Age-related Infertility

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KEYWORDS

• Aging • Infertility • Ovarian reserve • Advanced maternal age • Donor oocytes

KEY POINTS

- Fecundability decreases with increasing age.
- Evaluation for etiologies of infertility should be offered to women more than 35 years of age who have failed to conceive after 6 months.
- Abnormal tests for ovarian reserve should result in referral to an infertility specialist, as these patients need prompt evaluation and potentially more expedited and aggressive treatment.
- Oocyte donation provides the best chance for successful conception in patients with age-related infertility.
- Pregnancy at an advanced maternal age carries more risks for both mother and fetus, and patients should be fully informed and evaluated for potential complications before proceeding with infertility treatments.

INTRODUCTION

Societal shifts, triggered by a greater focus on education and careers, have resulted in a trend toward delayed childbearing in American women. Between 1970 and 2002, the percentage of first births in women more than 30 years of age increased 6-fold.[1–5] Along with the increase in maternal age has been an expansion in the number of women attempting to conceive at an age when the probability of conception (fecundability) is significantly decreased. The proportion of women who remain childless increases progressively with increased age at time of marriage: 6% at age 20 to 24 years, 9% at age 25 to 29 years, 15% at age 30 to 34 years, 30% at age 35 to 39 years, and 64% at ages more than 40 years.[6]

Although fertility declines with age of both men and women, the risk of infertility (ie, failure to achieve successful pregnancy after 12 months of attempt conception) has a stronger correlation with maternal age.[7] Historical studies have shown that fertility decreases at 32 years of age, with an increase in the rate of decline after 37 years of

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age.[7–9] A recent Danish study revealed peak fecundability at age 29 to 30 years in parous women and 27 to 28 years in nulliparous women. Furthermore, both the overall decrease in fecundability and the rate of decline in fecundability are greater in nulliparous women.[10]

The cause of age-related infertility is multifactorial. There is a demonstrated decrease in oocyte number as women progress through their reproductive years.[11,12] Furthermore, the rate of miscarriage and chromosomal abnormalities increases with increasing maternal age.[13] Aging is also associated with an increase in disorders that may impair fertility such as tubal disease, leiomyomas, and endometriosis.[14]

The impact of age-related behaviors, such as a decrease in sexual activity, on fertility is difficult to quantify. A French study of women with azoospermic husbands undergoing insemination revealed a decrease in pregnancy rates with increasing age. Cumulative pregnancy rates over 12 insemination cycles were 74% for women less than 31 years, 62% in women aged 31 to 35 years, and 54% in women more than 35 years of age.[15] However, a recent study showed that although timing of intercourse improved with age, both the frequency of intercourse and fecundability decreased with age.[10] This finding suggests that a decline in sexual behavior may contribute to, but is not the sole cause of, the decrease in fecundability seen with increasing age.

Reproductive aging is the natural process of declining fecundability as a woman progresses through the stages of puberty, fertility, the menopause transition, and menopause. However, the rate at which a woman moves through these stages can vary per individual.[16] Therefore, women of the same reproductive age can be at different stages in their reproductive lifespans. Because of this age-related decline in fertility, important consideration should be given to women planning or attempting to conceive in their later reproductive years. Current recommendations are to proceed with an evaluation for infertility after 6 months of attempted conception in a woman more than 35 years of age.[14]

DISCUSSION

Physiology of Reproductive Aging

Women are born with a finite number of oocytes. The peak in oocyte number occurs in utero, with 6 to 7 million oogonia at 16 to 20 weeks of gestation. From this point on, follicle number continues to decrease because of apoptosis of the nondominant follicles. At birth, 1 million to 2 million oocytes remain and only 300,000 to 500,000 are present when puberty begins. Follicle atresia increases at 37 years, when about 25,000 follicles remain. At the onset of menopause, fewer than 1000 follicles remain.[11,12,17]

The shrinking pool of oocytes results in decreased secretion of inhibin B from small preantral follicles. This loss of inhibition allows pituitary follicle-stimulating hormone (FSH) secretion to increase.[18,19] As FSH increases in the early follicular phase, aging ovaries show more rapid follicular development and an earlier selection of the dominant follicle.[20,21] This is clinically represented as a shorter follicular phase and irregular menstrual cycles, but these changes only become evident after significant ovarian aging has occurred.[22,23] Furthermore, the earlier increase in FSH level also frequently results in selection of more than 1 dominant follicle, explaining the increased rate of dizygotic twinning seen in natural conceptions at an advanced maternal age.[24]

The decrease in follicular number is coupled with a concurrent decrease in oocyte quality. An increased rate of chromosomal abnormalities and miscarriage has been shown with advancing maternal age (**Fig. 1**).[25–27] Studies suggest that most oocytes from women more than 40 years of age are chromosomally abnormal. The most