

Delayed Child-Bearing

This Committee Opinion has been prepared by the Genetics Committee, reviewed by the Reproductive Endocrinology and Infertility Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To provide an overview of delayed child-bearing and to describe the implications for women and health care providers.

Options: Delayed child-bearing, which has increased greatly in recent decades, is associated with an increased risk of infertility, pregnancy complications, and adverse pregnancy outcome. This guideline provides information that will optimize the counselling and care of Canadian women with respect to their reproductive choices.

Outcomes: Maternal age is the most important determinant of fertility, and obstetric and perinatal risks increase with maternal age. Many women are unaware of the success rates or limitations of assisted reproductive technology and of the increased medical risks of delayed child-bearing, including multiple births, preterm delivery, stillbirth, and Caesarean section. This guideline provides a framework to address these issues.

Evidence: Studies published between 2000 and August 2010 were retrieved through searches of PubMed and the Cochrane Library using appropriate key words (delayed child-bearing, deferred pregnancy, maternal age, assisted reproductive technology, infertility, and multiple births) and MeSH terms (maternal age, reproductive behaviour, fertility). The Internet was also searched using similar key words, and national and international medical specialty societies were searched for clinical practice guidelines and position statements. Data were extracted based on the aims, sample, authors, year, and results.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

Recommendations

1. Women who delay child-bearing are at increased risk of infertility. Prospective parents, especially women, should know that their fecundity and fertility begin to decline significantly after 32 years of age. Prospective parents should know that assisted reproductive technologies cannot guarantee a live birth or completely compensate for age-related decline in fertility. (II-2A)
2. A fertility evaluation should be initiated after 6 months of unprotected intercourse without conception in women 35 to 37 years of age, and earlier in women > 37 years of age. (II-2A)
3. Prospective parents should be informed that semen quality and male fertility deteriorate with advancing age and that the risk of genetic disorders in offspring increases. (II-2A)

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Key Words: Maternal age, delayed child-bearing, reproductive technology, oocyte donation, late maternal age

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4. Women ≥ 35 years of age should be offered screening for fetal aneuploidy and undergo a detailed second trimester ultrasound examination to look for significant fetal birth defects (particularly cardiac defects). (II-1A)
5. Delayed child-bearing is associated with increased obstetrical and perinatal complications. Care providers need to be aware of these complications and adjust obstetrical management protocols to ensure optimal maternal and perinatal outcomes. (II-2A)
6. All adults of reproductive age should be aware of the obstetrical and perinatal risks of advanced maternal age so they can make informed decisions about the timing of child-bearing. (II-2A)
7. Strategies to improve informed decision-making by prospective parents should be designed, implemented, and evaluated. These strategies should provide opportunity for adults to understand the potential medical, social, and economic consequences of child-bearing throughout the reproductive years. (III-B)
8. Barriers to healthy reproduction, including workplace policies, should be reviewed to optimize the likelihood of healthy pregnancies. (III-C)

INTRODUCTION

There is a growing trend in Canada for child-bearing to occur later in women's lives. Not only are more women aged > 30 years giving birth, but the proportion of first births occurring among women aged > 30 has been increasing steadily over the past 20 years.¹ Currently, 11% of first births occur in women aged ≥ 35 years.¹ This trend towards delayed child-bearing is also occurring in Western Europe, Australia, New Zealand, and the United States.²

Many of the reasons why women are choosing to postpone child-bearing reflect the availability of safe, effective, and reversible contraception, which has allowed women the reproductive autonomy to decide *if* and *when* they will have children. Biologically, the optimum period for child-bearing is between 20 and 35 years of age. After 35 years of age, fecundity decreases, and the chance of miscarriage, spontaneous abortion, pregnancy complications, and adverse pregnancy outcomes (including PTD and multiple birth) increases.³ As women age, many opt for fertility treatment to improve their chance of conception. The effectiveness of various reproductive technologies declines steadily after the age of 35, while the risk of pregnancy complications and adverse outcome increases with both

maternal age and the use of reproductive assistance.^{4,5} These pregnancy complications include ectopic pregnancy, spontaneous abortion, fetal chromosomal abnormalities, certain congenital anomalies, placenta previa, gestational diabetes, preeclampsia, multiple births, PTD, and Caesarean section. These in turn are associated with an increased risk of preterm birth and perinatal and maternal mortality and morbidity.⁶⁻¹⁰ Infants born preterm, especially multiples, are at increased risk of morbidity, mortality, and long-term disability.

If the trend towards delayed child-bearing continues, society can anticipate increased demand for reproductive assistance and associated increases in the need for more sophisticated prenatal, postpartum, and early development care. While a short delay in age at parenting poses little absolute risk for the individual woman, small shifts in population distribution curves affect large numbers of women, which has important implications for the health care system.

The SOGC hopes to alert care providers to the implications of this emerging public health issue and supports the urgent need for better public information to enable more informed reproductive choices.

DEFINITION OF DELAYED CHILD-BEARING

Fertility declines with increasing maternal age, especially after the mid-30s. For this reason, delayed child-bearing is traditionally defined as pregnancy occurring in women aged ≥ 35 years. This population has been referred to as advanced maternal age or late maternal age. In recent years, advances in ART have challenged the traditional age-related boundaries of reproduction, enabling even postmenopausal women to conceive and give birth.¹¹ Before ART, the oldest naturally conceived pregnancy was in a 57-year-old woman.¹² With use of ART and donor oocytes, the birth rate in older mothers has risen dramatically, and in one case, a 70-year-old woman has given birth. These women are defined as "very advanced maternal age" (44 years of age or older), "mature" gravida, or "extremely elderly" gravida.

INCIDENCE OF DELAYED CHILD-BEARING

Currently, the average age of a woman giving birth in Canada is 29 years, which represents a significant increase from previous decades.⁷ The proportion of first births occurring among women aged ≥ 35 has also increased from 4% in 1987 to 11% in 2005. At the same time, the proportion of first births occurring among women between 30 and 34 years increased from 18.9% in 1982 to 31.4% in 2006, and for the first time,

ABBREVIATIONS

ART	assisted reproductive technology
OR	odds ratio
ICSI	intracytoplasmic sperm injection
IUI	intrauterine insemination
LBW	low birth weight
PTD	preterm delivery
SGA	small for gestational age

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.¹⁰¹

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.¹⁰¹

the fertility rate of 30- to 34-year-old women exceeded the rate for women aged 25 to 29 years.¹³ Over the same time period, the proportion of live births to women between the ages of 35 to 39 and 40 to 44 years also increased, from 4.7% to 14.8%, and from 0.6% to 2.8% respectively.¹⁴

As women delay child-bearing and age at first birth increases, the total number of births to each woman decreases, and the size, composition, and future growth of the population is affected. The postponement of first births has been associated with smaller family sizes and increased childlessness, all of which contribute to the overall decline in fertility rate as experienced in Canada and other countries, including Spain, Sweden, the United Kingdom, and Australia. In Canada the fertility rate (average number of children per woman) of 1.66 (2007) is well below the replacement level of 2.1 children per woman.¹⁵

CAUSES OF DELAYED CHILD-BEARING

A number of factors have been proposed in the demographic and sociological literature to explain the phenomenon of delayed child-bearing, including safe, effective contraception, changes in societal expectations of women in post-secondary education and the workforce, and an increased population of women 35 to 44 years of age.¹²

Indeed, maternal education has been identified as one of the strongest predictors of use of contraception, timing of child-bearing, and the total number of children a woman will bear. In a study by Tough et al., financial security and

relationship factors (e.g., partner’s interest in and suitability for parenting) ranked as the 2 most important factors influencing readiness for child-bearing.¹⁶

A false sense of security is associated with advances in ART, and most women are unaware that technology cannot compensate completely for the effects of reproductive aging, except potentially through oocyte donation. A recent survey of 360 Canadian undergraduate women assessing their understanding of reproductive aging found that while most were aware of the drop in fertility with age, they significantly overestimated the likelihood of pregnancy at all ages and were not aware of the steep rate of fertility decline with age. These women also overestimated the chance of pregnancy loss at all ages, but they did not identify a woman’s age as the strongest risk factor for this event.¹⁷

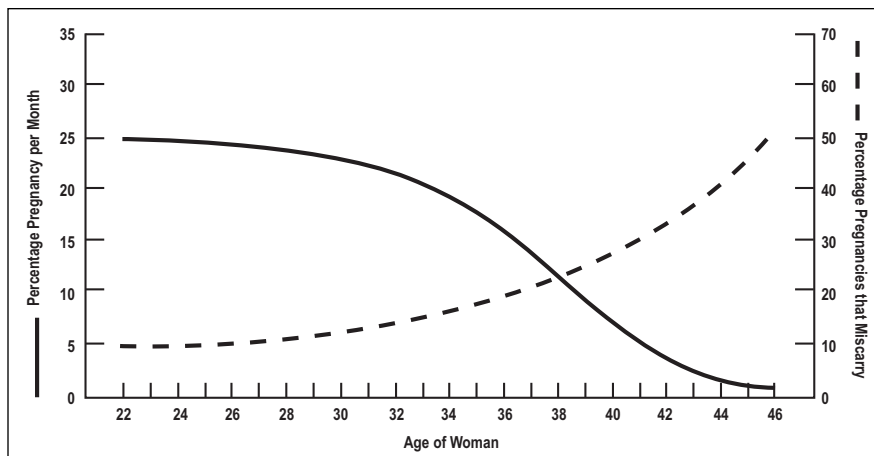
CONSEQUENCES OF DELAYED CHILD-BEARING

Delayed child-bearing is associated with an increased risk of infertility, maternal comorbidity, pregnancy and birth complications, and increased maternal and fetal morbidity and mortality. Women who start their families in their 20s and complete them by age 35 face significantly reduced risks.

MATERNAL AGE-RELATED SUBFERTILITY

Advancing maternal age is associated with a longer average time to achieve conception.¹⁸ Fecundability (i.e., the probability of achieving a pregnancy in one menstrual

Figure 1. Natural conception: schematic demonstrating trends in pregnancy and miscarriage rates according to age



Reproductive Ageing: Guidelines for First Line Physicians for Investigation of Infertility Problems (Canadian Fertility and Andrology Society;2004). Used with permission.

cycle) begins to decline significantly in the early 30s (about age 32), and typically subfecundability becomes more evident by age 37.¹⁹

The influence of female age on fertility has been clearly established by a number of observational studies that have consistently demonstrated a decline in pregnancy rates with advancing maternal age (Figure 1).^{7,20–22} Furthermore, cycles that result in pregnancy are less likely to progress to live births because of higher rates of aneuploidy and spontaneous abortion among older women.¹⁹

The progressive decrease in the number and quality of oocytes from fetal life until menopause is the cause of the age-related decline in female fertility. The oocyte pool peaks while the female fetus is in utero, reaching approximately 6 to 7 million at 20 weeks of gestation.²³ Subsequently, progressive atresia occurs so that the number of remaining oocytes is approximately 1 to 2 million at birth and 250 000 at the onset of puberty. During the reproductive years, there is continued atresia, which occurs at an accelerated rate after the age of 37 in the average woman.¹⁸ The average age of menopause is 51, at which time approximately 1000 oocytes remain.

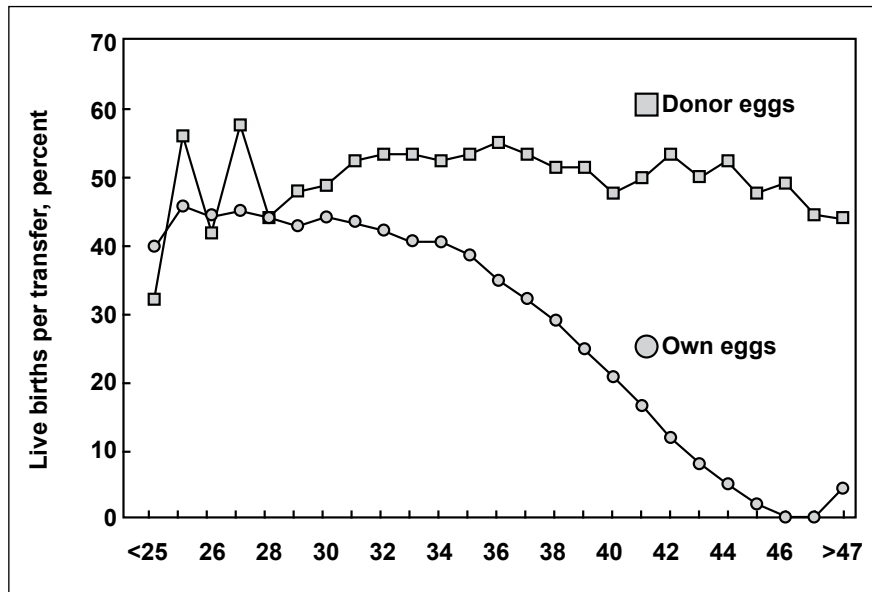
As the number of oocytes declines, so too does the quality, eventually reaching a threshold below which pregnancy is no longer possible. The decrease in quality is primarily due to an increased prevalence of aneuploid oocytes.¹⁸ Autosomal trisomy is the most frequent finding and is thought to be associated with age-related changes in the meiotic spindle that predispose to non-disjunction.²⁴ Chromosomally abnormal embryos account for the lower chances of pregnancy and the higher rates of spontaneous abortion.

In addition to ovarian factors, older women have an increased probability of underlying medical pathology that adversely affects fertility, such as endometriosis, fibroids, tubal disease, and polyps. These and other pathologies increase the likelihood of a history of ovarian surgery, radiation, or chemotherapy, which are threats to fertility. Older women are more likely to be obese, to have a chronic medical condition, and to have lifestyle issues, including decreased coital frequency, all of which may affect fertility.

INCREASED USE OF REPRODUCTIVE TECHNOLOGY

Women who delay child-bearing fall into 3 broad categories: (1) those who conceive without intervention, (2) those who still have fertilizable oocytes and conceive through use of ART, and (3) those who conceive after egg donation. Women who are < 37 years of age should be supported with expectant management for up to 6 months, after which a referral should be offered. For women aged ≥ 37, referral to a specialist is recommended without waiting 6 months for “spontaneous” conception, because ovarian reserve can further deplete during the waiting period. For women in categories 2 and 3, active treatment options may be initiated after appropriate investigations (which are beyond the scope of this guideline); these include controlled ovarian hyperstimulation with IUI, in vitro fertilization, and oocyte donation. While IUI and IVF can accelerate the time to conception, they cannot compensate for the natural decline of fertility due to age. With increasing maternal age, the chance of a woman progressing from the beginning of ART treatment to pregnancy and live birth using her own eggs decreases at every stage of ART

Figure 2. Percentages of transfers that resulted in live births for ART cycles using fresh embryos from own and donor eggs, by ART patient's age, 2006



Reproduced from Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Atlanta: Centers for Disease Control and Prevention;2006.

treatment (Figure 2).³ The live birth rate per cycle of IVF for example has been shown to drop from approximately 31% at age 35 to < 5% at age 42.²⁵

The only effective option for older women (> 40) with decreased ovarian reserve is oocyte donation.²⁵ In contrast to IVF with non-donor eggs, the success of IVF with donor eggs does not vary significantly according to the recipient's age up to age 50, after which declining rates of implantation, clinical pregnancy, and delivery are seen.^{26,27} In the largest study of delivery outcomes among recipients of donated eggs, (17 339 ART recipient cycles) no effect of recipient age was observed between ages 25 and 45 years; however, older recipient age was associated with statistically reduced rates of implantation, clinical pregnancy, and delivery.²⁷ This effect first appeared when women were in their late 40s and became more pronounced at age 50.²⁷ Pregnancy loss rates among recipients ≥ 45 years versus younger recipients were also slightly higher (3%).²⁷ Age-related uterine factors are proposed to play a role in these outcomes, with reduced uterine blood flow affecting uterine receptivity to both implantation and pregnancy maintenance.²⁷⁻³⁰

The risk of multiple births is substantially elevated in ART pregnancies. In Canada, the incidence of twin births increased by 35%, and triplets and higher order multiple births by over 250%, between 1974 and 1990.³¹ Multiple gestations are at greater risk of pregnancy loss, preterm birth, and maternal complications than singleton

pregnancies. Children of a multiple birth are at increased risk of neonatal mortality, developmental disabilities, and significant and lifelong special needs. Since the majority of multiple births are premature and consequently require additional medical attention before discharge, the effect on obstetric and neonatal intensive care resources and the health care system has been dramatic. Caring for multiples rather than singletons, has been associated with significant physical, economic, and psychological stress for families.^{7,32-37}

Recommendations

1. Women who delay child-bearing are at increased risk of infertility. Prospective parents, especially women, should know that their fecundity and fertility begin to decline significantly after 32 years of age. Prospective parents should know that assisted reproductive technologies cannot guarantee a live birth or completely compensate for age-related decline in fertility. (II-2A)
2. A fertility evaluation should be initiated after 6 months of unprotected intercourse without conception in women 35 to 37 years of age, and earlier in women > 37 years of age. (II-2A)

ADVANCED PATERNAL AGE

While the reproductive consequences of advanced paternal age (≥ 40 years of age at the time of conception)³⁸ are not as well-defined as the risks of advanced maternal age, the

Table 2. Risk of Down syndrome and other chromosome abnormalities in live births by maternal age

Maternal age (at term)	Risk		Maternal age (at term)	Risk		Maternal age (at term)	Risk	
	Down syndrome	Total chromosome abnormalities		Down syndrome	Total chromosome abnormalities		Down syndrome	Total chromosome abnormalities
25	1 in 1250	1 in 476	32	1 in 637	1 in 323	39	1 in 125	1 in 81
26	1 in 1190	1 in 476	33	1 in 535	1 in 286	40	1 in 94	1 in 63
27	1 in 1111	1 in 455	34	1 in 441	1 in 224	41	1 in 70	1 in 49
28	1 in 1031	1 in 435	35	1 in 356	1 in 179	42	1 in 52	1 in 39
29	1 in 935	1 in 417	36	1 in 281	1 in 149	43	1 in 40	1 in 31
30	1 in 840	1 in 385	37	1 in 217	1 in 123	44	1 in 30	1 in 21
31	1 in 741	1 in 385	38	1 in 166	1 in 105	≥ 45	≥ 1 in 24	≥ 1 in 19

Source: Hecht CA, Hook EB.1996

Reproduced from BC Prenatal Genetic Screening Program, Provincial Health Services Authority.

data suggest a decrease in fertility and an increase in genetic disorders in the offspring of older fathers.

The decreased fertility associated with advanced paternal age is related to a number of factors. These include decreased coital frequency, reduced sexual function, and poorer semen quality (decreased volume, sperm motility, and percent normal sperm). It is important to note, however, that standard sperm parameters do not necessarily correlate with fertilizing capacity and pregnancy rate.^{39,40}

Advanced paternal age is associated with an increased risk of new gene mutations.⁴¹⁻⁴³ During spermatogenesis, the male germ cells pass through more mitotic replications than female germ cells, creating greater opportunity for errors, which increase with paternal age. The conditions most strongly associated with advanced paternal age are those caused by single base substitutions resulting in autosomal dominant conditions such as, in decreasing order of frequency, achondroplasia, thanatophoric dysplasia, Apert syndrome, Pfeiffer syndrome, Crouzon syndrome, and multiple endocrine neoplasia 2A and multiple endocrine neoplasia 2B.⁴⁴ There is also evidence that advanced paternal age is associated with an increased risk of some congenital anomalies, schizophrenia, autism spectrum disorders, and some forms of cancer. For most of these conditions, the relative risk is ≤ 2 , and the mechanism is unknown.³⁸ There is no evidence that advanced paternal age is associated with increased risk of chromosomal abnormalities with the possible exception of trisomy 21 and Klinefelter syndrome.³⁸ Presently, there are no specific screening tests to target conditions related to advanced paternal age. When the male partner is aged ≥ 40 , the couple should be treated as any other couple and offered prenatal screening and diagnosis according to SOGC guidelines.

Recommendation

- Prospective parents should be informed that semen quality and male fertility deteriorate with advancing age and that the risk of genetic disorders in offspring increases. (II-2A)

MATERNAL AGE-RELATED RISK OF GENETIC CONDITIONS AND CONGENITAL ANOMALIES

Chromosomal Aneuploidy

The risk of fetal chromosome aneuploidy, primarily trisomies, increases with maternal age (Table 2).⁶ The biological basis for this observation is that oocytes reach metaphase I during the fetal period (5 months post-fertilization), and chromosomes remain aligned on the metaphase plate until the oocyte divides prior to ovulation. Age-related errors, largely due to dysfunction of the meiotic spindle, increase the risk of non-disjunction, which leads to unequal chromosome products at completion of division. This results in higher rates of aneuploid embryos, higher rates of spontaneous abortion, and lower chances of successful pregnancy outcome. It is estimated that after the age of 45, the majority of oocytes may be aneuploid.⁶

It is standard of care to offer all pregnant women, regardless of age, non-invasive screening for chromosomal aneuploidy using various combinations of ultrasound and maternal serum markers to adjust the mother's age-related risk.⁴⁵ Women whose screening tests suggest a high risk of aneuploidy are offered diagnostic invasive testing (amniocentesis, chorionic villus sampling).

With the exception of pregnancies conceived through the use of ICSI, the rate of chromosome abnormalities in couples undergoing ART treatment is similar to the rate in

spontaneously conceived pregnancies. The use of sperm from subfertile men and the ICSI procedure itself are thought to increase the risk of chromosomal abnormalities in children conceived using this method.^{46,47} Couples undergoing IVF-ICSI for male-factor infertility should receive information and be offered genetic counselling about the increased risk of de novo chromosomal abnormalities (mainly sex chromosomal anomalies) associated with their condition. Prenatal diagnosis by chorionic villus sampling or amniocentesis should be offered to these couples if they conceive.⁴⁷

Preimplantation genetic diagnosis with transfer of chromosomally normal embryos has been suggested as a way to increase rates of implantation and reduce risks of spontaneous abortion in older women and to avoid chromosomally abnormal births. However, despite the high number of aneuploid embryos that are selected out using this procedure, preimplantation genetic diagnosis for aneuploidy screening selection has not been found to be effective in improving pregnancy outcomes for women 35 to 41 years of age, and it is currently not recommended solely for advanced maternal age.^{48,49}

Gene Abnormalities

The effect of advanced maternal age on single gene disorders and epigenetic events, other than in the clinical area of assisted reproduction, is not well known. Epidemiologic studies have suggested a correlation between autism and advanced maternal and paternal age, but larger studies are needed to understand this association.⁵⁰

Congenital Malformations

The risk of certain non-chromosomal birth defects has been shown to increase with maternal age. In a study of > 1 million singleton infants born after 20 weeks of gestation who did not have a chromosomal abnormality, advanced maternal age (35 to 40 years) was associated with an increased risk for all types of heart defects (OR 1.12; 95% CI 1.03 to 1.22), tricuspid atresia (OR 1.24; 95% CI 1.02 to 1.50), right outflow tract defects (OR 1.28; 95% CI 1.10 to 1.49), hypospadias second degree or higher (OR 1.85; 95% CI 1.33 to 2.58), male genital defects excluding hypospadias (OR 1.25; 95% CI 1.08 to 1.45), and craniosynostosis (OR 1.65; 95% CI 1.18 to 2.30).⁵¹

Hollier et al., prospectively catalogued malformations detected at birth or in the newborn nursery over a 6-year period for 102 728 pregnancies, including abortions, stillbirths, and live births.⁴⁶ After excluding infants with chromosomal abnormalities, the incidence of structurally malformed infants increased progressively with maternal age. The OR for cardiac defects was 3.95 in infants of women

≥ 40 years of age compared with women 20 to 24 years of age.⁵² The risks of clubfoot and diaphragmatic hernia also increased as maternal age increased. Overall, the additional age-related risk of non-chromosomal malformations was approximately 1% in women ≥ 35 years of age.

Recommendation

4. Women ≥ 35 years of age should be offered screening for fetal aneuploidy and undergo a detailed second trimester ultrasound examination to look for significant fetal birth defects (particularly cardiac defects). (II-1A)

IMPACT OF MATERNAL AGE ON PREGNANCY OUTCOME

A large body of literature exists describing the impact of advanced maternal age on pregnancy outcome. When compared with younger women, women > 35 years are at increased risk of spontaneous abortion, ectopic pregnancy, placenta previa,^{8,52,53} pre-gestational diabetes, eclampsia,^{8,53,54} and pregnancy-induced hypertension,⁸ as well as Caesarean section^{8,52,55} and induction of labour.^{8,55,56} Perinatal and neonatal death and stillbirth also increase with increasing maternal age.⁵⁵ Some of these obstetrical complications appear to be related to the aging process alone, while others are related to coexisting factors such as multiple gestation, higher parity, and underlying chronic medical conditions (hypertension, diabetes mellitus and other chronic diseases) that become more prevalent with increasing age.^{8,52,55,56}

In September 2011, the Canadian Institute of Health Information published the results of a 3-year study (2006 to 2009)⁵⁷ which determined that advanced maternal age was associated with an increased risk of pregnancy complications and other adverse outcomes. The study linked the birth records and mothers' hospital records of > 1 million hospital live births. Findings included the following:

- Women > 40 were at least 3 times more likely to develop gestational diabetes and placenta previa than younger women
- More than 50% of first time mothers > 40 years of age were delivered by Caesarean section compared with 25% of women 20 to 24 years
- The incidence of chromosome disorders was 4-fold higher, and the rates of preterm birth and SGA were 20% and 7% higher in women ≥ 35 years than in women 20 to 34 years.

These data are consistent with the literature reviewed in these guidelines and provide additional support to the recommendations. They also further highlight the importance of increasing public awareness of this potentially preventable cause of maternal and neonatal morbidity.

The paper also suggests that the additional cost to the system associated with in-hospital births among older women (≥ 35 years) compared with younger women was \$ 61.1 million over the 3 years. The main cost drivers of maternity care are labour and delivery complications and/or interventions, Caesarean section, PTD, and length of hospital stay, all of which were higher in older than in younger women. This costing information has important implications for policy, planning, and provision of care in Canada.

Spontaneous Abortion

Older women have a higher rate of spontaneous abortion. These losses are both aneuploid and euploid, and most occur between 6 and 14 weeks' gestation. In a large study from Denmark, the calculated risk of spontaneous loss in women > 35 years of age was more than double that in women < 30 years of age (25% vs. 12%), and was $> 90\%$ in women ≥ 45 years of age.⁵⁸ The influence of maternal age on the spontaneous abortion rate was independent of parity and history of previous abortion, although these characteristics were also risk factors for pregnancy loss. Chromosomally abnormal embryos (mainly autosomal trisomies) account for the majority of spontaneous abortions in older women. In a recent study of over 2000 IVF pregnancies in which fetal cardiac activity was documented by transvaginal ultrasound, the pregnancy loss rate was significantly higher in older women, increasing from 5% in women < 30 years of age to 13% and 22% in women aged 35 to 39, and ≥ 40 years, respectively.^{59,60}

Ectopic Pregnancy

Ectopic pregnancy is a major source of maternal mortality and morbidity in early pregnancy. Maternal age ≥ 35 years is associated with a risk of ectopic pregnancy 4- to 8-fold greater than that of younger women.⁶⁰ This is due to an accumulation of risk factors over time, such as multiple sexual partners, pelvic infection, and tubal pathology.

Coexisting Medical Conditions

The 2 most common medical problems complicating pregnancy are hypertension (pre-existing and gestational) and diabetes mellitus (pre-gestational and gestational), and the risk of both of these complications increases with maternal age. The prevalence of medical and surgical illnesses, such as cancer and cardiovascular, renal, and autoimmune disease, increases with advancing age. As a

result, pregnant women ≥ 35 years of age have 2- to 3-fold higher rates of hospitalization, Caesarean section, and pregnancy-related complications than younger women.⁶¹⁻⁶⁷ Lifestyle factors, such as smoking and alcohol use during pregnancy have been associated with an increased risk of LBW, perinatal morbidity, and stillbirth in all age groups, and the risks are further elevated in older women.⁶⁸⁻⁷⁰

Hypertension

Although the maternal and fetal morbidity and mortality related to hypertensive disorders during pregnancy can be reduced with careful monitoring and timely intervention, these disorders are associated with an increased incidence of preterm birth, SGA infants, and Caesarean section. The incidence of chronic hypertension is 2- to 4-fold greater in women ≥ 35 years of age than in women 30 to 34 years of age.⁷¹ Rates of preeclampsia in the general obstetric population are 3% to 4%. They increase to 5% to 10% in women over 40, and up to 35 % percent in women > 50 years of age.⁷²

Diabetes

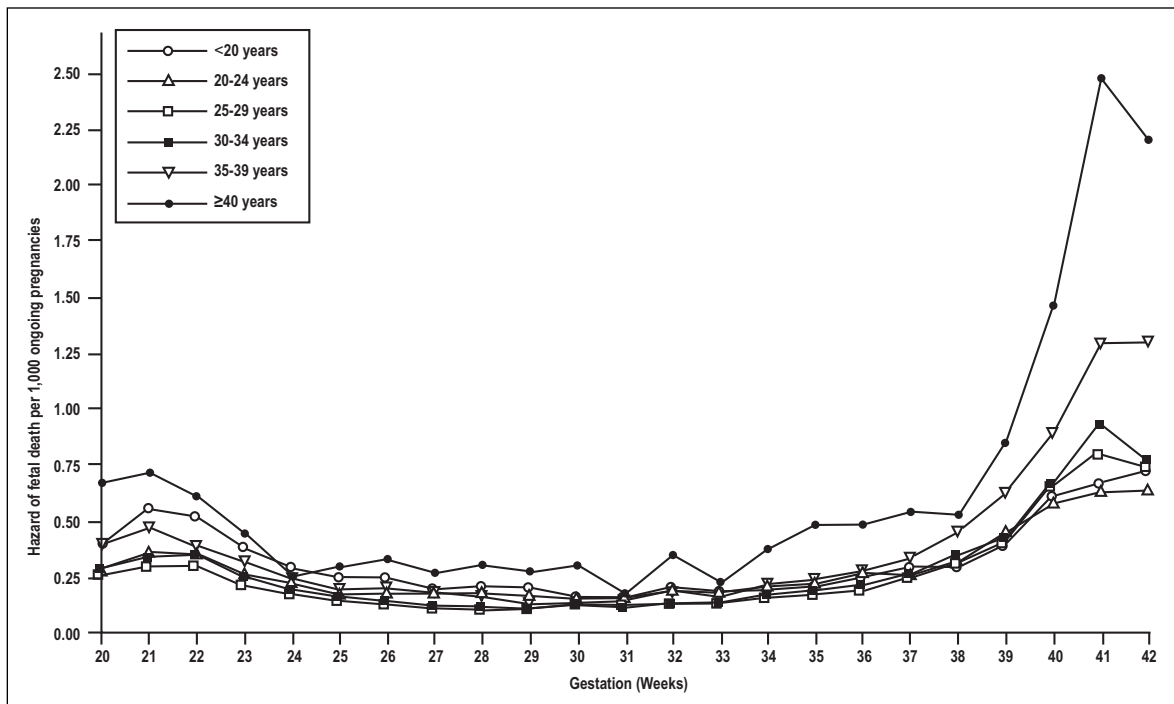
Pre-existing diabetes is associated with increased risks of congenital anomalies and perinatal morbidity and mortality, while the major complication of gestational diabetes is fetal macrosomia and its sequelae.⁷³ The prevalence of diabetes increases with maternal age. The incidence of both pre-existing diabetes mellitus and gestational diabetes is 3- to 6-fold higher in women ≥ 40 years of age than in women aged 20 to 29.^{53,65,73} The incidence of gestational diabetes is also 3- to 4-fold higher in older women (7% to 12 % in women > 40 ; 20% in women > 50) compared with the 3% incidence in the general obstetric population.

Placental Abnormalities

The prevalence of placental problems, such as placental abruption, placenta previa, and placenta accreta, is higher among older women.^{12,74} Multiparity accounts for a significant proportion of the excess risk in these disorders. For example, there is no significant correlation between maternal age and abruption when parity and hypertension are taken into account. Maternal age is, however, an independent risk factor for placenta previa. Nulliparous women ≥ 40 years of age have a 10-fold increased risk of placenta previa compared with nulliparous women aged 20 to 29 years, although the absolute risk is small (0.25% vs. 0.03%).⁷⁴

Placenta accreta occurs in approximately 1 of 2500 deliveries, and the incidence is as high as 10% in women with placenta previa. Advanced maternal age and previous Caesarean section are independent risk factors for placenta accreta.⁷⁴

Figure 3. Hazard (risk) of stillbirth for singleton births without congenital anomalies by gestational age, 2001–2002



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Perinatal Morbidity

Preterm and LBW infants are at increased risk of death, morbidity, and long-term disability. These disabilities include developmental disorders (e.g., cerebral palsy and blindness), respiratory problems, learning problems (e.g., lower IQ and lower academic achievement), and behavioural problems (e.g., attention deficit hyperactivity disorder).^{75–77}

Advanced maternal age has been associated with an increased risk of LBW (< 2500 g) and PTD. A large prospective study from Sweden compared birth outcomes in healthy nulliparous women delivering singletons at 35 to 40 years of age with those in women who were 20 to 24 years of age.⁷⁸ After adjusting for smoking, history of infertility, and other medical conditions, older maternal age was associated with a significantly higher risk of LBW and PTD: very LBW, < 1500 g (OR 1.9); moderate LBW, 1500 to 2499 g (OR 1.7); very preterm birth ≤ 32 weeks (OR 1.7); moderately preterm birth 33 to 36 weeks (OR 1.2); and SGA infant < 2 SD for GA (OR 1.7).

A subsequent prospective population-based study, also from Sweden, evaluated pregnancy outcome in over 32 000 women ≥ 40 years of age and confirmed an increased risk of PTD.⁵¹ After adjustment for confounders such as multiple gestation, smoking, parity, and maternal medical

diseases, the rates of PTD < 32 weeks for women 20 to 29, 30 to 39, and ≥ 40 years of age were 1.01, 1.80, and 2.24%, respectively.

Tough et al. compared birth weight and PTD rates in women aged ≥ 35 with those < 35 years.⁷² Among older mothers, the risk of LBW delivery was significantly higher in every weight category (< 2500 g, < 1500 g, < 1250 g, < 1000 g) (OR 1.1 to 1.6), as was the rate of PTD (< 37, < 35, < 32, and < 30 weeks of gestation) (OR 1.1 to 1.3). During the study period, delayed child-bearing accounted for 78% of the increase in the rate of LBW and 36% of the increase in the rate of PTD in the population. Maternal age was not related to changes in SGA, suggesting that the age effect was through pregnancy complications that led to PTD and LBW.

In 2005, Joseph et al.⁵⁶ published the results of a large population-based study of all singleton births (n = 157 445) in the province of Nova Scotia during 1988 to 1995. The risk of very preterm (< 32 weeks) and preterm (< 37 weeks) birth and SGA (3rd and 10th percentile) increased with advanced maternal age, showing a statistically significant excess risk for women ≥ 35 compared with 20 to 24 year olds.⁵⁶

Perinatal Mortality

Most large studies worldwide have reported that women ≥ 35 years of age are at greater risk of perinatal mortality than younger women, with relative risks of 1.2 to 4.5.⁷⁹ This excess perinatal mortality in older women is present even after controlling for risk factors such as hypertension, diabetes, antepartum bleeding, smoking, and multiple gestation, and is mostly due to unexplained stillbirths.^{47,79–85}

In a study of over 5 million singleton pregnancies in the United States, Reddy et al. reported the risk of stillbirth was 3.73, 6.41, and 8.65 per 1000 ongoing pregnancies in women < 35 , 35 to 39 years, and ≥ 40 years of age respectively, with the risk increasing sharply at 40 weeks of gestation (Figure 3).⁸³

Bahtiyar et al.⁸⁵ analyzed > 6 million singleton pregnancies in the United States to determine the influence of maternal age on stillbirth risk. After women with congenital anomalies and medical complications were excluded, older women were compared with a group of 25- to 29-year-old women with the lowest stillbirth risk. The odds of stillbirth at term increased significantly with advancing maternal age: 30 to 34 years, OR 1.24, (95% CI 1.13 to 1.36), 35 to 39 years, OR 1.45, (95% CI 1.21 to 1.74), and 40 to 44 years, OR 3.04 (95% CI 1.58 to 5.86).⁸⁵ Of note, the risk of stillbirth for women 40 to 44 years of age at 39 weeks was comparable to the risk for women 25 to 29 years old at 42 weeks. The authors concluded that advanced maternal age is an independent predictor of stillbirth and that antenatal testing in women ≥ 40 years of age should begin at 38 weeks' gestation. They also suggested delivery by 39 weeks in women > 40 years of age, since the cumulative risk of stillbirth in women 40 to 44 years of age at 39 weeks is the same as the risk in a 25- to 29-year-old at 42 weeks' gestation.⁸⁵

These data suggest that women ≥ 40 years of age should be considered biologically "post-term" at 39 weeks' gestation, and fetal monitoring (twice-weekly fetal assessment) should be initiated at 38 weeks in this age group.

Multiple Pregnancy

Advancing maternal age is associated with an increased prevalence of twin pregnancy, related to both a higher rate of naturally conceived twins and a higher use of ART in older women.⁸⁶ Data from the Centers for Disease Control and Prevention⁸⁷ show that between 1980 and 2006, twin birth rates rose 27% for mothers < 20 years compared with 80% for women aged 30 to 39, and 190% for mothers aged ≥ 40 years. In 2006, 20% of births to women aged 45 to 54 years were twins, compared with about 2% of births to women aged 20 to 24 years. These data mainly reflect the increased use of ART in older women.⁸⁶ The

overall twin birth rate increased 70% between 1980 and 2004, from 18.9 per 1000 to 32.1 per 1000 births, but it was essentially unchanged between 2004 and 2006, indicating a possible slowing of the upward trend. The rate of triplet and higher order multiple births (quadruplets, quintuplets and other higher order multiples per 100 000 live births), which climbed more than 400% during the 1980s and 1990s, also declined (by 21%) over the same period from the all-time high in 1998 (193.5 per 100 000 total births).⁸⁷ This is likely due in part to changes in practices in IVF clinics across the country.

There is a high risk of an adverse outcome for multiple births, and $> 12\%$ of twins and 30% of triplets are born at < 32 weeks, compared with 2% of singletons. The perinatal mortality rate is significantly higher among twins (29.8 per 1000) and triplets (59.6 per 1000) than among singletons (6.0 per 1000).^{86,87}

Caesarean Section

Women ≥ 35 years of age are more likely than younger women to be delivered by Caesarean section.^{25,50} The Caesarean section rate in women 40 to 45 approximates 50%, and this increases to approximately 80% in women aged 50 to 63 years, although the rate in the general obstetric population is about 25%.^{55,68,87}

The reasons for the high rate of Caesarean section in older women include an increased prevalence of medical complications, fetal malposition, cephalopelvic disproportion, induction of labour, a failed trial of labour, and uterine rupture.^{88–93}

In a study by Smith et al., a linear increase in ORs for Caesarean section with advancing maternal age (≥ 16 years) was demonstrated (adjusted OR for a 5-year increase in age: 1.49; 95% CI 1.48 to 1.50).⁹¹ During the study period (1980 to 2005), the proportion of women aged 30 to 34 years increased 3-fold, the proportion of women aged 35 to 40 years increased 7-fold, and the proportion of women aged > 40 years increased more than 10-fold. The authors used these data in a calculation model to determine the contribution of advanced maternal age to the overall Caesarean section rate and concluded that if the maternal age distribution had stayed at the 1980 level, 38% of the additional Caesarean sections would not have been performed.

There is also a lower threshold among both women and physicians for performing a Caesarean section in older women, and maternal request for Caesarean section is more common among older women.⁸⁸ There is a continuous negative relationship between age and uterine function throughout the child-bearing years.⁹⁰

Maternal Mortality

Maternal mortality increases with maternal age^{94–96} however, the risk of dying during childbirth is very low in developed countries (total maternal mortality rate in Canada 6.1 per 100 000 live births).⁹⁷ As the proportion of women who are delaying child-bearing to later in life continues to increase, age-specific increases in mortality may be observed.^{98,99}

Recommendations

5. Delayed child-bearing is associated with increased obstetrical and perinatal complications. Care providers need to be aware of these complications and adjust obstetrical management protocols to ensure optimal maternal and perinatal outcomes. (II-2A)
6. All adults of reproductive age should be aware of the obstetrical and perinatal risks of advanced maternal age so they can make informed decisions about the timing of child-bearing. (II-2A)

Benefits of Delayed Child-Bearing

There are advantages and disadvantages to parenting when older: there is more anxiety during pregnancy, but parents are more mature and likely to be more financially secure and to have higher levels of education. Multiple pregnancies have a slightly more favourable outcome in older women.

Overall, if older women can sustain a pregnancy, the pregnancy outcomes can be positive, and parents may be well prepared to cope with the physical and emotional stresses of pregnancy and parenting.⁵⁷ Older parents can bring experience, knowledge, and economic resources to the task of child raising, which may suggest a social advantage to delayed parenting.¹⁰⁰

SUMMARY

The proportion of women who delay child-bearing beyond the age of 35 years has increased greatly in recent decades. Pregnancy after 35 years has been associated with increased likelihood of infertility, miscarriage, spontaneous abortion, stillbirth, medical risks, operative delivery, and pregnancy complications. Advanced maternal age increases the risk for multiple births, PTD and/or LBW, each of which increases the potential need for additional medical care, and poses lifelong threats to development.

While most women have some awareness of the “biological clock” and realize that conception difficulties increase with age, many are unaware of the limitations of ART or the increased risk of adverse influences on child development associated with PTD and multiple birth. Given these gaps in reproductive knowledge and awareness, widespread pre-conception counselling and education are needed and

must be implemented so that the 95% of Canadians who anticipate parenting at some point can make informed decisions. Women (and men) need to be informed that age is the single most important determinant of female fertility, either natural or treated, and that ART cannot compensate for age-related decline in fertility.

There is an opportunity for SOGC to lead this initiative through the development and distribution of high-quality, respected, educational and public health materials.

In addition, communication strategies may be most effective if they align with the needs of government, policy makers, and employers who are vested in the development of a healthy, competent workforce, which may be threatened by delayed child-bearing and its consequences. There is an opportunity to improve public understanding about reproductive health and child-bearing between 25 and 35 years, the limits of ART, and the limitations of science to predict which families will be at risk when child-bearing is delayed. The influences of maternity leave, child care, work environments and relationship security on child-bearing decisions require further understanding (beyond the scope of this paper).

Recommendations

7. Strategies to improve informed decision-making by prospective parents should be designed, implemented, and evaluated. These strategies should provide opportunity for adults to understand the potential medical, social, and economic consequences of child-bearing throughout the reproductive years. (III-B)
8. Barriers to healthy reproduction, including workplace policies, should be reviewed to optimize the likelihood of healthy pregnancies. (III-C)

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APPENDIX. DELAYED CHILD-BEARING FACTS

Advanced maternal age (≥ 35 years) is associated with

- Decreased fertility and fecundity
- Increased risk of miscarriage
- Increased risk of ectopic pregnancy
- Increased risk of chromosomal aberrations and birth defects
- Increased risk of multiple pregnancy

Advanced paternal age (≥ 40 years) is associated with

- Decreased fertility and semen quality
- Increased risk of certain genetic disorders

Practice Points

- Pre-conceptional counselling is recommended for all couples when one or both partners are of advanced reproductive age.
- Pre-conceptional counselling and education at a government and public health level are required in order to inform younger women and men about the possible consequences of delaying child-bearing before they make the decision whether or not to do so.
- When women ≥ 35 years become pregnant, an early ultrasound to document location, number, and viability of the pregnancy should be undertaken.
- Prenatal screening for chromosome abnormalities and a second trimester ultrasound should be offered as is standard of care for all women.

Pregnancy in women of ≥ 35 years is associated with

- Increased risk of coexisting medical disorders
- Hypertensive disorders of pregnancy and preeclampsia
- Preexisting diabetes and gestational diabetes
- Increased risk of placenta previa
- Increased risk of LBW and PTD
- Increased risk of stillbirth
- Increased rate of Caesarean section

Practice Points

Women ≥ 35 years should

- Have a thorough history and physical examination.
- Have prenatal bloodwork that includes baseline liver and kidney function, as well as mammogram (> 40 years) and cardiology consultation > 45 years.
- Be monitored closely for hypertensive disorders of pregnancy and preeclampsia, and all should undergo screening for gestational diabetes.
- Have careful placental localization with ultrasound at the time of the second trimester scan, to be followed up at 28 weeks' gestation if low lying or previa.

A third trimester scan to document fetal growth and placental location should be considered.

The cumulative risk of stillbirth in women of 40 to 44 years of age at 39 weeks' gestation is nearly identical to the risk in those of 25 to 29 years of age at 42 weeks' gestation.

Therefore, a strategy of antenatal testing beginning at 38 gestational weeks with delivery by the completion of the 39th week for women > 40 years of age should be considered.