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REVIEW

The effects of advanced paternal age on fertility

Jason R Kovac, Josephine Addai, Ryan P Smith, Robert M Coward, Dolores J Lamb and Larry I Lipshultz

Modern societal pressures and expectations over the past several decades have resulted in the tendency for couples to delay conception. While women experience a notable decrease in oocyte production in their late thirties, the effect of age on spermatogenesis is less well described. While there are no known limits to the age at which men can father children, the effects of advanced paternal age are incompletely understood. This review summarizes the current state of knowledge regarding advanced paternal age and its implications on semen quality, reproductive success and offspring health. This review will serve as a guide to physicians in counseling men about the decision to delay paternity and the risks involved with conception later in life.
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INTRODUCTION

Women have long known that a natural limit to their ability to conceive a child exists. This window of fertility is limited by the availability of oocytes and the impending approach of menopause. This ticking biological clock is understood, expected, and even dreaded, by many females. On the other hand, men are seemingly untouched by the notion of this fertility precipice. In fact, men are traditionally viewed as immune to the ravages of age as it relates to fertility in both a physiological sense, and a social one. As improvements in reproductive technologies have pushed the frontiers of reproductive medicine, media reports of elderly men fathering children[1] have raised awareness and garnered acceptance of advanced paternal age (APA) in modern times.[1–4]

Societal pressures are partly to blame for the trend of couples delaying childbearing well into their mid- to late-thirties. Careers and educational aspirations, along with an increased life expectancy and the nearly ubiquitous use of contraception, have decreased accidental birth rates and increased parental age at first childbirth. Moreover, the success of *in vitro* fertilization has given many couples a type of 'reproductive security blanket' by assuring them that if the traditional methods of achieving conception are not successful, technology will come to their rescue.

With regard to advanced maternal age, preliminary data from the 2012 United States National Vital Statistics Report states that the number of births to women aged more than 35 years are at the highest levels since 1967.[5] Specifically, compared with the last census, the birth rates for women aged 40–44 increased by 2% and for those aged 35–39, it rose 3%.[5] Unfortunately, while statistics with regard to maternal age are well known, numerous difficulties exist in characterizing paternal age on a large scale.[6] Indeed, paternal information is often missing from the birth certificate and the age of the father is not reported in 14% of all births.[6] In those cases where the paternal age was reported, the rates of live births per 1000 men increased from 6.1 in 1980 to 8.2 in 2007 among men aged 45–49 years.[6] These statistics are mirrored in advanced countries around the world. For example, in Germany, the average age of married fathers has increased by nearly two years from 1991 to 1999.[7] More recently, in 2003, English fathers aged 35–54 accounted for 15% more births than they did 10 years ago.[8] Thus, these data point towards a worldwide trend of conceiving children later on in life.

One inherent difficulty with attempting to summarize data on APA is that it has no universal definition. The current population mean for paternal age is 27 years, and the most frequently used cutoff for APA is more than 40 years of age at the time of conception.[9] There currently exists a need for improved data collection, guidelines and outcome research based for APA. Moreover, an understanding of the unique factors and concerns surrounding APA is essential for management. Since guidelines for the counseling and evaluation of APA patients are yet to be formally designed, it is hoped that this review will serve as a framework for the future creation of such documents. Herein we summarize the current state of knowledge regarding APA and its effects on semen quality, reproductive success and offspring health.

EFFECT OF PATERNAL AGE ON SEMEN QUALITY

The primary technique used to diagnose and monitor male reproductive potential is semen analysis. The effect of paternal age on semen quality is currently controversial, and multiple epidemiologic studies have been conducted to examine this relationship.[4,10,11] The pioneering studies by Auger and colleagues[10] brought to light the decline in semen quality associated with both age and time in 1995. In their retrospective analysis of 1351 fertile men from 1973 to 1992, the authors concluded that while semen volume did not change over the period of time examined, the sperm concentration and motility decreased.[10] After adjusting for age, it was found that as men got older, each successive year accounted for a 2.6% decline in sperm concentration, a 0.3% decrease in motile sperm number, and a 0.7% decrease

Scott Department of Urology, Department of Molecular and Cellular Biology, The Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX 77030, USA
Correspondence: Dr JR Kovac (jason.kovac@bcm.edu) C/O Dr LI Lipshultz
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in the percentage of normal sperm morphology.[10] A later study by Fisch *et al.*[11] retrospectively reviewed data from three US sperm banks to determine whether sperm quality had decreased over time. From 1970 to 1994, semen analyses from 1283 consecutive patients were examined.[11] Whereas the concentration and motility were different among the three sperm banks, no decline in sperm counts over the 25-year period was identified when controlling for age and duration of abstinence.[11] These two large studies highlight the controversy surrounding the effects of paternal age on semen quality. In all of the studies dealing with APA and semen parameters reviewed here, the abstinence time was not specifically dealt with and cannot be excluded. Specifically, we have reviewed here the effects of APA on the various components of the semen analysis including semen volume and sperm concentration, motility and morphology.

Numerous studies have examined the relationship between paternal age and semen volume.[4] Unfortunately, these studies were hampered by the heterogeneous nature of the cohorts (i.e., healthy volunteers, sperm banks, infertility clinics) and the lack of information regarding abstinence periods, past medical history, prior medication or previous exposure to smoking or drugs. When studies controlled for these variables, most of them consistently demonstrated a decrease in semen volume as paternal age increased.[11–15] Specifically, in a series of studies, Homonnai *et al.*[13,16] reported a 30% decrease in semen volume from young men (~31 years) when compared with an older age group (~54 years). A subset analysis of a large retrospective review conducted by Fisch *et al.*[11] in 1996 looked back over 25 years, and when age was used as a modifier in a multiple regression model, semen volume was found to significantly decrease (0.15%) with increasing age.[11] In a more recent study by Hellstrom and colleagues,[14] the authors found that men aged 45–47.8 years had a median semen volume of 2.8 ml which then decreased significantly to 1.95 ml in the 56.6- to 80.1-year-old male. A retrospective review by Levitas *et al.*[15] found that peak semen volumes occurred between the ages of 30–35 years (3.5±1.8 ml) and were significantly different from those men greater than 55 years of age (2.2±1.2 ml).

In contrast to these findings, one study[17] examined 833 fertile men and found lower volumes in the younger (21–25 years) and older (46–50 years) cohorts compared with those of middle age (26–45 years). Several other studies did not find any differences among men of different ages in their semen volume,[18,19] while one reported an increase in volume with age.[20] As such, while the majority of studies suggest that a decrease in semen volume with paternal age occurs, the exact relationship is unclear.

With regard to sperm concentration, or sperm counts, a thorough review of the literature is detailed by Kidd *et al.*[4] Overall, the data are inconclusive. Specifically, several studies identified a decline in sperm concentration with age[10,21–23] with the report by Auger *et al.*[10] demonstrating a decrease in sperm concentration of 3.3% per year of advancing age. Similarly, the authors identified a 66% decrease occurring between the ages of 30 and 50. In contrast, other studies have illustrated an increase in concentration of 0.3%–3.3% per year of age[24–27] while another subset of reports details no association with paternal age.[14,18,28,29] The difficulty in analyzing concentration data, however, is the concomitant change in semen volume that may occur with APA.

Total sperm count, or total sperm number, is different from concentration and is defined as the total number of sperm in an entire ejaculate. A study by Eskenazi *et al.*[12] examined semen samples from 97 male volunteers obtained in the late 1990s and found that while men in their twenties had total sperm numbers of 345×10^6 per ejaculate, these numbers were significantly lower in men aged 60–69 years (215×10^6 per ejaculate).[12] Moreover, the amount of men with abnormal numbers of total spermatozoa significantly increased across age decades.[12] Cardona Maya and colleagues[30] who examined 1364 males and identified total sperm number to be inversely related to age,[30] echoed these findings in a more recent 2009 study. As such, it can be summarized that while the relationship between sperm concentration and APA is inconclusive, total sperm counts appear to decline with age.

When considering sperm motility, the majority of studies have utilized traditional light microscopy. Some studies, however, have employed a computer-assisted sperm analysis.[4] One of the studies that used a computer-assisted methodology found no change in sperm motility with APA,[31] as did several others using the traditional light microscopic technique.[18,32,33] The majority of studies, however, identified a decrease in motility as paternal age increased.[10,11,14,15,17,25] Specifically, Auger *et al.*[10] showed a 0.6% decrease in sperm motility for each year of age. Levitas *et al.*[15] found peak motility occurred when males were <25 years old (44.4%±21%) with the lowest motility (24.8%±18%) observed at an age >55 years. To add to the controversy, two studies found an increase in sperm motility in relation to increasing age, with a 0.06% increase for each year of age.[19,20] On the whole, however, there appears to be a preponderance of evidence to suggest that APA is associated with decreased sperm motility.

The data on the relationship between APA and sperm morphology is difficult to interpret given that morphology criteria have changed over time and are variable between laboratories. The majority of the studies suggest a decline with APA in the percentage of normal spermatozoa.[10,17,25,33,34] Auger *et al.*[10] identified a 0.9% loss of normal forms per year of age with a 4%–22% decline observed between men aged ⩾50 years and those who were less than 30 years old. While some studies failed to find any association between APA and sperm morphology,[18,28] the weight of the evidence suggests a decline in normal forms with increasing age.

Given that spermatogenesis consists of numerous cell divisions, as a man ages, there are exponentially more mitotic divisions within the germ cells resulting in elevated levels of DNA damage with age.[35] Indeed, compared with fertile men, infertile men exhibit poor sperm chromatin integrity as well as increased sperm DNA breaks as they age.[36–39]

Specifically, one study examined 66 men aged 20–57 years and identified significantly more breaks in the sperm DNA of older men (>35 years) compared with that of younger men.[39] Another study by Winkle *et al.*,[40] however, found no significant correlations between male age, semen parameters and sperm DNA fragmentation. These studies are interesting given the potential teratogenic effects of environmental pollutants and chemicals that could accumulate with age. In fact, air pollution has previously been linked to increased DNA damage in human spermatozoa in the absence of changes in other semen parameters.[41] However, the ability to establish a link between environmental toxins and male fertility is difficult.[42]

DNA damage may also result as a consequence of oxidative stress. This can occur owing to numerous conditions including repeated infections and obstruction. A cross-sectional, retrospective study by Rolf *et al.*[43] on 3698 infertile men (mean age: 33 years) identified an age-dependent increase in infections of the accessory sex glands. Given that infections lead to increased oxidative stress and elevated levels of reactive oxygen species have been identified in the spermatozoa of males of APA,[44] it is tempting to speculate that a relationship between oxidative stress, reactive oxygen species and APA exists.

EFFECT OF PATERNAL AGE ON REPRODUCTIVE SUCCESS

Much more is known about the female role in reproductive success than that of males. Advanced maternal age is traditionally defined as being greater than 35 years of age.[45] This definition for maternal age was established because it is the age at which women demonstrate a decreased ability to conceive, as well as a prolonged time to achieve pregnancy.[1] The concept of advanced maternal age is synonymous with 'ovarian aging' and is associated with lower oocyte numbers and quality; both of which lead to lower reproductive success. Unfortunately, the data on the effects of APA on reproductive success are less well described. It does appear, however, on the basis of available studies, that men of APA exhibit decreased levels of reproductive success.

Some of the work detailed above indicates that semen parameters, including semen volume, sperm motility and sperm concentration decline as men age. The decline in these parameters, however, does not prove that men of APA have a lower chance of inducing pregnancy or fertilization. These questions were addressed in a prospective study by Dunson *et al.* in 2004.[46] After controlling for female age, the authors found that the time to achieve pregnancy, as well as the rate of conception was adversely affected in the partners of men with APA.

Further evidence of this negative impact was identified in an observational study of pregnant women, in which a fivefold increase in the time to achieve pregnancy was observed when the man's age was >45 years.[47] Moreover, when compared with men <25 years old, men of APA (>45 years) were 4.6 times more likely not to induce pregnancy until after 1 year of regular unprotected intercourse. When those men who took longer than 2 years to induce a pregnancy with their partners were examined, men of APA (>45 years) were 12.5 times more likely to be included.[47] Interestingly, the effects of APA were not dependent on female age, suggesting that males alone contributed to this effect.[3,47]

Other studies demonstrated similar effects. For example, a prospective study from Europe examining 782 couples (women aged 18–40) who achieved pregnancy by intercourse alone, reported that when women reached their late thirties, male age became a significant factor in achieving pregnancy.[46] An Australian study looking at 585 couples found an increased risk of infertility in couples where the male partner was >35 years old, compared with couples in which the male was <35 years old.[48] In cases when intrauterine insemination was used to achieve pregnancy and female age was controlled, a paternal age of greater than 35 years was associated with a 50% lower pregnancy rate compared with that when the male was less than 30 years old.[49] A similar dependence on maternal age was observed in a study on 6188 randomly-selected women in which a paternal age of greater than 40 years was found to be a risk factor for infertility in women age 35 years or more.[50] The relationship between reproductive success and APA is not clear-cut, as some studies have suggested that no relationship exists. One such study from Denmark examined 10 886 women to determine what effects contribute to a time to achieve pregnancy of greater than one year. While the authors found a strong maternal effect, the paternal contribution was insignificant.[51]

The concept of paternal age affecting fertility has also been examined in the setting of assisted reproductive technologies (ARTs). Luna *et al.*[52] noted that fertilization rates with ART were significantly decreased in men who were more than 50 years of age. Furthermore, when *in vitro* fertilization (IVF) was examined retrospectively, Aboulghar *et al.*[53] also found a significantly lower fertilization rate with men older than 50 years. In a prospective study of 221 couples undergoing IVF and ART, Klonoff-Cohen and Natarajan[54] noted that pregnancy rates decreased as male age increased. Moreover, each additional year of paternal age was related to an 11% increase in the odds of not achieving pregnancy and a 12% increase of not having a successful live birth.[54] A retrospective cohort analysis of 1023 male partners participating in anonymous oocyte donation cycles showed a significant decrease in semen volume and total sperm motility with age.[55] These findings were compounded by the fact that in men of APA (>50 years), the authors identified an increase in pregnancy loss, blastocyst formation and lower live birth rates.[55] Other studies, however, have found no association between paternal age and ART outcomes. A retrospective analysis of 441 couples undergoing 558 oocyte donation cycles by Paulson *et al.*[56] identified a significant decline in sperm counts with APA; however, this was not reflected in fertilization or live birth rates.

As such, the effects of APA on reproductive outcomes remain controversial. A recent in-depth analysis by Dain *et al.*[57] does provide a comprehensive summary of the current literature. The authors examined 10 studies that examined APA and the effects on fertilization and pregnancy rates, implantations, miscarriages and live births.[57] They concluded that there was insufficient evidence to demonstrate an effect of APA on outcomes.[57] The authors did find a decrease in the rates of blastocyst embryo formation with APA and speculated that this might be due to the genomic changes that occur with APA.[57] Therefore, it appears that increased paternal age is associated with reduced fertility and that this effect is independent of whether conception is natural or assisted by IVF.

EFFECT OF PATERNAL AGE ON OFFSPRING HEALTH

The increased risks of chromosomal and genetic abnormalities in the offspring of women with advanced maternal age are well known, and as such, the decision to refer a female to a genetic counselor on the basis of age is common. Unfortunately, the paternal age at which offspring health is affected is unknown, making counseling difficult. When considering pregnancy outcomes, animal models identified a decreased pregnancy rate and increased rate of neonatal death when female mice were bred with older males.[58]

When newborn health was assessed *via* APGAR scores and birth weight in a large, retrospective, US study, it was found that APA had no effect on either of those variables.[1] While a Danish study found a slightly increased risk for lower APGAR scores in men >45 years old, only one study identified a role for APA on lower newborn birth weight with the majority of studies showing no effect.[1,59,60] APA has been related to increased complications faced by the mother. Indeed, female partners of men with APA (>45 years) are more likely to acquire hypertension, placental abruption and placenta previa.[61] Moreover, the highest rates of stillbirths and preterm births are observed in infants whose fathers had APA, suggesting that *in utero* development and survival are influenced by both maternal and paternal age.[61]

The concept of APA being associated with genetic syndromes was observed as early as 1955.[1,62] It has been postulated that as men age, repeated cycles of spermatogenesis contribute to the resultant increased likelihood of spontaneous, *de novo* mutations seen in men of APA.[63] The strongest association between spontaneous alterations and APA occurs in the form of single base-pair mutations, primarily because these small changes are less likely to be repaired by the intrinsic corrective machinery of the germ cells. Therefore, the genetic conditions most strongly associated with APA include those mutations caused by single base substitutions in genes such as *FGFR2*, *FGFR3* (fibroblast growth factor receptor) and the RET genes that

result in Pfeiffer syndrome, Crouzon syndrome, Apert syndrome, achondroplasia, thanatophoric dysplasia, as well as *MEN2A* and *MEN2B.*[9,64]

It is currently accepted that the most significant contribution of APA to a genetic condition occurs with the autosomal dominant disorder, achondroplasia.[65] The most common form of dwarfism, achondroplasia, is due to a mutation in the *FGFR3* gene. It has a general occurrence rate of 1 in 15 000 that is significantly less than the 1 in 1875 observed in males of APA ($\geqslant$50 years).[65] Examination of the genetic basis of the disorder found that 97%–99% of the *de novo* mutations leading to achondroplasia occurred due to a G-to-A transition mutation at base pair 1138 (G1138A, exon 10).[65] Since most sporadic cases of achondroplasia have the G1138A mutation inherited paternally,[66] the disorder has been used to highlight the concept that lifelong spermatogonial stem cell division contributes to high mutation frequencies in men of APA.[65] However, an elegant study using sperm DNA to examine the frequency of nucleotide substitutions in *FGFR3* found that the magnitude of the age-related mutations was not sufficient to explain the exponential increases of achondroplasia that occur with APA.[65]

More recently, an elegant review by Goriely and Wilkie[67] advanced the concept of 'Selfish Spermatogonial Selection'. In this theory, repetitive rounds of spermatogenesis and spermatogonial stem cell renewal results in random mutations within the testes.[67] Wild-type counterparts then surround these abnormal cells allowing an interaction between the two distinct populations.[67] Germline transmissions are then based upon the accumulation of mutations over multiple generations. While the deleterious mutations are rapidly eliminated, the neutral and mild mutations are potentially transmissible over several generations.[67] Specifically, functionally neutral mutations do not accumulate and pose low risk. Other more significant mutations, as those seen in the *FGF3R* gene, may confer a selective advantage to spermatogonial stem cells allowing accumulation [67] while milder mutations may offer a mild selective advantage that is enriched over time.

Trisomy 21, or Down syndrome, is also known to have an increased incidence with maternal age; however, the influence of paternal age is less well known.[1,68] It was recently found that trisomy 21 is primarily associated with APA when the female partner of the couple is >35 years old.[1] Other studies suggest the opposite, in that 20- to 24-year-old males had significantly higher adjusted prevalence ratios for trisomy 21 than fathers of APA.[1,69] APA has not been found to be associated with trisomy 18.[70,71] Fathers of APA were less likely to sire offspring with trisomy 13 and no relationship has been shown between APA and the birth of an offspring with anencephaly or encephalocele.[69] With regard to Klinefelter syndrome, the population risk is around 1 in 500,[72] and one study found this to be increased to 1 in 312 in men of APA >50 years old.[73] Other work has suggested that there is no significant relationship of APA with either the paternal or maternal age in Klinefelter syndrome.[1,74]

An association between increased rates of cancer in children of fathers with APA has been suggested. For example, childhood leukemia carries a risk of 1 : 25 000 within the general population; however, with APA the rate increases to 1 : 17 000, with a relative risk of 1.5.[75] An increase in non-Hodgkins lymphoma has been documented in cases of APA, independent of maternal age.[76,77] Similarly, Yip *et al.*[78] examined pediatric central nervous system tumors and found the risk of developing them to be 1 : 21 000 in the offspring of fathers with APA compared with that of the general population risk of 1 : 36 000. A case-controlled study conducted in North Korea examined the risk of breast cancer in offspring of fathers who had APA.[79] The authors found that APA increased the risk of breast cancer in female offspring, even when controlling for maternal age. Indeed, those women whose fathers were greater than 40 years had a 1.6-fold increase in breast cancer compared with those whose fathers were less than 30 years of age.[79] Controversy remains owing to an earlier case-controlled study comparing 1121 controls with 1253 breast cancer patients, which failed to identify an association between paternal age and breast cancer risk.[80]

Leo Kanner first described an association between paternal age and infantile autism in 1968.[81] Classified as a neurodevelopment disorder, autism usually presents by the age of three as social and behavioral abnormalities.[82] While the etiology of autism is not well understood, recent studies provide compelling evidence for a strong genetic link along with possible environmental influences.[83] Hultman *et al.*[83] examined a Swedish 10-year birth cohort (n=1 075 588) *via* linkage to a national autism patient registry to identify all reported autism cases (n=883). Following a meta-analysis, the authors found that the risk of autism increased with APA;[83] the increase was especially evident in the offspring of men >50 years old who were 2.2 times more likely to have autism than those children born to fathers aged 29 years or younger.[83] The authors concluded that a strong monotonic relationship existed between paternal age and autism, with fathers aged >50 years having a 2.7-fold increased risk of having an autistic offspring.[83] Similar findings were noted in a recent study by Kong *et al.*[84] who examined the genome-wide mutation rates of 78 Icelandic parent-offspring trios. Through whole genome sequencing, the authors discovered that mutations in single nucleotide polymorphisms were largely influenced by paternal age.[84] Simply put, paternal age determined the number of mutations that the offspring inherited. When considering these findings in the context of a series of studies published within the past year[85–87] implicating new paternal mutations as a cause of autism, it appears the links between APA, autism and other genetic diseases are likely to grow stronger in the future.

Other neuropsychiatric disorders such as schizophrenia and bipolar disorder have been studied in relationship to APA. A Swedish cohort of 50 087 adolescent males was investigated, and the authors deduced that APA was an independent risk factor for the development of schizophrenia.[88] Another Swedish cohort study identified 13 428 patients with a diagnosis of bipolar disorder on two separate hospital admissions.[89] After controlling for parity, maternal age, socioeconomic status and family history of psychiatric conditions, the offspring of men with APA (>55 years old) were 1.37 times more likely to be diagnosed with bipolar disorder.[89]

CONCLUSIONS

In modern times, couples have begun to push the limits of conception to the point that children are commonly born to parents of advanced maternal and paternal age. While the effects of maternal age are well described, APA carries both known[84] and unknown risks. Testicular function and sperm quality deteriorate with age. The development of ARTs, such as IVF with intracytoplasmic sperm injection, has allowed even the oldest of males, with the poorest of semen quality, to achieve conception. The risks involved, however, are only partially understood.[84–87] The offspring of fathers with APA exhibit increased rates of genetic abnormalities, cancers, autism and other psychiatric disorders.[1] Current practice guidelines[9] highlight a wide range of genetic disorders that may be increased with APA (**Table 1**). However, no screening or diagnostic evaluation currently exists to specifically test for disorders based on APA. If men of APA desire individualized

Table 1 A summary of the various conditions that may be affected in the offspring of men with advanced age. Further information and details are available in the source document from which this Table was adapted[9]

Condition	*Age (years)*	*Population risk*	*Adjusted risk with APA*
Achondroplasia	>50	1 : 15 000	1 : 1923
Apert	>50	1 : 50 000	1 : 5263
Crouzon	>50	1 : 50 000	1 : 6250
Neurofibromatosis 1	>50	1 : 3000–1 : 4000	1 : 810–1 : 1080
Retinoblastoma	>45	1 : 15 000–1 : 20 000	1 : 5,000–1 : 6667
Down syndrome (must use maternal age as baseline)	40–44	1 : 1200	1 : 876
Klinefelter syndrome	>50	1 : 500 men	1 : 312 men
Epilepsy	40–45	1 : 100	1 : 770
Schizophrenia	>50	1 : 100	1 : 22
Autism	>40	1 : 1000	1 : 174
Breast cancer	>40	1 : 8.5	1 : 5.3
Spontaneous miscarriage	>35	1 : 7	1 : 5.3
Preeclampsia	>44	1 : 62	1 : 50
Total risk (for the 86 examined congenital anomalies in Ref. 9)	>40	1 : 50	1 : 42

Abbreviation: APA, advanced paternal age.

genetic counseling, then an appointment should be arranged to address particular concerns.[9]

It is important to recognize that over time, the precision and accuracy of the semen analysis testing have improved. Proficiency programs are now in place allowing interlaboratory comparisons of accuracy.[42] The studies discussed in this review make comparisons that are clouded by regional variations as well as methodological bias; results further complicated by the baseline variability observed in the semen analyses of normal males.[42]

In conclusion, this review has summarized the current state of knowledge of advanced paternal age and its effects on semen quality, reproductive success and offspring health. We are currently moving towards an era where a man's reproductive age is considered as important as the females;[90] however, further work is required to elucidate the strength of these associations. It is our hope that this review will serve as a guide to physicians in counseling men about the decision to delay paternity and the risks involved with conception late in life.

COMPETING FINANCIAL INTERESTS

The authors have no competing financial interests.

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