MISE AU POINT / IN-DEPTH REVIEW

# ADVANCED PATERNAL AGE HOW DOES IT AFFECT FERTILITY AND PREGNANCY RELATED OUTCOMES ?

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**ABSTRACT** • When compared to maternal age, paternal age has not attracted the same attention throughout history. Advanced paternal age has been sometimes incriminated as a possible factor that can affect pregnancy and its outcomes. In this review, we discuss the effect of paternal age on fertility, miscarriage, chromosomal abnormalities, congenital anomalies, perinatal outcomes, and neurodevelopmental disorders. In fact, advanced paternal age is associated with decreased semen quality leading to lower pregnancy rates, longer time to conception, and a higher number of miscarriages. Additionally, an increase in the rate of adverse pregnancy outcomes, such as congenital anomalies and pre-eclampsia, is reported when the father's age is advanced. However, no significant effect on the outcome of assisted reproductive technology (ART) or the risk of trisomies, is confirmed.

Keywords : advanced; paternal; age; pregnancy

## INTRODUCTION

Advanced maternal age and its effect on pregnancy and conception has historically received the attention of both patients and health care providers. In turn, advanced paternal age effect on pregnancy is less well defined and has perhaps attracted less interest. For children born to women aged under 25 or those who are not married, birth certificates often lacked information on the father's age [1]. In fact, in 2013, the paternal age was not reported for 13 percent of all births that took place in the United States, and this rate increased to 32 percent when the woman's age was less than 20 and to 29 percent when the mother was not married [2]. However, paternal age is known to have important effects on fertility as well as pregnancy outcome. This is important to keep in mind particularly given the trend for delay in childbearing. For instance, the rate of births per 1000 men has decreased from 92.0 in 1980 to 55.7 in 2013 in the 20-24 years' category and from 123.1 to 90.6 in men aged 25 to 29 years. Contrarily, the rate of births per 1000 men showed significant rise in the 30-34 and 35-39 years' categories, with a rise from 91.0 to 101.8 and from 42.8 to 66.6, respectively [2]. It is not surprising then for the president of the American Society of Reproductive Medicine, Dr. R. Jeffrey Chang, to caution in his keynote speech at the millennium annual meeting of the society that *"the impact of age on reproductive health is a vital issue for the 21st century"*. The impact of advanced maternal age has been extensively reviewed as an important factor for women's reproductive health. The question of declining fertility as men age is an important one that needs additional research to resolve.

In this review we will discuss the effect of paternal age on fertility, miscarriage, chromosomal abnormalities, congenital anomalies, perinatal outcomes, and neurodevelopmental disorders among others.

## DISCUSSION

### Fertility

Numerous studies have demonstrated that increasing male age is associated with increased time to conception and possible failure to conceive [3,4,5]. Ford *et al*. conducted a large population-based study of over 8000 pregnancies that aimed at examining the effect of paternal age on time to conception, while adjusting for the mother's age. Their findings revealed that increasing father's age is associated with decreased conception rates within one year [4]. Also, following several investigations on a large population-based birth-cohort, Mutsaerts *et al*. concluded that advanced paternal age, especially above 35 years, is associated with increased time to pregnancy [5].

This effect of advanced paternal age on fertility has been attributed to numerous factors. For instance, sperm quality has been shown to decrease with increasing age. Brahem *et al*. examined the association between the age of the male and semen quality. Among their significant findings was a decrease in semen volume and vitality in the older population [6]. Zhu *et al*. reported no change in semen volume with increasing age. However, sperm motility, vitality, and the percentage of normal sperm decreased [7]. In turn, a decrease in sperm concentration or number of sperm with normal morphology has been demonstrated in a number of studies [8,9].

Coital frequency should be taken into consideration when studying pregnancy rates and time to conception. Using the results of the Massachusetts Male Aging Study (MMAS), Feldman *et al*. reported that the prevalence of complete erectile dysfunction tripled between ages 40 and 70 years [10]. This reflects the impact of age

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on impotence. Araujo *et al*. also used the data of the MMAS and observed that prior to age 40 the frequency of sexual activity in men was 6.5 times per month. This frequency decreased continuously as men reached their 40s, 50s, and 60s [11]. Decreased sexual activity, due to erectile dysfunction and lower androgen levels, is also associated with increasing paternal age [12]. However, the effect of sexual dysfunction on fertility can be modified by the use of assisted reproductive technology (ART) since the male germ cells are not affected by sexual dysfunction [12]. However, if there is no erection at all sperm will not follow all the maturation steps and modifications that take place in the epididymis and during the ejaculation process which could lead to less effective spermatozoa.

ART is an important tool towards achieving conception. Maternal age is a very influential factor affecting this objective. When compared to younger women, pregnancy and fertilization rates are significantly lower in women aged 43 years or more while live birth delivery rates also decrease significantly around the same age [13,14]. Two recent large retrospective studies analyzed the effect of advanced paternal age on the outcomes of assisted reproduction. No significant difference in reproductive outcomes, such as clinical pregnancy and live births rate, was reported when the father's age was advanced [15,16]. Similarly, Wu *et al*. reported that paternal age has no impact on fertilization rate and embryo quality at the cleavage stage [17].

To conclude this section, a systematic review including 12 studies was published in 2015 by Sagi-Dain *et al*. [18]. After analyzing several factors including semen parameters, rates of fertilization, miscarriages, live birth among others, the authors concluded that there is insufficient evidence to claim that advanced paternal age has an unfavorable effect on ART outcomes [18]. Hence, more studies are needed in this particular field in order to be able to draw solid conclusions that could be translated into practice.

**Miscarriage**

Compared to the effect of maternal age on miscarriage, paternal age has been less studied despite long-standing interest.

Advanced maternal age has been shown to be associated with increasing rates of miscarriage [19,20]. Thus, when the effect of paternal age on miscarriage risk is studied, there is a need to control for the confounding maternal age. A retrospective population-based multicenter study on infertility and subfecundity analyzed paternal and maternal ages together and referred to them as 'couple age'.

The risk of miscarriage was found to be the highest in couples where the woman is 35 years old or more and the man's age greater than 40. The study also showed that in couples where maternal age was less than 35, the highest risk of miscarriage occurred when the father's age exceeded 40 [21]. Moreover, a large cohort study of 23,821 pregnant women showed that *"pregnancies fathered by a man aged 50 or more years had almost twice the risk of ending in a fetal loss compared with pregnancies with younger fathers."* [22]. Based on the investigations available it seems that like advanced maternal age, advanced paternal age may increase the risk of spontaneous abortions albeit to a lesser extent.

**Chromosomal abnormalities**

Spermatogenesis continues throughout a male's life span unlike oogenesis that is limited to the human fetus except for the meiotic maturation that takes place after puberty. Spermatozoa are continuously produced, so the number of cell divisions and chromosomal replications that have taken place increase as men age, hence the greater possibility for error in males due to the larger number of mitotic replications in the germ cells when compared to females [23].

Aging males are believed to be the major contributors of de novo mutations introduced into the gene pool [23-25]. Additionally, multiple chromosomal aberrations have been associated with increasing male age. This includes more breaks in sperm DNA, a higher frequency of point mutations and aneuploidies [26-28]. For instance, Garcia-Ferreyra *et al*. studied the relationship between men's age and DNA damage. Among the findings of the study, men who were aged 50 years or more had a higher number of sperm with damaged DNA and higher aneuploidy rates in embryos [28]. Alshahrani *et al*. report that when compared to infertile men aged less than 40 years, those who are aged 40 or more have a greater percentage of sperm DNA fragmentation [26]. With that said, DNA fragmentation is not only the result of problems taking place during mitotic divisions but can also be due to unfavorable conditions that alter the sperm after its production, like oxidative stress.

Advanced paternal age has also been shown to be associated with an increase in new autosomal dominant mutations and diseases [29]. Examples include Apert, achondroplasia, Pfeiffer, and Marfan syndromes [30].

Regarding trisomies, Steiner *et al*. found that offsprings of younger fathers have a higher risk of aneuploidies [31]. Another study looked at the effect of paternal age in predicting the risk of trisomy 21 in the offspring of women younger and older than 35 years. The occurrence of trisomy 21 was significantly higher in older women when the father was 20 to 24 years old with an adjusted prevalence ratio of 2.27. When the father's age was more than 40 years, a slight increase in the prevalence of Down syndrome was noted in the older women group with a ratio of 1.35 [32].

De Souza *et al*. reported a higher risk of 47 XXY (Klinefelter syndrome) with advanced paternal age, in their case-control study [33].

What we can conclude is that data is scarce and sometimes contradictory which makes it impossible to reach generalizable conclusions that can be applied.

**Congenital anomalies**

An increase in congenital anomalies occurrence has been associated with advanced paternal age in some studies [34,35]. Yang *et al*. conducted a large population-based retrospective cohort study, which included over 5 million births, to study the effect of advanced paternal age on birth defects. After adjusting for possible confounders such as maternal age, maternal smoking and alcohol use during pregnancy, they reported an increase in the odds ratio for any birth defects in association with advanced paternal age [36]. More specifically an increased risk of heart defects, tracheoesophageal fistula, and other musculoskeletal/integumental anomalies was noted. Interestingly, infants born to fathers under 25 years of age were found to be at a higher risk of neural tube defects as well as omphalocele/gastroschisis [36]. In addition, congenital heart defects were reported to be more likely to occur in children born to fathers whose age was advanced [37]. A recent study by Su *et al*. showed a specific increase in the prevalence of patent ductus arteriosus (PDA) when the father's age is advanced [38].

**Preeclampsia and other adverse pregnancy outcomes**

The association between advanced maternal age and preeclampsia was well established in many studies [20, 39]. Some investigators have hypothesized a similar relationship between advanced paternal age and preeclampsia, particularly with the known relationship between paternal factors and preeclampsia [40].

Other adverse perinatal outcomes were studied in relation to advanced paternal age but the data is limited to few studies with some of them reporting an effect of advanced paternal age on stillbirth and preterm birth [41, 42]. In fact, the risk of very preterm birth, defined as less than 32 weeks of gestation, was found to be associated with advanced paternal age [41,42]. Alio *et al*. report a significant increase in the risk of stillbirth, preterm birth, and low birth weight in offsprings whose fathers are aged 45 years or more. However, a decreased risk of small for gestation age infants has been noted [41].

Regarding Caesarean delivery, their rate was shown to be increased with advanced maternal age [43]. When studying primiparous women, Faro *et al*. described an increased rate in Caesarean deliveries when the father's age was advanced especially over age 40 [44]. Their analysis was stratified by maternal age. Also, Tang *et al*. looked at deliveries by nulliparous women. A significant rise in the rate of Caesarean sections was observed with advanced paternal age independently of the mother's age [45].

**Neurodevelopmental disorders**

Schizophrenia has been studied in association with paternal age. An elevated risk in its occurrence was found in children of fathers with advanced age [46,47]. Regarding bipolar disorder, the data is not well established, with some studies reporting no association with paternal age [46]. Others describe an increased occurrence of bipolar disorder in offspring of fathers with advanced age [48]. In addition to an increased risk of bipolar disorder, D'Onofrio *et al*. noted higher incidence of attention-deficit/hyperactivity disorder and psychosis in offsprings born to fathers aged 45 years or more [48].

Autism spectrum disease is also considered to be associated with paternal age [46,47,48]. In one study fathers aged 40 years or more had 3.3 times increased odds of having a child with autism when compared to fathers aged less than 20 years [46]. Similarly, in another study, offspring of men aged more than 45 years were 3.45 times more likely to have autism than offspring of men aged between 20 and 24 years [48]. Maternal as well as paternal age was found to independently influence the incidence of autism [49]; however, Tsuchiya *et al*. reported that only increased paternal, but not maternal, age carried a higher risk of autism [50].

## CONCLUSION

In addition to the longstanding interest in the effect of maternal age on fertility and pregnancy outcomes, the corresponding effects of paternal age has recently attracted the attention of investigators. Studies have demonstrated that advanced paternal age is associated with lower pregnancy rates and longer time to conception. An increase in the risk of miscarriage has also been observed when the father is of an older age, and this risk rises further when both parents are of advanced age. Additionally, adverse pregnancy outcomes such as congenital anomalies, pre-eclampsia, preterm birth, and operative delivery have been studied as a function of paternal age, with some studies reporting an increase in rate with advancing age. On another note, advanced paternal age has generally been noted to be of no detrimental effect on the outcome of ART.


## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.


## REFERENCES


1. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Mathews TJ. Births: final data for 2011. Natl Vital Stat Rep 2013 Jun 28; 62 (1): 1-69, 72.
2. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. Natl Vital Stat Rep 2015 Jan 15; 64 (1): 1-65.
3. 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.
4. Ford WC, North K, Taylor H, Farrow A, Hull MG, Golding J. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. The ALSPAC Study Team (Avon Longitudinal Study of

Pregnancy and Childhood). Hum Reprod 2000 Aug; 15 (8): 1703-8.
5. Mutsaerts MA, Groen H, Huiting HG et al. The influence of maternal and paternal factors on time to pregnancy – a Dutch population-based birth-cohort study: the GECKO Drenthe study. Hum Reprod 2012 Feb; 27 (2): 583-93.
6. Brahem S, Mehdi M, Elghezal H, Saad A. The effects of male aging on semen quality, sperm DNA fragmentation and chromosomal abnormalities in an infertile population. J Assist Reprod Genet 2011 May; 28 (5): 425-32.
7. Zhu QX, Meads C, Lu ML, Wu JQ, Zhou WJ, Gao ES. Turning point of age for semen quality: a population-based study in Chinese men. Fertil Steril 2011 Sep; 96 (3): 572-6.
8. Hossain MM, Fatima P, Rahman D, Hossain HB. Semen parameters at different age groups of male partners of infertile couples. Mymensingh Med J 2012 Apr; 21 (2): 306-15.
9. 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.
10. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994 Jan; 151 (1): 54-61.
11. Araujo AB, Mohr BA, McKinlay JB. Changes in sexual function in middle-aged and older men: longitudinal data from the Massachusetts Male Aging Study. J Am Geriatr Soc 2004 Sep; 52 (9): 1502-9.
12. Sartorius GA, Nieschlag E. Paternal age and reproduction. Hum Reprod Update 2010 Jan-Feb; 16 (1): 65-79.
13. Shea LO, Hughes C, Mocanu EV. Advanced maternal age and assisted reproductive technologies in an Irish population. Ir Med J 2015 Sep; 108 (8): 243-6.
14. Yeh JS, Steward RG, Dude AM, Shah AA, Goldfarb JM, Muasher SJ. Pregnancy outcomes decline in recipients over age 44: an analysis of 27,959 fresh donor oocyte in vitro fertilization cycles from the Society for Assisted Reproductive Technology. Fertil Steril 2014 May; 101 (5): 1331-6.
15. Ghuman NK, Mair E, Pearce K, Choudhary M. Does age of the sperm donor influence live birth outcome in assisted reproduction? Hum Reprod 2016; 31 (3): 582-90.
16. Beguería R, García D, Obradors A, Poisot F, Vassena R, Vernaeve V. Paternal age and assisted reproductive outcomes in ICSI donor oocytes: is there an effect of older fathers? Hum Reprod 2014 Oct 10; 29 (10): 2114-22.
17. Wu Y, Kang X, Zheng H, Liu H, Liu J. Effect of paternal age on reproductive outcomes of in vitro fertilization. PLoS One 2015 Sep 9; 10 (9): e0135734.
18. Sagi-Dain L, Sagi S, Dirnfeld M. Effect of paternal age on reproductive outcomes in oocyte donation model: a systematic review. Fertil Steril 2015 Oct; 104 (4): 857-65. e1.
19. Ciancimino L, Laganà AS, Chiofalo B, Granese R, Grasso R, Triolo O. Would it be too late? A retrospective case-control analysis to evaluate maternal-fetal outcomes in advanced maternal age. Arch Gynecol Obstet 2014 Dec; 290 (6): 1109-14.
20. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol 2013 Dec; 42 (6): 634-43.
21. 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.
22. Nybo Andersen AM, Hansen KD, Andersen PK, Davey Smith G. Advanced paternal age and risk of fetal death: a cohort study. Am J Epidemiol 2004 Dec 15; 160 (12): 1214-22.
23. Crow JF. The origins, patterns and implications of human spontaneous mutation. Nat Rev Genet 2000 Oct; 1 (1): 40-7.
24. Genome of the Netherlands Consortium. Whole-genome sequence variation, population structure and demographic history of the Dutch population. Nat Genet 2014 Aug; 46 (8): 818-25.
25. Rahbari R, Wuster A, Lindsay SJ et al. Timing, rates and spectra of human germline mutation. Nat Genet 2016 Feb; 48 (2): 126-33.
26. Alshahrani S, Agarwal A, Assidi M et al. Infertile men older than 40 years are at higher risk of sperm DNA damage. Reprod Biol Endocrinol 2014 Nov 20; 12: 103.
27. Kong A, Frigge ML, Masson G et al. Rate of de novo mutations and the importance of father's age to disease risk. Nature 2012 Aug 23; 488 (7412): 471-5.
28. García-Ferreyra J, Luna D, Villegas L et al. High aneuploidy rates observed in embryos derived from donated oocytes are related to male aging and high percentages of sperm DNA fragmentation. Clin Med Insights Reprod Health 2015 Nov 11; 9: 21-7.
29. Reproductive Endocrinology and Infertility Committee; Family Physicians Advisory Committee; Maternal-Fetal Medicine Committee; Executive and Council of the Society of Obstetricians, Liu K, Case A. Advanced reproductive age and fertility. J Obstet Gynaecol Can 2011 Nov; 33 (11): 1165-75.
30. Auroux M. Age of the father and development. Contracept Fertil Sex 1993 May; 21 (5): 382-5.
31. Steiner B, Masood R, Rufibach K et al. An unexpected finding: younger fathers have a higher risk for offspring with chromosomal aneuploidies. Eur J Hum Genet 2015 Apr; 23 (4): 466-72.
32. Agopian AJ, Marengo LK, Mitchell LE. Predictors of trisomy 21 in the offspring of older and younger women. Birth Defects Res A Clin Mol Teratol 2012 Jan; 94 (1): 31-5.
33. De Souza E, Morris JK, EUROCAT Working Group. Case-control analysis of paternal age and trisomic anomalies. Arch Dis Child 2010 Nov; 95 (11): 893-7.
34. Urhoj SK, Mortensen LH, Nybo Andersen AM. Advanced paternal age and risk of musculoskeletal congenital anomalies in offspring. Birth Defects Res B Dev Reprod Toxicol 2015 Dec; 104 (6): 273-80.
35. Green RF, Devine O, Crider KS et al. Association of paternal age and risk for major congenital anomalies from the National Birth Defects Prevention Study, 1997 to 2004. Ann Epidemiol 2010 Mar; 20 (3): 241-9.
36. Yang Q, Wen SW, Leader A, Chen XK, Lipson J, Walker M. Paternal age and birth defects: how strong is the association? Hum Reprod 2007 Mar; 22 (3): 696-701.
37. Materna-Kiryluk A, Wiśniewska K, Badura-Stronka M, et al. Parental age as a risk factor for isolated congenital malformations in a Polish population. Paediatr Perinat Epidemiol 2009 Jan; 23 (1): 29-40.
38. Su XJ, Yuan W, Huang GY, Olsen J, Li J. Paternal age

and offspring congenital heart defects: a national cohort study. PLoS One 2015 Mar 25; 10 (3): e0121030.
39. Yogev Y, Melamed N, Bardin R, Tenenbaum-Gavish K, Ben-Shitrit G, Ben-Haroush A. Pregnancy outcome at extremely advanced maternal age. Am J Obstet Gynecol 2010 Dec; 203 (6): 558.e1-7.
40. Dekker GA. Pre-eclampsia – A disease of an individual couple. Pregnancy Hypertens 2014 Jul; 4 (3): 242-3.
41. Alio AP, Salihu HM, McIntosh C et al. The effect of paternal age on fetal birth outcomes. Am J Mens Health 2012 Sep; 6 (5): 427-35.
42. Zhu JL, Madsen KM, Vestergaard M, Basso O, Olsen J. Paternal age and preterm birth. Epidemiology 2005 Mar; 16 (2): 259-62.
43. Richards MK, Flanagan MR, Littman AJ, Burke AK, Callegari LS. Primary cesarean section and adverse delivery outcomes among women of very advanced maternal age. J Perinatol 2016 J Perinatol 2016 Apr; 36 (4): 272-7.
44. Faro R, Santolaya-Forgas J, Canterino JC, Oyelese Y, Ananth CV. Paternal age and risk for cesarean delivery. J Matern Fetal Neonatal Med 2012 Dec; 25 (12): 2713-16.
45. Tang CH, Wu MP, Liu JT, Lin HC, Hsu CC. Delayed parenthood and the risk of cesarean delivery – Is paternal age an independent risk factor? Birth 2006 Mar; 33 (1): 18-26.
46. Buizer-Voskamp JE, Laan W, Staal WG et al. Paternal age and psychiatric disorders: findings from a Dutch population registry. Schizophr Res 2011 Jul; 129 (2-3): 128-32.
47. McGrath JJ, Petersen L, Agerbo E, Mors O, Mortensen PB, Pedersen CB. A comprehensive assessment of parental age and psychiatric disorders. JAMA Psychiatry 2014 Mar; 71 (3): 301-9.
48. D'Onofrio BM, Rickert ME, Frans E et al. Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 2014 Apr; 71 (4): 432-8.
49. Sandin S, Schendel D, Magnusson P et al. Autism risk associated with parental age and with increasing difference in age between the parents. Mol Psychiatry 2015 Jun 9. doi: 10.1038/mp.2015.70. [Epub ahead of print]
50. Tsuchiya KJ, Matsumoto K, Miyachi T et al. Paternal age at birth and high-functioning autistic-spectrum disorder in offspring. Br J Psychiatry 2008 Oct; 193 (4): 316-21.