

# Male biological clock: a critical analysis of advanced paternal age

Ranjith Ramasamy, M.D.,<sup>a,b</sup> Koji Chiba, M.D., Ph.D.,<sup>a,b</sup> Peter Butler, B.A.,<sup>a</sup> and Dolores J. Lamb, Ph.D.<sup>a,b,c</sup>

<sup>a</sup> Center for Reproductive Medicine, <sup>b</sup> Scott Department of Urology, and <sup>c</sup> Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas

Extensive research defines the impact of advanced maternal age on couples' fecundity and reproductive outcomes, but significantly less research has been focused on understanding the impact of advanced paternal age. Yet it is increasingly common for couples at advanced ages to conceive children. Limited research suggests that the importance of paternal age is significantly less than that of maternal age, but advanced age of the father is implicated in a variety of conditions affecting the offspring. This review examines three aspects of advanced paternal age: the potential problems with conception and pregnancy that couples with advanced paternal age may encounter, the concept of discussing a limit to paternal age in a clinical setting, and the risks of diseases associated with advanced paternal age. As paternal age increases, it presents no absolute barrier to conception, but it does present greater risks and complications. The current body of knowledge does not justify dissuading older men from trying to initiate a pregnancy, but the medical community must do a better job of communicating to couples the current understanding of the risks of conception with advanced paternal age. (*Fertil Steril*® 2015;103:1402–6. ©2015 by American Society for Reproductive Medicine.)

**Key Words:** Male infertility, genetics

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In recent years, advanced paternal age has become an increasingly significant concern as men and women delay starting families. Pregnancy outcomes related to maternal age include low birth weight, premature birth, and pregnancy loss (1), as well as any number of risks of birth defects after parturition. It has also been shown that the rate of chromosomal abnormalities increases exponentially in the offspring of women over the age of 35 (2). The effects of advanced maternal age are better understood than the effects of paternal age. Although rarely discussed with patients, advanced parental age presents risks to offspring by increasing

the chances of introducing genetic abnormalities that may lead to the emergence of serious diseases or birth defects.

Although there is a trend toward increasing average age at which men father children (Fig. 1) (3), the nature and effects of advanced paternal age are less studied, but the literature suggests that paternal age presents serious problems to the couple seeking to conceive a child. Advanced paternal age is associated with declines in the motility and morphology of spermatozoa, as well as in the rate of pregnancy and incidence of pregnancy loss, which compounds the effect of advanced maternal age on this outcome. In a

study evaluating donor assisted reproductive technology cycles, advanced paternal age negatively impacts embryo development and reproductive outcome (4). Advanced paternal age also increases the relative risk of offspring developing conditions such as neurocognitive defects, some forms of cancers, and syndromes related to aneuploidies. Physicians and their patients must be better informed of the risks and problems associated with advanced paternal age, but discussion with older couples seeking to conceive is confounded by the lack of a clear definition of this condition. The age of 35 is a discrete time point after which risks of adverse reproductive outcome are significantly increased for women, but there is no consensus on the existence or identity of such a time point for men.

This review seeks to summarize the problems couples with an older male partner may encounter in attempting to conceive and the risks to offspring that arise with advanced paternal age, as well as the disagreement among clinicians of how to define advanced paternal age.

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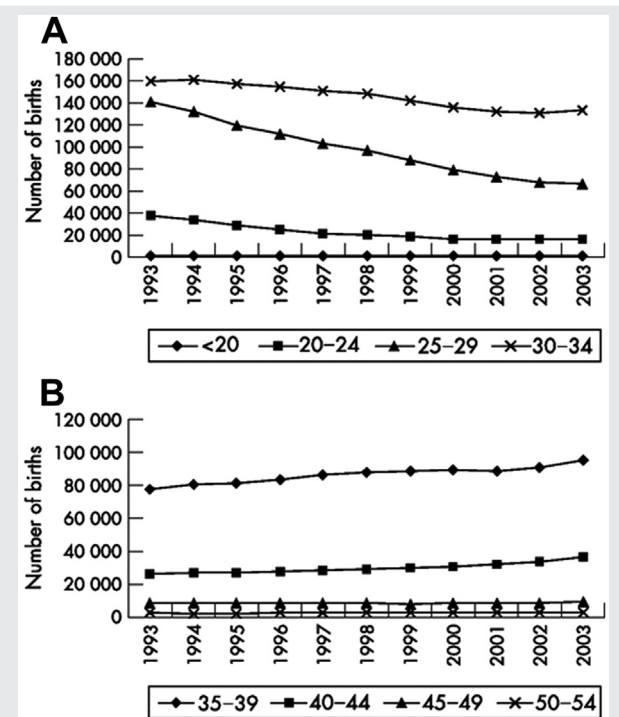
Reprint requests: Dolores J. Lamb, Ph.D., 1 Baylor Plaza, Alkek N730, Houston, Texas 77030 (E-mail: [dlamb@bcm.edu](mailto:dlamb@bcm.edu)).

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FIGURE 1



Trends in paternal age for live births within marriage in England and Wales, 1993–2003. (A) decreasing trends <35 years. (B) increasing trends 35–54 years. Source: Series FM1 no 32 (ONS, 2003). (Births to fathers over 54 years old account for less than 0.5% of live births within marriages and are not shown). Reproduced with permission from reference (3).

Ramasamy. Risks of advanced paternal age. *Fertil Steril* 2015.

## Barriers to Conception with Advanced Paternal Age

The impact of male age on fecundity remains controversial. A large population study, the Avon Longitudinal Study of Pregnancy and Childhood, investigated the effect of paternal age on time to conception (5). Compared with men <25 years old, the adjusted odds ratio for conception in  $\geq 12$  months was 0.5 in men  $\geq 35$  years of age, meaning that men older than 35 had a 50% lower chance of conceiving within 12 months than men <25 years of age, even after adjusted for maternal age. Admittedly, this conclusion is based on the conditional probability of conception within 6 or 12 months in couples who ultimately had a baby. This conclusion does not necessarily reflect the probability of conception in the population as a whole. Nevertheless, time to conception can provide a useful index of fecundity.

Several hormonal changes occur as a result of aging. T and sex hormone-binding globulin (SHBG) were measured in stored samples from 890 men in the Baltimore Longitudinal Study on Aging (6). After compensating for date effects, the investigators observed significant, independent, age-invariant, longitudinal effects of age on both free and total T. There was a steady decline in both concentrations together with increasing male age, accompanied by an increase in SHBG. Incidence of low T (<300 ng/dL) progressively

increased to about 20% in men over 60, 30% in those over 70, and 50% in those over 80 years of age (6). The decline in total and free T contributes to decreased libido and frequency of intercourse, impaired erectile function (7), and poor semen quality (8), all factors that may lead to decreased fecundity.

Several morphological changes that occur in testis histology and changes that occur in semen parameters with advanced age suggest evidence of deteriorating testicular function. The number of Leydig cells (9), Sertoli cells (10), and germ cells decreases with age (11). Semen analyses show a noticeable decrease in semen volume, sperm motility, and sperm morphology as men get older. Reports of the effect of advanced age on sperm density are inconsistent throughout the literature (8).

Spermatozoa from older men display less fertilizing potential after donor insemination (12), IUI (13), or IVF (14). One factor that might contribute to worse outcomes using assisted reproduction is increased DNA fragmentation. Several studies show that DNA fragmentation increases with male age (15, 16). In fact, in men between 60 and 80 years of age, the percentage of DNA fragmentation in ejaculated sperm is estimated to be 88% (15). A DNA fragmentation index above 30% is considered to be abnormal in most laboratories and potentially could be associated with less favorable outcomes with assisted reproduction (17). Both antioxidants (18) and varicocele repair were reported to decrease the probability of sperm DNA fragmentation (19), although from an evidenced-based medicine perspective many studies of significant sperm DNA fragmentation, in general, are conflicting and controversial.

Unfortunately, mature couples have an increased risk of miscarriage and preterm delivery. In a large retrospective population-based study of women aged 25–44 years in Denmark, Germany, Italy, and Spain (20), after adjustment for various factors (e.g., reproductive history, country), the investigators found that the risk of miscarriage was higher if the woman was  $\geq 35$  years old (as previously reported in a number of studies). However, the increase in risk was much greater for couples composed of a woman  $\geq 35$  years and a man  $\geq 40$  years. An association between paternal age and fetal loss strengthens the idea that paternal age influences the health of offspring via mutations of paternal origin. In another large prospective study of 23,821 pregnant women followed in the Danish National Birth Cohort study from 1997 to 1999 (21), pregnancies initiated by men 50 or older had a twofold increased risk of ending in fetal loss. This resulted in half the incidence of successful pregnancies initiated by younger fathers (after adjustment for maternal age, reproductive history, and maternal lifestyle during pregnancy). Taken together, these observations support the conclusion that the effects of paternal age on a couple's fecundity cannot be disregarded.

## Is There a Specific Age Threshold after Which Physicians Should Counsel Couples Regarding the Implications of Advanced Paternal Age on Outcomes?

Currently, in the absence of a clear definition, it is difficult for clinicians to engage patients in a meaningful discussion of

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