Female age-related fertility decline

Committee Opinion No. 589

The American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and The Practice Committee of the American Society for Reproductive Medicine

The fecundity of women decreases gradually but significantly beginning approximately at age 32 years and decreases more rapidly after age 37 years. Education and enhanced awareness of the effect of age on fertility are essential in counseling the patient who desires pregnancy. Given the anticipated age-related decline in fertility, the increased incidence of disorders that impair fertility, and the higher risk of pregnancy loss, women older than 35 years should receive an expedited evaluation and undergo treatment after 6 months of failed attempts to conceive or earlier, if clinically indicated. In women older than 40 years, more immediate evaluation and treatment are warranted. (Fertil Steril® 2014;101:633–4. ©2014 by American Society for Reproductive Medicine.)

The number of oocytes in the ovaries decreases naturally and progressively through the process of atresia. The maximum complement of oocytes is 6–7 million and exists at 20 weeks of gestation in the female fetus. The number of oocytes decreases to approximately 1–2 million oocytes at birth; 300,000–500,000 at puberty; 25,000 at age 37 years; and 1,000 at age 51 years, the average age of menopause in the United States (1–3). The fecundity of women decreases gradually but significantly beginning approximately at age 32 years and decreases more rapidly after age 37 years, reflecting primarily a decrease in egg quality in association with a gradual increase in the circulating level of follicle-stimulating hormone and decreases in circulating antimüllerian hormone and inhibin B concentrations (3, 4). The mechanisms involved are poorly understood but appear to include multiple factors encoded by genes on the X chromosome and the autosomes (5).

Age alone has an effect on fertility. Historical data suggest that, among populations that do not use contraception, fertility rates decrease with increasing age of women (Fig. 1). Because sexual activity also declines with age, it is difficult to separate out the effects of sexual behavior from age. However, a classic French study was able to separate behavioral and age effects by studying healthy women with husbands who had azoospermia and underwent donor insemination. The study found that pregnancy rates decreased progressively with increasing age of the recipient female patient (6). The cumulative pregnancy rate observed in up to 12 insemination cycles was 74% for women younger than 31 years and decreased to 62% for women aged 31–35 years and to 54% for women older than 35 years (6). A similar trend has been observed in analyses of data derived from in vitro fertilization (IVF) embryo transfer programs in the United States. The percentage of IVF cycle starts that resulted in live births was 41.5% in women younger than 35 years, 31.9% in women aged 35–37 years, 22.1% in women aged 38–40 years, 12.4% in women aged 41–42 years, 5% in women aged 43–44 years, and 1 % for women older than 44 years (7). In contrast, in patients who used eggs obtained from healthy, young donors, 51% of fresh transfers resulted in a live birth, regardless of the age of the recipient (7). As age increases, the risks of other disorders that may adversely affect fertility, such as leiomyomas, tubal disease, and endometriosis, also increase. Women with a history of prior ovarian surgery, chemotherapy, radiation therapy, severe endometriosis, smoking, pelvic infection, or a strong family history of early menopause may be at an increased risk of having a premature decrease in the size of their follicular pool and decline in fertility.

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Correspondence: Practice Committee, American Society for Reproductive Medicine, 1209 Montgomery Hwy., Birmingham, Alabama 35216 (E-mail: ASRM@asrm.org).

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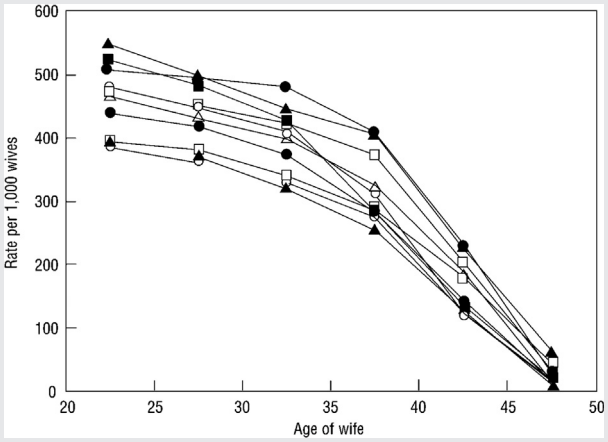
FIGURE 1



Marital fertility rates by 5-year age groups. The ten populations (in descending order at age 20–24 years) are Hutterites, marriages in 1921–1930 (▲); Geneva bourgeoisie, husbands born 1600–1649 (■); Canada, marriages in 1700–1730 (●); Normandy marriages in 1760–1790 (○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840–1859 (△); Normandy, marriages in 1674–1742 (●); Norway, marriages in 1874–1876 (□); Iran, village marriages in 1940–1950 (▲); Geneva bourgeoisie, husbands born before 1600 (○). From Menken J, Trussell J, Larsen U. Age and fertility. Science 1986;233:1389–94. Reprinted with permission from AAAS.

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The age-related decline in fertility is accompanied by significant increases in the rates of aneuploidy and spontaneous abortion (8). Autosomal trisomy is the most frequent finding and is related, at least in part, to changes in the meiotic spindle (9) that predisposes to nondisjunction (10). Even for morphologically normal embryos selected for transfer in IVF cycles, the prevalence of aneuploidy is high in women of advanced maternal age (11). The fetal loss rate also is significantly increased, even after fetal heart rate motion is detected by transvaginal ultrasonography (12). Although 9.9% of women younger than 33 years who conceive during IVF with a fresh embryo transfer have a pregnancy loss after 7 weeks of gestation with fetal heart activity observed, the rates of miscarriage progressively increase from 11.4% for women aged 33–34 years to 13.7% for women aged 35–37 years, 19.8% for women aged 38–40 years, 29.9% for women aged 41–42 years, and 36.6% for women older than 42 years (12). These data are similar to the increased rates of miscarriage reported nationally with IVF, where the rate of miscarriage increased progressively with age, from 13% in women younger than 35 years to 54% in women aged 44 years or older (7). Therefore, given the anticipated age-related decline in fertility, the increased incidence of disorders that impair fertility, and an increased risk of pregnancy loss, women older than 35 years should receive an expedited evaluation and undergo treatment after 6 months of failed attempts to conceive or earlier, if clinically indicated.

The fecundity of women decreases during the reproductive years primarily because of continual oocyte atresia and becomes significantly compromised before the onset of perimenopausal menstrual irregularity. Based on this conclusion, the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine make the following recommendations:

- Education and enhanced awareness of the effect of age on fertility is essential in counseling the patient who desires pregnancy.
- Women older than 35 years should receive expedited evaluation and treatment after 6 months of failed attempts to conceive or earlier, if clinically indicated.
- In women older than 40 years, immediate evaluation and treatment are warranted.

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