

## Secondary infertility and the aging male, overview

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**Introduction** Old men preparing themselves for marriage late in their lives might face infertility. Infertility in this group of men should be considered from a wider perspective, as they face any age-related health troubles that include, but are not limited to, androgen deficiency and psychological disorders that impede early conception. This review aims to shed light on the proper approach to this minority of secondarily infertile men.

**Material and methods** A comprehensive electronic English literature search was conducted, using various medical websites and books, for the factors that cause infertility in senior fathers. The physiology of geriatric males, together with their common comorbidities, were discussed.

**Results** Old men presenting with secondary infertility should be approached differently. Aging, itself, has a significant impact on male sexual function, sperm parameters, and fertility; all of which contribute to poor fecundability, decreased fertilizing capacity, increased time to pregnancy, increased rate of DNA damage, high abortion rates and increased prevalence of fetal developmental failures. The complexity and the unknowns of the aging male physiology, together with the interaction of obstinate diseases the patient might have, make the issue very difficult to tackle.

**Conclusions** Management should include the conventional way of treating young sufferers and further target the underlying causes, if known, along with the provision of geriatric, psychologic, and andrologic support.

**Key Words:** secondary male infertility ◊ old men ◊ androgen deficiency ◊ varicocele ◊ testosterone ◊ andropause

## INTRODUCTION

Secondary infertility is a situation in which parents fail to have more children after one year of trying. More specifically, secondary infertility is the inability of the mother to become pregnant once again, or to carry a pregnancy to term, following the birth of one or more biological children; provided that the birth of previous children did not involve any assisted reproductive technologies or fertility medications. About one-third of secondary infertility cases are related to male factors; another third are related to the female, whereas the remaining are concerned with problems in both the man and the woman, or remain unexplained. While it is primary infertility that attracts media attention, secondary infertility is just as common. According to statistics collected by the Center for Disease Control (CDC), 11% of couples in

USA, who already have a child, go on to experience secondary infertility. This represents approximately 4 million families, or about half of all infertility cases [1]. In some communities, as couples experiencing secondary infertility already have a child; their struggle is often downplayed or even ignored by friends, family, couples experiencing primary infertility, and even doctors. In contrast, in other communities where polygamy is common, it is not unusual for a fifty or sixty year old man who fathers children, to marry a young lady who in turn wishes to conceive. Testosterone plays an essential role in the sperm-generating process (spermatogenesis). Spermatogenesis is a sophisticated, long and very orderly process of cellular division and differentiation that is under the regulation of endocrine signals (GnRH, LH, Inhibin and FSH), paracrine signals derived from the interrelation of the different types of cells in the tubules and

interstitium, as well as autocrine signals of self-communication within the cell. In the testicular tubules, testosterone reaches concentrations 100 times higher than circulating testosterone. The effect of aging on the male reproductive system relies largely on the individual's characteristics, including acute and chronic diseases, urogenital traumas, as well as lifestyle and environmental factors. Age-related changes in the reproductive system include all aspects of reproductive function, from deregulation of the hypothalamic-pituitary-gonadal axis and of local auto/paracrine interactions, to effects on testicular stem cells, flaws in testicular architecture and spermatogenesis, and finally low testosterone secretion and poorly functioning sperms. Several theories place mitochondria at the top of cellular events related to aging; especially concerning the accumulation of oxidative damage to cells and tissues; a process in which these organelles play a notable role. However, oxidative stress is not the only process involved in mitochondrial-related aging; mitochondrial energy metabolism, changes in mitochondrial DNA or in mitochondrial-dependent testosterone production are also important. Evidently, all these issues are likely interdependent.

### How does age matter?

A review of the literature revealed that no age difference was taken into account while managing

**Table 1.** Causes of secondary male infertility

Testicular varicocele.
Genitourinary infections; TB, mumps, mycoplasma, smallpox, STD.
Genitourinary tract surgery, injury, malignant or benign tumors e.g. SPE**; or extirpation
Life style factors; cigarette and marijuana smoking, alcohol abuse.
Late-onset hypogonadism
Lubricants; astroglyde, lubafax, K-Y Jelly, Keri Lotion, surgilube, and saliva are spermatotoxic, whereas peanut oil, safflower oil, vegetable oil, and raw egg white, and petroleum jelly are not known to be spermatotoxic
Drugs; spironolactone, cyproterone, ketoconazole, cimetidine, tetracycline, nitrofurantoin, sulfasalazine, tamsulosin, fenasteride, colchicine, methadone, methotrexate, phenytoin, thioridazine, calcium channel blockers, and cytotoxic agents
Environmental factors; many pesticides, dibromochloropropane; exposure to lead, carbon disulfide, oxidant stresses and excessive heat
Psychological; emotional stress, old man syndrome
Blood diseases; sickle cell disease, thalassemia, hemochromatosis
Miscellaneous; diabetes mellitus, aging, obesity, anesthesia, starvation, myocardial infarction, hepatic coma, head injury, stroke, respiratory failure, congestive heart failure, sepsis, and burn .

STD\* sexual transmitted disease

SPE\*\* senile prostatic enlargement

secondarily infertile men, as most researchers and authors believe that the causes of primary and secondary male infertility are similar. For that reason, the same approach and investigations should be applied to either case. Other researchers found that until the age of 40, the man's age did not seem to have a significant effect. After 40, the quality of the semen diminished, possibly to an extent that leads to in vitro fertilization (IVF) treatment failure. Besides producing low-quality semen, age also affects the genetic quality of male sperm. In a study conducted at the Lawrence Livermore National Laboratory (LLNL) and the University of California at Berkeley, researchers discovered that genetic defects in the sperm increase with age in men, possibly leading to decreased fertility, increased chance of miscarriage and increased risk of some birth defects [2]. Current attempts to classify male infertility are semen analysis-based [3]. This article discusses additional approaches to senior fathers complaining of infertility in terms of history taking, blood tests and medical consultations to the relevant specialties.

### Clinical approach

For young men, before the age of Andropause [4] and senile prostate enlargement (SPE), the causes of secondary male infertility are due to low or absent sperm count, problems with sperm morphology and motility. Conventionally, the patient is examined for the presence of varicocele, questioned for relevant past surgeries, systemic illnesses, psychological disturbances and bad habits such as smoking and alcohol abuse. When older patients are concerned, all the aforementioned causes are looked at carefully; in addition, more investigations are made related to the health problems of aging men, including androgen deficiency of the aging male (ADAM) syndrome, irritable male syndrome, SPE and SPE medications (Table 1). As age passes, the negative impacts of an unhealthy lifestyle, bad habits and chronic illnesses accumulate.

### Highly relevant ailments Senile prostatic enlargement (SPE)

Prostate problems can affect pregnancy in a number of ways. An enlarged prostate may compromise normal ejaculation; this could be very disappointing for couples wishing to start a family later in life, especially when the husband's advanced age is concerned. Furthermore, the chronic prostatitis element of SPE makes ejaculation rather painful. Pregnancy occurs when the sperm meets the ovum. Around ovulation, the possibility of a woman's egg being fertilized is

within a time frame of 12 to 24 hours. When the time expires, the unfertilized ovum dissolves. If the aged husband was unable to cope with the frequency of intercourse required to target a viable ovum on time or had trouble with ejaculation, the woman's chance of pregnancy would be lost. A prostate removed due to cancer or SPE, could also be a cause of infertility; as the semen flows backward causing retrograde ejaculation. The medications used to control SPE symptoms have had negative influences on fertility. Tamsulosin, an alpha-adrenergic antagonist, has been reported to cause decreased sexual drive and abnormal ejaculation in the form of ejaculation failure, ejaculation disorder, retrograde ejaculation and decrease in ejaculation volume in 8–18% and impotence in 2.9% of the cases. Finasteride, a type II, 5-alpha reductase inhibitor is reported to cause abnormal sexual function (2.5%), erectile dysfunction (1.3%), ejaculation disorder (1.2%), and sperm DNA damage [5]. Interestingly, (Şalvarci et al. 2013) reported a case of secondary infertility due to the use of low-dose finasteride, based on DNA integrity which improved after drug cessation [6].

### Adam syndrome

Androgen deficiency of the aging male, or “Andropause” is a name given to late-onset hypogonadism (LOH). Testosterone levels in men older than 40 years can decrease at a rate of 1–2% per annum. Reports show that more than 50% of 80-year old men have testosterone levels consistent with hypogonadism [7]. LOH is a clinical and biochemical syndrome associated with advancing age and characterized by a cluster of symptoms related to senility and androgen hormone deficiency that includes diminished libido, depressed mood and cognition, reduced

sense of vitality and well-being, increased fatigue, and infertility. Andropause symptoms and erectile dysfunction are common among infertile men, affecting approximately 38% of this population [8]. In LOH patients, symptoms are reversed by androgen supplements. Moreover, there is an improvement in cavernous vasodilation and response to sildenafil in arteriogenic erectile dysfunction cases [9]; the veno-occlusive function is also improved [10].

### Irritable man syndrome (IMS)

IMS, sometimes called “the old man syndrome” is defined as a state of anxiety, anger, low level of tolerance, short temper, irritability, lack of libido, and infertility. These symptoms take place in elderly men as a result of aging-related biochemical changes, hormonal fluctuation, and stress. IMS symptoms are believed to be due to decreasing testosterone levels in old male mammals (Figure 1) [11].

### Testicular varicocele

Testicular varicocele is a dilatation of the pampiniform venous plexus within the scrotum. Approximately, 15–20% of the healthy fertile male population is estimated to have varicoceles; however, 30% of infertile men may have them [12]. It is the most correctable surgical cause of male subfertility. The mechanism by which a varicocele impairs sperm structure, function, and production is not known, but researchers believe it interferes with testicular thermoregulation. Varicocele has been reported to have a higher incidence in secondary infertility in males than in primary infertility. Data published by in 1993 by Gorelick et al., suggested that varicocele causes a progressive decline in fertility [13], whereas that prior fertility in a man with varicocele does not predict resistance to varicocele-induced impairment of spermatogenesis. This supports the clinical observation of dealing with more varicocele cases in secondarily infertile men than primary infertility cases.

### Diabetes mellitus

Over 124 million individuals worldwide suffer from Diabetes mellitus (DM) [14]. In communities where diabetes is common, men, as they get older, suffer from advanced diabetes-related reproductive complications. The prevalence of sexual dysfunction in diabetic men approaches 50%, presenting as testicular dysfunction, impotence, poor semen quality in the form of decreased sperm motility and concentration, abnormal morphology and increased seminal plasma abnormali-

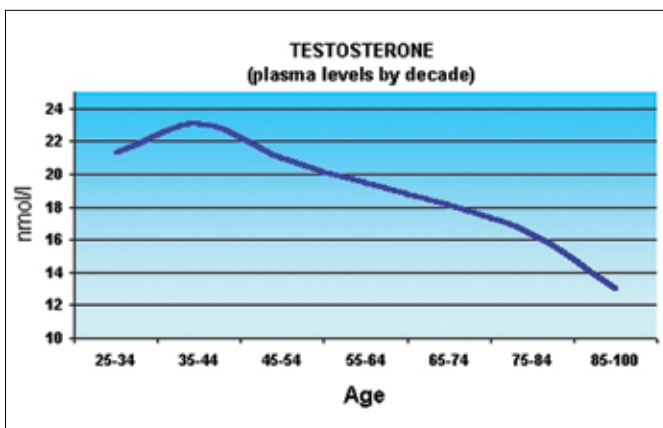


Figure 1. Testosterone chart.

ties leading to reduced fertility potential. Erectile dysfunction and retrograde ejaculation in diabetic men are primarily due to vasculogenic impotence and autonomic neuropathy of the bladder neck respectively [15]. Growing evidence indicates that oxidative stress is increased in diabetes due to the overproduction of reactive oxygen species (ROS), and the decreased efficiency of antioxidant defenses, a process that starts very early and worsens over the course of the disease. Diabetes-related oxidative stress may be the trigger for many alterations of sexual function, which can also include decreased testicular mitochondrial function with subsequent infertility [16].

## Senescence

Aging is likely to induce oxidative stress [17], and an increase in oxidative damage to the cells' nucleic acids [18]. Moreover, impairment of normal spermatogenesis and sperm function are the most common causes of male factor infertility [19]. Elevated levels of reactive oxygen species are seen in up to 30–80% of infertile men [20]. The role of free radicals in damaging sperm DNA has been studied extensively in the process of human reproduction. The excessive level of free radicals can cause detrimental effects on sperm function, and subsequent fertilization and offspring health. Oxidative stress develops when there is an imbalance between the generation of free radicals and the scavenging capacity of anti-oxidants in the reproductive tract. Furthermore, it has been shown to affect both standard semen parameters and fertilizing capacity in a wide spectrum of subfertility

conditions ranging from infertility and repeated miscarriages to birth defects and infant deaths. Based on the overwhelming evidence surrounding the noxious effects of free oxygen radicals on sperm function and integrity, antioxidant and anti-aging formulas have become prescribed to infertile old men; however, the exact mechanism of the action of dietary antioxidants and their optimal dietary supplementation have not been established [21].

## CONCLUSIONS

Old men presenting with secondary infertility should be approached comprehensively, as more clinical conditions that impair fertility might emerge with aging. The biology of senescence itself has a negative effect on fertility probabilities. Moreover, as the impact of existing chronic illnesses, such as diabetes mellitus and senile prostatic enlargement, on body health becomes more severe with time, potential fertility is diminished further. Endocrine profile, including testicular and hypothalamic hormones should be checked. Andrologic, psychologic and geriatric consultations should be requested if clinically indicated. Still, there remain unclear causes related to the aging of male physiology that affect sperm parameters and sexual function, leading to an increase in time to pregnancy and decreased fertility rates. The prescription of antioxidant and anti-aging supplements to infertile aged men is beneficial. We believe that secondary infertility in aged men is a developing subject that still has many gaps requiring large-scale studies.

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