Acta Scientific Clinical Case Reports

Volume 2 Issue 12 December 2021

Review Article

Age of Man and Reproduction

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Received: October 21, 2021

Published: November 11, 2021

Abstract

Objectives: To know if the age of man affects the fertilization capacity.

Methods: Retrospective and cross-sectional studies published between 2013 and 2018 from pub med library were used.

Results: Most of the retrospective and cross sectional studies on the effect of paternal age on reproduction show that aging in men is associated with decreased fertility.

Conclusion: More research is needed to resolve the controversy in the findings that evaluate the association between age in men and fertility, especially with maternal aging as a variable.

Keywords: Man; Reproduction; Fertilization Capacity

Inclusion criteria

The paper entails a review of paternal age on fertilization capacity. For the review, retrospective and cross-sectional studies published between 2013 and 2018 from pub med library were used. During the search, scholarly journals were selected based on the availability of full articles in the library and a combination of key words including paternal/male/men aging and fertility.

Review of paternal age on fertilization capacity in literature

Based on the review of the effects of paternal age on reproduction, Gunes, Hekim, Arslan and Asci (2016) [1] note that multiple environmental and genetic factors contribute to aging in male reproductive cells, which increase the risk of deformity and other diseases that reduce their fertilization capacity. In particular, aging alters spermatogenesis process and hormone levels in men gradually, which results in a decrease of both the quantity and quality of the spermatozoa. Besides, even the natural physiological changes of aging such as age-related comorbidities, obesity, and reduced physical activity contribute to lower fertilization capacity in men, mainly since they are associated with a decline in testosterone levels and early onset of gonadal senescence.

In particular, Sharma., *et al.* (2015) [2] point out that although many studies have evaluated the effect of aging on fertility in men, most studies offer controversial conclusions. Still, from their systematic review, Sharma., *et al.* (2015) [2] argue that aging reduces the semen quality in men through a combination of genetic diseases, altered testicular functions, epigenetic changes, chromosomal aneuploidies and DNA mutations. For instance, aging lessens the levels of certain reproductive hormones including Dehydroepiandrosterone (DHEA), Gonadotropin-Releasing Hormone (GnRH), and Testosterone. On the sperm, advanced age reduces motility and ejaculate volume, and often alters the morphology of the cells, which diminishes fertilization capacity. Noteworthy, from their review, Sharma., *et al.* (2015) [2] noted that although most researchers agree that alteration in sperm parameters is correlated with reduction in the fertility of older men, DNA fragmentation that occurs in men above 40 years is a better predictor of infertility.

While most scholars generally agree that paternal aging has a negative effect on the reproductive capacity of the sperm, few have observed the effects on the offspring. Accordingly, after a longitudinal study of 10 years, Preston, Jalme, Hingrat, Lacroix and Sorci (2015) [3] assert that older age in males is associated with lighter children. According to Preston., *et al.* (2015) [3], male gametes undergo senescent with age, which is a result of progressive deterioration in the spermatogenic machinery due to declining levels of reproductive hormones. The effect is sperms that are unable to deliver the necessary genetic load to females to give rise to offspring that are healthy compared to others from younger males. However, one of the most likely contributor of the reduced fertilization capacity of older sperms is the fact that male germline tend to undergo mutations associated with cell divisions over time. The mutation affects the spermatogenesis process, which in turn degrades the sperm DNA of older males affecting their capacity to give rise to healthier offspring.

Even in the absence of diseases or mutation-related triggers, Durairajanayagam (2018) [4] argues that advanced paternal age on its own has the ability to reduce the fertilization capacity of men. For example, from a review of 1,021 articles spanning 10 years, the author notes that the motility and total sperm count reduces significantly for men aged 34 years and above. Similarly, the fraction and concentration of sperms with normal morphology declines for males after 40 years of life. Motility and progressive parameters also reduce once men reach 43 years with the ejaculate volume significantly reducing past the age of 45 years. By age 55, the ration of Y: X chromosome is also altered in ejaculates. Thus, Durairajanayagam (2018) [4] concludes that even with other disease-related factors being constant, the progression of normal physiology with age in men affects the health of their sperm.

Moreover, the effect on age on fertility capacity for men has been observed even during Intracytoplasmic sperm injection (ICSI). In a retrospective cohort study that spanned a period of 3 years with 4,887 oocyte donation cycles, Beguería., *et al.* (2014) [5] found that old age in males affects sperm parameters negatively, which is a key measure of fertility capacity. For instance, the researchers observed that for every 5 years of age above 36 years for men, the volume to sperm decreased by a factor of 0.22 ml, the percentage of motility reduced by 1.2 percent, and the concentration of the spermatozoa increased but 3.1 million sperms per ml. The implication of the study findings is that even when the sperm is donated by young men below the age of 36 years, aging has almost similar degradation effects on the reproductive capacity. However, in a similar study evaluating the consequence of old age in males on the outcome of ICSI extracted through TESE (testicular sperm extraction) and cryopreserved, Tsai., *et al.* (2013) [6] found that the existing evidence linking aging with infertility is insufficient.

Comparatively in a similar study evaluating the effect of male age on the outcomes of ICSI, Wu., *et al*. (2016) [7] noted that paternal aging does not affect the number of 2-pronucleus zygotes, the quantity of fertilized oocyte, and the viability of embryos. Besides, from the retrospective study that involved 2,627 ICSI cycles, the authors also discovered that paternal age has no association with pregnancy outcomes such as miscarriage, preterm and live births, and implantation. Still, Wu., *et al.* (2016) [7] concluded that aging in fathers reduces the quality of embryos formed after fertilization.

Nevertheless, when *in vitro* fertilization (IVF) is evaluated, a varied effect of paternal age in different cohorts of mothers is observed. For instance, from a 5-year retrospective study with 9,991 IVF cycles, Wu, Kang, Zheng, Liu and Liu (2015) [8] concluded that fertilization rate, number of miscarriages, and the quality of the embryo do not differ with paternal age, mainly for women below 34 years. However, the researchers also observed that the rate of implantation decreased significantly for women above 34 years. Thus, the authors concluded that while paternal age might have a negative effect on fertility, the assumption is only true for mothers who are older, in which case maternal maturity above 34 years is a better explanation for the issues observed with aging and reproduction in males.

With the increased controversy in the findings on the association between infertility and paternal age, some researchers have sought to resolve the issue by examining the parameters of sperm on already infertile men. A case in point is the retrospective study with 472 infertile men classified into different age groups (group A: ≤ 30y; B: 31 - 40y, C: ≤ 40y and D: > 40y) [9]. In their study, Alshahrani., *et al.* (2014) [9] investigated the effects of aging on sperm parameters, mainly total antioxidant capacity (TAC) and reactive oxygen species (ROS). The authors noted that for men older than 40 years, ROS and TAC levels did not have any significant differences with samples from fertile individuals. However, Alshahrani., *et al.* (2014) [9] also discovered that infertile men over 40 years old had a higher incidence (24.4 ± 18.5%) of sperm DNA damage compared to normal fertile males at the same age or younger.

The association between paternal age and sperm DNA damage was also studied by Petersen., *et al.* (2018) [10] through a cross-sectional study with a sample of 2,178 men admitted for evaluation in an infertility clinic. From the research, the authors observed that despite the apparent correction between old age and sperm apoptosis, aging increased the abnormality of MMP (mitochondrial membrane potential) and sperm DNA fragmentation. Analytically, the association between sperm DNA degradation and aging is a function of the mitochondrial damage that is seen in older men due to age-related oxidative stress. In particular, higher ROS production tends to alter the permeability of the mitochondrial membrane and leading to sperm DNA fragmentation and sometimes the death of the spermatozoa.

Conclusion

In conclusion, most of the retrospective and cross sectional studies on the effect of paternal age on reproduction show that aging in men is associated with decrease in fertility. However, some indicate that when maternal age is used as a variable, then the age of men who do not have any diseases is not correlated to infertility. Still, some of the main aspects that have been noted to influence to association between paternal age and infertility or reproductive issues include older age above 34 - 40 years (different studies use varied age ranges), sperm DNA fragmentation, higher maternal age above 34 (some researchers use 36 years), altered testicular functions, epigenetic changes, and chromosomal aneuploidies. Accordingly, more research is needed to resolve the controversy in the findings that evaluate the association between age in men and fertility, especially with maternal aging as a variable.

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