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

reduced success with fertility treatments. Although the impact of those factors on reproduction has not been studied, infrequent coitus reduces natural conception, and ejaculatory abstention increases sperm DNA fragmentation (23). Improving erectile function would contribute to more frequent coitus and an improved sexual relationship during the stresses of infertility and fertility treatments. With the prominent exception of exogenous testosterone, lifestyle and certain treatment approaches improving erectile function have been associated with improved fertility. Exogenous testosterone causes oligospermia and even azoospermia (24); it is widely used by aging men, and its use may not be readily disclosed. It must be discontinued and sperm parameters usually normalize with the use of hCG-based stimulation regimens (25). Other treatments for the male partner, such as clomiphene citrate and aromatase inhibitors, can raise serum testosterone without negatively affecting sperm parameters (26).

Erectile Biochemistry and Physiology

Nitric oxide (NO) and its second messenger, cyclic guanosine monophosphate, are the most important mediators of penile vascular and sinusoidal smooth muscle relaxation. Sexual arousal stimulates penile nerves to activate neural NO synthase resulting in dilation of penile vessels, marked inflow of blood, and engorgement of penile sinusoids. Shear stress caused by the increase in penile blood flow activates endothelial NO synthase which relaxes smooth muscle surrounding the penile arteries and the sinusoids of the corpora cavernosa (CC). Distention of the CC together with muscular pressure from surrounding pelvic floor muscles occlude penile veins within and adjacent to the penile tunica, maintaining the erection. Muscular contractions of the pelvic floor muscles raise intracorporeal pressure (ICP) above vascular inflow pressure to provide maximal penile rigidity (27).

Erectile dysfunction (ED) has been reported to affect 10% of men at age 40 years and 80% over the age of 70 years (22), although the incidence is much lower in men without coronary artery disease (2% at age 40–49 years, rising to only 39% for men >70 years of age) (28). The reason that aging, vascular disease, and ED are so closely connected is that the underlying biochemical mechanisms are the same: oxidative stress (OS) leading to decreased vascular NO and damage to intracellular proteins, lipids, and cellular structures such as mitochondria; inflammation and insulin resistance, caused at least in part by OS; decreased physical activity and muscular bulk and strength; and decreased use. We will discuss age-related ED in the context of these interrelated mechanisms.

Decreased Physical Activity and Lean Muscle Mass

Physical activity progressively decreases with age. Erectile difficulties, ranging from mild to severe, are tenfold higher in sedentary men (29). The prevalence of ED in those men that engage in moderate exercise is associated with a two-thirds and a high degree of physical activity with more than 80% reduction of the incidence of ED (30). Sperm parameters have also been reported to be better in physically active men than in sedentary men (31).

Decreased Bulk and Strength of Pelvic Floor Muscles

Pressure within the CC (and therefore rigidity) solely from inflow of blood can not exceed systolic blood pressure, yet ICP up to 2–4 times systolic has been recorded in the male human (32). The bulbocarvernosal muscles partially surround the CC to augment erectile potency by constricting venous outflow and by directly increasing ICP (32). The ischiocavernosal muscles also overlie and insert onto the penile tunica to allow their contractions to improve erectile quality. In a cadaver study, relatively young sexually active men, PF muscles were more developed and their points of attachment to the tunica were thicker ($P<.01$) compared with older sexually less active men (33). In a thorough and exceptionally well designed study of pelvic floor exercises, erectile function normalized in 40% of subjects and improved in another 35% (34).

Decreased Use

Frequency of coitus decreases with age (21). The incidence of ED was twofold higher in men accustomed to a coital frequency of less than once per week (35). Shear stress increases NO release from the endothelium of systemic vessels, and the increase in blood flow with erection is much greater than in systemic vessels with exercise (36). In large vessels, in a nonhuman animal model, acute exercise increased vascular NO for 48 hours, but daily exercise increased NO fourfold, lasting for a week (37). These studies suggest that erections promote subsequent erectile potency, and that all measures that improve erectile function, including PDE5 inhibitors, have a secondary benefit by allowing better, more frequent, and more prolonged erections. However, the curative effect of frequent coitus on underlying ED remains unproven. More frequent coitus improves natural conception and decreases sperm DNA fragmentation (23), which increases with age (38, 39).

Testosterone

Low and low normal levels have been associated with ED, and serum testosterone correlates with vascular NO production (40). In hypogonadal men, testosterone supplementation improves erectile function and response to PDE5 inhibitors and reduces insulin resistance and central body fat distribution. Improvement of erectile function has been more consistent in younger than in older hypogonadal men (41). Testosterone levels may increase in obese men with exercise and weight loss (41) and with agents known to increase vascular NO (42). Exogenous testosterone reduces sperm production (24) and should not be used in men wishing to conceive.

Summary

Erectile function declines with age owing to increased body weight, decreased physical and sexual activity, increased

inflammation, decreased muscle mass, and increased oxidative stress, insulin resistance, and circulating glucose. DNA fragmentation increases with age and with less frequent ejaculation. Therefore, age-related decline in sexual function can contribute to delayed natural conception and greater need for and reduced success of fertility treatments. For all of these reasons, measures taken to improve sexual function in the aging man (27) will also help to fulfill their reproductive function.

REFERENCES

1. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2014. Natl Vital Stat Rep 2015;64:1–64.
2. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril 2015;103:e18–25.
3. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010;16:231–45.
4. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388–93.
5. Kidd SA, Eskenazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. Fertil Steril 2001;75:237–48.
6. Johnson SL, Dunleavy J, Gemmell NJ, Nakagawa S. Consistent age-dependent declines in human semen quality: a systematic review and meta-analysis. Ageing Res Rev 2015;19:22–33.
7. Sartorius GA, Nieschlag E. Paternal age and reproduction. Hum Reprod Update 2010;16:65–79.
8. Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, et al. Rate of de novo mutations and the importance of father's age to disease risk. Nature 2012;488:471–5.
9. Hauser R. The environment and male fertility: recent research on emerging chemicals and semen quality. Semin Reprod Med 2006;24:156–67.
10. Rolf C, Kenkel S, Nieschlag E. Age-related disease pattern in infertile men: increasing incidence of infections in older patients. Andrologia 2002;34:209–17.
11. Priskorn L, Jensen TK, Lindahl-Jacobsen R, Skakkebaek NE, Bostofte E, Eisenberg ML. Parental age at delivery and a man's semen quality. Hum Reprod 2014;29:1097–102.
12. Wang C, Festin MP, Swerdloff RS. Male hormonal contraception: where are we now? Curr Obstet Gynecol Rep 2016;5:38–47.
13. Rao PK, Boulet SL, Mehta A, Hotaling J, Eisenberg ML, Honig SC, et al. Trends in testosterone replacement therapy use among reproductive-age US men, 2003–2013. J Urol 2016 Oct 24. http://dx.doi.org/10.1016/j.juro.2016.10.063. [Epub ahead of print.]
14. de La Rochebrochard E, Thonneau P. Paternal age ≥40 years: an important risk factor for infertility. Am J Obstet Gynecol 2003;189:901–5.
15. Ford WC, North K, Taylor H, Farrow A, Hull MG, Golding J, Avon Longitudinal Study of Pregnancy and Childhood Study Team. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. Hum Reprod (Oxf) 2000;15:1703–8.
16. Hassan MA, Killick SR. Effect of male age on fertility: evidence for the decline in male fertility with increasing age. Fertil Steril 2003;79(Suppl 3):1520–7.
17. Paulson RJ, Milligan RC, Sokol RZ. The lack of influence of age on male fertility. Am J Obstet Gynecol 2001;184:818–22, discussion 822–4.
18. Frattarelli JL, Miller KA, Miller BT, Elkind-Hirsch K, Scott RT Jr. Male age negatively impacts embryo development and reproductive outcome in donor oocyte assisted reproductive technology cycles. Fertil Steril 2008;90:97–103.
19. Robertshaw I, Khoury J, Abdallah ME, Warikoo P, Hofmann GE. The effect of paternal age on outcome in assisted reproductive technology using the ovum donation model. Reprod Sci 2014;21:590–3.
20. de la Rochebrochard E, de Mouzon J, Thepot F, Thonneau P. Fathers over 40 and increased failure to conceive: the lessons of in vitro fertilization in France. Fertil Steril 2006;85:1420–4.
21. Brewis A, Meyer M. Marital coitus across the life course. J Biosoc Sci 2005;37:499–518.
22. O'Leary MP, Rhodes T, Girman CJ, Jacobson DJ, Roberts RO, Lieber MM, et al. Distribution of the Brief Male Sexual Inventory in community men. Int J Impot Res 2003;15:185–91.
23. Agarwal A, Gupta S, du Plessis S, Sharma R, Esteves SC, Cirenza C, et al. Abstinence time and its impact on basic and advanced semen parameters. Urology 2016;94:102–10.
24. Samplaski MK, Nangia AK. Adverse effects of common medications on male fertility. Nat Rev Urol 2015;12:401–13.
25. Wenker EP, Dupree JM, Langille GM, Kovac J, Ramasamy R, Lamb D, et al. The use of hCG-based combination therapy for recovery of spermatogenesis after testosterone use. J Sex Med 2015;12:1334–7.
26. Aydogdu A, Swerdloff RS. Emerging medication for the treatment of male hypogonadism. Expert Opin Emerg Drugs 2016;21:255–66.
27. Meldrum DR, Burnett AL, Dorey G, Esposito K, Ignarro LJ. Erectile hydraulics: maximizing inflow while minimizing outflow. J Sex Med 2014;11:1208–20.
28. Inman BA, Sauver JL, Jacobson DJ, McGree ME, Nehra A, Lieber MM, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc 2009;84:108–13.
29. Agostini LC, Netto JM, Miranda MV Jr, Figueiredo AA. Erectile dysfunction association with physical activity level and physical fitness in men aged 40–75 years. Int J Impot Res 2011;23:115–21.
30. Akkus E, Kadioglu A, Esen A, Doran S, Ergen A, Anafarta K, et al. Prevalence and correlates of erectile dysfunction in Turkey: a population-based study. Eur Urol 2002;41:298–304.
31. Vaamonde D, da Silva–Grigoletto ME, Garcia-Manso JM, Barrera N, Vaamonde-Lemos R. Physically active men show better semen parameters and hormone values than sedentary men. Eur J Appl Physiol 2012;112:3267–73.
32. Lavoisier P, Courtois F, Barres D, Blanchard M. Correlation between intracavernous pressure and contraction of the ischiocavernosus muscle in man. J Urol 1986;136:936–9.
33. Hsu GL, Hsieh CH, Wen HS, Hsu WL, Wu CH, Fong TH, et al. Anatomy of the human penis: the relationship of the architecture between skeletal and smooth muscles. J Androl 2004;25:426–31.
34. Dorey G, Speakman M, Feneley R, Swinkels A, Dunn C, Ewings P. Randomised controlled trial of pelvic floor muscle exercises and manometric biofeedback for erectile dysfunction. Br J Gen Pract 2004;54:819–25.
35. Koskimaki J, Shiri R, Tammela T, Hakkinen J, Hakama M, Auvinen A. Regular intercourse protects against erectile dysfunction: Tampere Aging Male Urologic Study. Am J Med 2008;121:592–6.
36. Meldrum DR, Gambone JC, Morris MA, Meldrum DA, Esposito K, Ignarro LJ. The link between erectile and cardiovascular health: the canary in the coal mine. Am J Cardiol 2011;108:599–606.
37. Haram PM, Adams V, Kemi OJ, Brubakk AO, Hambrecht R, Ellingsen O, et al. Time-course of endothelial adaptation following acute and regular exercise. Eur J Cardiovasc Prev Rehabil 2006;13:585–91.
38. Das M, Al-Hathal N, San-Gabriel M, Phillips S, Kadoch IJ, Bissonnette F, et al. High prevalence of isolated sperm DNA damage in infertile men with advanced paternal age. J Assist Reprod Genet 2013;30:843–8.
39. Humm KC, Sakkas D. Role of increased male age in IVF and egg donation: is sperm DNA fragmentation responsible? Fertil Steril 2013;99:30–6.
40. Akishita M, Hashimoto M, Ohike Y, Ogawa S, Iijima K, Eto M, et al. Low testosterone level is an independent determinant of endothelial dysfunction in men. Hypertens Res 2007;30:1029–34.
41. Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med 2013;10:245–84.
42. Meldrum DR, Gambone JC, Morris MA, Ignarro LJ. A multifaceted approach to maximize erectile function and vascular health. Fertil Steril 2010;94:2514–20.