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Review

How to overcome male infertility after 40: Influence of paternal age on fertility

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ABSTRACT

The recent trend toward delayed parenthood raises major safety concerns because of the adverse effects of aging on couple fertility. Studies have demonstrated that aging clearly affects female fertility, but can also affect male fertility. Although several theories have been proposed, the exact mechanisms responsible for the observed age-related decline in male fertility remain to be elucidated. It has been shown that advanced paternal age (PA) is associated with reduced semen volume as well as, reduced sperm count, motility and morphology. Recent studies have also reported that paternal aging is associated with a significant increase in the prevalence of both genomic and epigenomic sperm defects. In the context of natural and intrauterine insemination (IUI) conception, advanced paternal age has been associated with lower pregnancy rates and increased rates of spontaneous abortion (independent of maternal age). In IVF and oocyte donation programs, a significant decrease in late blastocyst development has been seen in those cycles using spermatozoa of men older than 55. However, no significant relationship between paternal age and IVF or ICSI pregnancy rates has been observed.

Although there are no treatments that can fully restore the age-related decline in male fertility, various measures have been shown to optimize male fertility potential. Specific therapies (e.g. varicocelectomy) and lifestyle changes (e.g. dietary antioxidant supplements) may help minimize some of the age-related deleterious effects on spermatogenesis, such as, oxidative stress and endocrine abnormalities.

Contents

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1. Introduction

As women age, their ovarian reserve and oocyte integrity (function and ploidy), gradually decrease. Taken together, these events explain the age-related decline in reproductive capacity (e.g. low rates of natural conception) and the poor results obtained with assisted reproduction technologies (ARTs) [1,2]. Women also experience an increased risk of pregnancy complications (perinatal morbidity and mortality) and of adverse perinatal and post-natal offspring outcomes as they age [3–5]. Finally, female fertility reaches a natural limit and altogether ceases with menopause. Unlike the abrupt decline in reproductive capacity seen in all women, men maintain a certain level of reproductive function lifelong but this function declines very gradually over time. Studies have shown that advanced paternal age (PA) is associated with changes in reproductive hormone production, sexual function, sperm production and fertility. Advanced PA has also been associated with adverse pregnancy outcomes, an increased risk of sperm de novo mutations, birth defects and offspring diseases.

2. Influence of paternal age on fertility

2.1. Age-related changes in reproductive hormones and sexual function

It has been reported that advanced PA is associated with progressive changes in several reproductive hormones. The most clinically relevant hormone alterations associated with male aging are increasing follicle-stimulating hormone (FSH) serum levels and decreasing testosterone serum levels. The increasing concentration of serum FSH in aged men has been linked to reduced Sertoli cell function, germ cell degeneration during meiosis and reduced daily sperm production [6]. The decreasing concentrations of serum testosterone levels in aged men has been linked to andropausal symptoms, such as, poor libido, fatigue and loss of cognitive functions [7].

Male sexual function and sexual frequency both decrease with aging [8–10]. Although male sexual dysfunction does not directly impact on male fertility potential, the infertility experienced by older couples may, in part, be due to a decline in sexual activity.

2.2. Age-related changes in conventional sperm parameters

Most studies have shown that paternal aging is associated with changes in semen parameters. Specifically, advancing PA is related to declining semen volume, sperm motility and morphology [11,12]. Although sperm concentration has not been consistently shown to decrease with aging, a decline in sperm count has been reported [2,3,13]. The underlying cause of the age-related decline in semen parameters has not been clearly defined. However, possible etiologies include age-related vascular insufficiency, increasing prevalence of co-morbidities (e.g. diabetes, hypertension), chronic infections (e.g. prostatitis), obesity, hormonal insufficiency and accessory gland dysfunction [14–17].

The significance of the observed age-related changes in semen parameters remains a subject of ongoing controversy. This is in part due to the notable biologic variability of conventional semen parameters and the fact that these parameters are poor predictors of male fertility potential [18,19]. As such, additional markers of male fertility potential (e.g. sperm DNA damage) have been examined to ascertain the observed relationship between age and semen quality.

2.3. Chromatin dispersion

A mature sperm has a chromatin tightly compacted, because more than 80% of the histones are replaced by protamines, during the spermatogenesis. Two types of protamines were investigated, Protamine 1 and Protamine 2, and a ratio close to 1 reflects the good quality of this compaction.

Chromatin dispersion may potentially result in lack of fertilization and/or early embryonic development defects. These are relatively common situations IVF/ICSI programs which lead to very early embryonic development arrests or spontaneous abortions in the first quarter. The mechanisms of DNA dispersion are still poorly known. Moreover chromatin dispersion exposes the nucleus to a greater vulnerability to oxidative stress.

Several studies demonstrated the impact of chromatin packaging in fertility and embryonic development [11–17].

There is really no consensus on the DNA dispersion level exposing to pathologic embryo development; some suggest a cut-off of 20% and others consider that more than 30% is potentially harmful.

2.4. Age-related changes in sperm chromatin and DNA integrity

Sperm chromatin and DNA tests measure nuclear chromatin compaction and DNA damage, respectively. These sperm function markers were first designed to increase our understanding of spermatogenesis, sperm physiology and reproductive biology [20–29]. More recently, tests of sperm chromatin and DNA damage have been used in the clinic, in the hope that these tests may provide a more accurate diagnosis than is possible with conventional semen parameters. Conventional sperm parameters (sperm concentration, motility and morphology) exhibit a high degree of biological variability and are only fair measures of fertility potential [18,30]. Sperm chromatin and DNA tests have also been studied in the