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ANDROLOGY

Review

The effects of aging on fertility in men

Erkeklerde yaşlanmanın fertilite üzerine etkileri

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ABSTRACT

The decline in the rate of childbirth observed in older couples gives rise to the question of whether there is a relationship between age and fertility. This question has been studied much more extensively for females than for males, perhaps because of the apparent lack of an age limit for males to have children. Investigating the effects of increased age on male fertility components, such as spermatogenesis, testicular histology and male reproductive histology, may help us understand the inverse relationship between age and birth rate. In this review, we have evaluated the literature regarding the effects of aging on fertility in an effort to determine how male reproductive capacity is affected by old age.

Key words: Age; male fertility; semen analysis; testicular histology; testicular endocrinology.

ÖZET

Yaşlı çiftlerde çocuk sahibi olma oranında görülen azalma akıllara yaş ve fertilite arasında herhangi bir ilişkinin olup olmadığını getirmektedir. Bu konu üzerine kadınlarda erkeklere nazaran daha çok çalışma mevcuttur. Bunun en önemli nedeni erkeklerde çocuk sahibi olmak için herhangi bir yaş sınırının olmamasıdır. Spermatogenez, testiküler histoloji ver erkek üreme sistemi gibi erkek fertilite parametreleri üzerine yapılacak araştırmalar ile yaş ve fertilite arasındaki bu ters ilişki daha iyi anlaşılabilir. Bu değerlendirmede ileri yaşın erkek üreme kapasitesi üzerine olan etkileri ile ilgili veritabanı değerlendirilmiştir.

Anahtar sözcükler: Erkek fertilitesi; semen analizi; testis histolojisi; testis endokrinolojisi; yaş.

Introduction

The fertility trends of the 21st century differ from those of the previous century. One of these fertility trends is an increase in the age of childbirth, which is due to increased life expectancy and the transformation of the role of women in society. In addition, most women today have fewer children than women did during the previous century.[1] Often, women attempting to have children later in life experience a loss of fecundity.[2] Indeed, maternal age is one of the most important factors in determining the success of assisted reproductive technology (ART).[3] Thus, there is growing evidence supporting a link between increased age and reduced fertility in women.

However, the effects of age on male fertility have been less well studied. No sudden or marked changes occur in the male reproductive system with aging, and the impact of advanced age on male fertility remains unclear. This has become an important research question because the age at which people have their first child is currently increasing in developed countries.[4]

Due to the increase in paternal age, determining the effects of age on male fertility has become a very important area of study. The purpose of this review is to describe and evaluate the available data regarding the effects of paternal age on fertility. Semen parameters, testicular histology and male reproductive endocrinology are all major components of male fertility. Thus, we have evaluated each of these components separately in our comprehensive assessment of the relationship between male age and fertility.

Age and semen analysis

It is noteworthy that the definition of a normal sperm count has changed from a reference value of 60 million/mL in the 1940s to the

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present value of 15 million/mL. This decline can be attributed primarily to environmental factors and is correlated with other genitourinary abnormalities that have become more prevalent during this time period, such as testicular cancer, cryptorchidism and hypospadias.[5] The risk of an individual being exposed to these environmental factors or developing these genitourinary abnormalities also increases with age. Evaluating the changes that occur in semen parameters in elderly men may represent a significant step towards improving our understanding of the effects of these environmental factors on the male reproductive system.

Semen analysis seems to be the main criterion by which the effects of age on fertility have been evaluated. For example, Jung et al.[6] compared semen parameters retrospectively in the elderly (>50 years of age) and in young men (21-25 years of age) and demonstrated a statistically significant decrease in normal sperm morphology, sperm motility and semen volume in elderly males. However, sperm concentrations and total sperm counts were not affected by age. In a large study group (a total of 6022 patients), Levitas et al.[7] examined the differences in semen parameters between various age groups. In that study, all patients had sperm concentrations greater than 20 million/mL. Levitas et al.[7] have evaluated similar parameters in patients of different ages and have found results similar to those from previous studies. Semen parameters were affected most dramatically in individuals over the age of 55, who exhibited significantly lower semen volume and sperm motility than patients in other age groups.

In keeping with these findings, Eskenazi et al.[8] demonstrated that males exhibit a decrease in semen volume by approximately 0.03 mL/year and decreases in motility and progressive motility by 0.7% and 3.1% per year, respectively. Kidd et al. have provided an evaluation of the effects of age on semen parameters in their previous review.[9] Similar to the aforementioned studies, they concluded that advancing age leads to a decline in semen volume, sperm motility and normal sperm morphology but does not affect sperm concentration.

A recently published cross-sectional population-based study investigated the relationship between age and semen parameters in Chinese men.[10] Their study included 998 patients between the ages of 20 and 60 and did not find a declining trend between age and semen volume, sperm concentration or total sperm numbers. However, their results revealed that increasing age led to changes in sperm motility, vitality and morphology in this population.

The aforementioned studies identified several common effects of age, including, perhaps most importantly, a decline in sperm motility and semen volume in elderly individuals. Alterations in sperm morphology and decreased vitality were other common findings. Although the observed reductions in sperm motility, vitality and semen volume and the observed alterations in sperm morphology might be predicted to lead to changes in fertility, additional research would be required to prove this definitively. In their multicenter study examining the effects of age on male fertility, De la Rochebrochard et al. identified a clear adverse effect on pregnancy outcomes for males over 40 years of age.[11] Examining men with reduced fertility who require ART may contribute to our knowledge of the effects of age on fertility.

De la Rochebrochard et al. demonstrated that paternal age over 40 years was an important risk factor for fertility in patients treated by conventional in vitro fertilization (IVF).[12] Indeed, the risk of failure in pregnancy was increased when the father was over 40 years of age, especially when the maternal age was greater than 35.

Nijs et al.[13] carried out a prospective study with 278 patients being treated with IVF or ICSI for the first time. In contrast to De la Rochebrochard`s study,[12] no significant changes in fertilization or baby take-home rates were observed in patients with older paternal age.

In a recent review, Dain et al.[14] examined the relationship between age and ART. A total of 10 studies were included, of which only one was a prospective study. Semen parameters, such as motility, concentration and morphology, did not show any decline with age. In addition to De la Rochebrochard`s study,[12] a prospective study by Klonoff-Cohen et al.[15] demonstrated a significant decrease in pregnancy rates in individuals of an advanced age. They concluded that each 1-year increment in paternal age was associated with an 11% increase in the odds of not achieving a pregnancy. Studies by Klonoff-Cohen et al.[15] and Frattarelli et al.[16] were the only studies reviewed by Dain et al. that demonstrated a statistically significant decrease in live birth rate in older individuals. Dain et al. concluded that there is insufficient evidence to demonstrate an unfavorable effect of paternal age on ART outcomes.[14]

Although many studies agree that increased age leads to a decline in sperm motility, morphology and semen volume, the effects of these alterations on fertility has not yet been established. Further research into the consequences of advanced male age on reproductive function is therefore required.

Age and testicular histology

Monitoring testicular volume and histology can provide an important means to examine the effects of aging on the male reproductive system. It has been suggested that these changes may, in turn, lead to decreased efficacy of spermatogenesis.[17] Well et al.[18] investigated the effects of age on testicular volume and showed that it peaks at 25 years of age. A slight but significant decline was observed through 80 and 90 years of

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age. Mahmood et al.[19] demonstrated that elderly men had significantly smaller testicular volumes than younger men. In addition, this observed volume decrease was directly correlated with the serum levels of inhibin B and the inhibin B/FSH ratio and was indirectly correlated with the serum levels of FSH. The association between serum testosterone (T) levels and testicular volume was weaker in elderly patients. The observed decrease in testicular volume was attributed to the age-related decrease in sertoli cell number.

Histologically, testes are characterized by a great deal of individual variability between young adulthood and old age.[20,21] Although testes can exhibit multiple different features during histological examinations, spermatozoa are commonly observed in the testes of even the very old men. The number of sertoli and leydig cells per testis declines by 40%[22] and 44%,[23] respectively, in elderly males, which may impair spermatogenesis in the elderly.[17]

Age and testicular endocrine function

The gradual slight decline in testicular T production with aging is well established, but the mechanisms underlying this effect are still not completely understood. Serum T is the most important circulatory parameter in determining the effectiveness of testicular steroidogenesis. In circulation, serum T is largely bound to plasma proteins; 40-50% is loosely bound to albumin, 50-60% is tightly bound to sex hormone binding globulin (SHBG) and the remaining 1-2% is unbound. The ratio of albumin-bound T to unbound T determines the total biologic activity of the circulating hormone. It is well established that serum T decreases in elderly males.[24] In addition, a concomitant rise in SHBG levels further reduces the levels of bioavailable T.[25] T is also present in the seminal fluid, where it is involved in the growth and maintenance of the male reproductive tract.[26-28] Eventually, the relative decline in T production seems to have a significant effect on spermatogenesis and sperm motility. Although the decline in androgenic stimulation may have an impact on male fertility, the association between the decline of serum T and male fertility remains to be determined.

Conclusion

The male reproductive system seems to change with aging, but the magnitude of the effects of these changes on male fertility has not been determined. Additional examinations of the semen parameters, testicular histology and testicular endocrinology of males of different ages will be required to evaluate the changes in reproductive capacity that occur in old age. However, the currently available evidence is insufficient to draw meaningful conclusions about these relationships, and further research is required.

Conflict of interest

No conflict of interest was declared by the authors.

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