Chapter 53
Are there reproductive consequences associated with advanced paternal age?

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Introduction

There is a progressive increase of paternal age at conception across the world. The birth rate among 35 to 49 year old American men in 2015 was 69.1 per thousand compared with 42.8 per thousand in 1980. Other countries have reported a similar trend that appears to be consistent across all races, ethnicities, regions and level of education. The impact of paternal aging on reproduction and offspring health has long been an important subject in Andrology.

Model to study aging-associated changes in male germ cell

A wide range of animal models, ranging from insects to worms, birds, fish and mammals, has been used to investigate the effects of paternal aging on male reproduction function. An ideal animal model should be long-lived and free from the systemic aging-related diseases, while maintaining other reproductive changes that emulate those in aging men. Rodent models have become the predominant species for determining the cellular and molecular changes that occur in the testis and epididymis with aging.

From mouse models we have learned that advanced age is associated with a quantitative reduction in spermatozoa, an increased number of vacuoles in Sertoli and germ cells, a thinning of the seminiferous epithelium, a reduction in the numbers of spermatocytes and spermatids, and an increase in germ cell mutations. An increase in reactive oxygen species (ROS) occurs with aging. Mice overexpressing catalase, an enzyme that helps reduce ROS, do not exhibit the age-dependent loss of spermatozoa, do not show aging-associated loss in testicular germ and Sertoli cells, and show reduced DNA lesions in spermatozoa.

The Brown Norway (BN) rat has become a commonly used model to study male reproductive aging since it has a long lifespan and is relatively free of age-related pathologies, including tumors and obesity. Striking age-related changes in the seminiferous tubules, Leydig cells and epididymides of these animals have been reported. The expression of several genes in the testis (in Leydig and germ cells) and in the epididymis is altered as a function of aging. Anomalies in the structure of the endoplasmic reticulum and nuclei of Sertoli cells, the niche-forming "nurse" cells that surround the germ cells and ensure their normal development (Chapter 7), are seen. In addition, large intracellular spaces are observed between Sertoli cells, rather than the normally embedded germ cells. The expression of genes and proteins associated with the formation of the blood-testis barrier declines prior to the barrier becoming "leaky" during aging. Effects of aging are also seen in hypothalamic-pituitary function. Importantly, the changes seen in testis and hypothalamic-pituitary functions in the BN rat with age reflect those reported in aging men.

Mating of male BN rats of increasing age to young females results in an increase in pre-implantation loss, a decrease in the average fetal weight, and an increase in neonatal deaths, indicating that the quality of spermatozoa decreases as BN male rats age. The basis for these age-related declines in reproductive function remains unclear; however, they may be a consequence of the effects of aging on gene expression and epigenetic marks of germ cells, increased sperm chromatin damage, and impaired epididymal functions (Chapter 18).

Impact of advanced paternal age in men on their progeny

Various studies have demonstrated that there is an age-related decline in conventional semen parameters, including semen volume, total sperm count, motility and morphology. Not surprisingly, natural fertility rates also decline as men age; conception at 1yr is 30% less for men >40yrs versus those <30yrs. Further, natural conceptions with men >35yrs are 1.26 times more likely to miscarry than those with men <35yrs. Pregnancies sired by fathers >45yrs showed an increased risk of late stillbirth, low birth weight and preterm birth.

Advanced paternal age and assisted reproductive outcomes

Although there are some conflicting data, overwhelming evidence indicates that advanced paternal age is associated with various adverse outcomes with assisted reproductive technologies (ARTs), including poor embryo quality, increased miscarriage rates, reduced fertilization, and decreased implantation, pregnancy, and live birth rates. One mechanism that has been proposed to contribute to the adverse reproductive outcomes in natural and assisted reproduction is impaired sperm chromatin integrity and increased DNA fragmentation rates. Indeed, the majority of studies have demonstrated an association of advanced paternal age with significant increase in DNA fragmentation.

Perinatal health

Advanced paternal age increases the risk of premature birth, gestational diabetes and newborn seizures. The odds ratio of birth defects significantly increases with each year of paternal age after adjustment for multiple confounders. These defects include cleft lip, diaphragmatic hernia, right ventricular outflow tract obstruction, and pulmonary stenosis.

Malignancies

The incidence of several cancers in progeny increases with advanced paternal age. For example, men >35yrs have a higher risk of having offspring who develop hematologic cancers compared with those whose fathers are <25yr. The risk of childhood acute lymphoblastic leukemia increases by 13% for every 5 years increase in paternal age. Other offspring malignancies associated with advanced paternal age include central nervous system tumors and breast cancer. One proposed mechanism for increased cancer risk with advanced paternal age is the telomere lengthening found in sperm as men age. Leukocyte telomeres are lengthened in the offspring of older fathers by 0.5 -2 times per year of paternal age [63-65]. While this may confer some health and longevity advantage, a higher risk for malignancy has been noted.

Mental health

Advanced paternal age is also linked to psychological and neurodevelopmental disorders in offspring. The relative risk of offspring diagnosed with schizophrenia increases progressively with paternal age from 34 years; this increased risk cannot be accounted for by other factors, such as family history of psychosis, maternal age,

parental education and social ability, family social integration, social class, birth order, birth weight or birth complications. Additionally, there is a greater risk of obsessive-compulsive disorder in offspring with advanced paternal age. Using paternal sibling comparisons, a 24-fold increase in bipolar disorder was noted in offspring born to fathers 20-24yrs versus those aged 45yrs or older. Offspring from men aged >40yrs were more than fivefold more likely to develop autism spectrum disorders compared to offspring of younger men.

Genetic disorders

An increase in several genetic diseases that occur with a low frequency in the general population is associated with advanced paternal age. These include Apert, Crouzon and Pfeiffer syndromes, achondroplasia and other conditions. Many of these disorders follow an autosomal dominant pattern, consistent with the opinion that these are mainly de novo mutations in the germline and are associated with severely debilitating phenotypes. Hence, prospective parents with advanced paternal age concerns should be informed and counselled for such risks.

Approximately 0.33% of infants are born with an altered number of chromosomes. Aneuploidies derive mainly from non-disjunction events during meiotic divisions and represent the most common heritable chromosomal anomaly. Though most constitutional aneuploidies originate in the female germline, all men produce approximately 3-5% of aneuploidy sperm; these include non-disjunction events, particularly in sex chromosomes, and are more likely to occur with aging. Most de novo structural chromosomal abnormalities are of paternal origin. Results from studies on the association of advanced paternal age and increased risks of offspring aneuploidies with structural chromosome anomalies are inconsistent. This is, in part, related to the fact that the vast majority of chromosome aneuploidies are not compatible with fetal development, leading to implantation failure or early miscarriage. Structural chromosomal rearrangements that are balanced are usually phenotypically normal and are thus undetected during childhood, while the vast majority of those that are unbalanced are not compatible with fetal development.

Mechanisms on advanced paternal age impact

Studies in animal models suggest that the constitution of the male germline is relatively robust, with far fewer spontaneous mutations compared to somatic tissues. This high level of genetic fidelity in part explains why even when men are exposed to chemotoxic agents or radiation, there is no dramatic increase in the incidence of birth defects, sperm DNA chromatin abnormalities or de novo germline mutations in their offspring. In contrast, paternal aging has been shown to be unique for the creation of de novo mutations in the male germline. Several mechanisms of age-induced de novo germline mutations have been proposed. Cumulative replication error from repeated cell divisions represents a significant source of germline mutation. Based on whole-genome sequencing studies of parent-offspring trios, approximately one to three de novo mutations are introduced to the germline mutational load of the offspring for each additional year in the father's age at conception. Selfish spermatogonial selection from preferentially amplified mitotic clonal expansion of mutated spermatogonial stem cells is another proposed theory to explain why several genetic diseases associated with advanced paternal age follow the autosomal dominant pattern. Age-related epigenomic modifications in men are speculated to increase the risk of some rare epigenetic disorders in offspring conceived with ARTs. Other proposed mechanisms involve post meiotic damage of sperm DNA secondary to the combined effects of increased ROS damaging chromatin and aberrant or inadequate repair of such damage by oocytes.

Looking forward

Though controversies exist, a preponderance of evidence from recent scientific literature affirms a negative impact of advanced paternal age on reproductive health. The first step to minimize or mitigate the negative impact of advanced paternal age is to comprehend the collective body of scientific evidence. The next step is to promote appropriate counselling to couples where the male partner is older than 40 years of age. There should be dialogues among investigators, healthcare providers, health policy makers and patients that focus on emerging data and their implications at the personal as well as societal levels.

Suggested reading

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