

# Age-Related Decline Of Male Fertility (ARDMF), The Other Side Of The Coin, A Review Article

Medhat Amer<sup>1,2,3</sup>, Emad Fakhry<sup>2\*</sup>

<sup>1</sup>Andrology Department, Faculty of Medicine, Cairo University, Egypt.

<sup>2</sup>Adam International Hospital, Cairo, Egypt.

<sup>3</sup>Egyptian Foundation of Reproductive Medicine and Embryology (EFRE).



Prof. Medhat Amer is Ex Chairman of the Andrology department, Cairo University, former President of the Andrology Mediterranean, Association and the Egyptian Society of Andrology is currently, He is Professor of Andrology and president of the Egyptian Society of Reproductive Medicine (ESRM); He is vice president of the Egyptian Foundation of Reproductive Medicine and embryology (EFRE), Chairman of one of the largest private Andrology and ART hospital and satellite clinics in the Middle East: Adam International Hospital devoted to male infertility, (ISO Q9001-2000). His research activities include over 70 published articles in international journals, covering all domains of male infertility.

## Abstract

**Background:** The effect of male age on male fertility is a debatable subject. Men never stop producing sperms, but there is a decline in sperm quality as a man ages. According to the World Health Organization (WHO) starting around the age of 35, semen parameters worsen. The sperm quality parameters naturally change with age: count, motility, morphology, DNA fragmentation, and genetic mutations. Paternal age is among the factors affecting a couple's chance of conceiving and their pregnancy outcomes. Pregnancy Rate, time to conception, miscarriage risk, adverse pregnancy outcomes, and Offspring health risks are all affected by male age. Some studies have shown that paternal age does not affect pregnancy outcomes using conventional in vitro fertilization (IVF) techniques, while others report decreased pregnancy and live birth rates with increased male age.

**Objective:** to discuss the effect of male aging on fertility and pregnancy outcome and also on the results of assisted reproduction.

**Conclusion:** Male Age has a significant role in his fertility potential and would affect pregnancy prognosis as well as ART results.

**Keywords:** aged male; male fertility; assisted reproduction.

## Introduction

The oldest man to father a baby was aged 96 years, so there shouldn't be an age limit for male fertility. Stories of men in their 60s or older fathering children would figure that male fertility is eternal, but that's a misconception. Men also experience the effects of aging with a decrease in fertility over time. Men, just like women, do face a biological clock. As early as 1955, Penrose L. questioned Advanced Paternal Age (APA) effects on male fertility (1). Although we haven't yet pinpointed exactly what age men are most fertile, we know that male fertility decline typically begins at the age of 35 and gets steeper at 40.

The Centers for Disease Control and Prevention (CDC) report that most men experience a significant age-related fertility decline after they reach the age of 40. Other studies show that the decline begins around age 35 (2). In one study that evaluated the relationship between age and semen parameters, they concluded that male fertility peaks between 30 and 35 and its decline begins at 35 (3).

## Semen Quality and Male Age

Men typically never stop producing sperm, but there is a measurable decline in sperm quality as a man ages. According to the World Health Organization (WHO) starting around the age of 35, men may see their semen parameters worsen (count, morphology, and motility).

The sperm quality parameters naturally change with age: count, motility, morphology, DNA fragmentation, and genetic mutations. Although scientific research has not found a direct decline in sperm count by age, some studies have found correlations. One study reported a decrease in sperm count of up to 2.6% per year of age. Findings are inconclusive of whether age directly impacts sperm count. According to research, sperm motility is expected to decrease by about 0.8% per year of age (4).

Studies show that sperm normal morphology decreases by about 0.65% per year of age (5). Studies show that sperm DNA fragmentation increases by 0.3% per year of age (6). Meiosis quality control is impaired with aging. More de

novo point mutations are observed in aged sperms which would reflect many offspring anomalies (7). In fact, young men's germ cells produce sperms after an average of 35 replications while the rounds of replications would be more than 800 rounds in a 50-year-old male which implicates more mutation occurrence (8).

Many mechanisms were proposed to explain this age-related deterioration in semen parameters. Free testosterone decreases by 50% between ages 20 and 80 years (9). A reduction in plasma levels of bioavailable testosterone below normal occurs in 35% above the age of 80 (10). A decrease in testicular perfusion with increasing age (11) with arteriosclerotic lesions of testicular arterioles was also reported (12). Rising seminal ROS (13) was reported in the aged male. A possible mechanism for decreased sperm quality is the imbalance of reactive oxygen species (ROS) and anti-oxidant production at the mitochondrial level (14). Disruption of the immune system occurs with advancing age (immunosenescence) and this increases the chance of infection and inflammation in the male reproductive tract with increasing age (15) with diminished semen quality and infertility in men.

## Adam International Hospital Experience

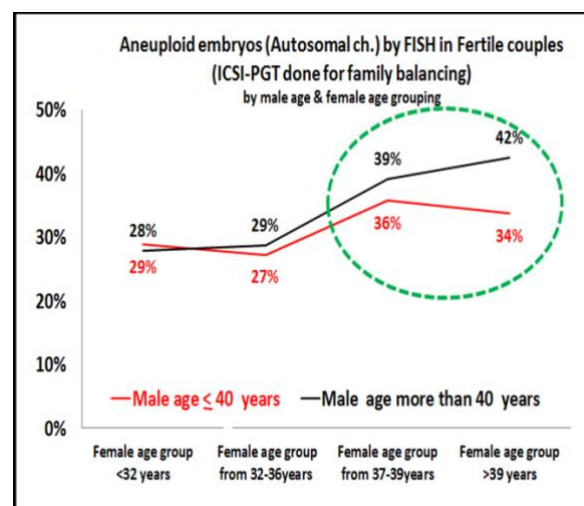
The following chart represents ICSI-PGT cases (done for family balancing) split by male age & female age grouping. Aneuploid embryos (Autosomal ch.) by FISH in those fertile couples were more in the older males (> 40 years) when compared with the younger ones. This increase was only noticed when the female partners of those older males were older than 36 years (but still no significance was detected P value = 0.134) Figure 1.

Paternal age is among the factors affecting a couple's chance of conceiving and their pregnancy outcomes.

- 1- Pregnancy Rate:** Men over the age of 35–40 typically experience a decrease in sperm health, which affects pregnancy rates, so men will generally see a 52%

decrease in fertility rate between their early 30s and their mid-to-late 50s.

- 2- **Time to conception:** Compared to men 25 years or younger, men 45 years or older are many times more likely to take over two years to conceive (16).
- 3- **Miscarriage risk:** Pregnancy loss between the 6 and 20-week gestation period increases by 27% in fathers 35 years or older. In a study published in 2002, they reported a high risk zone for pregnancy loss when paternal age is over 40 years even with wives aged 30-34 years. They also concluded that those males when married to females aged 35 years or more are in the highest risk zone with about 6 times more incidence of abortion as the young age group (17).
- 4- **Adverse pregnancy outcomes:** Pregnancies that involve a male over the age of 45 have an increased risk of birth complications. Alio et al. in 2012 reported that with increasing paternal age, the risk of preterm births, low birth weight, and stillbirth increased (18). Harlap et al. 2002, reported a weak association between increasing paternal age and preeclampsia and this was independent of maternal age (19).
- 5- **Offspring health risks:** The probability is still generally low, but studies show that older fathers may be more likely to have children with schizophrenia, bipolar disorder, autism, Down syndrome, or childhood leukemia. It is believed that sperm random mutations increase over the years, which can pass genetic mutations to a child and increase their chances of developing a psychological or neurocognitive disorder (20).



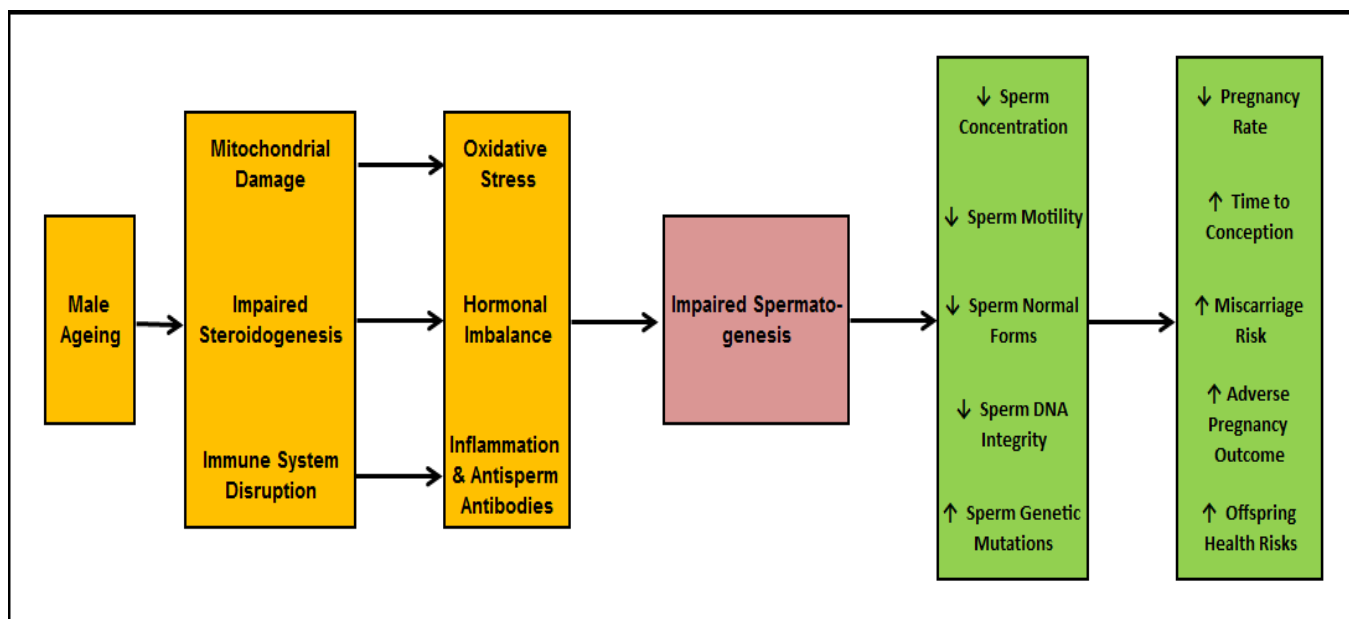
**Figure 1.** Aneuploid embryos % by FISH in fertile couples by male & female age grouping.

### Male Age & ART

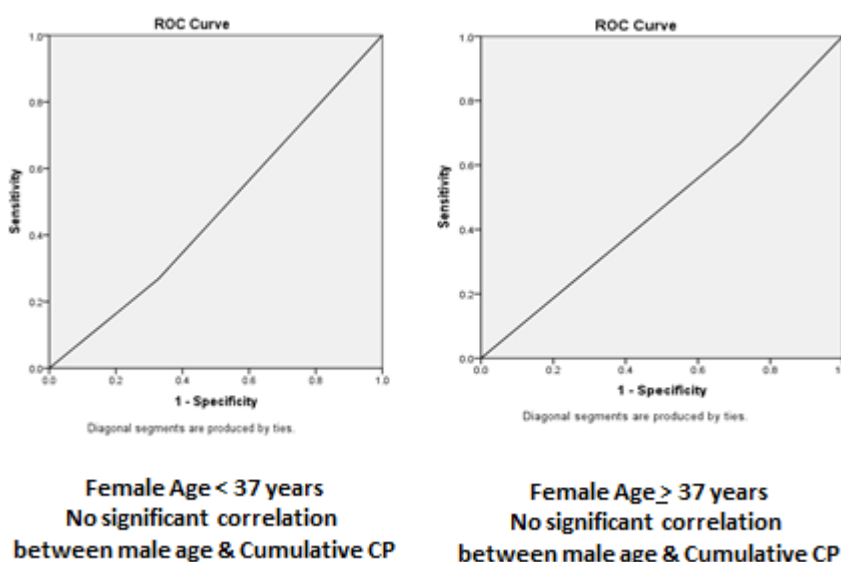
Few studies have investigated the effect of paternal aging on ART outcomes, they demonstrate discrepant results. Some studies have shown that paternal age does not affect pregnancy outcomes using conventional in vitro fertilization (IVF) techniques, while others report decreased pregnancy and live birth rates with increased male age (21).

An important study was concerned with couples going for IVF trials in France, taking into account the interaction between male and female ages, as older males are mostly married to older wives. The odds ratio of failure to conceive for paternal age 40 years or more was more significant when the women were older than 35 years as compared to younger males with the same female age groups (N.B. The same result was not noticed with younger wives whatever the male age was) (22).

In 2019, Cito et al, studied the effect of male age on ART outcome. They studied that effect in donor oocyte cycles. As the oocyte donation program represents a good method to reduce the confounding factors, since the quality of donor oocytes should be considered excellent. Sperm motility and fertilization rate were significantly lower in men older than 45 years than younger ones. However, statistical association between paternal age and other IVF outcomes, including cleavage and PRs, was not detected (23).



**Figure 2.** The causes and effects of semen profile changes in the aged male.



**Figure 3.** ROC curve showing the correlation between male age and cumulative clinical pregnancy rate according to female age grouping

In 2022, an important meta-analysis was published discussing the effect of male aging on ART outcome. This meta-analysis included a total 32,484 cycles from 16 autologous oocyte studies and 12 donor oocyte studies. In autologous cycles, a statistically significant positive effect of paternal age <40 years was noted in clinical pregnancy, live birth and miscarriage rates. Paternal age <50 years significantly reduced miscarriage rate, and increased blastocyst rate and number of

cleavage-stage embryos in donor oocyte cycles, where maternal age is controlled (24).

### Adam International Hospital Experience

This study represents ICSI-PGT correlation results for 1685 cases (done for family balancing in fertile couples) in Adam International Hospital. In the younger females < 37 years, no significant correlation was found between fertilization rate and male age but a

negative correlation was found regarding blastulation rate. While in the older females, no significant correlation with male age was found regarding fertilization or blastulation. No significant correlation was found between cumulative clinical pregnancy rate and male age in both young (<37y) and old females (>37y).

### Conclusion:

Male Age has a significant role on his fertility potential and would affect pregnancy prognosis as well as ART results.

### References:

1. Penrose LS (August 1955). "Parental age and mutation". *Lancet*. 269 (6885): 312–3. doi:10.1016/s0140-6736(55)92305-9. PMID 13243724.
2. Hassan MA, Killick SR. Effect of male age on fertility: evidence for the decline in male fertility with increasing age. *Fertil Steril*. 2003 Jun;79 Suppl 3:1520-7. doi: 10.1016/s0015-0282(03)00366-2. PMID: 12801554.
3. Stone BA, Alex A, Werlin LB, Marrs RP. Age thresholds for changes in semen parameters in men. *Fertil Steril*. 2013 Oct;100(4):952-8. doi: 10.1016/j.fertnstert.2013.05.046. Epub 2013 Jun 27. PMID: 23809502.
4. Slotter E, Schmid TE, Marchetti F, Eskenazi B, Nath J, Wyrobek AJ. Quantitative effects of male age on sperm motion. *Hum Reprod*. 2006 Nov;21(11):2868-75. doi: 10.1093/humrep/del250. Epub 2006 Jun 22. PMID: 16793993.
5. Levitas E, Lunenfeld E, Weisz N, Friger M, Potashnik G. Relationship between age and semen parameters in men with normal sperm concentration: analysis of 6022 semen samples. *Andrologia*. 2007 Apr;39(2):45-50. doi: 10.1111/j.1439-0272.2007.00761.x. PMID: 17430422.
6. Lahimer M, Montjean D, Cabry R, Capelle S, Lefranc E, Bach V, Ajina M, Ben Ali H, Khorsi-Cauet H, Benkhalifa M. Paternal Age Matters: Association with Sperm Criteria's- Spermatozoa DNA Integrity and Methylation Profile. *J Clin Med*. 2023 Jul 27;12(15):4928. doi: 10.3390/jcm12154928. PMID: 37568329; PMCID: PMC10420110.
7. Yatsenko AN, Turek PJ. Reproductive genetics and the aging male. *J Assist Reprod Genet*. 2018 Jun;35(6):933-941. doi: 10.1007/s10815-018-1148-y. Epub 2018 Mar 9. PMID: 29524155; PMCID: PMC6030011.
8. Crow JF. The origins, patterns and implications of human spontaneous mutation. *Nat Rev Genet*. 2000 Oct;1(1):40-7. doi: 10.1038/35049558. PMID: 11262873.
9. Hermann M, Berger P. Hormonal changes in aging men: a therapeutic indication? *Exp Gerontol*. 2001 Jul;36(7):1075-82. doi: 10.1016/s0531-5565(01)00113-9. PMID: 11404052.
10. Vermeulen A, Kaufman JM. Ageing of the hypothalamo-pituitary-testicular axis in men. *Horm Res*. 1995;43(1-3):25-8. doi: 10.1159/000184233. PMID: 7721258.
11. Suoranta H. Changes in the small blood vessels of the adult human testis in relation to age and to some pathological conditions. *Virchows Arch A Pathol Pathol Anat*. 1971;352(2):165-81. doi: 10.1007/BF00548374. PMID: 5313210.
12. Sasano N, Ichijo S. Vascular patterns of the human testis with special reference to its senile changes. *Tohoku J Exp Med*. 1969 Nov;99(3):269-80. doi: 10.1620/tjem.99.269. PMID: 5363446.
13. Cocuzza M, Athayde KS, Agarwal A, Sharma R, Pagani R, Lucon AM, Srougi M, Hallak J. Age-related increase of reactive oxygen species in neat semen in healthy fertile men. *Urology*. 2008 Mar;71(3):490-4. doi: 10.1016/j.urology.2007.11.041. PMID: 18342194.
14. Lissak A, Wiener-Megnazi Z, Reznick AZ, Shnizer S, Ishai D, Grach B, Lahav-Baratz S, Shiloh H, Koifman M, Dirnfeld M. Oxidative stress indices in seminal plasma, as measured by the thermochemiluminescence assay, correlate with sperm parameters. *Fertil Steril*. 2004 Mar;81 Suppl 1:792-7. doi: 10.1016/j.fertnstert.2003.08.015. PMID: 15019811.
15. Wigby S, Suarez SS, Lazzaro BP, Pizzari T, Wolfner MF. Sperm success and immunity. *Curr Top Dev Biol*. 2019;135:287-313. doi: 10.1016/bs.ctdb.2019.04.002. Epub 2019 May 15. PMID: 31155361; PMCID: PMC6784542.
16. Jimbo M, Kunisaki J, Ghaed M, Yu V, Flores HA, Hotaling JM. Fertility in the aging male: a systematic review. *Fertil Steril*. 2022 Dec;118(6):1022-1034. doi: 10.1016/j.fertnstert.2022.10.035. PMID: 36509505.
17. de la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. *Hum Reprod*. 2002 Jun;17(6):1649-56. doi: 10.1093/humrep/17.6.1649. PMID: 12042293.
18. Alio AP, Salihi HM, McIntosh C, August EM, Weldeselasse H, Sanchez E, Mbah AK. The effect of paternal age on fetal birth outcomes. *Am J Mens Health*. 2012 Sep;6(5):427-35. doi: 10.1177/1557988312440718. Epub 2012 May 7. PMID: 22564913.
19. Harlap S, Paltiel O, Deutsch L, Knaanie A, Masalha S, Tiram E, Caplan LS, Malaspina D, Friedlander Y. Paternal age and preeclampsia. *Epidemiology*. 2002 Nov;13(6):660-7. doi: 10.1097/00001648-200211000-00010. PMID: 12410007.

20. Janecka M, Mill J, Basson MA, Goriely A, Spiers H, Reichenberg A, Schalkwyk L, Fernandes C. Advanced paternal age effects in neurodevelopmental disorders-review of potential underlying mechanisms. *Transl Psychiatry*. 2017 Jan 31;7(1):e1019. doi: 10.1038/tp.2016.294. PMID: 28140401; PMCID: PMC5299396.
21. Marsidi AM, Kipling LM, Kawwass JF, Mehta A. Influence of paternal age on assisted reproductive technology cycles and perinatal outcomes. *Fertil Steril*. 2021 Aug;116(2):380-387. doi: 10.1016/j.fertnstert.2021.03.033. Epub 2021 Apr 25. PMID: 33910758.
22. de La Rochebrochard E, de Mouzon J, Thépot F, Thonneau P; French National IVF Registry (FIVNAT) Association. Fathers over 40 and increased failure to conceive: the lessons of in vitro fertilization in France. *Fertil Steril*. 2006 May;85(5):1420-4. doi: 10.1016/j.fertnstert.2005.11.040. Epub 2006 Apr 17. PMID: 16616749.
23. Cito G, Coccia ME, Picone R, Cocci A, Russo GI, Garaffa G, Fucci R, Bertocci F, Borrani E, Basile V, Micelli E, Criscuoli L, Serni S, Carini M, Natali A. Impact of advanced paternal age on the intracytoplasmic sperm injection (ICSI) outcomes in donor egg cycles. *Transl Androl Urol* 2019;8 (Suppl 1):S22-S30. doi: 10.21037/tau.2018.12.13
24. Murugesu S, Kasaven LS, Petrie A, Vaseekaran A, Jones BP, Bracewell-Milnes T, Barcroft JF, Grewal KJ, Getreu N, Galazis N, Sorbi F, Saso S, Ben-Nagi J. Does advanced paternal age affect outcomes following assisted reproductive technology? A systematic review and meta-analysis. *Reprod Biomed Online*. 2022 Aug;45(2):283-331. doi: 10.1016/j.rbmo.2022.03.031. Epub 2022 Apr 10. PMID: 35690546.