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Paternal Age Over 40 Years: The "Amber Light" in the Reproductive Life of Men?

Minireview

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In industrialized countries, many couples are choosing to delay childbearing, and the proportion of couples having children after age 30–35 years has increased. This has highlighted the effect of age on reproductive failure (van Balen et al, 1997). The effects of maternal age have been thoroughly investigated in the past few decades, and a major effect of maternal age over 35 years has been demonstrated on infertility, ectopic pregnancy, and miscarriage (van Noord-Zaadstra et al, 1991; van Balen et al, 1997; Nybo Andersen et al, 2000).

In contrast, little attention has been paid to the possible effects of paternal age. Most studies that have dealt with this factor have focused on changes in sperm characteristics with age, and physicians have tried to set an upper age limit for sperm donors. The American Society for Reproductive Medicine (1998) and the British Andrology Society (1999) have fixed the upper age limit for sperm donation at 40 years old on the basis of the increased risk of genetic abnormalities in children of older fathers (Bordson and Leonardo, 1991). In discussions of the effects of paternal age with a view toward setting age limits for sperm donors, the possibility that paternal age affects the likelihood of reproductive failure was not considered.

In other respects, some demographic studies have analyzed the effects of paternal age on effective fecundity, which is the probability of initiating a pregnancy leading to a live birth (Anderson, 1975; Mineau and Trussell, 1982; Goldman and Montgomery, 1989; Strassmann and Warner, 1998). These studies, based on large data sets from populations not using birth control methods, showed a decrease in effective fecundity with increasing paternal age. We reviewed the existing literature, analyzing the effect of paternal age on 2 major reproductive failures: infertility and miscarriage.

Methods

We searched MEDLINE, using the PubMed Searching system developed by the National Center for Biotechnology Information at the U.S. National Library of Medicine. We considered only references that dealt with studies of humans published in English. We selected articles analyzing reproductive failures on the basis of their having at least one of the following MEDLINE major keywords: infertility; fertility; fertilization; abortion, spontaneous; pregnancy outcome; fetal death; embryo loss; and pregnancy, ectopic. We selected references in which the term "paternal age" was a key word. We also included all references in which the term "paternal age" was present in the title or in the abstract, to reduce any search review bias toward the exclusion of nonsignificant results.

Our MEDLINE query[1] identified 35 references. We excluded 28 of these references because they were general reviews on the male reproductive tract (n = 4) or comments on another article (n = 1), they concerned infertile couples (n = 3), or they were irrelevant because they concerned diseases and malformations in the embryo and child (n = 5), paternal germ cell characteristics (n = 4), chromosomal analysis of dead fetuses (n = 4), professional and environmental exposure of the father (n = 3), teenage pregnancies (n = 2), the consequences of treatment for cryptorchidism (n = 1), or the consequences of consanguinity (n = 1). We therefore obtained a total of 7 relevant references from this MEDLINE search.

We checked the exhaustiveness of our list of references by cross-checking it with 1) references cited in these 7 articles, 2) the 7 sets of PubMed "related articles," and

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[1]After limiting our search to papers published in English, on humans, we used the following MEDLINE query: "paternal age"[All fields] AND ("infertility"[MESH Major Topic] OR "fertility"[MESH Major Topic] OR "fertilization"[MESH Major Topic] OR "abortion, spontaneous"[MESH Major Topic] OR "pregnancy outcome"[MESH Major Topic] OR "fetal death"[MESH Major Topic] OR "embryo loss"[MESH Major Topic] OR "pregnancy, ectopic"[MESH Major Topic]).

3) our reference database. We extended our search to all papers published since 1965 and identified 7 other references. Five of these 7 references were listed on MEDLINE. However, they were not found in our initial MEDLINE query because the term ''paternal age'' was absent. Unfortunately, we could not extend our MEDLINE search using synonyms such as ''male age,'' ''father age,'' or ''husband age'' because these terms are not phrases recognized by MEDLINE (PubMed does not actually perform adjacency searching but uses a list of recognized phrases against which search terms are matched).

Thus, in total, we identified 14 references that specifically analyzed the effects of paternal age on infertility and miscarriage (Table). Most of these papers (n = 11) concerned couples in the general population who were trying to conceive or who had conceived. In these papers, the authors adjusted for female factors (especially maternal age) by means of multivariate models. A few papers (n = 3) analyzed data from in vitro fertilization (IVF) programs involving ovum donation, to ensure efficient control for maternal factors as in these studies female donor factors were independent from paternal age. By considering such different data, we were able to compare the results of analyses with very different limitations: difficulties adjusting for confounders (especially for sexual confounders such as decreased frequency of intercourse with age) in natural reproduction and problems associated with gamete manipulation and selection bias in data from IVF with ovum donation.

Infertility

Infertility is defined as a failure to conceive in a couple trying to reproduce for ''some time.'' The World Health Organization has defined infertility as a period of 2 years without conception, but many couples actually seek medical advice after 1 year of infertility. Infertility is usually investigated by calculating time to pregnancy, which is the number of months required to achieve a recognized pregnancy for a couple having regular sexual intercourse in the absence of birth control methods. An increase in time to pregnancy may indicate changes in male and female gametogenesis, the transport of gametes in the male and female reproductive tracts, fertilization, migration of the zygote to the uterus, implantation, and the early survival of the conceptus until detection of the pregnancy (Baird et al, 1986). Thus, time to pregnancy is considered an accurate indicator of human fertility—not only for women but also for men (Joffe, 1997).

Joffe and Li (1994) carried out an analysis of a sample of men born in Britain in 1958, followed in a longitudinal study. They analyzed male and female factors affecting the time required to achieve a pregnancy in couples where the men (n = 2576) had fathered at least 1 child by the time of data collection in 1991, when all these men were aged 33 years. They used a multivariate Cox regression model to compare men who started attempting to father a pregnancy when they were 30 to 33 years old with those who attempted to father a pregnancy when they were less than 30 years old. They could not control for maternal age in their model because of incomplete data on female partner age. They found no difference in time to pregnancy between these 2 groups of men differing in paternal age, both of which consisted of men under the age of 33 years.

Olsen (1990) investigated the effects of maternal age and paternal age on the risk of taking more than 1 year to conceive for all pregnant women (n = 10 886) in two Danish cities from April 1984 to April 1987. A very weak effect of paternal age was observed in logistic regression analysis after controlling for maternal age. This author considered only pregnant women. This is a major limitation, which may have resulted in an underestimation of the effects of age, because of the exclusion or underrepresentation of sterile and less fecund couples (Juul et al, 2000).

The Australian Pregnancy and Lifestyle Study investigated sociodemographic, occupational, and environmental risk factors for infertility and miscarriage by interviewing couples (n = 585) who had planned a pregnancy (Ford et al, 1994). After 9 months of trying, 17.3% of couples had not yet achieved a pregnancy. The authors analyzed the effect of age on the risk of 9 months of infertility in a multivariate regression model in which partner's age effect was controlled. Taking less than 35 years as the reference age class, the authors showed that the risk of infertility was significantly higher in couples in which the man (odds ratio [OR], 2.31; 95% confidence interval [CI], 1.44–3.71) or the woman (OR, 2.19; 95% CI, 1.23–3.99) was more than 35 years old.

In the United Kingdom, the Avon Longitudinal Study of Pregnancy and Childhood was carried out between April 1991 and December 1992 on all couples expecting a baby in the Avon Health District. On the basis of planned pregnancies (n = 8515), Ford et al (2000) analyzed the probability of having conceived in a 6-month period and that of having conceived in a 12-month period. Multivariate logistic-regression analysis showed that the probability of conception decreased steadily with paternal age after controlling for maternal age. For example, for the probability of conceiving within a period of 12 months, the OR was 0.51 (95% CI, 0.31–0,86) for men aged 40 years and over when compared with fathers aged 24 years and younger. In this study, the authors analyzed paternal age at the time of conception rather than at the time when the couple started trying to conceive a child, leading to a potential overestimation of the effects of paternal age in cases in which the time to pregnancy was

Studies on the effect of paternal age on the risks of difficulties conceiving and miscarriage

Reference	Population studied	Reproductive outcome	Paternal age classes*	Paternal age effect?
Infertility				
Dunson et al, 2002	782 couples using natural family planning methods	Probabilities of pregnancy on various days of the menstrual cycle	19–26, 27–29, 30–34, 35–39, ≥40	+++
Paulson et al, 2001	558 IVF cycles with ovum donation	Clinical pregnancy	<38, 38–41, 42–46, >46	−
Watanabe et al, 2000	288 IVF cycles with ovum donation	Clinical pregnancy	<39 (ref), ≥39	+
Ford et al, 2000	8515 planned pregnancies	Infertility (6 and 12 months)	≤24 (ref), 25–29, 30–34, 35–39, ≥40	++
Gallardo et al, 1996	316 IVF cycles with ovum donation	Clinical pregnancy	31–40, 41–50, ≥51	−
Joffe and Li, 1994	2576 men aged 33 years who had fathered a child	Time to pregnancy	<30 (ref), 30–33	−
Ford et al, 1994	585 couples trying to conceive	Infertility (9 months)	<35 (ref), ≥35	++
Olsen, 1990	10 886 pregnancies	Infertility (12 months)	15–19 (ref), 20–24, 25–29, 30–34, 35–39, ≥40	−/+
Nieschlag et al, 1982	43 men who had fathered a child	Ovum penetration (HOP test)	24–37 (ref), 60–88	−
Miscarriage				
de La Rochobrochard and Thonneau, 2002	3174 planned pregnancies	Miscarriage	20–29 (ref), 30–34, 35–39, ≥40	+++
al-Ansary and Babay, 1994	Hospital patients: 226 miscarriages and 226 controls	Miscarriage	<30 (ref), 30–34, 35-39, 40–49, ≥50	++
Ford et al, 1994	484 planned pregnancies	Miscarriage (first trimester)	<35 (ref), ≥35	++
Wunsch and Gourbin, 1998	611 000 birth and death certificates	Late fetal death and neonoatal mortality	<35 (ref), ≥35	+
Selvin and Garfinkel, 1976	1.5 million birth and fetal death certificates	Late spontaneous abortion	. . .	+
Resseguie, 1976	Birth and fetal death certificates	Late spontaneous abortion	. . .	−

* In case of multivariate regression analysis, the reference class is indicated by ref.

long (resulting in older fathers) (Sallmen and Luukkonen, 2001).

A European multicenter study was recently conducted on a large cohort of couples (n = 782) using natural family planning methods to avoid pregnancy (Dunson et al, 2002). The authors estimated the probability of conception on various days in the menstrual cycle. This fertility indicator allowed the analysis of risk factors (such as maternal and paternal age) by taking into account sexual activity. The authors investigated paternal age by controlling for the maternal age effect. For couples in which the woman was aged 35 to 39 years, Dunson et al (2002) observed a decrease in the probability of conception for men in their late thirties or older. For a woman aged 35 years having intercourse on the most fertile day of the menstrual cycle, the probability of conception decreases from 0.29 if the man is aged 35 years to 0.18 if the man is aged 40 years.

A few studies have analyzed paternal age using data from IVF programs involving ovum donation. On the one hand, these data allowed analysis of paternal age without possible confusion with sexual activity. On the other hand, maternal factors were controlled more efficiently, because there was no relationship between paternal age and oocyte factors (such as age of the female donor or the number of oocytes retrieved). Watanabe et al (2000) analyzed 288 cycles performed at a French IVF center and concluded that the rate of clinical pregnancy decreased with increasing paternal age when 5 or fewer oocytes were retrieved. An analysis of 316 cycles from an American IVF center and 558 cycles from a Spanish IVF center showed no effect of male age on the rate of clinical pregnancy (Gallardo et al, 1996; Paulson et al, 2001). In these studies, the authors did not control for the number of oocytes retrieved, which is a key predictive factor.

Finally, Nieschlag et al (1982) investigated paternal age by comparing 23 grandfathers aged 60 to 88 years with 20 fathers aged 24 to 37 years. The men were recruited by newspaper advertisements and were asked to supply semen samples by masturbation after sexual abstinence for 2 to 7 days. The fertilizing capacity of the sperm was assessed by the Heterologous Ovum (HOP) test for 16 grandfathers and 20 fathers. The authors found no difference between the grandfathers and fathers in these 2 groups, each of which contained only a small number of subjects.

Miscarriage

As was stated by Nybo Andersen et al (2000), more than 13% of clinically recognized pregnancies end in fetal death. Most of these deaths occur during the first trimester of gestation and are defined as miscarriages. The term ''late fetal death'' is generally used to refer to deaths occurring after 20 weeks of gestation, and the term ''stillbirth'' is used for deaths occurring after 28 weeks of gestation.

In a case-control study carried out in a University Hospital in Saudi Arabia (n = 226 cases and 226 controls), Al-Ansary and Babay (1994) analyzed the risk factors for miscarriage before 24 weeks of gestation. After controlling for maternal age effect, they showed that the risk of miscarriage increased with paternal age, especially when fathers were aged more than 50 years. Surprisingly, these authors found no evidence of the well-documented effect of maternal age, possibly because of the small number (n = 38) of enrolled women who were aged 35 years or over.

Ford et al (1994) used a logistic regression model to analyze risk factors for first trimester miscarriage in couples (n = 484) who achieved a recognized pregnancy in the Pregnancy and Lifestyle Study (Ford et al, 1994). They considered only 2 age classes (<35 and ≥ 35 years), and, after controlling for maternal age effect, they found that the risk of miscarriage was higher in couples in which the man was aged 35 years or older, with an OR of 2.33 (95% CI, 1.41–3.84), than in men younger than age 35 years.

de La Rochebrochard and Thonneau (2002) analyzed data from a large study on subfecundity and infertility carried out in 4 European countries (n = 3174); they used a multivariate logistic regression model to analyze the risk of miscarriage. By controlling for maternal age, they concluded that the risk of miscarriage increased steadily with paternal age for men aged 40 years and older, especially if the mother was aged 35 years or older. Thus, in this study, compared with couples in which both partners were aged 20 to 29 years, the OR for women aged 35 years or older increased with paternal age from 3.38 (95% CI, 1.76–6.47) if the man was aged 35–39 years to 6.73 (95% CI, 3.50–12.95) if the man was aged 40 years or older.

In a paper published in 1976, Resseguie (1976) analyzed live births and fetal death certificates from Wisconsin for the years 1968 to 1971. That author compared the risk of late fetal death (after 20 weeks of gestation) for various paternal age classes by chi-square tests in subpopulations defined by birth order, maternal age class, and number of years of maternal education completed. No increase was observed in the risk of late fetal death with paternal age.

On the basis of more than 1.5 million live births and fetal death certificates from New York State for the years 1959–1967, Selvin and Garfinkel (1976) analyzed the risk of late fetal death (after 20 weeks of gestation) by multivariate logistic-regression analysis. After controlling for partner's age, they obtained an OR of 1.027 for a 1-year increase in paternal age and of 1.032 for a 1-year increase in maternal age. These authors concluded that paternal age and maternal age have independent and approximately equal effects on the risk of late fetal death. Neverthe-

less, this model is based on the assumption that the effect of age (both maternal and paternal) is linear. This assumption is controversial—the effect of age on the risk of reproductive failure is usually considered to follow a J-shaped curve (Nybo Andersen et al, 2000).

Wunsch and Gourbin (1998) recently studied the effect of paternal age on stillbirth (death after 28 weeks of gestation), neonatal mortality (death during the first 28 days of life), and postneonatal mortality (death in the first 12 months of life) by analyzing birth and death certificates from Belgium (1986–1990) and Hungary (1984–1988). After adjustment for confounding factors (especially maternal age), these authors concluded that paternal age 35 years or older increased the risks of stillbirth and of neonatal mortality.

Conclusion

Our analysis provides some evidence that increasing paternal age increases the risk of reproductive failure. Almost all of the published studies on the effects of paternal age on miscarriage have concluded that the risk of miscarriage and late fetal death were higher for couples in which the man was 35 to 40 years or older than in couples in which the man was younger than 35 years.

We found that some of the results of studies on paternal age and the risk of infertility were discordant. However, it appeared to us that this discordance resulted principally from the major limitations of inconclusive studies. These were mainly the limitation of observations to a particular male age interval (eg, under 33 years), lack of adjustment for major confounders (such as the number of oocytes retrieved in IVF with ovum donation studies), or consideration only of limited measures of the reproductive process (such as heterologous ovum tests). After detailed discussions of each of these studies, we concluded that, overall, the published studies provided evidence increased risk of infertility with paternal age. Furthermore, the effect of paternal age on infertility was investigated in very heterogeneous populations: couples from the general population who had tried to conceive or had conceived a child versus data for IVF with ovum donation. In both populations, an effect of paternal age was identified in men in their late thirties. Confirmation is required for the results obtained for IVF with ovum donation, but the overall concordance of results obtained for such different populations provides further evidence for the existence of a paternal age effect. This process of comparing results from very different populations has already been used to demonstrate the well-known effect of maternal age. Thus, conclusions concerning the effects of maternal age are based not only on studies of couples trying to conceive or who have conceived (van Balen et al, 1997) but also on data from studies of intrauterine insemination with donor spermatozoa (Schwartz and Mayaux, 1982).

In both types of reproductive failure investigated in these reviews, we concluded that the risk may be greater when the man is aged 40 years or older. The age of 40 has also been established as the upper age limit for sperm donors because of an increased risk of genetic abnormalities in children of these fathers (American Society for Reproductive Medicine, 1998; British Andrology Society, 1999). Paternal age over 40 years could thus be a cutoff in the reproductive life of men.

In the present review, we considered only the effect of paternal age in the general population and in cases of IVF with ovum donation (used to analyze the effects of paternal age because it concerned an infertile female population). Other unanswered questions remain concerning paternal age, such as its effect on success rates in assisted reproductive techniques (ART). On the basis of 821 intracytoplasmic sperm injections carried out in a New York infertility center, Spandorfer et al (1998) found no effect of paternal age on success rates after adjusting for the effects of maternal age by including only women under age 35 years. In contrast, by analyzing data from intrauterine artificial insemination with the husband's spermatozoa, Mathieu et al (1995) concluded that paternal age over 35 years was an important predictive factor of success, after controlling for maternal age. So, in ART, conclusions concerning the effects of paternal age may differ considerably according to the technique examined.

Various hypotheses that might account for the effect of paternal age on the risk of reproductive failure have been considered. For example, the possible contribution of paternal age to the occurrence of fetal trisomies has been disputed and remains controversial (Griffin et al, 1995; Sartorelli et al, 2001). Here, we present only the 2 major hypotheses: changes in sperm production and increased risk of mutation in male germ cells (Vermeulen and Kaufman, 1995; Tserotas and Merino, 1998).

Changes in semen with age were demonstrated in a recent exhaustive review, which concluded that semen volume, sperm motility, and sperm morphology deteriorated with age, following an analysis that compared men aged 50 years with men aged 30 years (Kidd et al, 2001). In line with the results obtained by Bonde et al (1998) in a cohort of 430 Danish couples, such age-related changes in sperm concentration and morphology may lead to an increase in time to pregnancy. However, a number of unresolved questions remain concerning changes in sperm characteristics with male age. In particular, Kidd et al (2001) were unable to draw firm conclusions concerning the possible existence of an age threshold or the shape of the relationship (eg, linearity) between age and changes in sperm characteristics. Moreover, studies on changes in sperm characteristics with age must be analyzed with care

because of possible confounders (especially duration of abstinence) and selection biases (especially in clinic-based studies).

Several authors have also concluded that the effects of paternal age may be mediated by a genetic mechanism, with an increase in the risk of autosomal dominant diseases (American College of Obstetricians and Gynecologists Committee, 1997; Tarin et al, 1998). Indeed diseases such as Apert syndrome, Marfan syndrome, and Waardenburg syndrome all show a strong paternal age effect (see review by Crow, 2000). The vast majority of underlying mutations associated with paternal age are single base-pair substitutions that may be a consequence of the greater ratio of germ cell divisions between males and females. Increased incidence of mutations with age could be the result of reduced fidelity of DNA replication and repair mechanisms. Other types of mutations (small intragenic deletions and chromosome rearrangements) do not show a paternal bias, with the exception of large deletions such as loss of chromosome 18q, 4p, and 5p. However, it remains to be determined whether a paternal age effect is associated with the paternal bias observed for these forms of chromosomal deletion and also with the paternal bias observed in the expansion of trinucleotide repeats in diseases such as Huntington disease and myotonic dystrophy (Crow, 2000). All of these factors could be expected to result in reduced fertility and an increased incidence of miscarriage.

In conclusion, our analysis of the existing literature on the effects of paternal age on the risk of reproductive failure suggests that 40 years could be considered to be the ''amber light'' in the reproductive life of men, just as 35 years is considered to be the ''amber light'' in the reproductive life of women (Gosden and Rutherford, 1995). Nevertheless, because of the relatively small number of published large-scale studies analyzing paternal age, our hypothesis of a cutoff age in male fertility must be confirmed by analyzing reproductive issues according to male and female ages in other large databases.

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