Human Reproduction Update, Vol.16, No.1 pp. 65–79, 2010
Advanced Access publication on August 20, 2009 doi:10.1093/humupd/dmp027

human reproduction update

Paternal age and reproduction

Gideon A. Sartorius[1,2] and Eberhard Nieschlag[1,3]

[1]Centre of Reproductive Medicine and Andrology of the University, Domagkstrasse 11, D-48149 Muenster, Germany [2]Present address: University Women's Hospital Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland

[3]Correspondence address. E-mail: eberhard.nieschlag@ukmuenster.de

TABLE OF CONTENTS

- Introduction
- Methods
- Results
  - Sociological/epidemiological aspects
  - Paternal age and reproductive hormones
  - Paternal age and sexual function
  - Paternal age, testicular morphology and semen parameters
  - Paternal age and toxicity/environmental factors
  - Paternal age and infections
  - Paternal age and genetics
  - Paternal age and fertility
  - Paternal age and pregnancy-associated complications
  - Paternal age and outcome of offspring
- Discussion and Conclusion
- Supplementary data

BACKGROUND: Due to various sociological factors, couples in developed countries are increasingly delaying childbearing. Besides ethical, economical and sociological issues, this trend presents us with several complex problems in reproduction. Although it is well-known that maternal age has a negative effect on fertility and increases the risk of adverse outcome during pregnancy and in offspring, the paternal influence on these outcomes is less well researched and not well-known.

METHODS: We performed a systematic search of PubMed, and retrieved original articles and review articles to update our previous survey in this journal.

RESULTS: This review highlights the link between male age and genetic abnormalities in the germ line and summarizes the knowledge about the effects of paternal age on reproductive function and outcome. Increasing paternal age can be associated with decreasing androgen levels, decreased sexual activity, alterations of testicular morphology and a deterioration of semen quality (volume, motility, morphology). Increased paternal age has an influence on DNA integrity of sperm, increases telomere length in spermatozoa and is suggested to have epigenetic effects. These changes may, at least in part, be responsible for the association of paternal age over 40 years with reduced fertility, an increase in pregnancy-associated complications and adverse outcome in the offspring.

CONCLUSION: Although higher maternal age can be an indication for intensive prenatal diagnosis, including invasive diagnostics, consideration of the available evidence suggests that paternal age itself, however, provides no rationale for invasive procedures.

Key words: aging male / semen parameters / fertility / genetic risk / pregnancy complications

Introduction

Reports about old fathers have a persistent fascination; the bible mentions Methusalem (father of Noah) fathering his son Lamech at the age of 187 years, and further sons and daughters after that before dying at the age of 782 (Old Testament, Genesis, 5.25–5.30). The oldest age of paternity noted in a scientific publication was 94 years (Seymour *et al.*, 1935). More recent examples of older fathers include the media mogul Rupert Murdoch who became a father at age 72 and the Spanish gynecologist and former head of the fertility, sterility

Table I Effects of male age on reproductive function: overview

Parameters of reproductive function	Effect of male age	Specific effects with increasing age
Reproductive hormones	Yes	FSH level: increasing, testosterone level: decreasing
Sexual function	Yes	Sexual activity: decreasing, male sexual dysfunction: increasing
Testicular morphology	Yes	Sertoli cells: number (n) decreasing, Leydig cells: n decreasing, germ cells: n decreasing, thickness of basal membrane of seminiferous tubules: increasing, testicular size: unchanged (until the eighth decade)
Semen: sperm parameters	Yes	Concentration: unchanged, motility: decreasing, morphology: normal forms: decreasing
Semen parameters: semen	Yes	Volume: decreasing, fructose level: decreasing, α-glucosidase level: decreasing, zinc level: decreasing, PSA level: decreasing
Infections of the accessory glands	Yes	Prevalence: increasing
Vascular disease	Yes	Vascularization of testicular parenchyma: decreasing
Genetics: sperm aneuploidies	Yes	Chromosomes 3,6,7,8,10,11,12,13,14,17: unchanged; 1,19,18,21, x,y: conflicting results
Genetics: aneuploidies in offspring	Yes	Trisomy 21: increasing, trisomy 13: decreasing, trisomy 18: unchanged, other trisomies: unchanged, sex chromosomes: unchanged
Genetics: DNA integrity	Yes	DNA damage: increasing
Genetics: telomeres (TL)	Yes	Telomere length in spermatozoa: increasing, TL in peripheral leucocytes: decreasing
Genetics: epigenetics	Yes	Methylations in somatic cells: increasing, methylations in germ cells: suggested
Fertility	Yes	Fertility: decreasing (male age effect in couples with female >35 years)
Miscarriage	Yes	Miscarriage rate: increasing (male age effect in couples with female >35 years)
C-section	Yes	C-section rate: increasing
Pre-eclampsia	Yes	Increasing for fathers younger than 25 and older than 35 years
Trophoblast disease	Yes	Increasing
Placenta previa/placental abruption	Inconclusive	Not conclusive
Preterm birth	Yes	Increasing in teenage fathers, conflicting results for higher paternal age
Adverse outcome in offspring	Yes	Increasing (clear evidence for certain diseases)

Overall summary of paternal age effects on parameters of reproductive function. Column 2 ('Effect of male age') sums up, whether paternal age (independent of whether low or high) has any known influence, whereas column 3 ('Specific effects with increasing age') shows specifically effects of increased paternal age.

and family planning unit of a maternity clinic in Madrid, Dr Julio Iglesias Senior. At age 89 he fathered a baby girl, who was born in 2006 and became a 61 year younger sister of the successful singer Julio Iglesias and an aunt to singer Enrique (Keeley, 2005).

Beyond anecdotal and mythical interest, the issue of fertility in advanced age is becoming more and more important as couples delay childbearing toward later stages in their lives. This is due to increased life expectancy, advances in assisted reproductive techniques (ART) and changing sociological factors, as for example planning to start a family which often only begins after establishment of professional careers.

Women experience an age-dependent increase in various adverse reproductive events such as infertility, pregnancy complications and perinatal maternal morbidity and mortality, as well as an impaired perinatal and post-natal outcome of the offspring (Schwartz and Mayaux, 1982; Cnattingius *et al*., 1992; Nybo Andersen *et al*., 2000; Pal and Santoro, 2003; Jacobsson *et al*., 2004; Cleary-Goldman *et al*., 2005). Although female fertility reaches a natural limit by the occurrence of menopause, male reproductive functions alter only slowly over a period of years and androgen production, spermatogenesis and sexual function are basically sustained lifelong, albeit with age-dependent alterations.

Increasing evidence shows that advanced paternal age is associated with changes in reproductive functions on different levels: the production of reproductive hormones, sexual function, semen production, fertility, pregnancy outcome and the incidence of some birth defects and diseases in offspring are all linked to paternal age (as reviewed in this journal by Kühnert and Nieschlag, 2004). The present overview updates their review 'Reproductive functions of the aging male' and refers to it for certain aspects omitted here. However, in order to cover all important effects of male age on reproduction, we repeat essential facts whereas other aspects, as for example pregnancy-associated complications are now covered more extensively (Table I).

Methods

This narrative review updates a previous overview (Kühnert and Nieschlag, 2004), including newly retrieved data based on a systematic PubMed search for literature published after January 2004 using the key words 'paternal age', 'male age', 'age' or 'aging' in combination with ([AND]) 'male fertility', 'fertility', 'semen', 'sperm', 'genetics', 'aneuploidy', 'mutation', 'epigenetics', 'telomere length' (TL) or 'DNA damage'. In addition we searched references cited in the retrieved articles. The main

search was completed by one author (G.A.S.) whereas screening of titles, abstracts and full text articles were completed by both authors. Suitable for inclusion were original articles of any design and review articles published in English, German and French as well as book chapters. The selection criteria were open and inclusive and aimed at covering the wide range of issues within the broad topic of this review.

The quality of studies included covers all evidence levels with the majority having evidence level B according to the rating system of the American College of Cardiology (Silber, 2006). Most of the studies retrieved and included were observational studies in which outcomes were assessed according to male age.

The selection of issues covered in this overview aimed at synthesizing the state of current knowledge relevant for clinicians in their daily work.

In order to keep our overview compact, we referred for certain aspects to recent reviews by other authors (e.g. fertility and environmental aspects) or to our previous review. Consulting the previous review will give additional, more detailed information of certain topics (e.g. semen parameters, aneuploidy), especially about the literature prior to 2004. However, as our article should be compact and comprehensive at the same time, we included some of the most relevant articles cited in our first overview according to the above mentioned selection criteria.

Results

Sociological/epidemiological aspects

Couples in the industrialized world are increasingly postponing childbearing. The mean age of childbearing mothers increased over the last decades, mainly due to a rising birth rate for women aged 35 and older (Fig. 1). To a certain extent this development is linked to ART and their medical implications, which, for example, are reflected in the dramatic increase of multiple deliveries in women of advanced age. US-American birth data from 2005 show that 1 out of 18 births to women aged 35 or above comprises a multiple delivery, compared with 1 out of 33 births to women under 35 years of age. The total number of births to women aged 50–54 years rose to 417 in 2005 ($n = 144$ in 1997), of which every second birth was part of a multiple delivery (Martin *et al*., 2007).

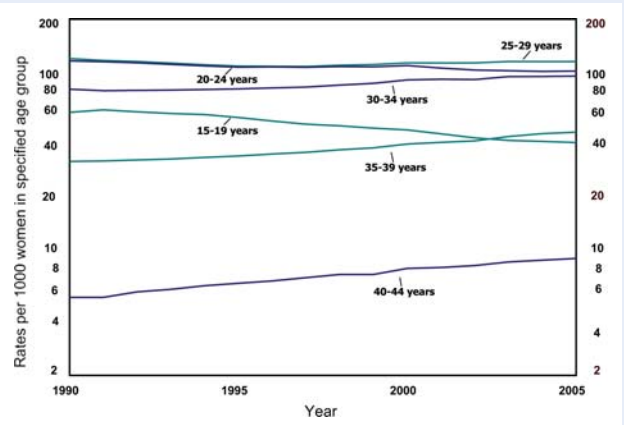

Figure 1 Birth rates by age of mother: USA, 1990–2005.

Rate per 1000 women in specified maternal age groups. Please note that the birth rates are plotted on a log scale (with permission from Martin *et al.*, CDC/NCHS, 2007).

The age of fathers is often not reported on birth certificates, thus paternal age is difficult to evaluate. However, the rate of paternity for men aged 30–49 years rose continuously since 1980, whereas paternity of men aged 25–29 has shown a decreased rate since 1980 (from 123.1 per 1000 men to 104.7 in 2005) (Martin *et al*., 2007).

Paternal age and reproductive hormones

Increasing male age has an impact on every level of the hypothalamo–pituitary–testicular axis, leading to decreased circulating androgen levels and ultimately to reduced androgenic effects at target organs (Juul and Skakkebaek, 2002; Kaufman and Vermeulen, 2005). Secondarily hypogonadal subjects can suffer from different, mostly unspecific symptoms, including sexual dysfunction. Of infertile men, 20–30% have low testosterone levels, but no positive effect of testosterone substitution on sperm production was shown in these subjects (Lombardo *et al*., 2005). Although the role of gonadotrophins and androgens on spermatogenesis is well-known and pharmaceutical modifications in this system are currently used for development of male hormonal contraceptives (Matthiesson and McLachlan, 2006), the impact of a secondary decrease of androgen levels on spermato-/spermiogenesis and fertility remains unclear. Increased concentration of follicle-stimulating hormone (FSH) in aged men has been linked to germ cell degeneration during meiosis, with a negative effect on daily sperm production (Johnson *et al*., 1990), a finding consistent with several studies linking increased FSH values to reduced sperm production, most probably due to reduced Sertoli cell function.

Paternal age and sexual function

Sexual activity decreases in older couples (Weinstein and Stark, 1994), partly due to the age-dependent increase in male sexual dysfunction (Handelsman, 2002; Mirone *et al*., 2004). Sexual dysfunction is not only prevalent in couples of more advanced age (Lindau *et al*., 2007), but also middle-aged couples, which often are still pursuing fertility (Nicolosi *et al*., 2006). Male sexual dysfunction in infertile couples can sometimes be the reason for infertility, but is more often either caused or aggravated by the fact of infertility and its own psychological implications (Shindel *et al*., 2008a, b). In reflection of its multifactorial causes, treatment options are broad, including psychosocial interventions, drug treatments such as, for example, oral phosphodiesterase type 5 inhibitors or transurethral/intracavernous application of prostaglandin E_1 or use of penile devices (vacuum erection device, penile prostheses) (McVary, 2007). Sexual dysfunction itself has no known influence on germ cells and its impact on infertility can be overcome by measures of ART (e.g. intrauterine insemination in case of impaired semen deposition). Nor is the use of phosphodiestarse-5-inhibitors known to influence semen parameters and they can be used by older men with erectile dysfunction and the wish for paternity (Kalsi *et al*., 2003).

Paternal age, testicular morphology and semen parameters

The impact of male age on histopathological aspects in the aging testes leads not only to reduced numbers of Sertoli cells, Leydig cells and germ cells, but also to other changes, as for example, thickening of the basal membrane of the tubuli seminiferi parallel to a reduction

of the seminiferous epithelium and defective vascularization of the testicular parenchyma (Kühnert and Nieschlag, 2004). This was further documented in testicular tissue from 30 men 60–102 years old (Dakouane *et al*., 2005).

Testicular size (which is a rough indicator of spermatogenesis) is not, however, a relevant factor in age groups seeking fertility, as the specific effects of age alone demonstrated a reduction in testicular volume only in the eighth decade of life (Handelsman and Staraj, 1985).

Studies published up to our review in 2004 evaluating the influence of age on semen parameters showed a deterioration of semen (volume, sperm, motility and morphology), but data concerning sperm concentration did not provide a uniform picture (Kühnert and Nieschlag, 2004). This was also confirmed in an earlier meta-analysis (Kidd *et al*., 2001). Although previous studies were based on small groups of older men, a large analysis of 1174 men over 45 years confirmed previous findings and a slight decrease in sperm counts (Hellstrom *et al*., 2006). Computer-assisted semen analysis of semen samples from older men objectively confirmed the decrease in sperm motility (Sloter *et al*., 2006).

The pathophysiological basis of age-impact on testes and semen parameters may be due to the specific effects of age alone, but can also be based on factors associated with age, as for example vascular diseases, obesity, infections of the accessory reproductive glands or an accumulation of toxic substances. However, elucidating the causative chain between such factors is extremely difficult, as confounding factors are almost impossible to differentiate. Obesity, for example, is associated with increased incidence of oligozoospermia and asthenozoospermia (Jensen *et al*., 2004; Hammoud *et al*., 2008), but whether life-style factors, the age-dependent increase in visceral fat or other obesity-associated metabolic factors cause the link remains unclear.

Semen volume and seminal fructose concentration decrease with age, possibly due to a seminal vesicle insufficiency, since the seminal vesicle contributes most to ejaculate volume (Rolf *et al*., 1996).

Factors leading to decreased sperm motility could be found in altered functions of post-testicular glands such as the prostate and, more probable, the epididymis, as the swimming ability of spermatozoa is acquired during epididymal transit and motility is dependent on dilution into seminal plasma (Gagnon and de Lamirande, 2006). Prostate-specific-antigen (PSA) and α-glucosidase, markers secreted by the prostate and the epididymis, respectively, decrease with age and are positively correlated to sperm motility (Elzanaty *et al*., 2002; Elzanaty, 2007). Age-dependent alterations of the epididymis might lead to disturbed mitochondrial functioning, as an important part of epididymal sperm maturation is the activation of sperm mitochondria (Aitken *et al*., 2007), which could by itself already be altered via genetic mechanisms, as highlighted below.

Paternal age and toxicity/environmental factors

Effects of environmental chemicals on male fertility are a major public concern, especially driven by reports about decreasing sperm quality over time. These reports are mainly based on publications of human data, some which have, in the meantime, been invalidated for methodological reasons (Handelsman, 2001; Fisch, 2008). Nevertheless, toxic substances may have a direct influence on cells involved in spermatogenesis or germ cell-DNA, whereby male age can play a role in different ways. Early short-term exposures to certain disruptive chemicals may have occurred only in certain age groups, whereas chronic exposure or accumulation of toxins over years may become relevant only in older men. Persistent effects of short-term exposures (e.g. early programming) are difficult to evaluate, whereas toxicity studies can reveal direct effects on spermatogenesis.

Paternal occupation can have an impact on semen parameters (Kenkel *et al*., 2001; Magnusdottir *et al*., 2005) and can be linked to certain birth defects or diseases in the offspring (Olshan *et al*., 1990, 1991; Whalley *et al*., 1995). Polychlorinated biphenyls are known to accumulate over time in men and were correlated with decreased sperm quality, especially reduced motility, whereas data about the relationship between pesticides or phthalates and human semen quality do not yet allow a definitive conclusion as highlighted in a recent review and the summary of an expert meeting about environmental challenges to reproductive health (Hauser, 2006; Woodruff *et al*., 2008). Air pollution was linked to increased DNA damage in human spermatozoa without affecting other semen parameters (Jafarabadi, 2007).

Although a contribution of environmental factors to the deterioration of human semen parameters in advancing age is readily accepted, especially by the public, solid evidence does not exist.

Paternal age and infections

Retrospective cross-sectional data of 3698 infertile men show an age-dependent increase in the prevalence of infections in the accessory glands associated with significantly lower sperm counts (Rolf *et al*., 2002). Male genital tract infections can have an influence on semen parameters via different mechanisms (Comhaire *et al*., 1999), including a direct disruption of spermatogenesis by chronic orchitis (Schuppe *et al*., 2008) or histomorphological changes potentially leading to obstructive oligo-/azoospermia (Heshmat and Lo, 2006).

Certain antibodies against spermatozoa in serum show an age-dependent increase (Kalaydjiev *et al*., 2002). The etiology of this increase remains unclear but may be associated with male genital tract infections. Changes not evident in classical semen evaluation are functional changes in the sperm cell caused by biochemical changes in the composition of the seminal plasma or the sperm cell membrane. Infections can lead to oxidative stress which can be evaluated by measuring reactive oxygen species (ROS) levels in seminal plasma. ROS levels show a significant, age-dependent increase in the aging male (Cocuzza *et al*., 2008) and may lead to DNA damage (Aitken and De Iuliis, 2007; Turner and Lysiak, 2008).

Paternal age and genetics

Paternal age and its association with certain syndromes was observed as early as 1955 (Penrose, 1955) and in the meantime the relation between paternal age and several x-linked recessive and autosomal-dominant disorders has been well confirmed (Crow, 2000). However, the demonstration of an effect of paternal age on cytogenetic disorders in epidemiological studies is rather difficult because of the small number of affected subjects for each syndrome and because chromosomally abnormal embryos are lost at different stages *in utero* leading to ascertainment bias. In addition, differentiation

of maternal and paternal effects is difficult, because of strong correlations in regard to age, lifestyle and environmental factors.

The direct evaluation of male gametes circumvents these difficulties. Besides the laborious sperm karyotyping technique, the development of fluorescence *in situ* hybridization allows direct analysis of spermatozoa for numerical (and structural) aberrations in large numbers of sperm (Sloter *et al*., 2000).

Despite contradictory reports, evidence suggests that increasing age is associated with a higher frequency of aneuploidies and point mutations, more breaks in sperm DNA, loss of apoptosis, genetic imprinting and other chromosomal abnormalities (Singh *et al*., 2003; Sloter *et al*., 2004; Thacker, 2004).

This might be due to the fact that male germ cells divide continuously and undergo many more mitotic replications than oocytes with their limited number of 22 replications before entering the meiotic prophase. It has been estimated that spermatogonial stem cells divide 30 times before puberty and from then on every 16 days (Crow, 2000). By the age of 50 years, 840 mitotic divisions would have occurred, with every single replication possibly causing a DNA copy error. Advancing paternal age is therefore considered as the major cause of new mutations in human populations (Crow, 1999) and could be responsible for an accumulation of mutations in the human gene pool, possibly leading to a higher incidence of recessive genetic disorders in the future.

Aneuploidies

Aneuploidies in sperm. Due to the implications for *in vitro* fertilization (IVF)/ICSI treatment, chromosomal anomalies in sperm of infertile men were increasingly evaluated in recent years. Infertile men have an increased frequency of chromosomally abnormal sperm and offspring, even when the somatic karyotype is normal. All chromosomes are susceptible to non-disjunction, with chromosomes 21, 22 and the gonosomes showing an increased rate of aneuploidy in sperm (Martin, 2006). However, data about age-dependent alterations of aneuploidy frequency are scarce and contradictory (Griffin *et al*., 1995). Most analyses were performed with ejaculated sperm, whereas one study evaluating testicular tissue found no increase in the aneuploidy rate in men between 60 and 90 years, in comparison to younger men undergoing testicular sperm extraction for obstructive azoospermia as long as testicular histology was normal (Dakouane *et al*., 2005). However, when spermatogenetic arrest was diagnosed, the aneuploidy rate increased significantly, but this appears to be a disease-specific and not an age-specific phenomenon.

A slight age-dependent increase in disomies of the sex chromosomes is controversially discussed (Naccarati *et al*., 2003; Kühnert and Nieschlag, 2004), whereas so far age effects on autosomes are not detectable (chromosomes 3,6,7,8,10,11,12,13,14,17) or equivocal (chromosomes 1,9,18, 21) (Luetjens *et al*., 2002). The age effect on diploidy remains controversial (Buwe *et al*., 2005).

Aneuploidies in the offspring. All autosomal monosomies are lethal and only fetuses with autosomal trisomies 13, 18 and 21 can survive to term. Trisomy 21 is the most common trisomy in newborns and its incidence is increased with higher maternal age, whereas the influence of paternal age is controversially discussed (Sloter *et al*., 2004; Yang *et al*., 2007; Crane and Morris, 2007). A recent evaluation of 3419 affected subjects, however, revealed that trisomy 21 and higher paternal age are only associated when mothers are aged 35 years or older. The paternal contribution to Down syndrome reached 50% when the mother was 40 or older (Fisch *et al*., 2003). But as only about 22% of all trisomies 21 survive to term and as the excess chromosome 21 originates from the father in only 5–10% (Hassold and Sherman, 2000), the risk for children of aged fathers still remains very low. Other studies reported an increased risk for teenage fathers in comparison with fathers aged 25–29 (Roecker and Huether, 1983; McIntosh *et al*., 1995).

The incidence of trisomy 18 in newborns is not affected by paternal age (Naguib *et al*., 1999), whereas fathers older than 39 years are less likely to have children with trisomy 13 (prevalence ratio 0.4, 95% CI: 0.16–0.96) in comparison to fathers aged 25–29 years (Archer *et al*., 2007).

Hatch *et al*. (1990) evaluated autosomal trisomies (all autosomes except chromosome 1) in spontaneous miscarriages and found no significant paternal age effects (Hatch *et al*., 1990).

Sex chromosomal aneuploidies reveal a higher paternal contribution (Hassold and Hunt, 2001) with variations from about 6% in 47, XXX to 50% in 47, XXY and 100% in 47, XYY cases (Buwe *et al*., 2005), but age effects in the paternally derived cases were not found in small groups of 47, XXY men (Sloter *et al*., 2004).We compared the parental age of 228 Klinefelter patients with that of 224 men with severe infertility but normal karyotype, and found no significant age relation, neither to the father nor to the mother (Lanfranco *et al*., 2004).

Structural chromosomal aberrations

Some single base substitutions in the RET gene (causing multiple endocrine neoplasia), FGFR2 gene (causing Apert's syndrome) or FGFR 3 gene (causing achondroplasia, Crouzon's and Pfeiffer's syndrome) increase with paternal age (Crow, 2000). The age-dependent increase in Apert's syndrome was linked to a premeiotic, positive selection in the male germ line, a paradoxical finding leading to an evolutionary conflict between a mutation advantageous on the testicular level but harmful for the affected organism (Goriely *et al*., 2003). Similarly, the incidence of achondroplasia is higher than expected from the frequency of mutated spermatozoa, possibly explained by a positive selection increasing the odds of the mutated sperm to fertilize an ovum (Tiemann-Boege *et al*., 2002). Recently, Dakouane Giudicelli *et al*. (2008) found an increased achondroplasia mutation frequency and G1138 mosaicism in testicular biopsies from men over 70 years old.

DNA integrity. DNA damage (fragmentation, abnormal chromatin packaging, protamine deficiency) negatively affects reproductive outcome in natural conception (Spano *et al*., 2000) and ART (Lopes *et al*., 1998), but spermatozoa from fertile men have also been shown to carry DNA damage (Zini *et al*., 2001; Zini and Libman, 2006). DNA damage was linked to different age-dependent pathogenic situations (e.g. systemic and genital infections, cancers, drugs, chemo- and radiotherapy, smoking, varicocele, hyperthermia), most of them associated with altered levels of ROS. However, independent of these factors, paternal age itself is also positively correlated with increased DNA damage in sperm donors and in men of infertile couples (Martin and Rademaker, 1987; McInnes *et al*., 1998; Sartorelli *et al*., 2001; Singh *et al*., 2003; Wyrobek *et al*., 2006; Vagnini *et al*., 2007).

Telomeres. Telomeres are repetitive DNA sequences located at the end of chromosomes, where they play an essential role in

chromosomal stability by distinguishing chromosomal ends from DNA double strand breaks. With every replication telomeres are shortened until a critical minimum is achieved, at which point cell proliferation stops and apoptosis may be induced. Telomere shortening is considered one of the aspects of cell senescence and is linked to age-related diseases and cancer-progression/suppression (Martien and Abbadie, 2007). In contrast, sperm cells show increasing telomere length (TL) with donor age, at least in a subset of sperm cells (Allsopp *et al*., 1992) and paternal age is associated with increasing TL in offspring with an estimated lengthening at a magnitude of half to more than double for the annual attrition per additional year of paternal age (Unryn *et al*., 2005; De Meyer *et al*., 2007; Kimura *et al*., 2008). The implications on the health of the offspring are unknown but a greater TL might represent a selection advantage. The increase of TL might be due to a selection during the numerous replications of germ-line stem cells, where only a subset of sperm with high TL resists the selection pressure of aging (Kimura *et al*., 2008), possibly mediated by oxidative stress (Forsyth *et al*., 2003).

However, TL could contribute to the reported age-related decrease in human sperm apoptosis, possibly negatively impacting naturally occurring control mechanisms serving to select healthy sperm (Singh *et al*., 2003).

Epigenetics. Epigenetics refers to heritable modifications in gene expression which by definition never involve DNA sequence modifications. Epigenetic abnormalities are associated with imprinting diseases (Gosden *et al*., 2003), molar pregnancies or certain childhood cancers. A paternal role in transmitting imprinting disorders is reported (Marques *et al*., 2004) and it is suggested that imprinting disorders are increased in babies from assisted reproduction. Genomic imprinting regulates whether the paternally or maternally inherited allele is expressed by silencing the reciprocal allele using methylation-induced blockage of target sequences or other mechanisms controlled by methylation (La Salle and Trasler, 2006). Influence of paternal age on methylation patterns was shown in rats (Oakes *et al*., 2003), and postulated in the human for diseases such as Huntington disease, Alzheimer's disease, autism or schizophrenia (Farrer *et al*., 1991, 1992; Reichenberg *et al*., 2006; Perrin *et al*., 2007).

Paternal age and fertility

Advancing age of the mother is known to be associated with reduced fertility and a prolongation in the 'time to conception' or 'time to pregnancy' (TTP) (Olsen, 1990; Schwartz and Mayaux, 1982). Reduced fertility in aging women is primarily due to 'ovarian aging' with reduced quality and reduced numbers of oocytes (decreased ovarian reserve) as well as an altered hormonal environment leading to ovulatory dysfunction. No abrupt and clear cutoff level can be defined, but rather a slow steady decline is seen between the ages of 20 and 37 years followed by an accelerated decline over subsequent years, so that spontaneous conceptions and deliveries after the age of 45 are rare, although there are population groups (like Bedouins) with the ability to conceive and deliver at later ages (Menken *et al*., 1986; Klein and Sauer, 2001; Laufer *et al*., 2004; Gielchinsky *et al*., 2006).

A paternal age effect on fecundity of a couple was documented in several studies, whereas Joffe and Li (1994) found no paternal age effect on TTP when evaluating men under 33 years of age with proven fertility.

One Danish study in 10 886 women analyzed the effect of parental age on the probability of a TTP longer than 12 months and detected a strong maternal age effect, but only a non-significant correlation with paternal age (Olsen, 1990). However, only couples after the 36th week of pregnancy ($n = 10\,886$) were included, probably causing an exclusion or underrepresentation of less fecund or sterile couples (De La Rochebrochard *et al*., 2003). In the British Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) study Ford *et al*. (2000) evaluated the probability of conceiving within 6 or 12 months and found a lower likelihood of conception in couples with older men [after adjustment for nine other variables independently related to TTP (including maternal age)]. Of 8515 planned pregnancies reaching at least 24 weeks of gestation, 74% were conceived in $\leq$6 months, 14% during the second 6 months and 12% after more than a year. Compared with men $<$25 years old, the adjusted odds ratios for conception within 12 months were 0.62 (95% CI: 0.40, 0.98) in men aged 30–34, 0.50 (95% CI: 0.31, 0.81) in men aged 35–39 and 0.51 (95% CI: 0.31, 0.86) in men $\geq$40 years.

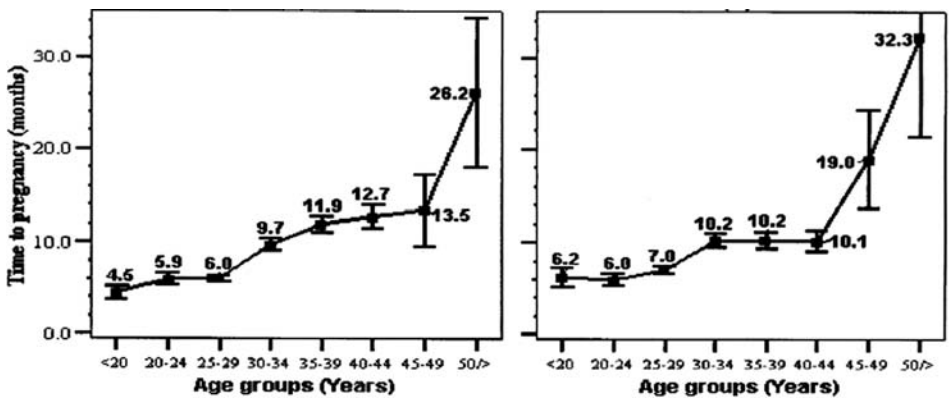

Figure 2 Paternal age effects on TTP.

Evaluation of 2112 pregnant women consecutively attending antenatal clinics in England. Results remain unchanged after adjustment for different confounding factors including maternal age. Left: paternal age at conception. Right: paternal age at the onset of attempting to achieve a pregnancy (with permission from Hassan and Killick, 2003).

Paternal age effects in this study are controversially discussed (at least for fathers <40 years) for different reasons including the potential overestimation of paternal age effect because age at the time of conception was evaluated rather than age at the time when the couple started trying to conceive a child (Sallmen and Luukkonen, 2001).

A prospective Australian study evaluating risk factors for infertility and miscarriage in 585 couples found a significantly increased risk of infertility after 9 months in male partners older than 35 years when compared with men younger than 35 years (OR 2.31, 95% CI: 1.44, 3.71) (Ford *et al.*, 1994).

These results were confirmed in retrospective data from 6188 randomly selected women, showing that paternal age over 40 years was a significant risk factor for infertility after 12 months, but only in women aged 35 years or older (adjusted OR 3.02 compared with men <40 years) (de La Rochebrochard and Thonneau, 2003).

Similar results were found in an evaluation of 2112 pregnant couples which showed that men >45 years old are 4.6-fold more likely to have a TTP of >1 year relative to men aged <25 years (Hassan and Killick, 2003) (Fig. 2).

However, the decline in male sexual activity can be an important bias for the analysis of paternal age effects on fertility, as the frequency of intercourse decreases with age (Araujo *et al.*, 2004), which—if the frequency is less than twice a week—increases the infertility rate in an age-dependent manner (Dunson *et al.*, 2004). However, this bias was avoided in a study evaluating 1938 couples who underwent IVF because of bilateral obstruction or absence of the uterine tubes. In accordance with former studies, an age-dependent increase in infertility, especially after the age of 37 was confirmed. When adjusted for maternal age effects the odds ratio of failure to conceive for paternal age >39 years compared with men <30 years was 1.70 (95% CI: 1.14–2.52). Taking into account an interaction between male and female age, the odds ratio of failure to conceive for paternal age >39 years was 2.0 (95% CI: 1.1–3.61) in couples with women aged 35–37 years, 2.03 (95% CI: 1.12–3.68) when women are 38–40 years old and 5.74 (95% CI: 2.16–15.23) for age 41 years and older (de La Rochebrochard *et al.*, 2006).

A prospective fecundability study evaluating 782 couples in Europe showed an age-dependent decline in fertility for men older than 35 years (Dunson *et al.*, 2002). The increased infertility in older couples were attributable primarily to a gradual decline in fertility rather than to an increase in absolute sterility, which was estimated age-independently at about 1% (Dunson *et al.*, 2004). This study showed that 43% of older couples (woman ≥35 years, man ≥40 years) with unexplained infertility after 12 months are still able to achieve a pregnancy if they try for another 12 menstrual cycles.

Increasing maternal age is associated with an increasing incidence of twin deliveries up to the age of ~37 years with a decrease thereafter (Collins, 2007). Increasing paternal age over 25 years is positively correlated with the incidence of twin deliveries (after controlling for maternal age) as shown in the Jerusalem Perinatal Study including 1115 twin deliveries out of a total of 91 235 deliveries (Kleinhaus *et al.*, 2008). As highlighted by the authors, this finding together with maternal age effects has to be considered in twin-studies, when data on twins is evaluated to investigate the etiology of diseases.

Although some studies show contradicting results, we conclude that increasing paternal age is associated with reduced fertility, at least in couples where men are older than 40 years and women are at least 35 years. The effects of paternal age in fertility are listed in the Supplementary Table 1.

Paternal age and pregnancy-associated complications

Miscarriage

Between 30 and 70% of all conceptions do not lead to a live birth, with most of them ending in spontaneous miscarriages occurring subclinically (Edmonds *et al.*, 1982; Wilcox *et al.*, 1988). A prospective study including 630 women intending to become pregnant showed an overall incidence of clinically recognizable spontaneous miscarriages before 20 weeks of gestation of 12% (50/407 pregnancies), which is slightly lower than generally reported (Regan *et al.*, 1989; Garcia-Enguidanos *et al.*, 2002).

A recent population-based case–control study including 603 women (18–55 years) whose most recent pregnancy had ended in first trimester miscarriage, detected high maternal age, previous miscarriage, previous termination and infertility, assisted conception, low pre-pregnancy body mass index, regular or high alcohol consumption, feelings of stress, changing partner and high paternal age as independent risk factors (Maconochie *et al.*, 2007).

Paternal effects

Chromosomal anomalies in the zygote can be caused by errors in maternal and paternal gametogenesis, during fertilization or during the first cellular divisions of the fertilized oocyte. As highlighted above, increased paternal age is associated with some chromosomal abnormalities in the spermatozoa and might thus play a role in the incidence of spontaneous miscarriages as well (Griffin *et al.*, 1995; Sartorelli *et al.*, 2001; Luetjens *et al.*, 2002; Morris *et al.*, 2002; Singh *et al.*, 2003). In an early investigation of $>1.5 \times 10^6$ birth and fetal death certificates recorded from 1959 to 1967 in New York State, the

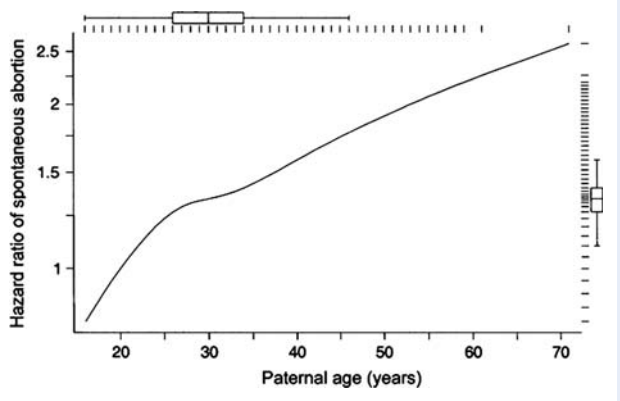

Figure 3 Hazard ratios of spontaneous miscarriages between 6 and 20 weeks according to paternal age adjusted for different confounders including maternal age (using prospective data from 5121 Californian women, men aged 20 years as referent).

Boxplots along the top and right side indicate data distribution according to each axis (with permission from Slama *et al.*, 2005).

risk of spontaneous miscarriage was attributed to maternal and paternal age to the same extent (Selvin and Garfinkel, 1976) with maternal and paternal effects being linear, although reproductive age patterns are usually represented as J- or U-shaped curves (Nybo Andersen *et al*., 2000; de la Rochebrochard and Thonneau, 2002).

In a retrospective analysis including more than 3174 European women, de la Rochebrochard and Thonneau (2003) showed a clear effect in couples of increasing maternal and paternal age, when compared with the reference group, which was composed of parents both aged 20–29 years. If the woman was 20–29 years old, the risk of miscarriage was not significantly influenced by the age of the man. If the woman was 30–34 years old, the risk of miscarriage was higher if the man was aged ≥40 years. If the woman was aged ≥35 years, the risk of miscarriage increased whatever the age of the man. When comparing the 'highest' risk group (woman ≥35 years, man ≥40 years) with the reference group, the risk of miscarriage was substantially higher with an odds ratio of 5.65 (3.20, 9.98). When comparing the 'highest' risk group with the 'high' risk group (woman ≥35 years, man <40 years or woman 30–34 years, man ≥40 years) the odds ratio was 1.97 (1.03, 3.77).

Another retrospective analysis of 2414 pregnancies with a 12.2% rate of spontaneous miscarriage confirmed deleterious paternal age effects with a significant increase in risk for spontaneous miscarriage when men were older than 35 years (Slama *et al*., 2003). Unexpectedly this difference was only seen among couples in which the woman's age was <30 years, which could be explained by the fact that maternal risk factors for spontaneous miscarriage might be better controlled by the adjustment for maternal age in younger than older women, in whom other factors, not adjustable by the maternal age, may mask the paternal age effect (Slama *et al*., 2005). However, retrospective evaluations of spontaneous miscarriages are limited due to an important recall bias (Wilcox and Horney, 1984).

A prospective study among 5121 Californian women analyzed 4645 live births and 491 spontaneous miscarriages that occurred after six completed gestational weeks (Slama *et al*., 2005). After adjustment for tobacco use as well as female alcohol and caffeine consumption, the hazard ratio of spontaneous miscarriage associated with paternal age of 35 years or more (compared with <35 years) was 1.27 (95% CI: 1.00, 1.61) with no modification by maternal age. Among women aged <30 years the hazard ratio of spontaneous miscarriage associated with paternal age ≥35 years was 1.56 for first trimester spontaneous miscarriage and 0.87 for early second trimester spontaneous miscarriage (Fig. 3). The findings suggested stronger effects of male age in the first trimester, a conclusion clearly stated as hypothetical due to small numbers. Albeit its non-significant nature, it is interesting as cytogenetic studies suggest that first trimester miscarriages are more likely to be caused by chromosomal anomalies.

Prospective data from 23 821 pregnant women in the Danish National Birth cohort showed that pregnancies fathered by men aged ≥50 years had almost twice the risk of ending in fetal death (<20 weeks of gestation) than pregnancies fathered by younger men (relative risk 1.88, 95% CI: 0.93, 3.82) (Nybo Andersen *et al*., 2004). The apparently increased risk for fetal death from fathers between 35 and 49 years was abolished after adjustment for maternal age.

In conclusion, there is clear evidence for an increasing risk of miscarriage and fetal death with higher paternal age.

Caesarean section

The Caesarean section rate increased continuously over the last decades and reached 30.2% in the USA in 2005 (Martin *et al*., 2007). The Caesarean delivery rate increases with maternal age (Rosenthal and Paterson-Brown, 1998; Ecker *et al*., 2001; Paulson *et al*., 2002; Ahmed *et al*., 2004; Dhillo *et al*., 2005) also in mothers in their sixth decade of life who conceived by IVF with oocytes of young donors (mean donor age: 27.5 years) (Paulson *et al*., 2002).

One Taiwanese study determined the independent effects of paternal age on the likelihood of Caesarean delivery, evaluating 310 574 singleton deliveries by nulliparous women (Tang *et al*., 2006). Within all maternal age groups a significant increase in the Caesarean delivery rate was seen according to rising paternal age. The overall risk for Caesarean delivery was twice as high in couples with the woman older than 35 and the man older than 40 years, compared with couples with both parents aged 20–29 years.

Summing up, there is a positive correlation of paternal age with the risk of Caesarean delivery, independent of maternal age and other confounding factors.

Pre-eclampsia

Pre-eclampsia is a multisystem disorder with an incidence between 2 and 7% in healthy nulliparous women (Sibai *et al*., 2005), but inconsistent definitions of pre-eclampsia across different studies make a direct comparison of results very difficult. Familial associations with very complex pathways of heredity are well documented (Albano *et al*., 1996; Cincotta and Brennecke, 1998; Cross, 2003; Ettinger *et al*., 2003). Maternal genes as well as fetal genes of either maternal or paternal origin may trigger pre-eclampsia, whereby the risk of a maternal contribution is stronger, as was shown in a population-based cohort study in men and women who were born after pre-eclamptic pregnancies (Esplin *et al*., 2001; Skjaerven *et al*., 2005). Affected mothers might carry susceptibility genes, but can also transmit independent genetic risk factors to their fetus, whereas affected fathers transmit only triggering fetal risk factors (Skjaerven *et al*., 2005). Men who fathered a pre-eclamptic pregnancy in one woman are more likely to father a pre-eclamptic pregnancy in other women (Lie *et al*., 1998). Another finding supporting the hypothesis of paternal contribution to pre-eclampsia is that long-term sperm exposure with the same partner is protective, although the risk increases in couples recently married or those who have limited sperm exposure to the same partner before conception (including barrier conception and artificial insemination) (Trupin *et al*., 1996; Li and Wi, 2000; Wang *et al*., 2002; Einarsson *et al*., 2003). Furthermore, the incidence of pre-eclampsia is dependent on paternal (and maternal) ethnicity, with the lowest rate in Asian men (Caughey *et al*., 2005).

Paternal age under 25 years and over 35 years increases the risk of pre-eclampsia when compared with fathers aged 25–34 years, as shown in the cohort of the Jerusalem Perinatal Study ($n = 81\,213$ deliveries) with a pre-eclampsia rate of 1.6%. The odds ratios were 1.24 (95% CI: 1.05, 1.46) for ages 35–44 and 1.80 (95% CI: 1.40–2.31) for age 45+. The odds ratio for fathers younger than 25 years was 1.25 (95% CI: 1.04, 1.51), and this was not an effect of recent marriage or a preponderance of groups with low probability of having previous sexual relationships (religious scholars), but might be

due to higher exposure to environmental causes of DNA damage or lower efficiency in apoptosis after DNA damage (Harlap *et al*., 2002).

The relation between parental age and 'new onset hypertension' (including gestational hypertension, pre-eclampsia and eclampsia) was retrospectively analyzed in 9 302 675 women giving live births in the USA between 1995 and 1998. Parental age was analyzed using the variable 'couple age' to reduce colinearity between maternal age and paternal age. Maternal age over 35 years was associated with an increased risk for new-onset hypertension when compared with couples in whom both partners were 20–34 years old. Maternal and paternal ages under 20 years were associated with a decreased risk for new-onset hypertension, except for couples with a very old father (above 45 years). But there was no significant association between paternal age and new-onset hypertension with stratification of maternal age (Chen *et al*., 2006).

In summary, paternal contributions to pre-eclampsia are clearly evident, and the only evaluation of paternal age effects shows a U-shaped increase of risk for pre-eclampsia with the highest risk in men aged 45 and older.

Gestational trophoblast diseases

Increased maternal age is a strong risk factor for gestational trophoblastic diseases (GTD) (Bracken, 1987; Altieri *et al*., 2003), whereas the data about paternal age effects are conflicting. In a case–control study of 132 women with hydatiform mole ($n = 108$) or choriocarcinoma ($n = 24$), higher paternal age was associated with GTD after adjusting for maternal age. Women whose husbands were 45 years and older had a relative risk of 4.9 (with 95% CI: 2.2–11.1), compared with women married to men younger than 40 years (La Vecchia *et al*., 1984). Higher paternal age (>45 years) showed a higher risk for complete hydatiform mole (adjusted relative risk 2.9; 95% CI: 0.9–9.1), whereas there was no increase for partial hydatiform mole (Parazzini *et al*., 1986). However, other case–control studies showed no influence after adjusting for confounding factors (Yen and MacMahon, 1968; Matsuura *et al*., 1984; Messerli *et al*., 1985; Brinton *et al*., 1989).

Placenta previa and placental abruption during pregnancy

Risk factors for uteroplacental bleeding disorders due to placenta previa and placental abruption include prior Caesarean delivery, pregnancy termination, intrauterine surgery, smoking, cocaine use, multifetal gestation, increasing parity, advanced maternal age and maternal ethnicity (Oyelese and Smulian, 2006; Odibo *et al*., 2007).

Although the influence of paternal genes on normal development and function of the placenta in humans and mice is known (Jinno *et al*., 1995; Miozzo and Simoni, 2002; Isles and Holland, 2005; Wagschal and Feil, 2006), the association between paternal characteristics and placenta previa or placental abruption has received little attention. A retrospective cohort study analyzed the connection between these pregnancy complications and missing paternal demographic data (age and ethnicity either alone or combined) in birth certificates of 26 336 549 births using US linked birth/infant death data from 1995 through 2001 (Getahun *et al*., 2006).

Although studies based on missing data can be strongly biased if the missing values do not occur randomly, this study still shows a probable influence of paternal age on uteroplacental abruption. This is in concordance with a retrospective population-based cohort study in 304 466 twins, where missing paternal information significantly increased the risk of placental abruption (as well as other adverse pregnancy outcome) (Tan *et al*., 2004).

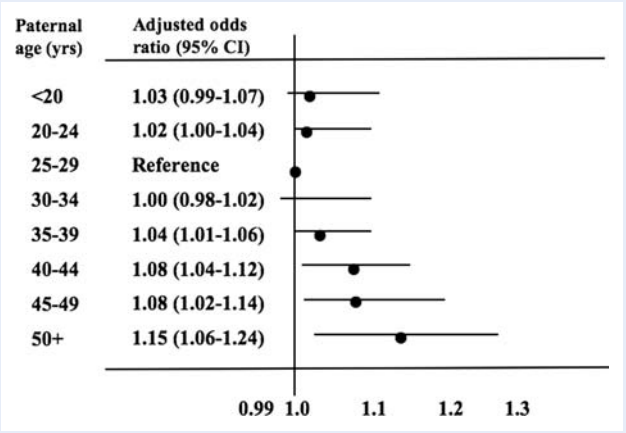

Figure 4 Relative risk of birth defects depending on paternal age. Retrospective analysis of 5 213 248 subjects in the USA. Increased risk for heart defects, circulatory/respiratory defects, diaphragmatic hernia, tracheo-oesophageal fistulas, musculo-sceletal anomalies (data extracted from Yang *et al*., 2007).

In summary, the evidence for influence of paternal age on placental disorders is poor, but available data suggest a link between paternal age and placental abruption.

Preterm birth

Spontaneous preterm birth before 34 weeks' gestation occurs in 3–7% of pregnancies and accounts for around 75% of neonatal mortality and 50% of long-term neurological impairment in children (Khan and Honest, 2007). Risk factors include history of preterm labor or preterm birth, history of preterm rupture of the membranes, history of cervical surgery, shortened cervical length, multiple gestation, polyhydramnion, uterine anomalies, genito-urinary infections, artificial reproductive technologies, low pre-pregnancy BMI, maternal smoking, low socioeconomic status and advanced maternal age (Astolfi and Zonta, 1999; Goffinet, 2005; Leitich, 2005; Reedy, 2007).

Studies on the effects of paternal age on pregnancy duration are contradictory. Several retrospective studies from Canada and the USA showed no effect of advanced paternal age (Basso and Wilcox, 2006; Olshan *et al*., 1995), whereas pregnancies induced by fathers younger than 20 years had a higher risk for preterm birth. This was confirmed in a recent retrospective cohort study of nulliparous women aged 20–29 years in the USA (Chen *et al*., 2008), where the preterm births in couples with teenage fathers were more frequent when compared with fathers aged 20–29 years (OR 1.15, 95% CI: 1.1, 1.2). The evaluation of older men did not reveal any influence of age on birth outcomes. A retrospective population-based analysis of 8 995 274 singleton pregnancies delivering at ≥20 weeks gestation in the USA in 1995–1997 showed an increase in preterm delivery among white women who were older than their male partners, but did not analyze paternal age as a variable on its own (Kinzler *et al*., 2002).

In contrast, three recent studies found an effect of paternal age on preterm birth (Astolfi *et al*., 2005; Astolfi *et al*., 2006; Zhu *et al*.,

2005a, b). Zhu *et al.* analyzed data of 70 347 singleton births in Denmark, but only women aged 20–29 years and fathers older than 19 years were included. After adjusting for maternal age and potential confounders, an increased risk of preterm birth was found which was most evident for very preterm births (<32 weeks of gestation). The odds ratio for preterm birth in women 20–24 years and men older than 50 years was 2.1 (95% CI: 1.3–3.5) compared with 20–24-year-old fathers. The OR for very preterm birth in the same age group was 3.4 (95% CI: 1.0–11.0). When children with congenital malformations were excluded, the associations between paternal age and preterm birth decreased. In their analysis of 1 510 823 birth records in Italy, Astolfi *et al.* showed similar effects with a steeper increase in odds ratios for very preterm births than for preterm births (34–37 weeks of gestation). The highest OR of 1.91 (95% CI: 1.08–3.38) was found in the group of women aged 20–24 and the men aged 45–49 compared with the reference group of men aged 25–29 years. The authors mention that the small number of adjusted covariates is a limiting aspect in this study as lifestyle factors, reproductive history and pregnancy-management have important influence on the preterm birth rate, but are not collected routinely in Italian birth records.

The differences between the Danish, Italian and USA populations could be caused by possible confounders, as for example socioeconomic factors related to paternal age which could have an influence, as the majority of men in the US study had their first child at an earlier age than in Europe. Another factor that may reduce the probability to detect a fathers' age-effect is that the proportion of deliveries before 32 weeks was twice as high as in Italy and Denmark.

In summary, evidence suggests that paternal age below 20 is associated with a higher incidence of preterm births, but it remains unclear whether higher paternal age has an effect on preterm deliveries, although there is some evidence that the risk for very preterm deliveries is increased in older fathers, at least in European populations.

Paternal age and outcome of offspring

In a large retrospective US study, paternal age below 20 is associated with adverse birth outcome as low APGAR scores, low birthweight, increased risk for small-for-gestational-age births and neonatal mortality (Chen *et al.*, 2008), whereas the same study found no influence of higher paternal age. This is in contrast with the Danish study showing a slightly increased risk for lower 1 and 5 min APGAR values in fathers older than 45 years compared with fathers 20–29 years of age. Only one study shows an influence of advanced paternal age on low birthweight (Reichman and Teitler, 2006), whereas most studies showed no effect.

Nonetheless, children of older fathers are not only more likely to have several diseases of clear genetic cause (Kühnert and Nieschlag, 2004; Lambert *et al.*, 2006), they show also an increased risk for multifactorial diseases such as birth defects (Olshan *et al.*, 1994; McIntosh *et al.*, 1995; Kazaura *et al.*, 2004; Bille *et al.*, 2005; Zhu *et al.*, 2005a, b; Archer *et al.*, 2007; Yang *et al.*, 2007), childhood cancers (Moll *et al.*, 1996; Hemminki *et al.*, 1999; Sharpe *et al.*, 1999; Murray *et al.*, 2002; Yip *et al.*, 2006), prostate cancer (Zhang *et al.*, 1999), breast cancer (controversial) (Colditz *et al.*, 1991; Choi *et al.*, 2005), diabetes mellitus type I (Bingley *et al.*, 2000; Cardwell *et al.*, 2005), multiple sclerosis (Montgomery *et al.*, 2004), some forms of cerebral palsy (Fletcher and Foley, 1993), schizophrenia (Malaspina, 2001), bipolar disorder (Frans *et al.*, 2008), autism (Reichenberg *et al.*, 2006), epilepsy (Vestergaard *et al.*, 2005), Alzheimer disease (Whalley *et al.*, 1995) and lower intelligence quotients (Malaspina *et al.*, 2005; Saha *et al.*, 2009). However, some of the reported associations need to be considered with caution for methodological reasons in the statistical analysis, especially in regard to the validity of the data sources (Kirby, 2007) (Fig. 4).

This concern also applies to the link between paternal age and longevity of the female offspring in a historical cohort of European aristocratic families (Gavrilov *et al.*, 1997). Daughters born to fathers aged 50–59 years were found to lose about 4.4 years of their lifespan compared with daughters born to younger fathers aged 20–29 years, whereas sons are not affected, which might indicate that paternal age has an influence on some longevity genes possibly located on the X chromosome, but this finding needs confirmation from data which is less vulnerable to confounding factors.

Discussion and Conclusion

Evaluating the influence of age on reproduction is difficult and conclusions remain vulnerable due to many possibly confounding cofactors. Not only do individual subjects age at different rates (biological versus chronological age), but effects of age on male reproduction may be caused by aging *per se*, or by mediators generated secondarily by age-related cofactors, as for example, vascular diseases, accumulation of toxic substances or infections of the reproductive accessory glands.

This review highlights male reproductive functions in regard to age with a special focus on fertility and pregnancy outcome. Not only higher maternal age but also increasing paternal age (at least over 40 years) is associated with lower fertility, an increase in pregnancy-associated complications (as miscarriage rate, preeclampsia, possibly uteroplacental bleeding disorders, preterm births and surgical deliveries) and an increase in adverse outcome in the offspring. These associations are the reason why the age of semen donors is now limited to 40 or 45 years in some countries.

These adverse health outcomes should be weighed up against potential social advantages for children born to older fathers who are more likely to have progressed in their career and to have achieved financial security. These higher socioeconomic levels might be associated with better health behavior. However, potential social disadvantages of increased paternal age should also be considered, such as less energetic parents and decreased likelihood of the child benefiting from long-term relationships with grandparents (Bray *et al.*, 2006).

Higher maternal age can be an indication for intensive prenatal diagnosis, including invasive diagnostics. Paternal age *per se*, however, is (so far) no reason for invasive procedures.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

Acknowledgements

The authors thank Susan Nieschlag M.A. for language editing the manuscript.

Funding

Gideon Sartorius is supported by grants of the Novartis Foundation, formerly Ciba-Geigy Jubilee Foundation, and in part by the Swiss National Research Foundation (grant PBBSB-116889) and the Lichtenstein-Stiftung, Basel, Switzerland.

References

Ahmed SF, Tucker P, Mayo A, Wallace AM, Hughes IA. Randomized, crossover comparison study of the short-term effect of oral testosterone undecanoate and intramuscular testosterone depot on linear growth and serum bone alkaline phosphatase. *J Pediatr Endocrinol Metab* 2004;**17**:941–950.

Aitken RJ, De Iuliis GN. Origins and consequences of DNA damage in male germ cells. *Reprod Biomed Online* 2007;**14**:727–733.

Aitken RJ, Nixon B, Lin M, Koppers AJ, Lee YH, Baker MA. Proteomic changes in mammalian spermatozoa during epididymal maturation. *Asian J Androl* 2007;**9**:554–564.

Albano C, Smitz J, Camus M, Bennink HC, Van Steirteghem AC, Devroey P. Pregnancy and birth in an in-vitro fertilization cycle after controlled ovarian stimulation in a woman with a history of allergic reaction to human menopausal gonadotrophin. *Hum Reprod* 1996; **11**:1632–1634.

Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB. Telomere length predicts replicative capacity of human fibroblasts. *Proc Natl Acad Sci U S A* 1992;**89**:10114–10118.

Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol* 2003; **4**:670–678.

Araujo AB, Mohr BA, McKinlay JB. Changes in sexual function in middle-aged and older men: longitudinal data from the Massachusetts Male Aging Study. *J Am Geriatr Soc* 2004;**52**:1502–1509.

Archer NP, Langlois PH, Suarez L, Brender J, Shanmugam R. Association of paternal age with prevalence of selected birth defects. *Birth Defects Res A Clin Mol Teratol* 2007;**79**:27–34.

Astolfi P, Zonta LA. Risks of preterm delivery and association with maternal age, birth order, and fetal gender. *Hum Reprod* 1999; **14**:2891–2894.

Astolfi P, De Pasquale A, Zonta L. Late childbearing and its impact on adverse pregnancy outcome: stillbirth, preterm delivery and low birth weight. *Rev Epidemiol Sante Publique* 2005;**53**:2S97–105.

Astolfi P, De Pasquale A, Zonta LA. Paternal age and preterm birth in Italy, 1990 to 1998. *Epidemiology* 2006;**17**:218–221.

Basso O, Wilcox AJ. Paternal age and delivery before 32 weeks. *Epidemiology* 2006;**17**:475–478.

Bille C, Skytthe A, Vach W, Knudsen LB, Andersen AM, Murray JC, Christensen K. Parent's age and the risk of oral clefts. *Epidemiology* 2005;**16**:311–316.

Bingley PJ, Douek IF, Rogers CA, Gale EA. Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. Bart's-Oxford Family Study Group. *BMJ* 2000;**321**:420–424.

Bracken MB. Incidence and aetiology of hydatidiform mole: an epidemiological review. *Br J Obstet Gynaecol* 1987;**94**:1123–1135.

Bray I, Gunnell D, Davey Smith G. Advanced paternal age: how old is too old? *J Epidemiol Community Health* 2006;**60**:851–853.

Brinton LA, Wu BZ, Wang W, Ershow AG, Song HZ, Li JY, Bracken MB, Blot WJ. Gestational trophoblastic disease: a case–control study from the People's Republic of China. *Am J Obstet Gynecol* 1989;**161**:121–127.

Buwe A, Guttenbach M, Schmid M. Effect of paternal age on the frequency of cytogenetic abnormalities in human spermatozoa. *Cytogenet Genome Res* 2005;**111**:213–228.

Cardwell CR, Carson DJ, Patterson CC. Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. *Diabet Med* 2005;**22**:200–206.

Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. *Obstet Gynecol* 2005;**106**:156–161.

Chen XK, Wen SW, Smith G, Leader A, Sutandar M, Yang Q, Walker M. Maternal age, paternal age and new-onset hypertension in late pregnancy. *Hypertens Pregnancy* 2006;**25**:217–227.

Chen XK, Wen SW, Krewski D, Fleming N, Yang Q, Walker MC. Paternal age and adverse birth outcomes: teenager or 40+, who is at risk? *Hum Reprod* 2008;**6**:1290–1296.

Choi JY, Lee KM, Park SK, Noh DY, Ahn SH, Yoo KY, Kang D. Association of paternal age at birth and the risk of breast cancer in offspring: a case control study. *BMC Cancer* 2005;**5**:143.

Cincotta RB, Brennecke SP. Family history of pre-eclampsia as a predictor for pre-eclampsia in primigravidas. *Int J Gynaecol Obstet* 1998;**60**:23–27.

Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, Saade GR, Eddleman KA, Klugman S, Dugoff L *et al.* Impact of maternal age on obstetric outcome. *Obstet Gynecol* 2005; **105**:983–990.

Cnattingius S, Forman MR, Berendes HW, Isotalo L. Delayed childbearing and risk of adverse perinatal outcome. A population-based study. *JAMA* 1992;**268**:886–890.

Cocuzza M, Athayde KS, Agarwal A, Sharma R, Pagani R, Lucon AM, Srougi M, Hallak J. Age-related increase of reactive oxygen species in neat semen in healthy fertile men. *Urology* 2008;**71**:490–494.

Colditz GA, Willett WC, Stampfer MJ, Hennekens CH, Rosner B, Speizer FE. Parental age at birth and risk of breast cancer in daughters: a prospective study among US women. *Cancer Causes Control* 1991;**2**:31–36.

Collins J. Global epidemiology of multiple birth. *Reprod Biomed Online* 2007;**15**:45–52.

Comhaire FH, Mahmoud AM, Depuydt CE, Zalata AA, Christophe AB. Mechanisms and effects of male genital tract infection on sperm quality and fertilizing potential: the andrologist's viewpoint. *Hum Reprod Update* 1999;**5**:393–398.

Crane E, Morris JK. Paternal age and birth defects: how strong is the association. *Hum Reprod* 2007;**22**:2349–2350.

Cross JC. The genetics of pre-eclampsia: a feto-placental or maternal problem? *Clin Genet* 2003;**64**:96–103.

Crow JF. Spontaneous mutation in man. *Mutat Res* 1999;**437**:5–9.

Crow JF. The origins, patterns and implications of human spontaneous mutation. *Nat Rev Genet* 2000;**1**:40–47.

Dakouane M, Bicchieray L, Bergere M, Albert M, Vialard F, Selva J. A histomorphometric and cytogenetic study of testis from men 29-102 years old. *Fertil Steril* 2005;**83**:923–928.

Dakouane Giudicelli M, Serazin V, Le Sciellour CR, Albert M, Selva J, Givdicelli Y. Increased achondroplasia mutation frequency with advanced age and evidence for G1138A mosaicism in human testis biopsies. *Fertil Steril* 2008;**89**:1651–1656.

de la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. *Hum Reprod* 2002;**17**:1649–1656.

de La Rochebrochard E, Thonneau P. Paternal age >or=40 years: an important risk factor for infertility. *Am J Obstet Gynecol* 2003; **189**:901–905.

de La Rochebrochard E, McElreavey K, Thonneau P. Paternal age over 40 years: the 'amber light' in the reproductive life of men? *J Androl* 2003; **24**:459–465.

de La Rochebrochard E, de Mouzon J, Thepot F, Thonneau P. Fathers over 40 and increased failure to conceive: the lessons of *in vitro* fertilization in France. *Fertil Steril* 2006;**85**:1420–1424.

De Meyer T, Rietzschel ER, De Buyzere ML, De Bacquer D, Van Criekinge W, De Backer GG, Gillebert TC, Van Oostveldt P, Bekaert S. Paternal age at birth is an important determinant of offspring telomere length. *Hum Mol Genet* 2007;**16**:3097–3102.

Dhillo WS, Chaudhri OB, Patterson M, Thompson EL, Murphy KG, Badman MK, McGowan BM, Amber V, Patel S, Ghatei MA *et al.* Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. *J Clin Endocrinol Metab* 2005;**90**:6609–6615.

Dunson DB, Colombo B, Baird DD. Changes with age in the level and duration of fertility in the menstrual cycle. *Hum Reprod* 2002; **17**:1399–1403.

Dunson DB, Baird DD, Colombo B. Increased infertility with age in men and women. *Obstet Gynecol* 2004;**103**:51–56.

Ecker JL, Chen KT, Cohen AP, Riley LE, Lieberman ES. Increased risk of cesarean delivery with advancing maternal age: indications and associated factors in nulliparous women. *Am J Obstet Gynecol* 2001; **185**:883–887.

Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PJ. Early embryonic mortality in women. *Fertil Steril* 1982;**38**:447–453.

Einarsson JI, Sangi-Haghpeykar H, Gardner MO. Sperm exposure and development of preeclampsia. *Am J Obstet Gynecol* 2003; **188**:1241–1243.

Elzanaty S. Association between age and epididymal and accessory sex gland function and their relation to sperm motility. *Arch Androl* 2007; **53**:149–156.

Elzanaty S, Richthoff J, Malm J, Giwercman A. The impact of epididymal and accessory sex gland function on sperm motility. *Hum Reprod* 2002;**17**:2904–2911.

Esplin MS, Fausett MB, Fraser A, Kerber R, Mineau G, Carrillo J, Varner MW. Paternal and maternal components of the predisposition to preeclampsia. *N Engl J Med* 2001;**344**:867–872.

Ettinger MP, Littlejohn TW, Schwartz SL, Weiss SR, McIlwain HH, Heymsfield SB, Bray GA, Roberts WG, Heyman ER, Stambler N *et al.* Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized, dose-ranging study. *JAMA* 2003; **289**:1826–1832.

Farrer LA, Cupples LA, Connor L, Wolf PA, Growdon JH. Association of decreased paternal age and late-onset Alzheimer's disease. An example of genetic imprinting? *Arch Neurol* 1991;**48**:599–604.

Farrer LA, Cupples LA, Kiely DK, Conneally PM, Myers RH. Inverse relationship between age at onset of Huntington disease and paternal age suggests involvement of genetic imprinting. *Am J Hum Genet* 1992; **50**:528–535.

Fisch H. Declining worldwide sperm counts: disproving a myth. *Urol Clin North Am* 2008;**35**:137–146. vii.

Fisch H, Hyun G, Golden R, Hensle TW, Olsson CA, Liberson GL. The influence of paternal age on down syndrome. *J Urol* 2003; **169**:2275–2278.

Fletcher NA, Foley J. Parental age, genetic mutation, and cerebral palsy. *J Med Genet* 1993;**30**:44–46.

Ford JH, MacCormac L, Hiller J. PALS (pregnancy and lifestyle study): association between occupational and environmental exposure to chemicals and reproductive outcome. *Mutat Res* 1994; **313**:153–164.

Ford WC, North K, Taylor H, Farrow A, Hull MG, Golding J. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. The ALSPAC Study Team (Avon Longitudinal Study of Pregnancy and Childhood). *Hum Reprod* 2000;**15**:1703–1708.

Forsyth NR, Evans AP, Shay JW, Wright WE. Developmental differences in the immortalization of lung fibroblasts by telomerase. *Aging Cell* 2003; **2**:235–243.

Frans EM, Sandin S, Reichenberg A, Lichtenstein P, Langstrom N, Hultman CM. Advancing paternal age and bipolar disorder. *Arch Gen Psychiatry* 2008;**65**:1034–1040.

Gagnon C, de Lamirande E. Controls of sperm motility. In De Jonge CC, Barratt CLR (eds). *The Sperm Cell: Production, Maturation, Fertilization, Regeneration*.Cambridge, UK; New York: Cambridge University Press, 2006, 108–133.

Garcia-Enguidanos A, Calle ME, Valero J, Luna S, Dominguez-Rojas V. Risk factors in miscarriage: a review. *Eur J Obstet Gynecol Reprod Biol* 2002; **102**:111–119.

Gavrilov LA, Gavrilova NS, Kroutko VN, Evdokushkina GN, Semyonova VG, Gavrilova AL, Lapshin EV, Evdokushkina NN, Kushnareva YE. Mutation load and human longevity. *Mutat Res* 1997; **377**:61–62.

Getahun D, Ananth CV, Vintzileos AM. Uteroplacental bleeding disorders during pregnancy: do missing paternal characteristics influence risk? *BMC Pregnancy Childbirth* 2006;**6**:2.

Gielchinsky Y, Mazor M, Simon A, Mor-Yossef S, Laufer N. Natural conception after age 45 in Bedouin women, a uniquely fertile population. *J Assist Reprod Genet* 2006;**23**:305–309.

Goffinet F. Primary predictors of preterm labour. *BJOG* 2005;**112**:38–47.

Goriely A, McVean GA, Rojmyr M, Ingemarsson B, Wilkie AO. Evidence for selective advantage of pathogenic FGFR2 mutations in the male germ line. *Science* 2003;**301**:643–646.

Gosden R, Trasler J, Lucifero D, Faddy M. Rare congenital disorders, imprinted genes, and assisted reproductive technology. *Lancet* 2003; **361**:1975–1977.

Griffin DK, Abruzzo MA, Millie EA, Sheean LA, Feingold E, Sherman SL, Hassold TJ. Non-disjunction in human sperm: evidence for an effect of increasing paternal age. *Hum Mol Genet* 1995;**4**:2227–2232.

Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT, Meikle AW. Male obesity and alteration in sperm parameters. *Fertil Steril* 2008; **90**:2222–2225.

Handelsman DJ. Estrogens and falling sperm counts. *Reprod Fertil Dev* 2001; **13**:317–324.

Handelsman DJ. Male reproductive ageing: human fertility, androgens and hormone dependent disease. *Novartis Found Symp* 2002;**242**:66–77; discussion 77–81.

Handelsman DJ, Staraj S. Testicular size: the effects of aging, malnutrition, and illness. *J Androl* 1985;**6**:144–151.

Harlap S, Paltiel O, Deutsch L, Knaanie A, Masalha S, Tiram E, Caplan LS, Malaspina D, Friedlander Y. Paternal age and preeclampsia. *Epidemiology* 2002;**13**:660–667.

Hassan MA, Killick SR. Effect of male age on fertility: evidence for the decline in male fertility with increasing age. *Fertil Steril* 2003; **79**:1520–1527.

Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet* 2001;**2**:280–291.

Hassold T, Sherman S. Down syndrome: genetic recombination and the origin of the extra chromosome 21. *Clin Genet* 2000;**57**:95–100.

Hatch M, Kline J, Levin B, Hutzler M, Warburton D. Paternal age and trisomy among spontaneous abortions. *Hum Genet* 1990; **85**:355–361.

Hauser R. The environment and male fertility: recent research on emerging chemicals and semen quality. *Semin Reprod Med* 2006; **24**:156–167.

Hellstrom WJ, Overstreet JW, Sikka SC, Denne J, Ahuja S, Hoover AM, Sides GD, Cordell WH, Harrison LM, Whitaker JS. Semen and sperm reference ranges for men 45 years of age and older. *J Androl* 2006; **27**:421–428.

Hemminki K, Kyyronen P, Vaittinen P. Parental age as a risk factor of childhood leukemia and brain cancer in offspring. *Epidemiology* 1999; **10**:271–275.

Heshmat S, Lo KC. Evaluation and treatment of ejaculatory duct obstruction in infertile men. *Can J Urol* 2006;**13**:18–21.

Isles AR, Holland AJ. Imprinted genes and mother-offspring interactions. *Early Hum Dev* 2005;**81**:73–77.

Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol* 2004;**104**:727–733.

Jafarabadi M. Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. *Hum Reprod* 2007;**22**:3263; author reply 3264.

Jensen TK, Andersson AM, Jorgensen N, Andersen AG, Carlsen E, Petersen JH, Skakkebaek NE. Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. *Fertil Steril* 2004;**82**:863–870.

Jinno Y, Ikeda Y, Yun K, Maw M, Masuzaki H, Fukuda H, Inuzuka K, Fujishita A, Ohtani Y, Okimoto T *et al*. Establishment of functional imprinting of the H19 gene in human developing placentae. *Nat Genet* 1995;**10**:318–324.

Joffe M, Li Z. Male and female factors in fertility. *Am J Epidemiol* 1994; **140**:921–929.

Johnson L, Grumbles JS, Bagheri A, Petty CS. Increased germ cell degeneration during postprophase of meiosis is related to increased serum follicle-stimulating hormone concentrations and reduced daily sperm production in aged men. *Biol Reprod* 1990;**42**:281–287.

Juul A, Skakkebaek NE. Androgens and the ageing male. *Hum Reprod Update* 2002;**8**:423–433.

Kalaydjiev SK, Dimitrova DK, Trifonova NL, Fichorova RN, Masharova NG, Raicheva YN, Simeonova MN, Todorova EI, Todorov VI, Nakov LS. The age-related changes in the incidence of 'natural' anti-sperm antibodies suggest they are not auto-/isoantibodies. *Am J Reprod Immunol* 2002;**47**:65–71.

Kalsi JS, Bahadur G, Muneer A, Ozturk O, Christopher N, Ralph DJ, Minhas S. Novel PDE5 inhibitors for the treatment of male erectile dysfunction. *Reprod Biomed Online* 2003;**7**:456–461.

Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005; **26**:833–876.

Kazaura M, Lie RT, Skjaerven R. Paternal age and the risk of birth defects in Norway. *Ann Epidemiol* 2004;**14**:566–570.

Keeley G. Expectant father Iglesias dies at 90. *The Times* 2005.

Kenkel S, Rolf C, Nieschlag E. Occupational risks for male fertility: an analysis of patients attending a tertiary referral centre. *J Int J Androl* 2001;**24**:318–326.

Khan KS, Honest H. Risk screening for spontaneous preterm labour. *Best Pract Res Clin Obstet Gynaecol* 2007;**21**:821–830.

Kidd SA, Eskenazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. *Fertil Steril* 2001; **75**:237–248.

Kimura M, Cherkas LF, Kato BS, Demissie S, Hjelmborg JB, Brimacombe M, Cupples A, Hunkin JL, Gardner JP, Lu X *et al*. Offspring's leukocyte telomere length, paternal age, and telomere elongation in sperm. *PLoS Genet* 2008;**4**:e37.

Kinzler WL, Ananth CV, Smulian JC, Vintzileos AM. Parental age difference and adverse perinatal outcomes in the United States. *Paediatr Perinat Epidemiol* 2002;**16**:320–327.

Kirby RS. Vital statistics: a poor source of data for investigating the association between paternal age and birth defects. *Hum Reprod* 2007;**22**:3265–3267.

Klein J, Sauer MV. Assessing fertility in women of advanced reproductive age. *Am J Obstet Gynecol* 2001;**185**:758–770.

Kleinhaus K, Perrin MC, Manor O, Friedlander Y, Calderon-Margalit R, Harlap S, Malaspina D. Paternal age and twinning in the Jerusalem Perinatal Study. *Eur J Obstet Gynecol Reprod Biol* 2008;**141**:119–122.

Kühnert B, Nieschlag E. Reproductive functions of the ageing male. *Hum Reprod Update* 2004;**10**:327–339.

La Salle S, Trasler JM. Epigenetic patterning in male germ cells: importance of DNA methylation to progeny outcome. In De Jonge CC, Barratt CLR (eds). *The Sperm Cell: Production, Maturation, Fertilization, Regeneration*. Cambridge, UK; New York: Cambridge University Press, 2006.

La Vecchia C, Parazzini F, Decarli A, Franceschi S, Fasoli M, Favalli G, Negri E, Pampallona S. Age of parents and risk of gestational trophoblastic disease. *J Natl Cancer Inst* 1984;**73**:639–642.

Lambert SM, Masson P, Fisch H. The male biological clock. *World J Urol* 2006;**24**:611–617.

Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* 2004;**364**:273–283.

Laufer N, Simon A, Samueloff A, Yaffe H, Milwidsky A, Gielchinsky Y. Successful spontaneous pregnancies in women older than 45 years. *Fertil Steril* 2004;**81**:1328–1332.

Leitich H. Secondary predictors of preterm labour. *BJOG* 2005; **112**:48–50.

Li DK, Wi S. Changing paternity and the risk of preeclampsia/eclampsia in the subsequent pregnancy. *Am J Epidemiol* 2000;**151**:57–62.

Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. *BMJ* 1998;**316**:1343–1347.

Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007;**357**:762–774.

Lombardo F, Sgro P, Salacone P, Gilio B, Gandini L, Dondero F, Jannini EA, Lenzi A. Androgens and fertility. *J Endocrinol Invest* 2005;**28**:51–55.

Lopes S, Sun JG, Jurisicova A, Meriano J, Casper RF. Sperm deoxyribonucleic acid fragmentation is increased in poor-quality semen samples and correlates with failed fertilization in intracytoplasmic sperm injection. *Fertil Steril* 1998;**69**:528–532.

Luetjens CM, Rolf C, Gassner P, Werny JE, Nieschlag E. Sperm aneuploidy rates in younger and older men. *Hum Reprod* 2002;**17**:1826–1832.

Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage–results from a UK-population-based case–control study. *BJOG* 2007;**114**:170–186.

Magnusdottir EV, Thorsteinsson T, Thorsteinsdottir S, Heimisdottir M, Olafsdottir K. Persistent organochlorines, sedentary occupation, obesity and human male subfertility. *Hum Reprod* 2005;**20**:208–215.

Malaspina D. Paternal factors and schizophrenia risk: de novo mutations and imprinting. *Schizophr Bull* 2001;**27**:379–393.

Malaspina D, Reichenberg A, Weiser M, Fennig S, Davidson M, Harlap S, Wolitzky R, Rabinowitz J, Susser E, Knobler HY. Paternal age and intelligence: implications for age-related genomic changes in male germ cells. *Psychiatr Genet* 2005;**15**:117–125.

Marques CJ, Carvalho F, Sousa M, Barros A. Genomic imprinting in disruptive spermatogenesis. *Lancet* 2004;**363**:1700–1702.

Martien S, Abbadie C. Acquisition of oxidative DNA damage during senescence: the first step toward carcinogenesis? *Ann N Y Acad Sci* 2007;**1119**:51–63.

Martin RH. Meiotic chromosome abnormalities in human spermatogenesis. *Reprod Toxicol* 2006;**22**:142–147.

Martin RH, Rademaker AW. The effect of age on the frequency of sperm chromosomal abnormalities in normal men. *Am J Hum Genet* 1987; **41**:484–492.

Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, Munson ML. Births: final data for 2005. *Natl Vital Stat Rep* 2007;**56**: 1–103.

Matsuura J, Chiu D, Jacobs PA, Szulman AE. Complete hydatidiform mole in Hawaii: an epidemiological study. *Genet Epidemiol* 1984; **1**:271–284.

Matthiesson KL, McLachlan RI. Male hormonal contraception: concept proven, product in sight? *Hum Reprod Update* 2006;**12**:463–482.

McInnes B, Rademaker A, Martin R. Donor age and the frequency of disomy for chromosomes 1, 13, 21 and structural abnormalities in human spermatozoa using multicolour fluorescence in-situ hybridization. *Hum Reprod* 1998;**13**:2489–2494.

McIntosh GC, Olshan AF, Baird PA. Paternal age and the risk of birth defects in offspring. *Epidemiology* 1995;**6**:282–288.

McVary KT. Clinical practice. Erectile dysfunction. *N Engl J Med* 2007; **357**:2472–2481.

Menken J, Trussell J, Larsen U. Age and infertility. *Science* 1986; **233**:1389–1394.

Messerli ML, Lilienfeld AM, Parmley T, Woodruff JD, Rosenshein NB. Risk factors for gestational trophoblastic neoplasia. *Am J Obstet Gynecol* 1985; **153**:294–300.

Miozzo M, Simoni G. The role of imprinted genes in fetal growth. *Biol Neonate* 2002;**81**:217–228.

Mirone V, Ricci E, Gentile V, Basile Fasolo C, Parazzini F. Determinants of erectile dysfunction risk in a large series of Italian men attending andrology clinics. *Eur Urol* 2004;**45**:87–91.

Moll AC, Imhof SM, Kuik DJ, Bouter LM, Den Otter W, Bezemer PD, Koten JW, Tan KE. High parental age is associated with sporadic hereditary retinoblastoma: the Dutch retinoblastoma register 1862–1994. *Hum Genet* 1996;**98**:109–112.

Montgomery SM, Lambe M, Olsson T, Ekbom A. Parental age, family size, and risk of multiple sclerosis. *Epidemiology* 2004;**15**:717–723.

Morris ID, Ilott S, Dixon L, Brison DR. The spectrum of DNA damage in human sperm assessed by single cell gel electrophoresis (Comet assay) and its relationship to fertilization and embryo development. *Hum Reprod* 2002;**17**:990–998.

Murray L, McCarron P, Bailie K, Middleton R, Davey Smith G, Dempsey S, McCarthy A, Gavin A. Association of early life factors and acute lymphoblastic leukaemia in childhood: historical cohort study. *Br J Cancer* 2002;**86**:356–361.

Naccarati A, Zanello A, Landi S, Consigli R, Migliore L. Sperm-FISH analysis and human monitoring: a study on workers occupationally exposed to styrene. *Mutat Res* 2003;**537**:131–140.

Naguib KK, Al-Awadi SA, Moussa MA, Bastaki L, Gouda S, Redha MA, Mustafa F, Tayel SM, Abulhassan SA, Murthy DS. Trisomy 18 in Kuwait. *Int J Epidemiol* 1999;**28**:711–716.

Nicolosi A, Buvat J, Glasser DB, Hartmann U, Laumann EO, Gingell C. Sexual behaviour, sexual dysfunctions and related help seeking patterns in middle-aged and elderly Europeans: the global study of sexual attitudes and behaviors. *World J Urol* 2006;**24**:423–428.

Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;**320**:1708–1712.

Nybo Andersen AM, Hansen KD, Andersen PK, Davey Smith G. Advanced paternal age and risk of fetal death: a cohort study. *Am J Epidemiol* 2004;**160**:1214–1222.

Oakes CC, Smiraglia DJ, Plass C, Trasler JM, Robaire B. Aging results in hypermethylation of ribosomal DNA in sperm and liver of male rats. *Proc Natl Acad Sci U S A* 2003;**100**:1775–1780.

Odibo AO, Cahill AG, Stamilio DM, Stevens EJ, Peipert JF, Macones GA. Predicting placental abruption and previa in women with a previous cesarean delivery. *Am J Perinatol* 2007;**24**:299–305.

Olsen J. Subfecundity according to the age of the mother and the father. *Dan Med Bull* 1990;**37**:281–282.

Olshan AF, Breslow NE, Daling JR, Falletta JM, Grufferman S, Robison LL, Waskerwitz M, Hammond GD. Wilms' tumor and paternal occupation. *Cancer Res* 1990;**50**:3212–3217.

Olshan AF, Teschke K, Baird PA. Paternal occupation and congenital anomalies in offspring. *Am J Ind Med* 1991;**20**:447–475.

Olshan AF, Schnitzer PG, Baird PA. Paternal age and the risk of congenital heart defects. *Teratology* 1994;**50**:80–84.

Olshan AF, Ananth CV, Savitz DA. Intrauterine growth retardation as an endpoint in mutation epidemiology: an evaluation based on paternal age. *Mutat Res* 1995;**344**:89–94.

Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. *Obstet Gynecol* 2006;**107**:927–941.

Pal L, Santoro N. Age-related decline in fertility. *Endocrinol Metab Clin North Am* 2003;**32**:669–688.

Parazzini F, La Vecchia C, Pampallona S. Parental age and risk of complete and partial hydatidiform mole. *Br J Obstet Gynaecol* 1986;**93**:582–585.

Paulson RJ, Boostanfar R, Saadat P, Mor E, Tourgeman DE, Slater CC, Francis MM, Jain JK. Pregnancy in the sixth decade of life: obstetric outcomes in women of advanced reproductive age. *JAMA* 2002; **288**:2320–2323.

Penrose LS. Parental age and mutation. *Lancet* 1955;**269**:312–313.

Perrin MC, Brown AS, Malaspina D. Aberrant epigenetic regulation could explain the relationship of paternal age to schizophrenia. *Schizophr Bull* 2007;**33**:1270–1273.

Reedy NJ. Born too soon: the continuing challenge of preterm labor and birth in the United States. *J Midwifery Womens Health* 2007;**52**:281–290.

Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ* 1989;**299**:541–545.

Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, Rabinowitz J, Shulman C, Malaspina D, Lubin G *et al.* Advancing paternal age and autism. *Arch Gen Psychiatry* 2006;**63**:1026–1032.

Reichman NE, Teitler JO. Paternal age as a risk factor for low birthweight. *Am J Public Health* 2006;**96**:862–866.

Roecker GO, Huether CA. An analysis for paternal-age effect in Ohio's Down syndrome births, 1970-1980. *Am J Hum Genet* 1983;**35**:1297–1306.

Rolf C, Behre HM, Nieschlag E. Reproductive parameters of older compared to younger men of infertile couples. *Int J Androl* 1996;**19**:135–142.

Rolf C, Kenkel S, Nieschlag E. Age-related disease pattern in infertile men: increasing incidence of infections in older patients. *Andrologia* 2002; **34**:209–217.

Rosenthal AN, Paterson-Brown S. Is there an incremental rise in the risk of obstetric intervention with increasing maternal age? *Br J Obstet Gynaecol* 1998;**105**:1064–1069.

Saha S, Barnett AG, Foldi C, Burne TH, Eyles DW, Buka SL, McGrath JJ. Advanced paternal age is associated with impaired neurocognitive outcomes during infancy and childhood. *PLoS Med* 2009;**6**:e40.

Sallmen M, Luukkonen R. Is the observed association between increasing paternal age and delayed conception an artefact? *Hum Reprod* 2001; **16**:2027–2028.

Sartorelli EM, Mazzucatto LF, de Pina-Neto JM. Effect of paternal age on human sperm chromosomes. *Fertil Steril* 2001;**76**:1119–1123.

Schuppe HC, Meinhardt A, Allam JP, Bergmann M, Weidner W, Haidl G. Chronic orchitis: a neglected cause of male infertility? *Andrologia* 2008; **40**:84–91.

Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. Federation CECOS. *N Engl J Med* 1982;**306**:404–406.

Selvin S, Garfinkel J. Paternal age, maternal age and birth order and the risk of a fetal loss. *Hum Biol* 1976;**48**:223–230.

Seymour F, Duffy C, Korner A. A case of authentic fertility in a man of 94. *JAMA* 1935;**105**:1423–1424.

Sharpe CR, Franco EL, de Camargo B, Lopes LF, Barreto J, Johnsson R, Mauad M. The influence of parental age on the risk of Wilms' tumour. *Paediatr Perinat Epidemiol* 1999;**13**:138–143.

Shindel AW, Nelson CJ, Naughton CK, Mulhall JP. Premature ejaculation in infertile couples: prevalence and correlates. *J Sex Med* 2008a; **5**:485–491.

Shindel AW, Nelson CJ, Naughton CK, Ohebshalom M, Mulhall JP. Sexual function and quality of life in the male partner of infertile couples: prevalence and correlates of dysfunction. *J Urol* 2008b;**179**:1056–1059.

Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005; **365**:785–799.

Silber S. A new and rapid scoring system to assess the scientific evidence from clinical trials. *J Interv Cardiol* 2006;**19**:485–492.

Singh NP, Muller CH, Berger RE. Effects of age on DNA double-strand breaks and apoptosis in human sperm. *Fertil Steril* 2003;**80**:1420–1430.

Skjaerven R, Vatten LJ, Wilcox AJ, Ronning T, Irgens LM, Lie RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ* 2005;**331**:877.

Slama R, Werwatz A, Boutou O, Ducot B, Spira A, Hardle W. Does male age affect the risk of spontaneous abortion? An approach using semiparametric regression. *Am J Epidemiol* 2003;**157**:815–824.

Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, Swan SH. Influence of paternal age on the risk of spontaneous abortion. *Am J Epidemiol* 2005;**161**:816–823.

Sloter ED, Lowe X, Moore ID, Nath J, Wyrobek AJ. Multicolor FISH analysis of chromosomal breaks, duplications, deletions, and numerical abnormalities in the sperm of healthy men. *Am J Hum Genet* 2000;**67**:862–872.

Sloter E, Nath J, Eskenazi B, Wyrobek AJ. Effects of male age on the frequencies of germinal and heritable chromosomal abnormalities in humans and rodents. *Fertil Steril* 2004;**81**:925–943.

Sloter E, Schmid TE, Marchetti F, Eskenazi B, Nath J, Wyrobek AJ. Quantitative effects of male age on sperm motion. *Hum Reprod* 2006; **21**:2868–2875.

Spano M, Bonde JP, Hjollund HI, Kolstad HA, Cordelli E, Leter G. Sperm chromatin damage impairs human fertility. The Danish first pregnancy planner study team. *Fertil Steril* 2000;**73**:43–50.

Tan H, Wen SW, Walker M, Demissie K. Missing paternal demographics: A novel indicator for identifying high risk population of adverse pregnancy outcomes. *BMC Pregnancy Childbirth* 2004;**4**:21.

Tang CH, Wu MP, Liu JT, Lin HC, Hsu CC. Delayed parenthood and the risk of cesarean delivery—is paternal age an independent risk factor? *Birth* 2006;**33**:18–26.

Thacker PD. Biological clock ticks for men, too: genetic defects linked to sperm of older fathers. *JAMA* 2004;**291**:1683–1685.

Tiemann-Boege I, Navidi W, Grewal R, Cohn D, Eskenazi B, Wyrobek AJ, Arnheim N. The observed human sperm mutation frequency cannot explain the achondroplasia paternal age effect. *Proc Natl Acad Sci U S A* 2002;**99**:14952–14957.

Trupin LS, Simon LP, Eskenazi B. Change in paternity: a risk factor for preeclampsia in multiparas. *Epidemiology* 1996;**7**:240–244.

Turner TT, Lysiak JJ. Oxidative stress: a common factor in testicular dysfunction. *J Androl* 2008;**29**:488–498.

Unryn BM, Cook LS, Riabowol KT. Paternal age is positively linked to telomere length of children. *Aging Cell* 2005;**4**:97–101.

Vagnini L, Baruffi RL, Mauri AL, Petersen CG, Massaro FC, Pontes A, Oliveira JB, Franco JG Jr. The effects of male age on sperm DNA damage in an infertile population. *Reprod Biomed Online* 2007; **15**:514–519.

Vestergaard M, Mork A, Madsen KM, Olsen J. Paternal age and epilepsy in the offspring. *Eur J Epidemiol* 2005;**20**:1003–1005.

Wagschal A, Feil R. Genomic imprinting in the placenta. *Cytogenet Genome Res* 2006;**113**:90–98.

Wang JX, Knottnerus AM, Schuit G, Norman RJ, Chan A, Dekker GA. Surgically obtained sperm, and risk of gestational hypertension and pre-eclampsia. *Lancet* 2002;**359**:673–674.

Weinstein M, Stark M. Behavioral and biological determinants of fecundability. *Ann N Y Acad Sci* 1994;**709**:128–144.

Whalley LJ, Thomas BM, Starr JM. Epidemiology of presenile Alzheimer's disease in Scotland (1974–1988) II. Exposures to possible risk factors. *Br J Psychiatry* 1995;**167**:732–738.

Wilcox AJ, Horney LF. Accuracy of spontaneous abortion recall. *Am J Epidemiol* 1984;**120**:727–733.

Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *N Engl J Med* 1988;**319**:189–194.

Woodruff TJ, Carlson A, Schwartz JM, Giudice LC. Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary. *Fertil Steril* 2008;**89**:281–300.

Wyrobek AJ, Eskenazi B, Young S, Arnheim N, Tiemann-Boege I, Jabs EW, Glaser RL, Pearson FS, Evenson D. Advancing age has differential effects on DNA damage, chromatin integrity, gene mutations, and aneuploidies in sperm. *Proc Natl Acad Sci U S A* 2006; **103**:9601–9606.

Yang Q, Wen SW, Leader A, Chen XK, Lipson J, Walker M. Paternal age and birth defects: how strong is the association? *Hum Reprod* 2007; **22**:696–701.

Yen S, MacMahon B. Epidemiologic features of trophoblastic disease. *Am J Obstet Gynecol* 1968;**101**:126–132.

Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol* 2006; **35**:1495–1503.

Zhang Y, Kreger BE, Dorgan JF, Cupples LA, Myers RH, Splansky GL, Schatzkin A, Ellison RC. Parental age at child's birth and son's risk of prostate cancer. The Framingham Study. *Am J Epidemiol* 1999; **150**:1208–1212.

Zhu JL, Madsen KM, Vestergaard M, Basso O, Olsen J. Paternal age and preterm birth. *Epidemiology* 2005a;**16**:259–262.

Zhu JL, Madsen KM, Vestergaard M, Olesen AV, Basso O, Olsen J. Paternal age and congenital malformations. *Hum Reprod* 2005b; **20**:3173–3177.

Zini A, Libman J. Sperm DNA damage: clinical significance in the era of assisted reproduction. *CMAJ* 2006;**175**:495–500.

Zini A, Bielecki R, Phang D, Zenzes MT. Correlations between two markers of sperm DNA integrity, DNA denaturation and DNA fragmentation, in fertile and infertile men. *Fertil Steril* 2001;**75**:674–677.

Submitted on September 18, 2008; resubmitted on July 13, 2009; accepted on July 20, 2009