiple pregnancies although multiple births can be identified in the current data set. One reason is that we could not link multiple births to the same mother. Treating them as unmatched singletons in regression would violate the assumption of independence of subjects required by regression model. The other reason is that our data set does not provide information on characteristics of multiple births (i.e. birth order for multiple births), use of assisted reproductive technology and socioeconomic status that demonstrated to influence the incidence of multiple pregnancies or alter the association between advanced maternal age and perinatal mortality.[114,115] Since etiologic factors for multiple pregnancies are very complex, lack of this important information makes it difficult to examine accurately the relationship between older maternal age and stillbirth risk for multiple births.

Finally, due to the lack of unique identification number for women in the data set, we were unable to account for the potential non-independence of study subjects that result from the possibility of giving more than one birth for a woman during the study period. This introduces the possibility of violating the assumption of logistic regression method and thus introducing some bias into the estimates from the model. However, the very large number of births or women in the study data set will make it unlikely that these would be an important bias associated with this issue.

5.7 Conclusion

Our study demonstrated an increased risk of stillbirth among women with advanced maternal age after accounting for important cofactors. The study also found that older mothers having their first delivery or younger mothers with parity of more than three had the highest adjusted stillbirth risk. Women with prior stillbirth had an increased risk of stillbirth in a subsequent pregnancy. This suggests that careful prenatal surveillance and appropriate obstetrical interventions should be provided to this high risk population.

We failed to find a major effect of paternal aging on stillbirth risk. The observation in literature that the effect of increased mutations on germ cells caused by male aging is stronger on first trimester fetal losses could be one of the explanations. However, further investigations are needed to focus on the mechanisms of advanced paternal age influencing late fetal death.

5.8 Implications

Currently more and more women delay childbirth to their late 30s due to pursue higher educational and career goals. Modern women with advanced maternal age are different from older mothers in past decades in many aspects including socioeconomic status and reproductive behavior. The possibility of having a healthy baby for these women is becoming an important public health issue for health care providers, couples who intend to conceive and even communities. The predicted risk of having a stillbirth under certain conditions provided by this study should help health care providers in their preconception counseling for women at advanced maternal age regarding pregnancy expectations or possible reproductive outcomes, and thus allow women to make an informed decision on conception.

Women at older age, even when healthy, believe that their babies are more vulnerable than those of their younger counterparts during pregnancy and labor. They are more likely to experience maternal anxiety and some of them might not get pregnant because of the fear of adverse pregnancy outcomes such as congenital anomalies, miscarriage and stillbirth. The perception of higher pregnancy risk for older women may partially result from studies that focused on the overwhelming negative aspects of delayed childbearing. Our study showed that while stillbirth risk increases by maternal age, it is mostly pronounced for nulliparas. Older multiparas who have no other risk factors such as medical conditions, pregnancy complications and previous adverse pregnancy outcomes can experience a much lower risk of stillbirth. Even for older nulliparas, the stillbirth risk can be lower than predicted if they are healthy, in high SES and have good life styles, which have been demonstrated to be associated with better prenatal outcomes. Our finding should encourage older women to challenge the same conventional perceptions about stillbirth risk and maternal age and positively face the conception, pregnancy and delivery.

A cautious attitude for pregnancies of older women is common among health care providers and this is reflected by more frequently applied antepartum testing and higher rates of peripartum interventions such as labor induction and Cesearen Section. Advanced maternal age alone is usually a criterion for such a high risk approach. However, many healthy women with older maternal age are able to carry their pregnancies to term without problem.[182] Our findings suggest that risk assessment of pregnancy among older women be done by considering parity and other common risk factors for pregnancy. Guidelines of obstetrical interventions should consider the actual risk for older women with different obstetrical situations, especially for older women who have no risk factors, for example, women without chronic diseases and pregnancy complications, in their second and subsequent pregnancies. To meet the needs, perhaps more evidence based studies on interventions for those otherwise healthy women are anticipated to guide the management of pregnancy for this specific obstetrical population.

In addition, geographical variations in stillbirth rate presented by this national data would guide health policy makers to take some specific measurements in the areas with a higher stillbirth rate, for example, initiating audit procedures for each stillbirth to identify avoidable cases, so that the national stillbirth rate can be further reduced.

5.9 Future research

Based on our study and literature review, several foci of research are recommended to further strengthen the association between maternal age and stillbirth.

First, the exact mechanism of how advanced maternal age increases stillbirth risk is not fully understood. Therefore, we require further research on biological changes of aging uterus and pathways linking older age to relevant risk factors for stillbirth. The excess risk of stillbirth among older mothers could only be reduced by our better understanding of the etiology and the obstetrical care and interventions required to decrease this risk.

Second, socioeconomic status, life style factors, and medical conditions including the use of assisted reproductive technology (ART) impact the association between maternal age and stillbirth risk. A lack of information on these factors in the common vital statistics data sets makes it impossible in a population-based study to control comprehensively for confounding effects. It would be useful to link vital statistics to other different datasets such as hospitalization, census or survey datasets.

Third, a limited focus has been placed on examining the effect of late paternity on stillbirth risk. We clearly need more studies to investigate the role of late paternity in the risk of stillbirth and explore possible biological or genetic explanations on the relationship. We also need more studies to explore the effect of older paternal age on the relationship between advanced maternal age and adverse pregnancy outcomes since late paternity usually accompanies with late maternity.

Finally, studies on the relationship between advanced maternal age and stillbirth due to different causes including unexplained antepartum stillbirth separately would help to better understand the mechanisms behind the difference in stillbirth risk between older and younger mothers or different causes of deaths. An accurate assessment of the underlying cause of a fetal death would be particularly important in these studies. We highly encourage studies using data set with a high proportion of carefully performed autopsies including pathological examinations of both fetus and placenta.

REFERENCES

1. Cnattingius S, Stephansson O. The epidemiology of stillbirth. Semin Perinatol 2002; 26:25- 30.

2. Astolfi P, Zonta LA. Delayed maternity and risk at delivery. Paediatr Perinat Epidemiol 2002;16:67-72.

3. Martin JA, Hoyert DL.The national fetal death file. Semin Perinatol 2002;26:3-11.

4. Health Canada. Canadian perinatal health report 2003. Ottawa: Minister of Public Works and Government Services Canada; 2003.

5. Dodd JM, Robinson JS, Crowther CA, Chan A. Stillbirth and neonatal outcomes in South Austrilia, 1991-2000. Am J Obstet Gynecol 2003;189:1731-6.

6. Fretts RC, Usher RH. Causes of fetal death in women of advanced maternal age. Obstet Gynecol 1997;89:40-5.

7. Kiely L, Paneth N, Susser M. An assessment of the effects of maternal age and parity in different components of perinatal mortality. Am J Epidemiol 1986;123:444-54.

8. Ferraz EM, Gray RH. A case-control study of stillbirth in northeast Brazil. Int J Gynaecol Obstet 1991;34:13-9.

9. Cnattingius S, Berendes HW, Forman MR. Do delayed childbearers face increased risks of adverse pregnancy outcomes after the first birth? Obstet Gynecol 1993;81:512-6.

10. Whitley E, Doyle P, Roman E, Stavola BD. The effect of reproductive history on future pregnancy outcomes. Hum Reprod 1999;14:2863-7.

11. Frias AE Jr, Luikenaar RA, Sullivan AE, Lee RM, Porter TF, Branch DW et al. Poor obstetric outcome in subsequent pregnancies in women with prior fetal death. Obstet Gynecol 2004;104:521-6.

12. Samueloff A, Xenakis Em, Berkus MD, Huff RW, Langer O. Recurrent stillbirth: Significance and characteristics. J Reprod Med 1993;38 :883-6.

13. Hughes PM, Turton P, Evans CD. Stillbirth as risk factors for depression and anxiety in the subsequent pregnancy: cohort study. BMJ 1999;318:1721-4.

14. Turton P, Hughes P, Evans CDH, Fainman D. Incidence, correlates and predictors of post-traumatic stress disorders in the pregnancy after stillbirth. Br J Psychiatry 2001;178:556-60.

15. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995. Am J Obstet Gynecol 2001;184:694-702.

16. Huang DY, Usher RH, Kramer MS, Yang H, Morin L, Fretts RC. Determinants of unexplained antepartum fetal deaths. Obstet Gynecol 2000;95:215-21.

17. Smulian JC, Ananth CV, Vintzileos AM, Scorza WE, Knuppel RA. Fetal deaths in the United States. Influence of high-risk conditions and implications for management. Obstet Gynecol 2002;100:1183-9.

18. Oron T, Sheiner E, Shoham-Vardi I, Mazor M, Katz M, Hallak M. Risk factors for antepartum fetal death. J Rep Med 2001;46:825-30.

19. Fledman GB. Prospective risk of stillbirth. Obstet Gynecol 1992;79:547-53.

20. Petitti,D.B. The epidemiology of fetal death. Clin Obstet Gynecol 1987;30:253-8.

21. Naeye RL. Maternal age, obstetric complications, and the outcome of pregnancy. Obstet Gynecol 1983;61:210-6.

22. 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;15:2433-7.

23. Cleary-Goldman J, Malone FD, Vidaver J et al. Impact of maternal age on obstetric outcome. Obstet Gynecol 2005;105:983-90.

24. Joseph KS, Allen A, Dodds L, Turner LA, Scott H, Liston R. The perinatal effects of delayed childbearing. Obstet Gynecol 2005;105:1410-8.

25. Raymond EG, Cnattingius S, Kiely JL. Effects of maternal age, parity, and smoking on the risk of stillbirth. Br J Obstet Gynaecol 1994;101:301-6.

26. Fretts RC, Schmittdiel J, Mclean FH, Usher RH, Marlene BG. Increased maternal age and the risk of fetal death. N Engl J Med 1995:333:953-7.

27. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study.[see comment]. BMJ 2000; 320:1708-12.

28. Conde-Agudelo A, Belizan JM, Diaz-Rossello JL. Epidemiology of fetal death in Latin America. Acta Obstet Gynecol Scand 2000;79:371-8.

29. Viegas OA, Leong WP, Ahmed S, Ratnam SS. Obstetrical outcome with increasing maternal age. J Biosoc Sci 1994;26:261-7.

30. Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL. Delayed childbearing and the outcome of pregnancy. N Engl J Med 1990;322:659-64.

31. Bianco A, Stone J, Lynch L, Lapinski R, Berkowitz G, Berkowitz RL. Pregnancy outcome at age 40 and older. Obstet Gynecol 1996;87:917-22.

32. World Health Organization. International statistical classification of diseases and related health problems: tenth revision (volume 2). Geneva: World Health Organization; 1993. p.129-33.

33. Joseph KS, Allen A, Kramer MS, CyrM, Fair M. Changes in the registration of stillbirths <500g in Canada, 1985-95. Paediatr Perinat Epidemiol 1999;13:278-87.

34. Centre of Disease Control. Vital statistics database 2004. Available from: URL:http://www.cdc.gov/nchs/vital.htm.

35. Zupan J. Perinatal Mortality in developing countries. N Engl J Med 2005;352;2047-8.

36. Goldenberg RL,Kirby R, Culhane JF. Stillbirth: a review. J Matern Fetal and Neonatal Med 2004;16:79-94.

37. Gadow EC, Castilla EE, Lopez Camelo J, Queenan JT. Stillbirth rate and associated risk factors among 869750 Latin American hospital births 1982-1986. Int J Gynecol Obstet 1991;35:209-14.

38. Khandait DW, Ambadekar NN, Zodpey SP, Vasudeo ND. Maternal age as a risk factor for stillbirth. Indian J Public Health 2000;44:28-30.

39. Winbo I, Serenius F, Dahlquist G, Kallen B. Maternal risk factors for cause-specific stillbirth and neonatal death. Acta Obstet Gynecol Scand 2001;80:235-44.

40. Cunningham FG, Gant NF, Leveno KJ, et al. Williams Obstetrics. 21st ed. New York: McGraw-Hill; 2001. p. 208,1073-8.

41. Heinonen S, Kirkinen P. Pregnancy outcome after previous stillbirth resulting from causes other than maternal conditions and fetal abnormalitie. Birth 2000;27:33-7.

42. Lekea-Karanika, Tzoumaka-Bakoula C, Golding J. Previous obstetric history and subsequent pretrm delivery in Greece. Eur J Obstet Gynecol Reprod Biol. 1990;37:99-109.

43. Naeye RL, Blanc WA. Unfavorable outcome of pregnancy: repeated losses. Am J Obstet Gynecol 1973;116:1133-7.

44. Aliyu MH, Salihu HM, Keith LG, Ehiri JE, Islam MA, Jolly PE. High parity and fetal

morbidity outcomes. Obstet Gynecol 2005;105:1045-51.

45. Little RE, Weinberg CR. Risk factors for antepartum and intrapartum stillbirth. Am J Epidemiol 1993;137:1177-89.

46. Goldman GA, Kaplan B, Neri A, Hecht-Resnick R, Harel L, Ovadia J. The grand multipara. Eur J Obstet Gynecol Reprod Biol 1995;61:105-10.

47. Bai J, Wong F, Bauman A, Mohsin M. Parity and pregnancy outcomes. Am J Obstet Gynecol 2002;186:274-8.52. Abu-Heija AT, Chalabi HE. Great grand multiparity: is it a risk? Int J Gynaecol Obstet
1997; 59:213-6.

48. Brunner J, Melander E, Krook-Brandt M, Thomassen PA. Grand multiparity as an obstetric risk factor: A prospective case-control study. Eur J Obstet Gynecol Reprod Biol 1992;47:201-5.

49. Ananth CV, Wilcox AJ, Savitz DA, Bowes WA Jr, Luther ER. Effect of maternal age and parity on the risk of uteroplacental bleeding disorders in pregnancy. Obstet Gynecol 1996;88:511-6.

50. Devalera E. Abruptio placentae. Am J Obstet Gynecol 1968;100:599-606.

51. Evaldson GR. The grand multipara in modern obstetrics. Obstet Gynecol Invest 1990;30:217-23.

52. Abu-Heija AT, Chalabi HE. Great grand multiparity: is it a risk? Int J Gynaecol Obstet 1997; 59:213-6.

53. Babinszki A, Kerenyi T, Torok O, Grazi V, Lapinski RH, Berkowitz RL. Perinataloutcome in grand and great grand multiparity: Effects of parity on obstetric risk factors. Am J Obstet Gynecol 1999;181:669-74.

54. Toohey JS, Keegan KA Jr, Morgan MA, Francis J, Task S, deVeciana M. The dangerous multipara: fact or fiction? Am J Obstet Gynecol 1995;172:683-6.

55. Haglund B, Cnattingius S, Nordstrom ML. Social differences in late fetal death and infant mortality in Sweden 1985-86. Paediatr and Perinat Epidemiol 1993;7:33-44.

56. Yerushalmy J. Age of father and survival of offspring. Human Biol 1939;11:342-56.

57. Nybo Andersen AM, Hansen KD, Andersen PK, Davey Smith G. Advanced paternal age and risk of fetal death: a cohort study. Am J Epidemiol 2004;160:1214-22.

58. Resseguie LJ. Paternal age, stillbirths and mutation. Ann Hum Genet 1976 Nov;40(2):213-9.

59. Kinzler WL, Ananth CV, Smulian JC, Vintzileos. Parental age difference and adverse perinatal outcomes in the United States. Paediatr and Perinat Epidemiol 2002;16:320-7.

60. Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, Swan SH. Influence of paternal age on the risk of spontaneous abortion. Am J Epidemiol 2005;161:816-23.

61. de la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. Hum Reprod 2002;17:1649-56.

62. Slama R, Werwatz A,Boutou O, Ducot B, Spira A, Hardle W. Does male age affect the risk of spontaneous abortion? An approach using semiparametric regression. Am J Epidemiol 2003; 157:815-24.

63. Thacker PD. Biological clock ticks for men, too: genetic defects linked to sperm of older fathers. JAMA 2004;291:1683-5.

64. Guildea ZE, Fone DL, Dunstan FD, Sibert JR, Cartlidge PH. Social deprivation and the causes of stillbirth and infant mortality. Arch Dis Child 2001;84:307-10.

65. Stephansson O, Dickman PW, Johansson AL, Cnattingius S. The influence of socioeconomic status on stillbirth risk in Sweden. Int J Epidemiol 2001;30:1296-301.

66. Vintzileos AM, Ananth CV, Smulian JC, Scorza WE, Knuppel RA. Prenatal care and black-white fetal death disparity in the United States: heterogeneity by high risk conditions. Obstet Gynecol 2002;99:483-9.

67. Zeitlin J, Combier E, Caunes FD, Papiernik E. Socio-demographic risk factors for perinatal mortality. Acta Obstet Gynecol Scand 1998;77:826-35.

68. Olsen J, Frische G. Social differences in eproductive health: A study on birth weight, stillbirths and congenital malformations in Denmark. Scand J Soc Med 1993;21:90-7.

69. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol 2004;103:219-24.

70. McCowan LME, Buiat RG, North RA. Perinatal morbidity in chronic hypertension. Br J Obstet Gynecol 1996; 102:123-9.

71. Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961-1988. Obstet Gynecol 1992;79:35-9.

72. Yadav S, Saxena U, Yadav R, Gupta S. Hypertensive disorders of pregnancy and maternal and fetal outcome. A case controlled study. J Indian Med Assoc 1997;95:548-51.

73. Martin JN, Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. Am J Obstet Gynecol 1999;180 (6 Pt 1):1373-84.

74. Kochenour NK. Other causes of fetal death. Clin Obstet Gynecol 1987;30:312-21.

75. Cundy T, Gamble G, Townend K, Henley PG, MacPherson P, Roberts AB. Perinatal mortality in Type 2 diabetes mellitus. Diabet Med 2000;17:33-9.

76. Mabie WC, Pernoll ML, Biswas MK. Chronic hypertension in pregnancy. Obstet Gynecol 1986; 67:197-205.

77. Branch DW. Immunologic disease and fetal death. Clin Obstet Gynecol 1987;30:295-311.

78. Cunningham FG, Cox SM, Harstad TW, Mason RA, Pritchard JA. Chronic renal disease and pregnancy outcome. Am J Obstet Gynecol 1990;163:453-9.

79. Simpson LL. Maternal medical diseases: risk of antepartum fetal death. Semin Perinatol 2002; 26:42-50.

80. Allen VM, Joseph K, Murphy KE, Magee LA, Ohlsson A. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population based study. BMC Pregnancy Childbirth 2004 Aug 6 ;4(1):17.

81. Aslan H, Gul A, Cebeci A. Neonatal outcome in pregnancies after preterm delivery for HELLP syndrome. Gynecol Obstet Invest 2004;58:96-9.

82. Ananth CV, Savitz DA, Bowes WA Jr. Hypertensive disorders of pregnancy and stillbirth in North Carolina, 1988 to 1991. Acta Obstet Gynecol Scand 1995;74:788-93.

83. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. Am J Obstet Gynecol 1990;163:460-5.

84. Abdella TN, Sibai BM, Hays JM Jr, Anderson GD. Relationship of hypertensive disease to abruptio placentae. Obstet Gynecol.1984;63:365-70.

85. Zuspan FP. New concepts in the understanding of hypertensive diseases during pregnancy: an overview. Clin Perinatol 1991;18:653-9.

86. Jacobs DJ, Vreeburg SA, Dekker GA, Heard AR, Priest KR, Chan A. Risk factors for hypertension during pregnancy in South Australia. Aust N Z J Obstet Gynaecol 2003;43:421-8.

87. Tricomi V, Kohl SG. Fetal death in utero. Am J Obstet Gynecol 1957;74:1092-7.

88. Gruenberger W, Gerstner GJ. The causes of antepartum fetal death: a clinico-pathological study. Clin Exp Obstet Gynecol 1980;7:210-4.

89. Bell R, Parker L, MacPhail S, Wright C. Trends in the cause of late fetal death, 1982-2000. BJOG 2004;111:1400-7.

90. Sibai BM, Abdella TN, Anderson GD. Pregnancy outcome in 211 patients with mild chronic hypertension. Obstet Gynecol 1983;61:571-6.

91. Connell FA, Vadheim C, Emanuel I. Diabetes in pregnancy: a population-based study of incidence, referral for care, and perinatal mortality. Am J Obstet Gynecol 1985;151:598-603.

92. Clausen TD, Matthiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. Diabetes Care 2005;28:323-8.

93. Robson S, Chan A, Keane RJ, Luke CG. Subsequent birth outcomes after an unexplained stillbirth: preliminary population-based retrospective cohort study. Aust N Z J Obstet Gynecol 2001; 41:29-35.

94. Sheiner E, Levy A, Katz M, Mazor M. Pregnancy outcome following recurrent spontaneous abortions. Eur J Obstet Gynecol Reprod Biol. 2005;118;61-5.

95. Lau TK, Li CY. A perinatal audit of stillbirth in a teaching hospital in Hong Kong. Aust N Z J Obstet Gynecol 1994;34:416-21.

96. Kristensen J, Vestergaard M, Wisborg K, Kesmodel U, Secher NJ. Pre-pregnancy weight and the risk of stillbirth and neonatal death. BJOG 2005;112:403-8.

97. Nohr EA, Bech BH, Davies MJ, Frydenberg M, Henriksen TB, Olsen J. Prepregnancy obesity and fetal death: a study within the Danish National Birth Cohort. Obstet Gynecol 2005; 106:250-9.

98. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med 1998; 338:147-52.

99. Stephansson O, Dickman PW, Johansson AL, Cnattingius S. Maternal weight, pregnancy weight gain, and the risk of antepartum stillbirth. Am J Obstet Gynecol 2001;184:463-9.

100. Fretts RC. Etiology and prevention of stillbirth. Am J Obstet Gynecol 2005;193:1923-35.

101. Alonso A, Soto I, Urgelles MF, Corte JR, Rodriguez MJ, Pinto CR. Acquired and inherited thrombophilia in women with unexplained fetal losses. Am J Obstet Gynecol 2002;187:1337-42.

102. Many A, Elad R, Yaron Y, Eldor A, Lessing JB, Kupferminc MJ. Third-trimester unexplained intrauterine fetal death is associated with inherited thrombophilia. Obstet Gynecol 2002;99:684-7.

103. Gris JC, Quere I, Monpeyroux F, Mercier E, Ripart-Neveu S, Tailland ML. Case-control study of the frequency of thrombophilic disorders in couples with late foetal loss and no thrombotic antecedent. Thromb Haemost 1999;81:891-9.

104. Preston FE, Rosendaal FR, Walker ID, Briet E, Berntorp E, Conard J. Increased fetal loss in women with heritable thrombophilia. Lancet 1996;348:913-6.

105. Weiner Z, Beck-Fruchter R, Weiss A, Hujirat Y, Shalev E, Shalev SA. Thrombophilia and stillbirth: possible connection by intrauterine growth restriction. BJOG 2004;111:780-3.

106. Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus EC, Hamulyak K. Increased risk for fetal loss in carriers of the factor V Leiden mutation.
Ann Intern Med 1999;130:736-9.

107. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A. Increased frequency of genetic thrombophilia in women with complications of pregnancy.
N Engl J Med 1999;340:9-13.

108. Agorastos T, Karavida A, Lambropoulos A, Constantinidis T, Tzitzimikas S, Chrisafi S. Factor V Leiden and prothrombin G20210A mutations in pregnancies with adverse outcome. J Matern Fetal Neonatal Med 2002 Oct;12(4):267-73.

109. Wright VC, Chang J, Jeng G, Macaluso M. Assisted reproductive technology surveillance-United States, 2003. MMWR Surveill Summ 2006 May 26;55(4):1-22.

110. Imaizumi Y. Infant mortality rates in single, twin and triplet births, and influencing factors in Japan, 1995-98. Paediatr Perinat Epidemiol 2001;15:346-51.

111. Westergaard T, Wohlfahrt J, Aaby P, Melbye M. Population based study of rates of multiple pregnancies in Denmark, 1980-94. BMJ 1997;314:775-9.

112. Ventura SJ, Martin JA, Curtin SC, Menacker F, Hamilton BE. Births: final data for 1999. Natl Vital Stat Rep 2001 Apr 17;49(1):1-100.

113. Russell RB, Petrini JR, Damus K, Mattison DR, Schwarz RH. The changing epidemiology of multiple births in the United States. Obstet Gynecol 2003;101:129-35.

114. Lynch A, McDuffie R, Murphy J, Faber K, Leff M, Orleans M. Assisted reproductive interventions and multiple birth. Obstet Gynecol 2001;97:195-200.

115. Zhang J, Meikle S, Grainger DA, Trumble A. Multifetal pregnancy in older women and perinatal outcomes. Fertil Steril 2002;78:562-8.

116. 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.

117. Bardis N, Maruthini D, Balen AH. Modes of conception and multiple pregnancy: a national survey of babies born during one week in 2003 in the United Kingdom. Fertil Steril 2005;84:1727-32.

118. Reynolds MA, Schieve LA. Trends in embryo transfer practices and multiple gestation for IVF procedures in the USA, 1996-2002. Hum Reprod 2006;21:694-700.

119. Oakley L, Doyle P. Predicting the impact of in vitro fertilisation and other forms of assisted conception on perinatal and infant mortality in England and Wales: examining the role of multiplicity. BJOG 2006;113:738-41.

120. Salihu HM, Aliyu MH, Rouse DJ, Kirby RS, Alexander GR. Potentially preventable excess mortality among higher-order multiples. Obstet Gynecol 2003;102:679-84.

121. Westergaard HB, Johansen AM, Erb K, Andersen AN. Danish National In-Vitro Fertilization Registry 1994 and 1995: a controlled study of births, malformations and cytogenetic findings. Hum Reprod 1999;14:1896-902.

122. Dhont M, De Sutter P, Ruyssinck G, Martens G, Bekaert A. Perinatal outcome of pregnancies after assisted reproduction: a case-control study. Am J Obstet Gynecol 1999; 181:688-95.

123. Bergh T, Ericson A, Hillensjo T, Nygren KG, Wennerholm UB. Deliveries and children born after in-vitro fertilisation in Sweden 1982-95: a retrospective cohort study. Lancet 1999; 354:1579-85.

124. Wang JX, Norman RJ, Kristiansson P. The effect of various infertility treatments on the risk of preterm birth. Hum Reprod 2002;17:945-9.

125. McDonald SD, Murphy K, Beyene J, Ohlsson A. Perinatel outcomes of singleton pregnancies achieved by in vitro fertilization: a systematic review and meta-analysis. J Obstet Gynaecol Can 2005;27:449-59.

126. Tan SL, Doyle P, Campbell S, Beral V, Rizk B, Brinsden P. Obstetric outcome of in vitro fertilization pregnancies compared with normally conceived pregnancies. Am J Obstet Gynecol 1992;167:778-84.

127. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 2004;103:551-63.

128. Breart G. Delayed childbearing. Eur J Obstet Gynecol Reprod Biol 1997;75:71-3.

129. Heffner LJ. Advanced maternal age---how old is too old? N Engl J Med 2004;351;1927-9.

130. Fleiss JL, Levin B, Cho Paik M. Statistical methods for rates and proportions. 3rd ed. Hoboken,New Jersey: Wiley-Interscience; 2003. p.598-610.

131. Altman DG. Practical statistics for medical research. London England: Chapman and Hall; 1991. p. 404.

132. Cnattingius S, Forman MR, Berendes HW, Isotalo L. Delayed childbearing and risk of adverse perinatal outcome: a population-based study. JAMA 1992;268:886-90.

133. Donoso E, Villarroel L. [Reproductive risk of women over 40 years old]. [Spanish]. Rev Med Chil 2003;131:55-59.

134. Heimann F, Messerer D, Baltzer J. [Pregnancy, labor and fetal outcome in females over 40 years of age]. [German]. Geburtshilfe und Frauenheilkunde 1993;53:411-5.

135. Lammer EJ, Brown LE, Anderka MT, Guyer B. Classification and analysis of fetal deaths in Massachusetts. JAMA 1989;261:1757-62.

136. Pugliese A, Vicedomini D, Arsieri R. [Perinatal outcomes of newborn infants of mothers over 40 years old. A case-control study]. [Italian]. Minerva Ginecologica 1997;49:81-4.

137. Rasmussen S, Albrechtsen S, Irgens LM, Dalaker K, Maartmann-Moe H, Vlatkovic L et al. Risk factors for unexplained antepartum fetal death in Norway 1967-1998. Early Hum Dev 2003;71:39-52.

138. Sheiner E, Hallak M, Shoham-Vardi I, Goldstein D, Mazor M, Katz M. Determining risk factors for intrapartum fetal death. J Reprod Med 2000;45:419-24.

139. 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.

140. Wen SW, Lei HZ, Kramer MS, Sauve R. Determinants of intrapartum fetal death in a remote and indigent population in China. J Perinatol 2004;24:77-81.

141. Dildy GA, Jackson GM, Fowers GK, Oshiro BT, Varner MW, Clark SL. Very advanced maternal age: pregnancy after age 45. Am J Obstet Gynecol 1996;175:668-74.

142. Salihu HM, Shumpert MN, Slay M, Kirby RS, Alexander GR. Childbearing beyond maternal age 50 and fetal outcomes in the United States. Obstet Gynecol 2003;102:1006-14.

143. Cassell KA, O'connell CM, Baskett TF. The origins and outcomes of triplet and quadruplet pregnancies in Nova Scotia: 1980 to 2001. Am J Perinatol 2004;21:439-45.

144. Gardner MO, Goldenberg RL, Cliver SP, Tucker JM, Nelson KG, Copper RL. The origin and outcome of preterm twin pregnancies. Obstet Gynecol 1995;85:553-7.

145. Hur YM, Kwon JS. Changes in twinning rates in South Korea: 1981-2002. Twin Res Hum Genet. 2005;8:76-9.

146. Fair ME, Cyr M, Allen CA, Wen SW, Guyon G, MacDonald RC. An assessment of the validity of a computer system for probabilistic record linkage of birth and infant death records in Canada. Chronic Diseases in Canada 2000;21:8-13.

147. Statistics Canada. Vital Statistics-Stillbirth Database. [Cited 2005 Jul 15]; Available from: URL:http://www.statcan.ca/english/sdds/3234.htm.

148. Joseph KS, Kramer MS. Recent trends in infant mortality rates and proportions of low-birth-weight live births in Canada. CMAJ 1997;157:535-41.

149. Joseph KS, Kramer MS. Recent trends in Canadian infant mortality rates: effect of changes in registration of live newborns weighing less than 500 g. CMAJ 1996;155(8):1047-52.

150. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.

151. Rubin DB. Multiple imputation for non-response in surveys. New York: New York: John Wiley & Sons Inc; 1987.

152. Yuan YC. Multiple imputation for missing data: Concepts and new development. SAS Users Group International (SUGI); P267-25.

153. Kirz DS, Dorchester W, Freeman RK. Advanced maternal age: the mature gravida. Am J Obstet Gynecol 1985;152:7-12.

154. Galstian A, Beer AE, Roberts JM. Immunology of preeclampsia. In: Coulam CB, Faulk WP, McIntyre JA,eds. Immunological obstetrics. New York, NY: W W Norton Medical Books, 1992:502-16.

155. Linn S, Schoenbaum SC, MonsonRR. The relationship between induced abortion and outcome of subsequent pregnancies. Am J Obstet Gynecol 1983;146:136-40.

156. MacDonald IR, Maclennan HR. A consideration of the treatment of elderly primigravidae. J Obstet Gynaecol Br Emp. 1960;67:443-50.

157. Kane SH. Advancing age and the primigravida. Obstet Gynecol. 1967;29:409-14.138.

158. Morrison I. The elderly primigravida. Am J Obstet Gynecol. 1975;121:465-70.

159. Blickstein I, Lancet M, Kessler I. Re-evaluation of the obstetrical risk for the older primipara. Int J Gynaecol Obstet. 1987 Apr;25(2):107-12.

160. Prysak M, Lorenz RP, Kisly A. Pregnancy outcome in nulliparous women 35 years and older. Obstet Gynecol 1995;85:65-70.

161. Stein A. Pregnancy in gravidas over age 35 years. J Nurse Midwifery 1983;28:17-20.

162. Sipila P, von Wendt L, Hartikainen-Sorri AL. The grand multipara---still an obstetrical challenge? Arch Gynecol Obstet 1990;247(4):187-95.

163. Chibber R. Unexplained antepartum fetal deaths: what are the determinants? Arch Gynecol Obstet 2005 Apr;271(4):286-91.

164. Seidman DS, Dollberg S, Stevenson DK, Gale R. The effects of parity and socio-economic status on obstetric and neonatal outcome. Arch Gynecol Obstet 1991;249(3):119-27.

165. Aliyu MH, Jolly PE, Ehiri JE, Salihu HM. High parity and adverse birth outcomes: exploring the maze. Birth 2005; 32:45-59.

166. Simonsen SM, Lyon JL, Alder SC, Varner MW. Effect of grand multiparity on intrapartum and newborn complications in young women. Obstet Gynecol 2005;106:454-60.

167. Scholl TO, Hediger ML, Huang J, Johnson FE, Smith W, Ances IG. Young maternal age and parity. Influences on pregnancy outcome. Ann Epidemiol 1992 Sep;2(5):565-75.

168. Williams MA, Lieberman E, Mittendorf R, Monson RR, Schoenbaum SC. Risk factors for abruptio placentae. Am J Epidemiol 1991;134:965-72.

169. Woolf CM. Stillbirths and parental age. Obstet Gynecol 1965;26:1-8.

170. Selvin S, Garfinkel J. Paternal age, maternal age and birth order and the risk of a fetal loss. Hum Biol 1976; 48:223-30.

171. Astolfi P, De Pasquale A, Zonta LA. Late paternity and stillbirth risk. Hum Reprol 2004; 19:2497-501.

172. Penrose LS. Parental age and mutation. Lancet 1955 Aug 13; 269(6885):312-3.

173. Boue A, Boue J, Cropp A. Cytogenetics of pregnancy wastage. Adv Hum Genet 1985;14:1-57.

174. Burgoyne PS, Holland K, Stephens R. Incidence of numerical chromosome anomalies in human pregnancy estimation from induced and spontaneous abortion data. Hum Reprod 1991;6:555-65.

175. Tarin JJ, Gomez-Piquer V, Manzanedo C, Minarro J, Hermenegildo C, Cano A. Long-term effects of delayed motherhood in mice on postnatal development and behavioural traits of offspring. Hum Reprod 2003; 18:1580-7.

176. Sairam S, Costeloe K, Thilaganathan B. Prospective risk of stillbirth in multiple-gestation pregnancies: a population-based analysis. Obstet Gynecol 2002;100:638-41.

177. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology. 1995 Jul;6(4):356-65.

178. Royston P. A strategy for modeling the effect of a continuous covariate in medicine and epidemiology. Stat Med. 2000;19:1831-47.

179. Khan KS, Chien PF, Dwarakanath LS. Logistic regression models in obstetrics and gynecology literature. Obstet Gynecol. 1999;93:1014-20.

180. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. Ann Intern Med. 1993;118:201-10.

181. 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;156:493-7.

182. Neumann M, Graf C. Pregnancy after age 35: Are these women at high risk? AWHONN Lifelines 2003;7:424-30.

Appendix A: Literature search strategy

1.stillbirth$.tw.

2. fetal death$.tw.

3. exp *Fetal Death/an, mo, cl, pa, co, di, pc, px, ec, sn, ep, eh, td, et, ge [Analysis, Mortality, Classification, Pathology, Complications, Diagnosis, Prevention & Control, Psychology, Economics, Statistics & Numerical Data, Epidemiology, Ethnology, Trends, Etiology, Genetics]

4. (perinatal mortality or perinatal death$).tw.

5. or/1-4

6. increas$ maternal age.tw.

7. advanced maternal age.tw.

8. exp *"Maternal Age 35 and over"/

9. delayed childbearing.tw.

10. older mother$.tw.

11. or/6-10

12. 5 and 11

13. risk.tw.

14. exp risk/

15. (relative risk or risk ratio$ or RR).tw.

16. (odds ratio$ or ORs).tw.

17. or/13-16

18. cohort stud#.tw.

19. case control stud#.tw.

20. exp cohort studies/

21. exp case control studies/

22. (prospective or retrospective).tw.

23. or/18-22

24. 12 and 17

25. 12 and 23

26. 12 and 17 and 23

Appendix B: Data extraction form for systematic review

Stillbirth and Maternal Age: Systematic Review

SECTION 1: Document Identification:

Reviewer's Initials ______ **Reference Manager ID#**_____ **Source** ________________

Lead Author ______________ **Journal** ____________________ **Year of publication** ________

Language of publication 1. English 2. Other: ______________________________

Country(ies) of Study Origin ________________________ **Study year**__________________

Source(s) of funding for the study (if available): ____

Medium:
1. Full journal Publication 2. published abstract 3. Editorial 4. Letter/comment 5. book 6. conference proceedings 7. Grey literature

SECTION2: Method of Study

Study design: 1.Cohort, prospective 2. Cohort, retrospective 3. Case Control 4. Other: ___________

Database: 1. Population based 2. Hospital based 3. Other: ______________________________

Study population:
Plurality: 1. Singletons 2. Multiple pregnancy 3. Both
Parity: 1. Nullipara 2. Multipara 3. Both

Stillbirth included:

Gestational age:	1. ≥ 20 weeks	2. ≥ 22 weeks	3. ≥ 28 weeks	4. Other: ________________	
Birth weight :	1. All	2. ≥ 500g	3. ≥ 1000g	4. Other: ________________	
Type:	1. All	2. Antepartum	3. Intrapartum	4. Unexplained	5. Other: ____

Confounders Adjusted for in the analysis:
1. None
2. Comobidities: 1) Hypertension 2) Diabetes 3) Other:________________________________
3. Placental complications: 1) Placenta previa 2) Abruption 3) Cord problem 4) Other: __________
4. Obstetrical history: 1) Previous SB 2) Parity 3) Other ______________________________
5. SES: 1)Education 2) Race 3) Other ______________________________________
6. Behavior: 1)Smoking 2) Drinking 3) Drug using 4) Other: ____________________
7. Other: ____

Effect modifiers considered in the analysis:
1. No 2. Yes specify____

Additional information about the method of study:

____

SECTION3: Results

Section A: Observed Outcomes

Variable	# of Total births	# of Live births	# of Stillbirths	Stillbirth Rate (‰)	Crude OR	*Adjusted OR
Maternal age (Years):						
1. <20						
2. 20-24						
3. 25-29						
4. 30-34						
5. 35-39						
6. ≥ 40						
Total						

Factors adjusted for:

Section B: Notes

Appendix C: Sample of birth certificates

Registration No

Amendment No

Service Request No. | Pre-Registration No.

Alberta
REGISTRIES

- *This is a* ***permanent legal record.*** • *Certificates are prepared according to this information and in compliance with legislation.* • *Type or print clearly in* ***black ink only.*** • *Do not sign this form until it is* ***completed in full.***

Registration of Birth

Child

1. Last Name of Child *(restrictions apply - see Information Guide before completing)*

Full Given Name(s)

2. Sex
☐ Male
☐ Female

3. Date of Birth *(month name, day, year)*

4. Time of Birth
______ Hour : ______ Minutes ☐ AM ☐ PM

6. Place of Birth a) Name of Hospital *(if not in hospital, give exact location)*

b) City/Town/Village *(if rural, give nearest city/town/village)*
, Alberta

7. Kind of Birth
☐ Single ☐ Twin
☐ Triplet
☐ Other ______

8. Order of Birth *(multiple births only)*
☐ 1st ☐ 2nd
☐ 3rd ☐ ______

9. Birth Weight *(in grams)*

10. Duration of Pregnancy *(completed weeks)*

Children born to this Mother *(include this birth)*
11. Number of Live Births
12. Number of Stillbirths *(excluding miscarriages)*

13. a) Type of Birth Attendant
☐ Physician ☐ Midwife ☐ Other: *(specify)*

b) Name of Birth Attendant

See Information Guide

14. Are parents married to each other *(at conception, birth, or any time in between)*? ☐ Yes ☐ No

15. If parents are not married to each other, indicate **Mother's** marital status
☐ Never Married ☐ Divorced ☐ Widowed ☐ Married

Mother

16. Currently Used Last Name of Mother

17. Legal Maiden Last Name

Full Legal Given Name(s)

18. Alberta Personal Health Number

19. Date of Birth *(month name, day, year)*

20. Place of Birth *City/Town/Village* *Province/Country*

21. Usual Residence *Street Address* *City/Town/Village*

Province/State *Country* *Postal/Zip Code* Telephone No. *(daytime)*

(If different than Usual Residence)
22. Mailing Address *Street Address/PO Box No.* *City/Town/Village*

Province/State *Country* *Postal/Zip Code*

23. **I certify** the above to be correct to the best of my knowledge and request, jointly with the father listed *(if applicable)*, the last name of the child be registered as named above.

X ______________________ ______________________
Signature of Mother *Date (month name, day, year)*

or Informant: I certify the above to be correct to the best of my knowledge.

X ______________________ ______________________
Signature of Informant *Relationship to Child*

Father

See Information Guide before completing

24. Legal Last Name of Father

Full Legal Given Name(s)

25. Alberta Personal Health Number

26. Date of Birth *(month name, day, year)*

27. Place of Birth *City/Town/Village* *Province/Country*

28. **I acknowledge** that I am the natural father of this child and jointly request, with the mother, the last name of the child be registered as named above.

X ______________________ ______________________
Signature of Father *Date (month name, day, year)*

REG 3216 (98/03)

Last Name of Child

Your options for registering the last name of your child are restricted by legislation.

The restrictions are determined by the

- *Mother's Marital Status,*
- *Father's Information, and*
- *Signatures recorded on this registration.*

Carefully ***read*** *the* ***Registering a Birth Information Guide*** *for a full explanation* ***before completing*** *this registration form.*

Notations *(Vital Statistics Use Only)*

Hospital Certification

I certify this registration was accepted by me at *(name of hospital)*

____

at ______________________, Alberta

dated ______________________

X ______________________
Signature of Hospital Registrar

This information is being collected for the purposes of Vital Statistics records in accordance with the Vital Statistics Act. Questions about the collection of this information can be directed to the Freedom of Information and Protection of Privacy Coordinator for Alberta Registries, Research and Program Support, 3D Commerce Place 10155-102 Street Edmonton, Alberta T5J 4L4, (403)427-2683

Alberta
GOVERNMENT SERVICES
Registries

- This is a permanent legal record.
- Type or print clearly in black ink only.
- Do not sign this form until it is completed in full.

Registration No.	
Amendment No.	
Service Request No.	Pre-Registration No.

Registration of Stillbirth

Child

1. Last Name of Child (restrictions apply - see Information Guide before completing)
Full Given Name(s)
2. Sex ☐ Male ☐ Female
3. Date of Stillbirth (month name, day, year)
5. Place of Stillbirth a) Name of Hospital (if not in hospital give exact location) b) City/Town/Village (if rural, give nearest city/town/village)
6. Kind of Birth ☐ Single ☐ Twin ☐ Triplet ☐ Other: ______
7. Order of Birth (multiple births only) ☐ 1st ☐ 2nd ☐ 3rd ☐ ____
8. Birth Weight (in grams)
9. Duration of Pregnancy (completed weeks)
Children born to this Mother (include this birth)
10. Number of Live Births
11. Number of Stillbirths (excluding miscarriages)
12. a) Type of Birth Attendant ☐ Physician ☐ Midwife ☐ Other: (specify)
b) Name of Birth Attendant

See Information Guide ▶ 13. Are parents married to each other (at conception, birth, or any time in between)? ☐ Yes ☐ No
14. If parents are not married to each other, indicate Mother's marital status ☐ Never Married ☐ Divorced ☐ Widowed ☐ Married

Mother

15. Currently Used Last Name of Mother
16. Legal Maiden Last Name
Full Legal Given Name(s)
17. Alberta Personal Health Number
18. Date of Birth (month name, day, year)
19. Place of Birth City/Town/Village Province/Country
20. Usual Residence Street Address City/Town/Village
Province/State Country Postal/Zip Code Telephone No. (daytime)
(if different than Usual Residence) 21. Mailing Address Street Address/PO Box No. City/Town/Village
Province/State Country Postal/Zip Code
22. I certify the above to be correct to the best of my knowledge and request jointly with the father listed (if applicable), the last name of the child be registered as named above.
X
Signature of Mother Date (month name, day, year)
or Informant: I certify the above to be correct to the best of my knowledge.
X
Signature of Informant Relationship to Child

Father

See Information Guide before completing
23. Legal Last Name of Father
Full Legal Given Name(s)
24. Alberta Personal Health Number
25. Date of Birth (month name, day, year)
26. Place of Birth City/Town/Village Province/Country
27. I acknowledge that I am the natural father of this child and request jointly with the mother, the last name of the child be registered as named above.
X
Signature of Father Date (month name, day, year)

Disposition Information To be completed by Funeral Director/Hospital

28. Method of Disposition ☐ Burial ☐ Cremation ☐ Department of Anatomy ☐ Mausoleum ☐ Fetal/Infant Death (disposition by hospital)
29. Proposed Date of Disposition (month name, day, year)
30. Name of Cemetery, Crematorium or Place of Disposition
Address
31. Name of Funeral Home, Hospital, or Person in Charge of Remains
Address
Telephone Number

Hospital/District Registrar Certification

Burial Permit Issued by (name of facility)
Date Issued (month name, day, year)
I certify this registration was accepted by me at (name of facility)
at ______, Alberta
dated ______
X
Signature of Hospital/District Registrar

Notations (Vital Statistics Use Only)

This information is being collected for the purposes of Vital Statistics records in accordance with the Vital Statistics Act. Questions about the collection of this information can be directed to the Freedom of Information and Protection of Privacy Coordinator for Alberta Registries, Research and Program Support, 3D Commerce Place, 10155-102 Street, Edmonton, Alberta T5J 4L4. (780) 427-7013.

REG 3218 (98/03)

Alberta
REGISTRIES

Registration No
Amendment No
Service Request No / Pre-Registration No

- *See back of form before completing*
- *This is a **permanent legal record***
- *Type or print clearly in **black ink only***

Medical Certificate of Stillbirth

Personal Information of the Child

1 Last Name of Child
Full Given Name(s)
2 Sex ☐ Male ☐ Female
3 Date of Stillbirth *(month name, day, year)*
4 Place of Stillbirth a) Name of Hospital *(if not in hospital give exact location)* b) City/Town/Village *(if rural give nearest city/town/village)* , Alberta

Medical Certificate of Stillbirth

(Check One)

Medical Cause of Stillbirth

Part 1 — For examples see back of form — Fetal / Maternal

Immediate Cause of stillbirth, giving (a)
due to (or as a consequence of)
Antecedent Cause(s) if any, next (b) ☐ ☐
due to (or as a consequence of)
state the ***Underlying Cause*** last (c) ☐ ☐

Part 2 — Fetal / Maternal
Other Significant Conditions contributing to stillbirth but not causally related to the immediate cause (a) above ☐ ☐ / ☐ ☐

Autopsy Particulars

5 Autopsy being held? Yes ☐ No ☐
If Yes Does the cause of stillbirth stated above take into account autopsy finding? Yes ☐ No ☐
6 Will further information relating to the cause of stillbirth be available later? *(see back of form re Interim Certificate)* Yes ☐ No ☐

Delivery and Labour

7 Manipulative, instrumental or other operative procedure for delivery? ☐ Yes ☐ No
8 Was fetus dead before such procedure? ☐ Yes ☐ No
9 Nature of procedure *(low, middle or high forceps, version and extraction, caesarian section, craniotomy, etc)*
10 Did death occur *before* labour? Yes ☐ No ☐ *during* labour? Yes ☐ No ☐
11 Labour induced? ☐ Yes ☐ No *If Yes, specify method(s)*

Certification (Attending Physician, Medical Examiner)

12 I certify that I *was / was not* in attendance at this stillbirth and that the statements herein are true and correct to the best of my knowledge

X
Signature of Attending Physician or Medical Examiner — *Date (month, day, year)*

13 Designation ☐ Attending Physician ☐ Medical Examiner
14 Name of Attending Physician or Medical Examiner (please print)
15 Mailing Address *Street Address/P.O. Box No / City/Town/Village / Province / Postal Code*
16 Business Telephone Number

***Notations** (Vital Statistics Use Only)*

Hospital Certification

I certify this registration was accepted by me at *(name of hospital)*
at .... Alberta
dated
X
Signature of Hospital Registrar

This form is required before a burial permit can be issued

This information is being collected for the purposes of Vital Statistics records in accordance with the Vital Statistics Act. Questions about the collection of this information can be directed to the Freedom of Information and Protection of Privacy Coordinator for Alberta Registries, Research and Program Support, 3D Commerce Place, 10155 102 Street, Edmonton, Alberta T5J 4L4, (403)427-2683

REG 3219 (96/03)