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Advanced Reproductive Age and Fertility

This clinical practice guideline has been prepared by the Reproductive Endocrinology and Infertility Committee, reviewed by the Family Physicians Advisory Committee and the Maternal-Fetal Medicine Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Key Words: Ovarian aging, advanced reproductive age, assisted reproductive technology

Abstract

Objective: To improve awareness of the natural age-related decline in female and male fertility with respect to natural fertility and assisted reproductive technologies (ART) and provide recommendations for their management, and to review investigations in the assessment of ovarian aging.

Options: This guideline reviews options for the assessment of ovarian reserve and fertility treatments using ART with women of advanced reproductive age presenting with infertility.

Outcomes: The outcomes measured are the predictive value of ovarian reserve testing and pregnancy rates with natural and assisted fertility.

Evidence: Published literature was retrieved through searches of PubMed or Medline, CINAHL, and The Cochrane Library in June 2010, using appropriate key words (ovarian aging, ovarian reserve, advanced maternal age, advanced paternal age, ART). Results were restricted to systematic reviews, randomized controlled trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and incorporated into the guideline to December 2010.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care. Recommendations for practice were ranked according to the method described in that report (Table).

Benefits, harms, and costs: Primary and specialist health care providers and women will be better informed about ovarian aging and the age-related decline in natural fertility and about options for assisted reproductive technology.

Recommendations

1. Women in their 20s and 30s should be counselled about the age-related risk of infertility when other reproductive health issues, such as sexual health or contraception, are addressed as part of their primary well-woman care. Reproductive-age women should be aware that natural fertility and assisted reproductive technology success (except with egg donation) is significantly lower for women in their late 30s and 40s. (II-2A)
2. Because of the decline in fertility and the increased time to conception that occurs after the age of 35, women > 35 years of age should be referred for infertility work-up after 6 months of trying to conceive. (III-B)

3. Ovarian reserve testing may be considered for women ≥ 35 years of age or for women < 35 years of age with risk factors for decreased ovarian reserve, such as a single ovary, previous ovarian surgery, poor response to follicle-stimulating hormone, previous exposure to chemotherapy or radiation, or unexplained infertility. (III-B)
4. Ovarian reserve testing prior to assisted reproductive technology treatment may be used for counselling but has a poor predictive value for non-pregnancy and should be used to exclude women from treatment only if levels are significantly abnormal. (II-2A)
5. Pregnancy rates for controlled ovarian hyperstimulation are low for women > 40 years of age. Women > 40 years should consider IVF if they do not conceive within 1 to 2 cycles of controlled ovarian hyperstimulation. (II-2B)
6. The only effective treatment for ovarian aging is oocyte donation. A woman with decreased ovarian reserve should be offered oocyte donation as an option, as pregnancy rates associated with this treatment are significantly higher than those associated with controlled ovarian hyperstimulation or in vitro fertilization with a woman's own eggs. (II-2B)
7. Women should be informed that the risk of spontaneous pregnancy loss and chromosomal abnormalities increases with age. Women should be counselled about and offered appropriate prenatal screening once pregnancy is established. (II-2A)
8. Pre-conception counselling regarding the risks of pregnancy with advanced maternal age, promotion of optimal health and weight, and screening for concurrent medical conditions such as hypertension and diabetes should be considered for women > age 40. (III-B)
9. Advanced paternal age appears to be associated with an increased risk of spontaneous abortion and increased frequency of some autosomal dominant conditions, autism spectrum disorders, and schizophrenia. Men > age 40 and their partners should be counselled about these potential risks when they are seeking pregnancy, although the risks remain small. (II-2C)

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INTRODUCTION

Social trends in Canada and around the world have led to women delaying child-bearing into their 30s and, in some cases, their 40s. The average age of women giving birth has increased from 27 to 29.3 over the last 20 years.[1] In 2006, the fertility rate for women aged 30 to 34 was the highest of any age group, surpassing that of the previous highest group, women aged 25 to 29.[2] The percentage of first-time mothers who are > 30 years of age increased steadily from 11% in 1987 to 26% in 2005.[1] During the same period, there was a significant rise in first-time mothers > 35 years of age, from 4% in 1987 to 11% in 2005, and a corresponding decrease in the group who are < 25 years.[1] Similar trends have been seen in other parts of the world.[3]

Ovarian function declines as women approach their later reproductive years until menopause, and increasing age is associated with lowered fecundity and infertility. Women experience a decline in natural fertility that begins in the mid-30s, and they will often reach sterility many years before the complete cessation of menses.[4] Although ART may aid some couples who present with fertility issues, it will not compensate for the decline in natural fertility that occurs with delayed child-bearing.[5] ART is also invasive, expensive, and not covered by most provincial health plans for this indication. In addition, complications of pregnancy increase for both the mother and the offspring with advanced maternal age.[6]

Women and their health care providers should be aware of the effects of age on reproductive potential.

ABBREVIATIONS

AFC	antral follicle count
AMH	antimüllerian hormone
ART	assisted reproductive technology
COH	controlled ovarian hyperstimulation
FSH	follicle-stimulating hormone
IUI	intrauterine insemination

OVARIAN AGING

The loss of oocytes from the ovaries is a continual process that begins in utero. The ovaries in the female fetus contain 6 to 7 million oocytes at approximately 20 weeks' gestation. At birth, 1 to 2 million oocytes remain, and only 300 000 to 500 000 are present at the onset of puberty.[7] This process continues until menopause, when only a few hundred oocytes remain.[8] During the reproductive years, 400 to 500 oocytes will be ovulated; the majority of oocytes are lost through apoptosis, or programmed cell death. Earlier research suggested that a more accelerated process of decline occurs in the last 10 to 15 years before menopause, beginning around the age of 38 years.[9] However, more recent data suggest that oocyte loss occurs at the same rate through the reproductive lifetime, with the slope of decline remaining fairly consistent until menopause.[10]

As the ovarian follicular pool decreases, women will experience infertility, sterility, cycle shortening, menstrual irregularity, and finally menopause (Figure 1).[10] In Western countries, the mean age of menopause is 51, and 1% will experience premature ovarian failure before age 40.[11] There appears to be a fixed interval through these stages of ovarian function. Women who experience an earlier menopause will have an earlier loss of fertility[12]; therefore, approximately 10% of women will have decreased ovarian function in their early to mid-30s.[13]

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
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	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.[95]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[95]

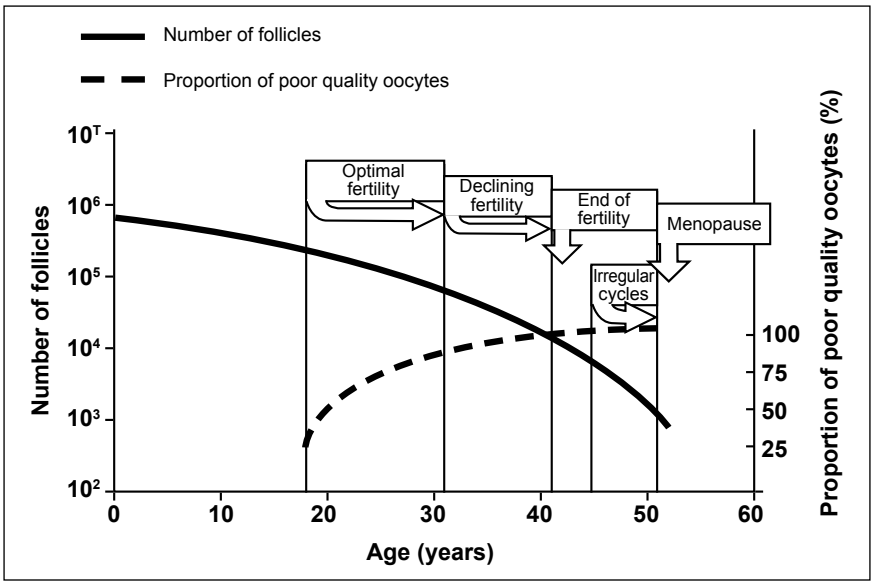
Child-bearing usually ends 10 years before menopause, and this time period is consistent regardless of the age of menopause.[14,15] Cycle irregularity will usually occur 6 to 7 years before menopause,[14] regardless of the age of menopause, coinciding with approximately 10 000 follicles remaining.[8]

As the total number of remaining follicles decreases, there is a corresponding decrease in the available follicular cohort. As a consequence of a smaller follicular cohort, there is a decline in inhibin-B, which is produced by the granulosa cells in the early follicular phase.[16] There is an inverse correlation between FSH and inhibin-B, which is likely due to a loss in negative feedback; the rise in FSH during the early follicular phase is one of the earliest signs of ovarian aging.[17] This initial stage may not be clinically apparent, or present only as infertility, because ovarian hormone production remains constant, and women continue to ovulate and have regular cycles. The first clinical signs of ovarian aging may be shortening of menstrual cycles, which is due to a shorter follicular phase. More rapid follicular development leads to earlier recruitment of a dominant follicle.[18] As this transition continues, women will notice that their cycles lengthen and become more irregular as they enter the menopause transition and ovulation is less consistent.[8] Once women start to notice clinical signs of ovarian aging such as cycle shortening or irregularity, their fertility may already be greatly diminished. One review article found that women who were sterile after age 35 had already demonstrated lower fecundity before the age of 30.[12] Markers of ovarian reserve may be useful to predict an earlier menopause or menopause transition for women who do not yet have clinical signs or symptoms of ovarian aging but who may already have decreased fertility.

When menopause occurs, there are often a few hundred follicles remaining. There is still ovarian activity and estrogen production during the first year after menopause.[14] Although the mean age of menopause in Western countries is 51, there is a significant range, from 40 to 60 years of age. Sibling and twin studies have shown a significant genetic component to the age of menopause.[19] Smoking has been associated with a decreased follicular pool and earlier menopause.[14]

Oocyte quality also appears to be affected by age. Studies on IVF oocytes have shown that the rate of oocyte aneuploidy increases with age.[20] The rate is low in women < age 35 (10%), but increases to 30% at the age of 40, to 40% at the age of 43, and to 100% in women > age 45.[20] These were gonadotropin stimulated oocytes, and therefore may not reflect the rate of aneuploidy in oocytes from a dominant follicle recruited during a non-stimulated or natural cycle; however, this correlates with the increase in chromosomally abnormal pregnancies and spontaneous abortions with age. The decline in oocyte quality may be in the formation and function of the spindles, which appear to be more diffuse.[21] This may result in chromosomes being less tightly arranged and may therefore lead to meiotic errors. Data also suggest that the selection process may deteriorate with age, allowing

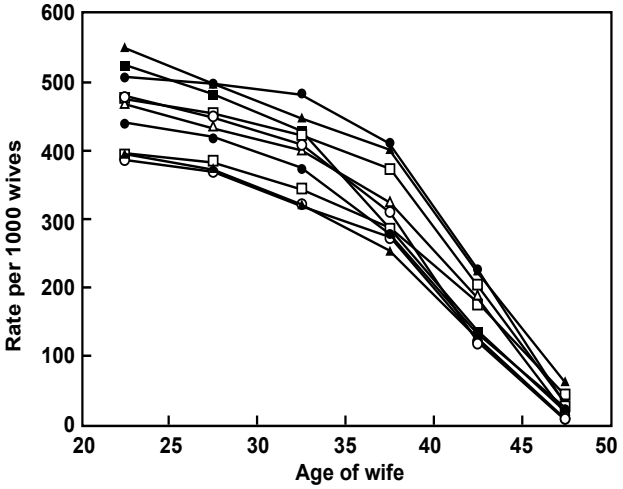
Figure 1. Schematic representation of the number of primordial follicles present in the ovaries and the chromosomal quality of oocytes in relation to female age and corresponding reproductive events.



Graph was drawn after Hansen et al. and de Bruin et al.

Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009;30:465–93.12 Copyright 2009, The Endocrine Society. Reproduced with permission.

Figure 2. Natural fertility by age



The ten populations (in descending order at age 20 to 24) are Hutterites, marriages 1921–30 (▲); Geneva bourgeoisie, husbands born 1600–49 (■); Canada, marriages 1700–30 (●); Normandy, marriages 1760–90 (○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840-59 (△); Normandy, marriages 1674–1742 (●); Norway, marriages 1874–76 (□); Iran, village marriages, 1940–50 (▲); Geneva bourgeoisie, husbands born before 1600 (○).

Menken J, Trussell J, Larsen U. Age and infertility. Science 1986; 233(4771):1389–1394.4 Reprinted with permission from AAAS.

poorer quality oocytes the opportunity to develop into the dominant follicle, or to be selected during an IVF cycle. The selection of the available follicular cohort may be less discriminating, allowing follicles to mature which should have undergone atresia.[22] Other proposed mechanisms include cumulative damage to the oocyte with age and decreasing quality of granulosa cells.[23]

FEMALE ADVANCED REPRODUCTIVE AGE AND INFERTILITY

Population studies have consistently noted that the decline in birth rates begins when women reach the age of 35 (Figure 2).[4] On average, women will deliver their last child at age 41, with a range of 23 to 51.[24] Natural population studies may not take into account non-reproductive factors, such as desire to prevent pregnancy, coital frequency, aging partners, and other medical conditions that may affect live birth rates. In addition, conditions such as fibroids and endometriosis are more frequent in later reproductive years. These studies therefore may not offer a full reflection of a woman's maximum fertility potential. Natural fertility studies of patients who had recently discontinued contraception have shown that younger women have a higher fecundity rate, and therefore conceive sooner than older women.[25]

The incidence of infertility and sterility increases as the age of the female partner increases. Although the true incidence of sterility is difficult to determine because of non-reproductive factors such as voluntary childlessness, population studies can provide some insight. In one study of 7 populations in which contraception use is rare and in which there is a low incidence of premarital conceptions, the percentage of women who remained childless was higher in those who married later.[4] Only 6% of women who married in their early 20s remained childless, while 64% of women who were not married until their 40s remained childless. Studies in the Hutterite population confirm an increase in infertility with age, escalating from 11% after age 34 to 33% by age 40 and to 87% by age 45.[26]

Although social changes have led to women delaying their reproduction, concomitant advances in reproductive sciences have led to increased options for fertility treatment and ART. Unfortunately, this may give women false optimism that they can delay pregnancy while pursing their education and careers with the expectation that ART will help them to conceive if they have difficulty conceiving later. However, success rates for ART treatment for women using their own eggs are directly linked to the age of the women,[27] and many women may not realize that older women are successful using ART to achieve pregnancy later in life only with donor eggs. Computer models have demonstrated that the current ART success rates cannot compensate for the loss in natural fertility that occurs in a women who has delayed child-bearing from 30 to 35 years of age.[5]

Studies on donor insemination confirm an age-related decline in pregnancy rates. Most of the earlier donor insemination studies were performed in couples with severe male factor infertility. These studies are thought to be a good reflection of female fertility because non-reproductive factors such as coital frequency are removed. A negative effect on pregnancy rates is seen in women > age 30, and is even more pronounced for women > age 35.[28–31] One study of almost 3000 cycles showed cumulative pregnancy rates of 62% for women < 30 years of age, and 44% for women aged ≥ 30 years after 12 cycles. Younger women often conceive quickly, and more cycles of treatment were often needed for women aged ≥ 35 years.[29,31]

Pregnancy rates collected from ART treatment cycles show the significant impact of female age on success. The 2007 Canadian live birth rate after IVF was 37.4% for women < 35 years of age, 26.5% for women aged 35 to 39 years, and 11.4% for women aged ≥ 40 years.[32] ART reports from the United States show similar age-related success rates.[33] Age is the most significant prognostic factor for IVF success.

Age-associated infertility appears to be primarily related to ovarian aging and the diminishing ovarian follicle count. The uterine endometrium has the capacity to maintain a pregnancy throughout a woman's reproductive years and, with newer technologies such as egg donation, even beyond the natural reproductive years. Age does not affect the endometrium's response to hormonal stimulation.[34] Pregnancy rates from donor egg cycles also confirm that the age of the recipient does not affect pregnancy rates.[33]

Recommendations

1. Women in their 20s and 30s should be counselled about the age-related risk of infertility when other reproductive health issues, such as sexual health or contraception, are addressed as part of their primary well-woman care. Reproductive-age women should be aware that natural fertility and assisted reproductive technology success (except with egg donation) is significantly lower for women in their late 30s and 40s. (II-2A)
2. Because of the decline in fertility and the increased time to conception that occurs after the age of 35, women > 35 years of age should be referred for infertility work-up after 6 months of trying to conceive. (III-B)

ASSESSMENT OF OVARIAN AGING

Ovarian aging will have begun before women notice any clinical changes to their menstrual cycles; therefore, they are often unaware that they may be at greater risk of infertility. Ovarian reserve testing has been explored as a means to determine a woman's fertility potential and provide an assessment of ovarian aging. Although chronological age alone serves as a good marker of ovarian reserve, some women will experience a decline in their natural fertility sooner than average, while some older women may maintain above average ovarian function. Identification of these two groups, in which ovarian reserve is inconsistent with chronological age, may be useful for counselling and planning treatment.[35]

Many tests of ovarian reserve have been tried. However, testing has mainly been performed on infertile populations, with little data on the distribution in the normal fertile population. Ovarian reserve testing cannot be used to predict infertility or time to infertility; therefore, its application to the general population as a screening tool is untested. Most studies have used these tests to try to predict a woman's ovarian response and prognosis with fertility treatment and IVF. Overall, markers of ovarian

reserve have been shown to correlate with egg quantity and response to ovarian stimulation, but not with egg quality.

The most commonly used test of ovarian reserve is the cycle day 3 or basal FSH level. An elevated basal FSH level (> 14 IU/L) is the first sign of ovarian aging that can be detected in women, and usually occurs in women aged 35 to 40.[36] Physiologically, the follicular pool is reduced to approximately 10% of the levels present at puberty.[9] The rise in basal FSH is due to a loss in ovarian feedback (inhibin-A and B) as the available follicular cohort diminishes. Basal FSH levels are easy to obtain, and no special skills are required to perform the test or interpret the results; therefore, it is easily accessible. However, basal FSH levels have been shown to be predictive for poor response to ovarian stimulation and for non-pregnancy only when the levels are extremely elevated.[35] Although a high threshold may improve the usefulness of the test in predicting a poorer prognosis, only a small number of women will have abnormal tests at this threshold. In addition, it has been associated with a false positive rate of 5%.[35] Elevated basal FSH levels are also less predictive of pregnancy for women < age 35.[37,38]

An ovarian antral follicle count can be performed early in the menstrual cycle. Antral follicles between 2 mm and 10 mm can be identified by transvaginal ultrasound performed by an experienced sonographer using a vaginal transducer with a minimum frequency of 7 MHz.[39] Antral follicles are sensitive to FSH and are considered to be representative of the available follicle pool. The number of antral follicles seems to correlate with the number of primordial follicles in the ovary, with a decline in primordial follicles being reflected in a lower number of antral follicles.[24] In later reproductive years, the proportion of antral follicles to total follicles may increase as the ovary allows a higher proportion of follicles to be selected. This may reflect a loosening of the selection process.[14] The decline in AFC may not be as steep as the decline in fertility. Although decline in AFC is correlated with both the menopause transition and ovarian response to stimulation, it is not a good predictor of pregnancy.[35]

Antimüllerian hormone is produced by the granulosa cells of pre-antral and small antral follicles but not dominant follicles.[12] AMH levels decrease with decreasing AFC, which in turn is a marker of the primordial follicle count. Levels remain consistent throughout the menstrual cycle[40] and become undetectable in women after menopause.[41] Although AMH provides moderate value in prediction of ovarian response in IVF, it is a poor predictor of pregnancy.[35] Currently, AMH testing is not widely available across Canada.

The clomiphene challenge test is performed by administering 100 mg of clomiphene daily from day 5 to day 9 of the cycle. FSH is measured on day 3 and on day 10. If an adequate response to clomiphene is generated, the rise in FSH will be suppressed by the release of estradiol and inhibin-B by developing follicles. Systematic reviews have not shown a benefit to the clomiphene challenge test over basal FSH or AFC.[35] Inhibin-B and basal estradiol have not been shown to be more useful predictors of poor response or pregnancy than basal FSH.[35] However, basal estradiol levels are often screened in conjunction with FSH and can confirm correct timing in the menstrual cycle. An elevated estradiol level may also falsely suppress FSH levels.

Ovarian reserve tests performed before ART treatment is begun may be useful for counselling, but they have a poor predictive power for pregnancy.[12] AFC and AMH have been shown to be useful for prediction of poor ovarian response with IVF.[12] Although significantly abnormal results are associated with lower pregnancy rates (< 5%), only about 3% of women will have results in this category.[35] In general, ovarian reserve testing is useful for predicting egg quantity and ovarian response to stimulation but has little value for the prediction of egg quality. Therefore, although these tests may be useful for counselling before ART treatment, testing should not be used to exclude women from ART treatment, and abnormal tests do not preclude the possibility of pregnancy. These test results can be used to obtain individual prognostic information to help to guide the choice of treatment and best use of resources.

Ovarian reserve testing may be considered in women > age 35 to screen for age-related infertility, although its results may be useful only for counselling and to aid women in their decision-making process. Testing in women < 35 years may be considered if they have risk factors for decreased ovarian reserve, such as a single ovary, previous ovarian surgery, poor response to FSH, previous exposure to chemotherapy or radiation, or unexplained infertility.[42] Although markers of ovarian reserve are not good predictors of pregnancy rate with ART for women < 35,[38] identification of these women may prompt shorter delay to infertility investigations and treatment.

Recommendations

3. Ovarian reserve testing may be considered for women ≥ 35 years of age or for women < 35 years of age with risk factors for decreased ovarian reserve, such as a single ovary, previous ovarian surgery, poor response to follicle-stimulating hormone, previous exposure to chemotherapy or radiation, or unexplained infertility. (III-B)

4. Ovarian reserve testing prior to assisted reproductive technology treatment may be used for counselling but has a poor predictive value for non-pregnancy and should be used to exclude women from treatment only if levels are significantly abnormal. (II-2A)

TREATMENT OF AGE-RELATED INFERTILITY

Fertility treatment for age-related infertility is aimed at increasing monthly fecundity and decreasing the time to conception. Women may be offered controlled ovarian hyperstimulation with clomiphene citrate or gonadotropins, or IVF to improve their chances of pregnancy and decrease time to pregnancy. Both treatments are intended to increase the number of mature oocytes each month to balance decreasing oocyte quality, but they do not address the underlying issue of oocyte quantity or quality. The only effective treatment for age-related infertility and declining oocyte quality is oocyte donation.

In reality, pregnancy and live birth rates with COH in older women are low. In one retrospective review of more than 4000 treatment cycles using clomiphene citrate and intrauterine insemination, pregnancy rates were 7% for women aged 38 to 40, 4% for women 41 to 42, and 1% for women > 42.[43] A small study of 130 cycles of COH with gonadotropins and IUI found a live birth rate of 6% for women aged 38 to 39, and 2% for women > 40.[44] All live births happened within the first or second cycles. Older women may consider 1 to 2 cycles of COH if they do not want to try IVF as a first-line treatment, but they should move on to IVF quickly if they are unsuccessful within the first couple of cycles.[45]

Although chance of success diminishes with age, IVF still offers higher pregnancy and live birth rates than COH, although significantly lower rates than oocyte donation. In 2007, live birth rates were 11.4% per cycle for women aged > 40 in Canada.[32] One study of women aged > 40 undergoing IVF, showed that for women aged ≥ 42, live birth rates drop to below 5%.[46] In this study, no live births were reported in 54 cycles for women aged ≥ 45. A separate study found a significant drop in IVF live birth rates in women aged ≥ 43 and over. Live birth rates were 7.4% for women 40 to 42 years of age, and only 1.1% for women ≥ 43 years. Miscarriage rates were 43.1% in the younger age group and 65.2% in the older age group.[47]

Oocyte donation offers women with an intact uterus the opportunity to carry a pregnancy despite declining ovarian function or menopause. In Canada, the 2004 *Assisted Human Reproduction Act* regulates all reproductive technologies, including the use of donor gametes. Specifically, the Act prohibits the sale of eggs, sperm, or surrogacy services.[48] Compensation to donors for receiptable expenses such as medications and parking are allowed,[49] although the specific regulations are not yet available. Many countries, including the United States, rely on paid, often anonymous, egg donors to ensure an adequate supply to meet the significant demand for this treatment option. However, as this practice is prohibited in Canada, Canadian women must rely on altruistic egg donors, usually family members, close friends, or colleagues. Unfortunately, many women will not know an appropriate donor, so egg donation may not be an option for them. Other women turn to reproductive tourism and seek treatment in the United States or Europe.

Pregnancy rates with oocyte donation are based on the age of the donor, not the recipient.[33,50] Pregnancies and live births have been reported in women into their 60s[51]; however, the use of donor eggs for women after the age of 50 is controversial. There are increased rates of obstetrical and maternal complications with increasing maternal age, including maternal death, hypertension, prematurity, fetal and neonatal death, and operative delivery.[52–55] At least one death immediately after delivery has been reported in a 50-year-old woman who conceived with oocyte donation.[56] However, many of these studies show these risks are already increased in women > age 40, and treatment is offered to women between the ages of 40 and 50 without significant debate. Many clinicians feel the natural age of menopause is an appropriate maximum age for offering oocyte donation, although others argue this is an arbitrary cut-off point.[57] In Canada, there are no regulations that set an age limit for oocyte donation, although many clinics have set the age of menopause as the maximum age for this treatment.

Recommendations

5. Pregnancy rates for controlled ovarian hyperstimulation are low for women > 40 years of age. Women > 40 should consider IVF if they do not conceive within 1 to 2 cycles of controlled ovarian hyperstimulation. (II-2B)
6. The only effective treatment for ovarian aging is oocyte donation. A woman with decreased ovarian reserve should be offered oocyte donation as an option, as pregnancy rates associated with this treatment are significantly higher than those associated with controlled ovarian hyperstimulation or in vitro fertilization with a woman's own eggs. (II-2B)

EARLY PREGNANCY AND MATERNAL COMPLICATIONS

Advanced reproductive age is associated with early and later pregnancy complications in addition to infertility. Age is a recognized risk factor for spontaneous abortion. Although the risk of clinical pregnancy loss is low in women < 30 years of age (7% to 15%), it begins to rise for women aged 30 to 34 (8% to 21%) and women aged 35 to 39 (17% to 28%), and it increases dramatically for women aged ≥ 40 (34% to 52%).[15] Data from the Canadian ART clinics also show an increase in spontaneous pregnancy loss after ART treatment. Pregnancy loss rates after clinical intrauterine pregnancy ranged from 10.4% for women aged < 35 to 16.4% for women aged 35 to 39, and increased to 33% for women aged ≥ 40.[27]

An increased risk of chromosomal abnormalities also occurs with age. Much of the increased risk of early pregnancy loss may be due to the increased rate of chromosomally abnormal conceptions. The previously discussed underlying mechanisms for ovarian aging and declining egg quality leading to increased oocyte aneuploidy may lead to an increased rate of chromosomal abnormalities in resultant embryos and pregnancies. The age-related risks for Down syndrome increase from 1 in 1477 for women at age 20 to 1 in 939 at age 30, 1 in 353 at age 35, 1 in 85 at age 40, and 1 in 39 at age 44. The age-related risk for all chromosomal abnormalities rises from 1 in 526 for women at age 20 to 1 in 384 at age 30, 1 in 204 at age 35, 1 in 65 at age 40, and 1 in 2 at age 45.[58]

Pregnancy in women > 40 years of age is also associated with a higher risk of obstetrical complications, including operative delivery, gestational diabetes, preeclampsia, IUGR, and low birth weight.[6] Pre-conception screening for significant medical conditions such as hypertension or diabetes should be considered for women at high risk before fertility treatment is begun.

Recommendations

7. Women should be informed that the risk of spontaneous pregnancy loss and chromosomal abnormalities increases with age. Women should be counselled about and offered appropriate prenatal screening once pregnancy is established. (II-2A)
8. Pre-conception counselling regarding the risks of pregnancy with advanced maternal age, promotion of optimal health and weight, and screening for concurrent medical conditions such as hypertension and diabetes should be considered for women > age 40. (III-B)

ADVANCED PATERNAL AGE

Although significant focus has been placed on female reproductive aging, there is also an age-related decline in sperm function and male fertility. Although "andropause" is not a clearly defined event for men as menopause is for women, there is a decline in testicular function, which includes declining testosterone levels each year.[59] Sperm parameters including semen volume, motility, and morphology decrease with age, although a decline in sperm concentration has not been shown.[60]

Studies trying to delineate the effects of male age on natural fertility often have not accounted for female age. One study has suggested that the odds of conception decrease 3% per year, while other studies have shown that the effect of male age alone on natural monthly conception is small.[61,62] Similarly, studies in ART treatment have often not controlled adequately for maternal age.[63,64] One study suggested that male age > 35 years may have an effect on IUI, but most studies suggest that male age does not affect IVF/ intracytoplasmic sperm injection pregnancy rates despite lower motility and fertilization rates.[65,66] There was also no difference seen in egg donation cycles.[67,68] In couples undergoing ART treatment, it appears that the effect of paternal age on the number of cleavage-stage embryos is small.[69] However, a significant decrease in the rate of blastocyst embryo formation on day 5 and in the number of cryopreservable embryos has been noted.[70,71]

Paternal age > 40 years does appear to be associated with risk of spontaneous abortion, even when maternal age is controlled for.[72,73] For chromosomal abnormalities, the effect of maternal age is such a significant factor, the paternal age effect is small in comparison and is not found at all in many studies after maternal age is controlled for.[74–77] However, recent studies suggest that, either alone or in combination with a maternal effect, paternal effect may increase the risk of Down syndrome.[78] Although there has been conflicting evidence for an association with pre-term birth and low birth weight, a study conducted in the United States and a population study undertaken in Alberta did not find this association after multiple and logistic regression analysis.[79–81] Advanced paternal age has been associated with autosomal dominant disorders such as Alport syndrome, achondroplasia, and neurofibromatosis.[82–87] The estimated risk for autosomal dominant disorders in offspring of fathers ≥ 40 years of age is thought to be < 0.5%.[78]

Autism spectrum disorders and schizophrenia have been associated with advanced paternal age through larger cohort and population database studies. A large Danish prospective study on autism with one million children

found a relative risk 1.6 for fathers > 40 to 44 years of age, and an Israeli cohort study found an OR 5.75 for fathers aged 40 to 49.[88,89] A large US study found an association between autism and both maternal and paternal age, with a relative risk of 1.3 for every 10-year increase in paternal age.[90] The link between paternal age and schizophrenia was initially felt to be constitutional: people with this condition tend to marry and reproduce later in life. A cohort of almost 90 000 children in Jerusalem was linked to the Israeli Psychiatric Registry. The relative risk for offspring with schizophrenia was 2.0 for fathers aged 45 to 49, and 3.0 for fathers > age 50.[91] This finding has been seen across other studies in other ethnic populations, including populations in Denmark, Sweden, and Japan.[92–94]

The American College of Medical Genetics does not recommend additional prenatal testing solely on the basis of advanced paternal age (defined as ≥ 40), although prenatal counselling about the potential risks of advanced paternal age should be undertaken.[78]

Recommendation

9. Advanced paternal age appears to be associated with an increased risk of spontaneous abortion and increased frequency of some autosomal dominant conditions, autism spectrum disorders, and schizophrenia. Men > age 40 and their partners should be counselled about these potential risks when they are seeking pregnancy, although the risks remain small. (II-2C)

CONCLUSIONS

Female reproductive aging is a common cause of infertility in women in their late 30s and 40s. Health care providers should counsel women about the realities of the biological clock and ensure they have realistic expectations about natural and assisted fertility rates if they choose to delay child-bearing into their later reproductive years.

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