ADVANCED PATERNAL AGE

Age that may lead to the accumulation of de novo mutations, male infertility and increased genetic risks on the offspring.

Risk factor

♂ Male

About Advanced paternal age

The advanced paternal age may lead to the accumulation of de novo mutations, male infertility and increased genetic risks on the offspring. Nevertheless, the effect of paternal age on semen quality and reproductive function is controversial, because there is no universal definition for advanced paternal ageing. Aging is a multifactorial and complex process leading to progressive impaired cellular functions and hence increased vulnerability to diseases. In this context, advanced paternal age would lead to the accumulation of de novo mutations, male infertility and increased genetic risks on the offspring (Pic. 1).

In addition to increased risk of male infertility, paternal age has also been demonstrated to impact reproductive and fertility outcomes including a decrease in in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) success rate and increasing rate of preterm birth. Increasing paternal age has shown to increase the incidence of different types of disorders like autism, schizophrenia, bipolar disorders, and childhood leukemia in the progeny. It is thereby essential to educate the infertile couples on the disturbing links between increased paternal age and rising disorders in their offspring, to better counsel them during their reproductive years.

Testicular functions and reproductive hormones

Age-affected testicular atrophy is a result of hypothalamic-pituitary-testicular (HPT) axis alterations that disturb the functions of various reproductive hormones (Pic. 2). Advanced paternal age has also been associated with changes in different hormonal levels. Leydig cells are responsible for testosterone production. Increased follicle-stimulating hormone (FSH) serum levels and decreasing testosterone levels are the most common clinically relevant alterations associated with male ageing.

The number of Leydig cells tends to reduce with increasing paternal age. The average total number of Leydig cell nuclei decrease by half in age group of 50–76 years compared to age group of 20–48 years. Reduced number of Leydig cells plays a key role in incidence and pathogenesis of andropause in aging men. The decreased number of Leydig cells also contribute to reduced levels of total testosterone and free testosterone (1.2%) serum levels in paternal group >50 years.

Sperm parameters

Several mechanisms have been proposed to explain how aging in males may cause changes in semen parameters (Pic. 3). These changes can be related to seminal vesicle inadequacy which reduces semen volume or changes in prostate, in terms of prostate atrophy such as reduction in water and protein content which might affect sperm motility and ejaculate volume.

DNA integrity and ART outcomes

Sperm DNA damage is associated within lower probability of conception and a longer time to conception. Studies suggest that DNA damage is a better predictor of pregnancy than the conventional semen parameters.

Positive correlations have been reported between an increased sperm DNA fragmentation (damaged genetic information), reduced motility and ART outcomes leading to lower pregnancy rates and higher miscarriages.
Such DNA integrity reduction was shown to be correlated to advanced paternal age (especially for ages beyond 40 years), supporting the overall negative effect of ageing fathers on IVF/ICSI success rate and hence ART outcomes.

Sperm DNA integrity (absence of DNA damage) is not only important for successful IVF but also for normal embryonic development. It has been recently shown that the advanced paternal age and its adverse effects on sperm DNA integrity also interfere with early embryonic development.

**DNA mutations**

In contrast to egg cell maturation (oogenesis), sperms divide (or spermatogenesis occurs) continuously throughout reproductive lifetime and hence accumulates greater number of cell divisions. The paternal contribution to offspring novo mutations was estimated to increase by 4% per year. At the age of 20, a sperm would have undergone 150 chromosomal replications (a part of cell cycle), and at the age of 50, it would have gone through 840 replications. This increases the probability of replication errors in the germ line leading to the accumulation of mutations and hence increased de novo mutation rate in spermatozoa. This problem is further aggravated when age-sensitive processes such as DNA replication and repair are compromised due to an increasing age. On average, the rate of de novo mutation increases by two base pairs every successive year.

**Chromosomal aneuploidies**

Chromosomal aneuploidy is the presence of an abnormal number of chromosomes in a cell. Chromosomal aneuploidy is caused in a sperm when it undergoes meiosis (reproductive cells cycle) but the chromosomes are not equally divided in daughter cells because of disjunction. Most of the aneuploid embryos die in-utero and hence chromosomal aneuploidy is the leading cause of failed pregnancy. However, 1% of aneuploid pregnancies lead to live birth which accounts for a large number of congenital birth defects and/ or mental retardation.

On average, 10% of sperm cells of healthy male population have chromosomal aneuploidies and include chromosome 21 and 22. However, this number increases with paternal age (Pic. 4). The incidence of sex chromosome disomy 18 significantly increases among older men (>50 years) when compared to younger men. McIntosh et al. reported increased risk of up to two fold among fathers of 50 years and older when compared to the fathers of age group 25–29 years.

**Epigenetics of male aging**

Epigenetics is stable heritable modification on histone tails but not the DNA sequence that leads to altered gene expression (process by which genetic instructions are used to synthesize proteins). Unlike DNA mutations, epigenetic patterns can be disrupted or silenced by various environmental and endogenous factors such as nutrition, age, drug/toxin exposure and phenotypic variation. Therefore, both spermatogenesis and spermiogenesis (processes of sperm cell development) processes are marked by successive steps of epigenetic reprogramming of the male gamete which is influenced by several environmental factors. These epigenetic events may impair or inhibit key steps of fertilization, implantation and/or the embryo development.

**Symptoms**

The decreasing testosterone levels in aging men are linked to andropausal symptoms, such as poor libido, fatigue and loss of cognitive function. Both male sexual function and sexual frequency decrease with age and the infertility experienced by many older men may in part be related to the decline in sexual activity.

**Associated diseases**

Many genetic disorders in offspring have been associated to increasing paternal age:

- schizophrenia
- bipolar disorder (mental disorder that causes periods of depression and periods of elevated mood)
- autism (impairment in social interaction, verbal and non-verbal communication, and restricted and repetitive behavior)
- Klinefelter syndrome (set of symptoms that result from two or more X chromosomes in males)
- achondroplasia (form of short-limbed dwarfism)
- Apert syndrome (congenital disorder characterized by malformations of the skull, face, hands and feet)

**Complications**
Increased paternal age affects testicular function, reproductive hormones, sperm parameters, sperm DNA integrity, telomere length (a region at the end of chromosome), de novo mutation rate, chromosomal structure and epigenetic factors.

**Paternal age, intraretine insemination success and live birth rates**

Reports have shown a decrease in assisted pregnancy rate with increasing paternal age. Male age ≥ 35y is associated with decreased clinical pregnancy rate. Significant decline in artificial conception rate has been showed when pregnancy rate decreased from 12.3% per cycle in men aged <30 to 9.3% in men ≥45 years. With increasing paternal age, the live birth rate decreases, showing a decrease in artificial pregnancy rate.

**Spontaneous abortions**

Spontaneous abortion is defined as loss of pregnancy occurring before 20 weeks of gestation. It is seen in 10-15% of clinically recognized pregnancies. Increasing paternal age is significantly associated with the risk of spontaneous abortions.

**Pre-eclampsia and advanced paternal age**

Pre-eclampsia refers to the onset of hypertension and either proteinuria (proteins in the urine) or end-organ dysfunction after 20 weeks of gestation in a previously normotensive woman. A significant association has been reported between increasing paternal age and preeclampsia.

**Pre-term birth and low birth weight and increasing paternal age**

Pre-term delivery is defined by the occurrence of delivery before the completion of 37 weeks of gestation. Pre-term birth is responsible for causing 27% neonatal deaths worldwide, leading to over a million deaths annually. It is also associated with more than 70% of early life morbidity and mortality, making it one of the largest health problems in reproductive health. With increasing paternal age, the risk of preterm births increases. The odds ratio for preterm increased with increasing paternal age.

Low birth weight is a leading cause of infant mortality in the United States. It is associated with attention deficit hyperactivity disorder (ADHD), blindness, epilepsy, chronic lung disease, cerebral palsy, all of them leading to long term health problems. In comparison to the paternal age group of 25–29 years, age group >45 years has 19% increased likelihood of low birth weight and 13% increased risk of preterm (between 33 and 37 weeks of gestation) birth.

**Still-birth/fetal death and increasing paternal age**

Still-birth defines a fetal death that occurs prior to the expulsion from its mother. The paternal age group >45 years has 48% increased risk of still-birth (uterofetal death ≥28 weeks) compared to the 25–29 years group.

For pregnancies fathered by men aged ≥ 50 years, both the risks for early fetal death (≤20 weeks of gestation) and late fetal death increased with the hazard ratio of 1.38 and 3.94 respectively. In comparison to the paternal age group of 25–29 years, age group >45 years has 22% increased risk of stillbirth.

**Risk factors**

- age over 40 years
- exposure to environmental toxins

**Prevention**

The sperm parameters do not change until males reach the age of 34 years.

**How it can affect fertility**

**Advanced paternal age and time to pregnancy/male fecundity**
Fecundity is defined as the likelihood of achieving a pregnancy in a defined period of time. Using time to conception as an index to measure male fecundity, there is a significant decline in male fecundity with advanced paternal age after adjusting maternal age and other confounding factors.

For men older than 40 years, the odds ratios for conception in <12 months are 0.62 for 30–34 years old, 0.50 for 35–39 years old and 0.51 compared to the reference age group (<25 y). Association of paternal age with fertility is contradictory. This may be attributed to the decline in male sexual activity as frequency of intercourse decreases with age. The general consensus is that paternal age is associated with reduced fertility especially in couples where men are older than 40 years and age of the women is at least 35 years.

**Prognosis**

In conclusion, advanced paternal age increases the DNA fragmentation in sperm negatively affecting the IVF/ICSI success rates, ART outcomes as well as early embryo development.

**Find more about related issues**

**Diagnoses**

**Azoospermia**
Complete absence of sperm in the ejaculate of a man.
Learn more at: [www.fertilitypedia.org/therapy/diag/azoospermia](http://www.fertilitypedia.org/therapy/diag/azoospermia)

**Erectile dysfunction**
The inability (that lasts more than 6 months) to develop or maintain an erection of the penis during sexual activity.
Learn more at: [www.fertilitypedia.org/therapy/diag/erectile-dysfunction](http://www.fertilitypedia.org/therapy/diag/erectile-dysfunction)

**Idiopathic male infertility**
A condition in which fertility impairment occurs spontaneously or due to an unknown cause.
Learn more at: [www.fertilitypedia.org/therapy/diag/idiopathic-male-infertility](http://www.fertilitypedia.org/therapy/diag/idiopathic-male-infertility)

**Gallery**

**Pic. 1: Main factors involved in impaired male infertility due to reproductive aging**

**Pic. 2: Effect of advancing paternal age on reproductive hormones**

<table>
<thead>
<tr>
<th>Name of the hormone</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>↓</td>
</tr>
<tr>
<td>Dihydrotestosterone (DHT)</td>
<td>No Change</td>
</tr>
<tr>
<td>Estrogen</td>
<td>↓</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>↑</td>
</tr>
<tr>
<td>Gonadotropin-Releasing Hormone (GnRH)</td>
<td>↓</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
<td>↑</td>
</tr>
<tr>
<td>Sex hormone-binding globulin (SHBG)</td>
<td>↑</td>
</tr>
<tr>
<td>Testosterone</td>
<td>↓</td>
</tr>
</tbody>
</table>
Sources

“Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring” — by Sharma et al. licensed under CC BY 4.0

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“Advanced paternal age is a risk factor for schizophrenia in Iranians” — by Naserbakh et al. licensed under CC BY 2.0

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