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► **To cite this version:**

Elise de La Rochebrochard, Ken Mcelreavey, Patrick Thonneau. Paternal Age Over 40 Years: The “Amber Light” in the Reproductive Life of Men?. *Journal of Andrology*, 2003, 24 (4), pp.459-465. <10.1002/j.1939-4640.2003.tb02694.x>. <hal-02264970>

HAL Id: hal-02264970

<https://hal.science/hal-02264970v1>

Submitted on 8 Aug 2019

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La Rochebrochard Elise (de), McElreavey Ken, Thonneau Patrick, 2003, "Paternal age over 40 years: the "amber light" in the reproductive life of men?", **Journal of Andrology** [now known as: Andrology], 24(4), p. 459-465.
DOI: 10.1002/j.1939-4640.2003.tb02694.x

**Paternal age over 40 years:
the "amber light" in the reproductive life of men?**

ELISE DE LA ROCHEBROCHARD ^{*}, KEN McELREAVEY [†], PATRICK THONNEAU [‡]

From the Departments of

^{*} Public Health – Epidemiology – Human Reproduction, INSERM Unit 569, Bicêtre Hospital,
94275 Le Kremlin-Bicêtre, France

[†] Reproduction, Fertility and Populations, Pasteur Institute, 75015 Paris, France

[‡] Human Fertility Research Group, INSERM, La Grave Hospital, 31052 Toulouse, France

Correspondence to: Dr P. Thonneau, Human Fertility Research Group, La Grave Hospital,
Place Lange, 31059 Toulouse Cedex 9, France

Running head: de La Rochebrochard *et al.*, Paternal age over 40 years

Abstract

Background. Although paternal age may be a risk factor for reproductive failure, unlike maternal age it has received little attention. We reviewed the existing literature, analyzing the effect of paternal age on two main reproductive failures: infertility and miscarriage.

Methods. We searched MEDLINE with the keyword “paternal age” and checked the exhaustiveness of our list of references.

Results. We found that published studies provided evidence that increasing paternal age could be a risk factor for reproductive failure. Several studies indicated that the risk of infertility increases in men in their late thirties. Furthermore, increased risk of miscarriage and late fetal deaths has been found when fathers were aged 35-40 years and over.

Conclusions. The age of 40 years may be the male equivalent of the so-called “amber light” at 35 years in the reproductive life of women. Confirmation of the existence of a “cut-off age” in male fertility requires further investigation in large scale studies.

Key words. Spontaneous abortion / Fertility / Fetal death / Infertility / Paternal age

Introduction

In industrialized countries, many couples are choosing to delay childbearing and the proportion of couples having children after the age of 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 last few decades and a major effect of maternal age over 35 years on infertility, ectopic pregnancy and miscarriage has been demonstrated (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 dealing 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 and the British Andrology Society have fixed the upper age limit for sperm donation at 40 years (American Society for Reproductive Medicine, 1998; British Andrology Society, 1999) based on 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 to 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 fecundability, 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 fecundability with increasing paternal age.

We reviewed the existing literature, analyzing the effect of paternal age on two 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 in 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 / pregnancy, ectopic. We selected references in which the term ‘paternal age’ was a key words. We also included all references in which the term ‘paternal age’ was present in the title or in the abstract in order to reduce any ‘search review’ bias toward the exclusion of non-significant 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 because they were irrelevant as 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 seven relevant references from this MEDLINE search.

We checked the exhaustiveness of our list of references by cross-checking it with: (i) references cited in these seven articles, (ii) the seven sets of PubMed ‘related articles’, and (iii) our reference database. We extended our search to all papers published since 1965, and identified seven other references. Five of these seven 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', 'husband age', because these terms are not 'MEDLINE recognized phrases' (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 two years without conception but many couples actually seek medical advice after one 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 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 ($n=2,576$) had fathered at least one child by the time of data collection in 1991, when all these men were aged 33 years (Joffe and Li, 1994). They used a multivariate Cox regression model to compare men who started attempting to father a pregnancy when they were 30-33 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 two groups of men differing in paternal age, both consisting of men under the age of 33 years.

Olsen investigated the effects of maternal age and paternal age on the risk of taking more than one year to conceive for all pregnant women ($n=10,886$) in two Danish cities from

April 1984 to April 1987 (Olsen, 1990). 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, due to the exclusion or under-representation of sterile and less fecund couples (Juul *et al.*, 2000).

The Australian Pregnancy and Lifestyle Study (PALS) 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 nine months of trying, 17.3% of couples had not yet achieved a pregnancy. The authors analyzed the effect of age on the risk of nine months of infertility in a multivariate regression model in which partner's age effect was controlled. Taking <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 of 2.31, 95% CI: 1.44, 3.71) or the woman (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 (ALSPC) was carried out between April 1991 and December 1992 on all couples expecting a baby in the Avon Health District. Based on planned pregnancies ($n=8,515$), W. Ford *et al.* analyzed the probability of having conceived in a six-month period and that of having conceived in a 12-month period (Ford *et al.*, 2000). 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, when compared with fathers aged ≤ 24 years. In this study, the authors analyzed paternal age at the time of conception rather than that 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 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 analysis of risk factors (such as maternal age and paternal age) by taking account of sexual activity. The authors investigated paternal age by controlling for maternal age effect. For couples in which the woman was aged 35-39 years, Dunson *et al.* 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 *in vitro* fertilization (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, number of oocytes retrieved). Watanabe *et al.* analyzed 288 cycles performed at a French IVF center and concluded that the rate of clinical pregnancy decreased with increasing paternal age when five or less oocytes were retrieved (Watanabe *et al.*, 2000). 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.* investigated paternal age by comparing 23 grandfathers aged 60-88 years with 20 fathers aged 24-37 years (Nieschlag *et al.*, 1982). The men were recruited by newspaper advertisements and were asked to supply semen samples by masturbation after sexual abstinence for 2-7 days. The fertilizing capacity of the sperm was assessed by the Heterologous Ovum Test (HOP test) for 16 grandfathers and 20 fathers. The authors found no difference between the grandfathers and fathers in these two groups, each of which contained only a small number of subjects.

Miscarriage

As stated by Nybo Andersen *et al.*, more than 13 percent of clinically recognized pregnancies end in fetal death (Nybo Andersen *et al.*, 2000). 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' 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 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 over 50 years (al-Ansary and Babay, 1994). Surprisingly, these authors found no evidence of the well-documented effect of maternal age, possibly due to the small number ($n=38$) of enrolled women who were aged 35 years or over.

J. Ford *et al.* 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 two age classes ($<35 / \geq 35$ years), and after controlling for maternal age effect, they found that the risk of miscarriage was higher in couples in which the man was 35 years old or older, with an OR of 2.33 (95% CI: 1.41, 3.84), than in men under the age of 35 years.

de La Rochebrochard and Thonneau analyzed data from a large study on subfecundity and infertility carried out in four European countries ($n=3,174$); they used a multivariate logistic regression model to analyze the risk of miscarriage (de La Rochebrochard and Thonneau, 2002). By controlling for maternal age, they concluded that the risk of miscarriage increased steadily with paternal age for men aged 40 years and over,

especially if the mother was aged 35 years or over. Thus in this study, compared to couples in which both partners were aged 20-29 years, the OR for women aged ≥ 35 years 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 over.

In a paper published in 1976, Resseguie analyzed live births and fetal death certificates from the State of Wisconsin (USA) for the years 1968 to 1971 (Resseguie, 1976). The 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.

Based on more than 1.5 million live births and fetal death certificates from New York State for the years 1959-1967, Selvin and Garfinkel analyzed the risk of late fetal death (after 20 weeks of gestation) by multivariate logistic regression analysis (Selvin and Garfinkel, 1976). After controlling for partner's age, they obtained an OR of 1.027 for a one-year increase in paternal age and of 1.032 for a one-year increase in maternal age. Selvin and Garfinkel concluded that paternal age and maternal age have independent and approximately equal effects on the risk of late fetal death. Nevertheless, 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 usually being considered to follow a J-shaped curve (Nybo Andersen *et al.*, 2000).

Wunsch and Gourbin 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 post-neonatal mortality (death in the first 12 months of life) by analyzing birth and death certificates from Belgium (1986-1990) and Hungary (1984-1988) (Wunsch and Gourbin,

1998). After adjustment for confounding factors (especially maternal age), Wunsch and Gourbin concluded that paternal age ≥ 35 years 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 the published studies on the effects of paternal age on miscarriage concluded that the risk of miscarriage and late fetal death were higher for couples in which the man was 35-40 years old or older than in couples in which the man was younger than 35.

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 limitation of observations to a particular male age interval (for example 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). Following 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 types of population, 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 40 years or older. Forty years 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 cut-off in the reproductive life of men.

In these reviews, 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). Based on 821 ICSI carried out in a New York infertility center, Spandorfer *et al.* found no effect of paternal age on success rates after adjusting for the effects of maternal age by including only women under the age of 35 years (Spandorfer *et al.*, 1998). In contrast, by analyzing data from intrauterine artificial insemination with the husband's spermatozoa, Mathieu *et al.* concluded that paternal age over 35 years was an important predictive factor of success, after controlling for maternal age (Mathieu *et al.*, 1995). 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 two 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 comparing men aged 50 years with men aged 30 years (Kidd *et al.*, 2001). In line with the results obtained by Bonde *et al.* 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 (Bonde *et al.*, 1998). However, a number of unresolved questions remain concerning changes in sperm characteristics with male age. In particular, Kidd *et al.* were unable to draw firm conclusions concerning the possible existence of an age threshold or the shape of the relationship (e.g. 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 which 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, 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 if 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 these factors could be expected to result in reduced fertility and 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, due to the relatively small number of published large scale studies analyzing paternal age, our hypothesis of a ‘cut-off 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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Notes

(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])

Table. 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 <i>et al.</i> , 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 <i>et al.</i> , 2001	558 IVF cycles with ovum donation	Clinical pregnancy	<38 / 38-41 / 42-46 / >46	-
Watanabe <i>et al.</i> , 2000	288 IVF cycles with ovum donation	Clinical pregnancy	<39 (ref) / ≥39	+
Ford <i>et al.</i> , 2000	8,515 planned pregnancies	Infertility (6 and 12 months)	≤24 (ref) / 25-29 / 30-34 / 35-39 / ≥40	++
Gallardo <i>et al.</i> , 1996	316 IVF cycles with ovum donation	Clinical pregnancy	31-40 / 41-50 / ≥51	-
Joffe and Li, 1994	2,576 men aged 33 years who had fathered a child	Time to pregnancy	<30 (ref) / 30-33	-
Ford <i>et al.</i> , 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 <i>et al.</i> , 1982	43 men who had fathered a child	Ovum penetration (HOP test)	24-37 (ref) / 60-88	-
MISCARRIAGE				
de La Rochebrochard and Thonneau, 2002	3,174 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 <i>et al.</i> , 1994	484 planned pregnancies	Miscarriage (first trimester)	<35 (ref) / ≥35	++
Wunsch and Gourbin, 1998	611,000 birth and death certificates	Late fetal death and neonatal 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)'.