Effects of age on fertility and sexual function

Michael L. Eisenberg, M.D.[a] and David Meldrum, M.D.[b]

[a] Department of Urology, Stanford University School of Medicine, Stanford; and [b] Department of Reproductive Medicine, Division of Reproductive Endocrinology and Infertility, University of California, San Diego, California

As paternal age increases in the developed world, more attention has been given to the effects of age on male reproductive and sexual function. Although the biologic potential for reproductive continues for most of a man's life, changes in sperm production do occur. In addition, erectile function changes with age, caused by the same factors that lead to other vascular disease. (Fertil Steril® 2017;107: 301–4. ©2016 by American Society for Reproductive Medicine.)
Key Words: Infertility, erectile dysfunction, semen analysis, hypogonadism

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/14119-23224

AGE AND REPRODUCTIVE FUNCTION

The age of paternity is rising in the United States. Over the past three decades, the birth rate for fathers under the age of 30 years has declined and for fathers 30 years and older has increased (1). For example, in 1980, the birth rate for fathers aged 25–29 years was 123.1 births per 1,000 men, and in 2014 it fell to 89.7 (a decline of more than 27%). In contrast, the birth rate per 1,000 fathers aged 30–34 years increased from 90.1 to 103.9 (an increase of 15%). For older fathers, the increase was more dramatic. Among fathers 35–39, 40–44, and 45–49 years, the birth rates increased 61%, 63%, and 52%, respectively. Moreover, the popular literature is rife with celebrities and other men having children beyond the seventh decade of life. Though biologically feasible, the extent of the effects of age on male sexual and reproductive function have been questioned.

Age and Spermatogenesis

Semen quality is routinely used to assess male fertility potential (2, 3). Although studies have questioned the reliability of semen analysis, it remains a standard component of a male fertility evaluation (2, 4). Several groups have examined the effects of male age on semen quality and have reported general declines with advancing age. In 2001, Kidd et al. reviewed the literature from 1980 to 1999 (5). Sixteen studies of semen volume, 21 studies of sperm concentration, 19 studies of sperm motility, and 14 studies of sperm morphology were examined. The authors noted heterogeneity in the literature, with the most consistent declines identified for semen volume, motility, and morphology. In contrast, a reliable association between male age and sperm concentration was not identified. The authors compared 30- and 50-year-old men and reported decreases in semen volume (3%–22%), sperm motility (3%–37%), and percentage of normal sperm (4%–18%). Indeed, the decline in semen volume is commonly reported by older men presenting with ejaculatory disorders.

A recent meta-analysis was performed by Johnson et al. in 2015 (6). They identified 90 studies examining 93,839 subjects included in 110 data sets. The authors reported declines in semen volume, total sperm count, motility, progressive motility, and sperm morphology with increasing age. They reported summary regression coefficients of r[volume] = −0.103 (95% confidence interval [CI] −0.136 to −0.069), r[total count] = −0.053 (−0.092 to −0.013), r[motility] = −0.138 (−0.191 to −0.083), r[progressive motility] = −0.200 (−0.286 to −0.111), and r[morphology] = −0.090 (−0.134 to −0.045). Similar to the findings of Kidd et al., a nonconsistent decline in sperm concentration was identified with the confidence interval of the summary coefficient crossing unity (r[concentration] = −0.014 (−0.055 to 0.026)). Their results were consistent with the decline in semen volume masking a decline in sperm concentration that would have otherwise been observed.

In addition, the authors identified an increase in sperm DNA fragmentation (r[DNA] = −0.209 (−0.287 to

Received October 11, 2016; revised and accepted December 16, 2016.
M.L.E. is an advisor to Sandstone, Glow, and EmbraceHer. D.M. has nothing to disclose.
Reprint requests: Michael L. Eisenberg, M.D., Department of Urology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, California 94305-5118 (E-mail: eisenberg@stanford.edu).

Fertility and Sterility® Vol. 107, No. 2, February 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.12.018

−0.128)). Elevated sperm DNA damage is more common in infertile men than in fertile men and may relate to impaired fertility outcomes. Although sperm DNA fragmentation is not currently recommended by the American Society for Reproductive Medicine in the first line evaluation of male fertility, it may provide addition information for couples considering intrauterine insemination, in vitro fertilization (IVF), or intracytoplasmic sperm injection, particularly for older male partners (2).

When examining current studies of changes in semen quality with age, it is important to consider the subject population under study. While several studies have been criticized for inclusion of patients visiting clinics for infertility, the study by Johnson et al. accounted for subject source (patients/clinic-based studies vs. donors/volunteers). Regardless of recruitment population, the authors reported a similar trend suggesting that the impact of male age on spermatogenesis is consistent and broadly generalizable.

The causes of these changes in semen quality with age are not definitively known. However, researchers have hypothesized that accumulated DNA damage, exposure to environmental toxicants, infections, hormonal-related declines, and altered accessory sexual gland function may contribute (6–10). One may also wonder if increasing paternal age could affect the reproductive health of their male offspring, but it has not been shown to affect spermatogenesis in sons (11). Another important point to mention is the increasing use of testosterone therapy in recent years, especially among reproductive-age men, which has severe negative effects on spermatogenesis (12, 13).

Paternal Age and Unassisted Conception

Several studies have examined the effects of increasing paternal age on the time to pregnancy (TTP). In a retrospective study of 6,188 European couples, the authors identified an effect of paternal age on conception which was dependent on maternal age (14). Using a cutoff for paternal age of ≥40 years of age, couples with a female partner <30 or 30–34 years of age did not show a significant effect of paternal age on not conceiving within 12 months (odds ratios [ORs] 1.18, 95% CI 0.60–2.32; and 1.17, 95% CI 0.63–2.18; respectively). In contrast, among couples with women 35–39 years of age, risks of delayed conception were significantly higher when paternal age was ≥40 years than when paternal age was <40 years, with an adjusted OR of 2.21 (95% CI 1.13–4.33).

A cross-sectional study of all couples expecting a baby completed questionnaires at 18 weeks of gestation from 1991 to 1992 (15). Of 8,515 planned pregnancies, 74% were conceived in ≤6 months, 14% in the 2nd 6 months, and 12% after more than 1 year. After adjusting for female age, body mass index, smoking, housing, education, oral contraceptive use, alcohol consumption, and cohabitation, the likelihood of conception within 6 or 12 months was lower for older men. Compared with men <25 years old, the ORs for conception in ≤12 months in men aged 30–34, 35–39, and ≥40 years were 0.62 (95% CI 0.40–0.98), 0.50 (0.31–0.81), and 0.51 (0.31–0.86), respectively.

In a study of 2,122 pregnant women in the United Kingdom, the authors found that increasing male age was associated with significantly rising TTP and declining conception rates. A fivefold increase in TTP occurred with men's age >45 years. Relative to men <25 years old, those >45 years were 4.6-fold and 12.5-fold more likely to have a TTP of >1 or >2 years, respectively. Similar results were identified when restricting the analysis to partners of young women, suggesting the effects were not driven by female partner age (16).

Paternal Age and Assisted Conception

Several groups have examined the effect of paternal age on assisted conception. Given that maternal age often increases with paternal age, several groups have attempted to examine the effect of paternal age in isolation by examining only donor-egg cycles. Paulson et al. examined 441 donor-egg cycles (17). Although the authors saw a decline in sperm counts, they did not see an effect on fertilization rate or live birth rate.

Frattarelli et al. examined data from infertile couples undergoing 1,023 anonymous oocyte donation cycles (18). The authors found no difference in fertilization rate, day 2 embryo arrest, day 3 embryo arrest, and day 3 embryos with ≥7 cells when stratifying by paternal age. However, they did identify a lower rate of blastocyst formation in older fathers. Based on their data, the authors concluded that sperm from men >50 years of age was associated with some measures of impaired embryo development and higher rates of embryo loss that resulted in a lower live birth rate. Because the fetal genome becomes active only after the 4- to 8-cell stage, the increased DNA fragmentation with increasing male age could account for reduced blastocyst formation. Robert Shaw examined 237 donor oocyte cycles and reported a decline in pregnancy and live birth rate with increasing male age (19).

Another strategy to attempt to account for female factors in IVF is to isolate analyses to couples utilizing IVF owing to tubal disease, hoping to eliminate the confounding uterine and ovarian factors that may obscure the effect of paternal age. De La Rochebrochard et al. used this strategy when examining 1,938 couples undergoing IVF for tubal disease (20). Comparing men >39 and <30 years of age, the authors identified a 1.7 higher odds of failing to conceive for the older men. Moreover, the trend held across female ages, such that the odds were elevated for female partners 35–38 (OR 2.0, 95% CI 1.1–3.6), 39–40 (2.0, 1.1–3.7), and ≥41 (5.7, 2.2–15.7) years of age.

Summary

The literature supports an association between sperm production and age whereby semen volume, sperm motility, and sperm morphology decline. In addition, the bulk of evidence supports a decline in male fertility with increasing age when assessing unassisted or assisted reproduction.

AGE AND ERECTILE FUNCTION

Coital frequency and erectile function decrease with age (21, 22) in association with delayed conception and