

## Review Article

# Male Fertility and Sexual Competence are Both Decreased by Age

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## Abstract

Diminishing fertility in couples, over the last decades, is largely attributable to the drop in female fertility. However, increasing numbers of men, whose fertility theoretically lasts well into old age, are seeking fertility treatment at older ages; yet there are debates on sperm production and the impact of male age on fecundity. The aging process leads to andropause, affecting testicular tissue and reducing the major functional compartments of Sertoli and Leydig cells. A drop of the Sertoli cell number can affect spermatogenesis, while a fall of the Leydig cell number affects the production of testosterone, both of which could lead to reduce fecundity in men.

## Keywords

- Andropause
- Male aging
- Sertoli cells
- Leydig cells
- Spermatogenesis
- Testosterone

## INTRODUCTION

All physiological functions of organisms decrease as we age. A diminishing in male gonadal hormonal activity arouses the phenomena of “male menopause” or “male perimenopausal state”. We now determine this state as “andropause”. It occurs mainly in middle age and elderly men, when testosterone production and its plasma concentrations are reduced. This phenomenon could be accompanied by impaired spermatogenesis. Reduced levels of testosterone affect most male systems and tissues, including the central nervous system, endocrine and cardiovascular systems, muscles, bones, sexual and fertility functions.

Andropause development stems from the gradual and slow aging process of testicular tissue. This tissue structure may be functionally separated into two major compartments. The first one is seminiferous tubules with Sertoli cells and spermatogenic cells; both of them are an inalienable part of the spermatogenic process. The hypothalamic follicle stimulating hormone (FSH) acts on the Sertoli cells mainly to increase spermatogenesis. The second one is an interstitial tissue containing a Leydig cell section and testosterone production. Hypothalamic gonadotropin, a luteinizing hormone (LH), acts on the Leydig cells mainly to increase steroidogenesis. The control of male fertility requires accurate endocrine, paracrine and autocrine communications along the hypothalamus-pituitary-gonad (HPG) axis [1]. Actions of both gonadotropins are influenced by hypothalamic gonadotropin releasing hormone (GnRH). Kisspeptins, via the activation of kisspeptin receptor Gpr54 represent the main gatekeeper of the hypothalamic GnRH. Direct production and activity of kisspeptin in testis and its involvement in the control of Leydig cells, germ cells progression and sperm functions was shown [1]. Functionality of the Sertoli cells and spermatogenesis

are directly dependent upon androgen influence and the function of Leydig cells; therefore, one testicular compartment closely depends on the second one. The aging process, leading to andropause, affects both compartments. As the female climacteric syndrome is partially reversible by oestrogen treatment [2], the question arises whether testosterone replacement therapy really provides a helpful analogy for man?

## Sertoli cell compartment

The adult seminiferous tubule contains epithelium of 5 to 8 layers of cells. The Sertoli cells organize this epithelium. Each Sertoli cell has unique tight junctions (TJ) and basal adherens junctions (AJ), side by side with its neighbors, at the basal domain of Sertoli cells to create the blood-testis barrier (BTB). BTB must open periodically to permit germ cell movement to ensure the successful and continual production of spermatozoa, and also plays a crucial role in spermatogenesis [3,4]. At the age of 20-48 years about 500 million Sertoli cells could be found in the testis; however, this number critically decreases to about 300 million at the age of 50-85 years [5]. A drop in the Sertoli cell number can affect the integrity of BTB, reducing the entrance of sperm-germ cells to the spermatogenetic process, sperm quality and its production rate [6]. Reduction in the Sertoli cell count, as well, as a diminished function of these cells in aging men lead to decreased fertility. In a convenience sample of healthy men from a non-clinical setting, semen volume and sperm motility decreased continuously between 22-80 years of age [7]. There was no significant difference in sperm density, but both median semen volume and total sperm output per ejaculation reduced by 47% and 64%, respectively in older men [8].

An oocyte donor program, from 500 males, revealed that all sperm parameters, such as: sperm volume, concentration

of spermatozoa, total count, motility and progressive motility of spermatozoa, gradually decline with male age [9]. Although male aging is associated with a significant decline in total sperm count, this change is not reflected in a decreased fertilization rate or a decreased live birth rate in the oocyte donation model [10], or in the pregnancy rate of regular in vitro fertilization (IVF) patients [11]. However, others report that pregnancy and live birth delivery are all inversely related to increasing paternal age [12,13], even in oocyte donation programs [14]. Risk of spontaneous abortion, similarly associated with paternal age, was higher in those older than 35 years, as compared to a paternal age of less than 35 [15,16].

Semen samples collected from men, between the ages of 20 to 57 years, were correlated; it was found that there was an increasing percentage of sperm with highly damaged DNA in men aged 36–57 years, as compared with those aged 20–35 years [17]. Sperm DNA damage is associated with a significantly increased risk of pregnancy loss, as was shown after classical IVF and intra-cytoplasm sperm injection (ICSI) [18,19].

Analysis of 17 000 intrauterine insemination (IUI) cycles shows a miscarriage rate of 13.7% per pregnancy in men younger than 30 years old, versus 32.4% in men older than 45 years old [20]. Increasing paternal age is significantly associated with delayed conception and diminished pregnancy in a large population of fertile couples, which is evidence of declining fecundity in older men [21–23]. Most studies suggest that this age-dependent effect could be a reason for failures in both natural and IVF cycles. Moreover, advanced paternal age was associated with increased risks of birth defects, including: heart defects, tracheo-oesophageal atresia, musculoskeletal/integumental anomalies, Down's syndrome, achondroplasia and other chromosomal anomalies [24,25].

### Leydig cell compartment

The number of Leydig cells in both testes of a 20-year-old male is up to 700 million and diminishes by half by the age of 60 [26], as plasma testosterone levels decline. With an increase of age, there is a decline in the Leydig cell count and/or a dysfunction in hypothalamic-pituitary homeostatic control, or both, leading to an abnormal secretion of LH, resulting in a low testosterone production. Cross sectional and prospective studies show a decline in testosterone that starts in early middle age and then progresses in a linear manner [27–30]. This decline in plasma testosterone concentration is due to an age-associated increase in the plasma concentration of the sex hormone binding globulin (SHBG, which is synthesized in the liver), resulting in a more marked drop in the bioavailable testosterone amount [31–33].

Normal testosterone levels are 270–1070 ngr/dL or 9–38 nmol/L [34]. Levels of 8–12 nmol/L are related to the grey zone. Testosterone concentration at 10.4 nmol/L (300 ng/dL) was found to be critical for the sexual function in men; however, there is a variation between individuals [35]. An abnormally low concentration of testosterone (hypotestosteronemia) may be the result of a testicular dysfunction (primary hypogonadism), or a hypothalamic-pituitary dysfunction (secondary hypogonadism). These types of hypogonadism could be either congenital,

or acquired. Concentrations of bioavailable testosterone decrease by as much as 50% between the ages of 25 to 75 years [36]. It has been proposed that with respect to bioavailable concentrations, as many as 50% of men over the age of 50, are hypotestosteronemic, as compared to the peak of early morning concentrations in young men [37]. By the age of 80 years, serum total testosterone concentrations have fallen about 75% and free testosterone concentrations to about 50% of what they were at the age of 20 [38].

Clinical manifestations of androgen deficiency may be divided into three major groups: physical, brain/behavioral and sexual. Physical manifestations of androgen deficiency include loss of bone mineral density, muscle wasting and weakness, loss of male body hair, gynecomastia and small or shrinking testes. Brain/behavioral manifestations of androgen deficiency include decreased cognitive functions and memory, depressed mood, irritability, low energy, poor motivation, sleep disturbance, increased sleepiness and reduced libido. Sexual manifestations of androgen deficiency include erectile dysfunction and infertility.

### Metabolic disorders

Metabolic disorders could also affect testosterone bulk. The presence of obesity is associated with lower concentrations of bioavailable testosterone [39]; insulin concentrations have been found to be indirectly correlated with SHBG and testosterone concentrations [40]. Overweight men who had a BMI over 25 had a nearly 22% lower sperm concentration and 24% lower total sperm count, as compared to healthy weighted men [41], and positively related to estradiol levels [42]. Adipose tissue is capable of aromatizing testosterone to estradiol, and it is speculated that a reduced total testosterone production in obese men results in affecting the function of the seminiferous epithelium, as well as the synchrony of spermatogenesis. Estrogens exhibit high impact on proliferative and apoptotic events in testis, thus resulting as a local key modulators for the production, transport and maturation of spermatozoa [1]. Male aging is associated with an increase in body fat and reduced muscle mass and strength. This could be explained by an age-associated decline in growth hormone concentrations, which itself is associated with an increase in sex hormone binding globulin and, therefore, a reduction in bioavailable testosterone [43]. Profound hypotestosteronemia in younger men results in accelerated bone loss and osteoporosis [44]. In older men, bioavailable testosterone concentrations are positively correlated with bone mineral density at the radius, spine, and hip [45], and men with hypotestosteronemia have been reported to be at an increased risk of hip fracture [46].

An article from 1944 described symptoms reversed by testosterone replacement, but not by placebo, seen in men suffering from an age associated decline in testosterone concentrations [47]. It was demonstrated data of a treated group for three years, with almost 100 healthy men over the age of 65 years with testosterone patches, which sufficiently raised their serum testosterone concentrations into the range appropriate for men in their 20s. The overall effects on bone mineral density were no different from those obtained with the placebo [48]. However, a significant increase in lean body mass and a fall in fat mass were observed [49]. Data on the effects of testosterone

replacement therapy on bone metabolism in hypotestosteronemic men suggest beneficial effects [50]. There is a consensus that testosterone supplementation in hypotestosteronemic men improves fat free mass, muscle bulk, and strength [51,52]. Testosterone administration to men with hypogonadism also improved cardiovascular risk factors [53].

### Sexual and cognitive behavior

A decline in sexual interest and potency is usually associated with aging [54]. Such changes in sexual behavior are androgen dependent, but are not proven in all cases. Affective symptoms have long been associated with low levels of testosterone, whereas depressed mood is significantly correlated with low concentrations of bioavailable testosterone in older men [55]. Some longitudinal uncontrolled studies of hypotestosteronemic men have shown that symptoms of depression, anger, irritability, sadness, nervousness, friendliness, sense of wellbeing, and energy levels significantly improved with androgen treatment [56,57]. Fatigue may also occur with low levels of testosterone. During one prospective study, symptoms significantly improved with supplementation and decreased during androgen withdrawal; another showed significant improvements in energy levels and tiredness [58].

Although the proportion of men complaining of erectile dysfunction rises dramatically with age, only 50% of men between the ages of 50 and 70 years complain of potency loss [59]. Erectile dysfunction in elderly men is often of nonhormonal etiology, while testosterone deficiency accounts for 645% of all cases [60].

Androgens also have an important role in the development of cognitive functioning; in men, strong correlations exist between testosterone concentrations and visuospatial abilities in certain domains [61]. Administration of pharmacological doses of exogenous testosterone to aging men has been shown to be associated with improved visuospatial skills [62].

### Analysis for the determination of male fecundity and hypotestosteronemia

What the clinician needs for the correct management of infertility in middle-aged and elderly men is a diagnosis. Infertility is not a diagnosis - it is only a symptom. Semen analysis is routinely used to evaluate the male partner in infertile couples. The analysis of semen only occasionally gives the clinician a diagnosis as, for the most part, to the changes that take place in semen are largely non-specific. Over time it has become clear that the relationship between infertility and sperm numbers, sperm movement and sperm morphology is not a simple one. Pregnancy is known to occur with men having both very low sperm counts and poor sperm motility [63]. Sperm numbers can raise and fall sharply among otherwise fertile men. For this reason, sperm analysis should be prepared at least twice, with an interval of week or ten days.

One common reason to test testosterone is to determine both male age and infertility. The test may also be necessary if hypotestosteronemia is suspected. A low level of testosterone in a male is associated with impotence and results in changes of the penile tissues causing erectile dysfunction [64], which could also be one of the reasons for the failure to ejaculate and infertility.

## CONCLUSION

Men should be offered treatment with testosterone replacement therapy with hypotestosteronemia with symptoms of androgen deficiency, when contraindications have been excluded. However, it should be kept in the mind that for IVF male partners this kind of testosterone replacement therapy has to be avoided for its suppression of spermatogenesis [65,66].

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