Age-related Infertility

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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 age.8

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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.

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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. 

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

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. However, a recent study showed that although timing of intercourse improved with age, both the frequency of intercourse and fecundability decreased with age. 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. 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.

**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.

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. As FSH increases in the early follicular phase, aging ovaries show more rapid follicular development and an earlier selection of the dominant follicle. 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. 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.

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. Studies suggest that most oocytes from women more than 40 years of age are chromosomally abnormal. The most
common chromosomal abnormality seen with increasing age is trisomy. The increase in aneuploidy in older oocytes is due to meiotic nondisjunction. A study evaluating oocytes from naturally cycling young women (20–25 years of age) and older women (40–45 years of age) revealed that 79% of the older oocytes had meiotic spindle abnormalities compared with 17% in the younger group. Furthermore, the rate of significant chromosomal abnormalities in live births is 1 in 500 in women less than age 30 years, 1 in 80 at age 35 years, and 1 in 20 at age 45 years.

Tests of Ovarian Reserve

Measures of ovarian reserve attempt to quantify a woman’s reproductive potential by estimating the number of remaining oocytes. Ovarian reserve tests have been used along with menstrual history to estimate where a woman is in the process of reproductive aging. Measures of ovarian reserve predict oocyte yield following ovarian hyperstimulation and predict pregnancy following assisted reproductive technology (ART) in older women. A small study suggests that measures of ovarian reserve may be predictors of natural fertility among women more than 30 years of age; however, definitive, larger studies are lacking. Tests of ovarian reserve aid in counseling and selection of appropriate treatment of women with infertility.

- Early follicular phase FSH: A decrease in oocyte number results in decreased negative feedback from inhibin B and a resultant increase in FSH secretion in the early follicular phase. An early follicular (cycle day 3) FSH cutoff value of greater than 10 IU/L has a high specificity (80%–100%) but lower sensitivity (10%–30%) for predicting poor ovarian response to stimulation. FSH levels can be measured in serum or in urine.
- Early follicular phase estradiol: Estradiol alone has limited utility in determining ovarian reserve. However, early follicular estradiol levels can aid in the interpretation of FSH values. With earlier selection of a dominant follicle, as seen with reproductive aging, estradiol levels increase in the early follicular phase and may suppress FSH secretion. Therefore, increased estradiol levels (>60–80 pg/mL) with normal FSH values (<10 IU/L) suggest diminished ovarian reserve. Women with increased FSH and estradiol levels are poor-prognosis patients for ART.
- **Clomiphene citrate challenge test (CCCT):** The CCCT measures FSH levels before (cycle day 3) and after (cycle day 10) 5 days of stimulation with 100 mg of clomiphene citrate (cycle days 5–9). A decrease in inhibin B secretion from a small cohort of follicles provides less negative feedback on clomiphene-induced pituitary hormone release, resulting in an increased cycle day 10 FSH value.\(^{36}\) The CCCT has higher sensitivity (13%–66%) but lower specificity (67%–100%) than basal FSH values alone.\(^{37}\)

- **Inhibin B:** Inhibin B is secreted from the granulosa cells of the small antral follicles in the follicular phase. However, it has limited utility as a measure of ovarian reserve because it varies widely throughout the cycle\(^{38,39}\) and must be measured during the early follicular phase.

- **Antimullerian hormone (AMH):** AMH, also secreted from the granulosa cells or preantral follicles, is important in recruitment of the dominant follicle. AMH declines with age, and values less than 0.7 ng/mL have been correlated with decreased fecundability in natural cycles and poor response to stimulation with ART.\(^{30,40,41}\) AMH is unaffected by cycle day.\(^{42}\) Cutoff values between 0.2 and 0.7 ng/mL have a sensitivity of 40% to 97% and a specificity of 78% to 92% in predicting poor response to ovarian stimulation.\(^{29}\)

- **Antral follicle count (AFC):** AFC is the determination of all follicles with a mean diameter 2 to 10 mm by transvaginal ultrasonography in the early follicular phase. Histologic studies have correlated AFC with number of remaining primordial follicles.\(^{43}\) A low AFC, less than 3 to 10 total follicles, has been associated with decreased success in achieving pregnancy following ART.\(^{44}\) An AFC of fewer than 3 to 4 follicles has a sensitivity of 9% to 73% and a specificity of 73% to 100% for predicting poor response to ovarian stimulation.\(^{29}\) Thus, AFC is best suited to help predict a patient who may have a poor response to stimulation with ART.

**Management and Treatment**

When using tests of ovarian reserve to determine a woman’s reproductive potential, results should be compared with that of a woman her own age.\(^{45}\) However, absolute cutoff values should be used when predicting ovarian response to stimulation. For example, an AMH level of 1.0 ng/mL in a 30-year-old woman suggests low ovarian reserve for her age. However, that patient would be unlikely to have poor oocyte yield (<4 oocytes) in response to controlled ovarian hyperstimulation. Therefore, tests of ovarian reserve should be interpreted with caution, because abnormal results do not define sterility, especially among young women. The predictive value of such tests appears to depend on the woman’s age. However, an abnormal test indicates a need for a prompt evaluation and potentially a more aggressive approach in management.

There is no specific treatment of diminished ovarian reserve. The only treatment option to overcome age-related infertility is in vitro fertilization (IVF) with donor oocytes. Note that measures of ovarian reserve do not predict oocyte quality. A woman’s risk of having a fetus affected by aneuploidy is driven by maternal age not ovarian reserve.\(^{46}\)

Patients seeking pregnancy at an older age, patients more than 35 years of age without conception after 6 months of unprotected intercourse, or patients with diminished ovarian reserve should all be seen by an infertility specialist. In general, an infertility evaluation includes determination of ovulatory status, tests of ovarian reserve, evaluation of tubal and uterine anatomy, and semen analysis. If these tests return normal, then empirical treatment is usually undertaken with controlled ovarian hyperstimulation, intrauterine insemination, or in vitro fertilization. However, these options are often limited by the woman’s age-related potential for reproduction.
The mean age of all patients undergoing IVF is 36 years.\textsuperscript{47} Sixty-four percent of all IVF cycles are in women aged 30 to 39 years, with 24% of cycles in women aged 40 years and older.\textsuperscript{47} The live birth rate per IVF cycle is directly correlated with maternal age. Recent US Centers for Disease Control and Prevention data for all fresh, nondonor IVF cycles in 2011 reported a live birth rate of 40% in women less than 35 years of age. This rate decreases as women age: 32% at 35 to 37 years, 22% at 38 to 40 years, 12% at 41 to 42 years, 5% at 43 to 44 years, and less than 1% in women older than 44 years (Fig. 2).\textsuperscript{47}

Even with IVF, the likelihood of successful ongoing pregnancy is compromised by age. After the age of 30 years, the probability for ongoing pregnancy decreases by about 1.5% per year.\textsuperscript{48} The rate of implantation decreases by more than two-thirds after the age of 40 years, likely reflecting poor embryo quality.\textsuperscript{49} Miscarriage rates after IVF cycles are 15% in women less than 35 years old, 25% in women at age 40 years, and more than 70% in women more than 44 years of age.\textsuperscript{47} The likelihood of success with IVF decreases because of a diminished response to stimulation, a lower chance of proceeding to oocyte retrieval and embryo transfer, and both lower pregnancy rates and live birth rates per transfer.\textsuperscript{47} Poor embryo quality and increasing aneuploidy rates with older oocytes cannot be overcome with IVF alone. Results of studies evaluating chromosomal screening before embryo transfer have shown that there is a decline in reproductive potential of embryos even after controlling for aneuploidy.\textsuperscript{50}

The use of IVF with donor oocytes has expanded the reproductive options of many women, especially those with age-related infertility. Pregnancy success rates are much higher and miscarriage rates are lower than in age-matched controls. When using donor oocytes, the live birth rate per embryo transfer is 55% across all age groups.\textsuperscript{47} An analysis of cycles from the Society of Assisted Reproductive Technology (SART) database revealed that age affects IVF outcomes with donor oocytes. The live birth rate in recipients less than the age of 35 years was 56%, whereas the live birth rate for recipients aged 45 to 49 years and greater than 50 years was 52% and

![Fig. 2. Live birth rates per IVF cycle. (Data from Centers for Disease Control and Prevention, American Society for Reproductive Medicine Society for Assisted Reproductive Technology. 2011 assisted reproductive technology: national summary report. Atlanta (GA): Centers for Disease Control and Prevention; 2013.)](image-url)
48%, respectively. However, the absolute live birth rates were still high. The 2012 recommendations for gamete donation by the American Society for Reproductive Medicine (ASRM) provide current guidelines for screening oocyte donors and evaluation of the recipient. Indications for oocyte donation include:

- Hypergonadotropic hypogonadism
- Advanced reproductive age
- Diminished ovarian reserve
- Genetic carriers
- Poor oocyte or embryo quality with previous failed IVF cycles

The recipient of the donor oocytes needs to be evaluated and screened before proceeding with the cycle. The increased risks for maternal complications in older women underscore the importance of this evaluation. Recommended screening includes:

- Complete medical history and physical examination
- Psychological evaluation by a qualified mental health care provider, with partner if applicable
- Assessment of the uterine cavity, either with saline-infused sonography, hysterosalpingogram, or hysteroscopy
- Infectious disease screening: human immunodeficiency virus (HIV)-1/HIV-2 antibodies, hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, serologic testing for syphilis, Neisseria gonorrhoeae and Chlamydia trachomatis nucleic acid testing (NAT)
- Preconception screening: rubella and varicella titers, blood type and Rh factor, antibody screen
- If the recipient is more than the age of 45 years, further recommendations include a thorough medical evaluation with cardiovascular testing and referral to maternal fetal medicine to discuss risks with pregnancy at an advanced age

The partner of the recipient also requires evaluation with:

- Semen analysis
- Blood type and Rh factor
- Infectious disease screening: HIV-1/HIV-2 antibodies, hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, serologic testing for syphilis
- Genetic screening as indicated per ethnicity

Screening potential oocyte donors is required regardless of whether the donor is known or anonymous. The preferable age for oocyte donors is between 21 and 34 years, and proven fertility is highly desirable. Appropriate screening includes:

- Complete medical history and physical examination
- Psychological evaluation by a qualified mental health care provider, with partner if applicable
- Genetic screening for cystic fibrosis and any additional diseases based on ethnicity
- Infectious disease screening: HIV-1/HIV-2 antibodies, hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, serologic testing for syphilis, N gonorrhoeae and C trachomatis NAT
- Blood type and Rh factor
- Verification of no recent tattoos or body piercings within the past 12 months

Furthermore, it is important to disclose all risks to the potential donor, including ovarian hyperstimulation syndrome (1%–2% of donor cycles), ovarian torsion, and...
risk of bleeding or infection with oocyte retrieval.\textsuperscript{52} Data do not show an association between repetitive oocyte donation and future cancer development or diminished ovarian reserve. However, ASRM recommends limiting oocyte donation to 6 total cycles.\textsuperscript{53}

Another potential option for patients of advancing age is the option for elective oocyte cryopreservation. The technique of oocyte vitrification has made oocyte cryopreservation for social reasons a possibility.\textsuperscript{54,55} Although not a treatment of age-related infertility, oocyte cryopreservation is a preventative measure in attempt to conserve a woman’s reproductive potential. Success rates after oocyte cryopreservation are based on data from oocyte donation programs. The live birth rates per 6 oocytes frozen at age 30 and 35 years are estimated at 24\% and 18\%, respectively.\textsuperscript{56} Note that the effectiveness of oocyte cryopreservation for older or infertile women has not been proved.

### Maternal and Fetal Risks

Pregnancy at an advanced maternal age has been correlated with an increased risk of specific adverse pregnancy outcomes. Advanced maternal age has been shown to be an independent risk factor for miscarriage, chromosomal abnormalities, congenital abnormalities, gestational diabetes, severe preeclampsia, placenta previa, and cesarean delivery. Furthermore, maternal age of 40 years or more was associated with a further increase in risk for placental abruption, preterm delivery, low birth weight, intrauterine growth restriction, stillbirth, and perinatal mortality.\textsuperscript{57–60} One potential explanation for the increase in perinatal complications with advancing maternal age may be a failure of the uterine vasculature to adapt to the increased hemodynamic demand with pregnancy.\textsuperscript{61} In addition, older patients are at an increased risk for multiple gestations, both in natural and assisted cycles, increasing the overall rate of perinatal complications. Pregnancy at an advanced maternal age is high risk, and antenatal testing during pregnancy is recommended.

It is difficult to draw conclusions about the impact that pregnancy with donor oocytes may have on maternal and fetal risks associated with advancing age. As previously discussed, the probability of live birth is 55\% across all maternal ages with the use of donor oocytes.\textsuperscript{47} Furthermore, the risk of miscarriage and chromosomal abnormalities is decreased in this population compared with women using their own oocytes.\textsuperscript{62} However, the associations with preeclampsia, gestational diabetes, stillbirth, intrauterine growth restriction, and perinatal mortality likely persist because of impaired placentation and progressive uterine vascular endothelial damage with age.\textsuperscript{57,59–62} Furthermore, oocyte donation in women of older age, especially women in their 50s, poses unique ethical issues. Therefore, ASRM has recommended that oocyte donation be discouraged when the recipient is more than the age of 50 years with any underlying medical problems or more than the age of 55 without such issues.\textsuperscript{62}

### SUMMARY

With the societal shift toward delayed childbearing, it is important for providers to remember that age is still the best marker for reproductive potential. However, patients of advancing age are capable of achieving pregnancy, especially in the era of advanced reproductive technology and donor oocytes. Pregnancy at an advanced maternal age has risks. Patients should be fully counseled and educated regarding options for conception and the implications of advancing age on both maternal and fetal outcomes.
REFERENCES