

Fertility and the Aging Male

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In the United States since 1980, the birth rate in women aged > 35 years has increased by nearly 60%, whereas the birth rate for women aged 20 to 34 years has increased by only 10%. The trend in parenthood at an older age has also been seen in men. Since 1980, the fertility rate for men in their 30s has increased by 21% and for men aged 40 years and older, the rate has increased nearly 30%. In contrast, the fertility rate in men younger than age 30 years has decreased by 15%. Age-related infertility will continue to be a problem. A basic understanding of the issues is critical for health care professionals so that they can effectively counsel patients who are considering a delay in childbearing for social reasons or for those seeking fertility treatments. This review details the changes in fertility seen in the aging male. [Rev Urol. 2011;13(4):e184-e190 doi: 10.3909/riu0538]

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Key words: Fertility • Aging male • Miscarriage rates • Age-related infertility

In recent decades, infertility has impacted an increasing number of couples. Approximately 10% of couples in the United States are defined as infertile based on the inability to conceive after 12 months of unprotected intercourse.^{1,2} In addition to the increased rates of obesity and medical illness found in reproductive-aged women, intentionally delayed childbearing is a trend among professional couples.³ In the United States since 1980, the birth rate in women older than age 35 years increased by nearly 60%, whereas the birth rate for women aged 20 to 34 years increased by only 10%.⁴ This trend, in addition to an age-related decline in fertility, has led to an increased need for advanced reproductive technology for couples.⁵⁻⁷

The trend for parenthood at an older age has also been seen in men. Since 1980, the fertility rate for men in their 30s has increased by 21% and for men aged \geq 40 years,

the rate has increased nearly 30%. In contrast, the fertility rate in men younger than age 30 years has decreased by 15%.⁴ The idea that robust fertility for a man will continue well past a woman's decline in fertility is untrue. Although the female ovarian reserve is perhaps the most crucial component of a couple's per cycle fecundity, the age of the male partner also has significant impact on reproduction. Beyond the fact that older men tend to have older female partners, increasing male age is associated with increased time to conception. This reflects the age-related increase in acquired medical conditions, decreases in semen quality, and increasing rates of DNA fragmentation seen in sperm. In addition, there is an association between age of the male partner and the incidence of birth defects and chromosomal abnormalities.

Age-related infertility will continue to be a problem secondary to women delaying childbearing while obtaining advanced education and establishing a professional career. A basic understanding of these issues is critical for health care professionals so that they can effectively counsel patients who are considering a delay in childbearing for social reasons or for those seeking fertility treatments.

The Aging Female Partner

Studies that have attempted to assess the impact of male age on fertility have been confounded by the age of the female partner. It is well documented that women have a natural and inevitable decline in fecundity with age. An interesting example is Tietze's natural history study of the Hutterite population in North America.⁸ This sect strictly condemns contraception, and therefore serves as an ideal population to observe changes in fertility with age. The study showed that 11% of women were

infertile by age 34, 33% by age 40, and 87% by age 45. Further studies have shown that, although there is a mild decrease in fertility in women in their late 20s, a more appreciable deterioration occurs after age 30, and fertility rapidly declines after age 35. In fact, per-cycle fecundity drops from a peak of 25% to 30% per month in the early to mid 20s, to < 5% at age 40.

From a physiologic perspective, the greater impact of age on female fertility is understandable. Compared with an average ejaculate that may contain > 40 million sperm, the female fetus has a peak of 6 to 7 million oocytes at approximately 20 weeks of gestation. This number falls through fetal development and at birth there are 1 to 2 million viable oocytes remaining. By the time she reaches puberty, there are only 300,000 to 500,000 oocytes remaining. During the 35 to 40 years of a woman's reproductive life, she will ovulate 400 to 500 of these oocytes and the rest will be lost to atresia. The ovary has no capacity to regenerate oocytes. This is in stark contrast to the male, who can produce upwards of 100 million sperm a day.

Changes in Sexual Function in the Aging Male

Studies have consistently shown that increasing male age is associated with an increased time to pregnancy and decreased pregnancy rates. However, only a few studies have examined these outcomes while adjusting for female age. Ford and colleagues performed a secondary data analysis of the Avon Longitudinal Study of Pregnancy and Childhood, a large population-based study in the United Kingdom. Surveys from 8559 pregnancies were used to determine the effect of age on time to pregnancy. After adjusting for female age, conception during a 12-month period was 30% less likely for men over age 40 years as compared with men younger than age 30 years.⁹

In addition to female age, coital frequency and sexual functioning are variables that affect time to conception and pregnancy rates. Decreased sexual activity can decrease the chances of conception,¹⁰ and erectile dysfunction (ED) increases with age.¹¹ Decreased coital frequency with age is due in part to diminished sexual functioning; however, sexual dysfunction itself has no known influence on germ cells and its impact on infertility can be overcome by measures of assisted reproductive technology.¹² In a study of 1290 men aged 40 to 70 years who enrolled in the Massachusetts Male Aging Study (MMAS), sexual functioning and coital frequency were assessed. Between ages 40 and 70, the probability of having severe ED increased threefold and the probability of moderate ED increased twofold.¹³ In the same cohort followed for an average of 9 years, coital frequency was assessed in 1085 men. After adjusting for baseline sexual function, men engaged in sexual activity an average of 6.5 times per month prior to age 40. This frequency decreased by one to two times per month after age 50 and by another one to two times per month after age 60.¹⁴

In a survey study of 1976 British women controlled for female age, coital frequency, social history, and weight, an even stronger age effect on pregnancy rate was found than in the study by Ford and colleagues. This study reported a five times greater increase in time to pregnancy in men aged 45 years and older compared with men aged < 25 years. The increased time to pregnancy was similar even when restricting the analysis to men whose female partners were aged < 25 years.¹⁵

To evaluate pregnancy rates in different age groups, a French study examined 901 cycles of intrauterine artificial insemination. They found that the most significant factor contributing to probability of pregnancy was the age of the male partner. After

six cycles, men aged ≥ 35 years had fertility rates of 25% compared with fertility rates of 52% in men aged < 35 years, representing a 52% decrease in fertility rate.¹⁶

Alteration in Semen Parameters

Male factor infertility is a term that encompasses a host of different conditions relating to sperm function that may make it difficult for a sperm to fertilize an egg under normal conditions. Problems in male factor fertility may be due to changes in semen quality as assessed by the semen analysis.

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Sperm Concentration

In 1969, Sasano and Ichijo first described the decrease in sperm concentration as men age. They reported that 90% of seminiferous tubules in men in their 20s and 30s contained spermatids, whereas men in their 40s and 50s had spermatids in 50% of their seminiferous tubules. Only 10% of seminiferous tubules from men aged > 80 years contained spermatids.¹⁷ However, recent publications indicate that, of all the sperm parameters, changes in sperm concentration with advancing male age are the least consistent.¹⁸⁻²⁰ There are

studies that report a decrease in sperm concentration of up to 3.3% per year of age,²¹ but other data report no change in sperm concentration up to age 50.²² Some have even suggested increases in sperm concentrations with age. A study of 20,411 men found a statistically significant increase in concentration of 0.7% per year of age. This amounts to an increase in concentration of 14% over a 20-year period.²³ In a study of 1283 men who cryobanked sperm prior to vasectomy, sperm concentrations were found to be lower at both

extremes of age as compared with men aged 26 to 45 years.²⁴

Motility

In contrast to concentration, evidence consistently indicates that sperm motility decreases with advancing age. Studies that adjusted for duration of abstinence revealed statistically significant decreases in motility of 0.17% to 0.6% decrease per year of age^{21,24} resulting in a 3% to 12% decline in motility over 20 years. More recently, Slotter and colleagues used computer-assisted semen analysis in a population of 90 men aged 22 to 80 years with no history of infertility. Motility decreased 0.8% per year of age and linear motion decreased 0.2% per year.²⁵

Because motility is acquired during sperm transit through the prostate and the epididymis, the decrease in motility is suspected to be due to age-related decline in the function of these posttesticular glands.¹² Age-dependent alterations of the epididymis may also

cause alterations in sperm mitochondrial functioning, which is paramount for sperm motility.²⁶

Morphology

Similar to motility, morphology appears to decrease with advancing male age. Studies indicate declines in normal sperm morphology of 0.2% to 0.9% per year of age, resulting in a 4% to 18% decrease in normal morphology over a 20-year period.^{21,23,27} It is important to recognize the limitations in comparing sperm morphology data across studies secondary to differences in morphology criteria used by different investigators.

Seminal Volume

Evidence suggests there is a mild decrease in seminal volume with increasing age, although the clinical significance of this finding is marginal. The decrease in volume may be related to seminal vesicle insufficiency because seminal vesicle fluid composes most of the ejaculate volume.^{12,18} Prostatic changes, including smooth muscle atrophy, may also affect semen volume and sperm motility.

The reports showing a decrease in volume have only identified a modest change of 0.15% to 0.2% per year of age. This accumulates to a 3% to 4% decrease in seminal volume over a 20-year period.^{23,24} Other large population-based studies have shown no difference in volume with age.^{19,22} Most data suggest that the most pronounced changes occur in men aged > 45 years. Semen volume drops from a median of 2.80 mL in those aged 45 to 47.8 years to 1.95 mL in men aged > 56.6 years.^{20,28}

Other Semen Parameters

The association between age, the epididymal and accessory sex gland

products, and their relation to sperm motility has also been examined. The specific seminal markers investigated were glucosidase secreted by the epididymis, prostate-specific antigen (PSA) and zinc secreted from the prostate, and fructose secreted by seminal vesicles. Glucosidase, PSA, zinc, and fructose were significantly lower in men aged > 50 years compared with men aged between 21 and 30 years. In a multiple regression analysis, glucosidase and PSA showed positive association with progressive motility, whereas zinc levels showed an inverse relationship with motility. The author concluded that the decline in sperm motility observed in men aged > 50 years might be due to changes in epididymal and accessory sex gland function.²⁹

DNA Fragmentation

There has been a fair amount of recent literature pertaining to DNA sperm fragmentation and its effects on fertility. The evidence to date shows an increasing rate of fragmentation with increasing age. This is hypothesized to be a result of increasing oxidative stress over time, and is supported by animal models that show decreased epididymal antioxidant capacity with increasing age.^{30,31} Sperm DNA fragmentation is seen in men of all age groups.³² The debate regarding the clinical significance of DNA fragmentation is ongoing, but many fertility centers have adopted evaluation of fragmentation as a part of their evaluation for otherwise unexplained infertility. Although the use of testicular sperm aspiration in combination with intracytoplasmic sperm injection in couples with otherwise unexplained infertility has been suggested when a high fragmentation index is found, the current evidence is not sufficient to recommend such invasive therapies.³³⁻³⁵

Medical Conditions and Environmental Factors

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The risk of developing a medical condition or of being exposed to environmental toxins increases with age. For men, viral orchitis and sexually transmitted infections can lead to infertility due to germinal cell damage, ischemia, or the immune response to the infection.^{37,38} Epididymal obstructions can result from postinflammatory changes in relation to gonococcal or chlamydial infections.³⁹

Men with a history of chronic illness such as sickle cell disease, chronic renal insufficiency, cirrhosis, celiac sprue, or malnutrition of any cause may have primary as well as secondary hypogonadism.⁴⁰⁻⁴² Finally, men who develop medical problems later in life may be exposed to medications that can adversely affect sperm functioning. Common medications that can impact semen parameters include antihypertensives (spironolactone and calcium channel blockers), H₂ blockers (cimetidine), and antiandrogen treatments for the prostate (flutamide).⁴³ Exposure to these medical conditions and medications all increase with increasing age and men with infertility should be appropriately screened.

Anatomic Changes

Testicular size is a surrogate marker of spermatogenesis.⁴⁴ The size of the testis is relatively unchanged until the

8th decade,⁴⁵ at which point the testicular volume is 31% lower than in men aged 18 to 40 years.⁴⁶ In addition, evidence exists that testicular

perfusion,^{17,47} Leydig cell numbers,^{17,48,49} and Sertoli cell numbers decline with age,⁵⁰ whereas accumulation of the aging pigment lipofuscin increases with age.

Germinal epithelium supports normal spermatogenesis.⁵¹ Histologic changes in aging germinal epithelium include thickening of the basement membrane and tunica propria in seminiferous tubules, progressive tubular fibrosis, decreased diameter of the tubules, thinning of spermatogenic epithelium, and eventual obliteration of the tubules.⁵¹⁻⁵³ Tubular sclerosis occurs secondary to progressive fibrosis of the tunica propria and manifests as either interstitial fibrosis or severe sclerosis of the small arteries and arterioles in association with hyperplastic paratubular Leydig cells.⁵³

Hormonal Changes

There is an overall disruption of the hypothalamic-pituitary-testicular (HPT) axis as a man ages and it is often referred to as late-onset hypogonadism. This disruption is due to a combination of changes in testicular and germinal histology and HPT axis hormone levels. High levels of intratesticular testosterone, secreted by the Leydig cells, are necessary for spermatogenesis. Testosterone levels decrease with age, in what is termed the *andropause*, and this decline is initiated at approximately age 40.¹³ The exact physiology for declining testosterone has not been established. Declining testosterone may be due to alterations

of the HPT axis with aging, decreasing numbers of Leydig cells, or both. For men enrolled in MMAS, total testosterone declined at 0.8% per year of age, whereas both free and albumin-bound testosterone declined at about 2% per year. Sex hormone-binding globulin (SHBG) increased at 1.6% per year. The increase in SHBG likely results in a further decline in testosterone levels. Dehydroepiandrosterone, dehydroepiandrosterone sulfate, cortisol, and estrone showed significant declines, whereas dihydrotestosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin increased over time.⁵⁴

Another recent study from the MMAS cohort controlled for confounding factors such as chronic illness, body mass index (BMI), medications, and lifestyle when analyzing testosterone levels. The authors report that chronic disease and high BMI significantly decreased testosterone concentrations, whereas smoking tended to increase total, free, and bioavailable testosterone concentrations.⁵⁵

Finally, declining testosterone may cause decline in libido, ED, and difficulty achieving ejaculation. The level of testosterone does appear to influence sexual function. Testosterone replacement therapy was found to improve erectile function for hypogonadal men in a randomized, placebo-controlled, double-blind, parallel group, multicenter study,⁵⁶ although exogenous testosterone obviously has severe adverse effects on spermatogenesis.

Birth Defects

There is concern that the increased rate of DNA fragmentation previously discussed leads to an increase in fetal abnormalities. It is difficult to demonstrate the effects that DNA fragmentation and paternal age have on genetic disorders for several reasons. Genetic disorders are rare, which makes studying them difficult.

Although more men are having children at later ages, the number of older fathers is still relatively small, further impeding studying these rare outcomes. Many studies do not control for maternal age or lifestyle and health issues, which may confound their results.

One study that showed an association between paternal age and a genetic mutation examined men aged 22 to 80 years. The results revealed associations between age and the frequencies of sperm with DNA fragmentation and fibroblast growth factor receptor 3 gene (*FGFR3*) mutations. *FGFR3* mutation causes achondroplasia. The study found no associations between male age and sperm with aneuploidies or diploids. Specifically, there was no link between paternal age and Down syndrome, Klinefelter syndrome, Turner syndrome, XYY syndrome, Apert syndrome (*FGFR2* mutation), or sex ratio.⁵⁷ There is ongoing debate in the literature regarding the contribution of paternal age to trisomies in the offspring. A study of 3419 offspring with trisomies showed a paternal age effect only when the maternal age was ≥ 35 years. This effect was strongest when maternal age was > 40 years. When maternal age was > 40 years, the paternal contribution to Down syndrome was as important as the maternal age effect.⁵⁸

There has been recent evidence of increased rate of first trimester spontaneous abortion with older paternal age. For paternal age ≥ 35 years, the risk of spontaneous abortion between 6 and 20 weeks of gestation was 1.27. This elevated risk was seen even when evaluating only those couples where the maternal age was < 30 years. When divided by trimester, the risk of first trimester miscarriage was 1.56 and risk was 0.87 for second trimester loss.⁵⁹ Spontaneous abortion was likely due to chromosomal abnormalities. It

is plausible that, because spermatogenesis continues throughout a man's life, such continued replication can result in mutations. This was illustrated by Singh and colleagues, who studied semen samples that were collected from men between the ages of 20 and 57 years visiting fertility clinics. They found that the percentage of sperm with highly damaged DNA was statistically significantly higher in men aged 36 to 57 years than in those aged 20 to 35 years.⁶⁰

Conclusions

It is clear that aging has a significant impact on male sexual function, sperm parameters, and fertility. These changes contribute to decreased fecundability, increased time to conception, and increased miscarriage rates. Despite the evidence discussed in this article, there are clearly many unknowns with regard to male aging and fertility. There is opportunity for further research in nearly all areas discussed in this article. Further research will allow better understanding of the changes in the male reproductive axis and the impact on all areas of male fertility in relation to age. ■

The authors report no real or apparent conflicts of interest.

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Main Points

- The age of the male partner has significant impact on reproduction. Older men tend to have older female partners, and increasing male age is associated with increased time to conception. This reflects the age-related increase in acquired medical conditions, decreases in semen quality, and increasing rates of DNA fragmentation seen in sperm.
- The risk of developing a medical condition or of being exposed to environmental toxins increases with age. For men, viral orchitis and sexually transmitted infections can lead to infertility due to germinal cell damage, ischemia, or the immune response to the infection.
- Declining testosterone may cause decline in libido, erectile dysfunction, and difficulty achieving ejaculation. The level of testosterone does appear to influence sexual function.
- Aging has a significant impact on male sexual function, sperm parameters, and fertility, which all contribute to decreased fecundability, increased time to conception, and increased miscarriage rates. There are clearly many unknowns that remain with regard to male aging and fertility. Further research will allow a better understanding of age and its impact on all areas of male fertility.

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