Paternal age and reproduction

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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

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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 tech-
niques (ART) and changing sociological factors, as for example plan-
ning 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 peri-
natal 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 pro-
duction of reproductive hormones, sexual function, semen pro-
duction, 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 repro-
duction, 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
‘mutation’, ‘epigenetics’, ‘telomere length’ (TL) or ‘DNA damage’. In
addition we searched references cited in the retrieved articles. The main

### Table I: Effects of male age on reproductive function: overview

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

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.
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).

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 Vermueken, 2005). Secondly 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 (Lombarido 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 (Matthiessen 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 E1 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 phosphodiesterase-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-/azoosperma (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 chromosome 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 diplody 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 G13B 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, chemotheraphy, 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; McIntosh 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 ≤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 ≥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 paternal 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; Luettjens et al., 2002; Morris et al., 2002; Singh et al., 2003).

In an early investigation of >1.5 × 10⁶ birth and fetal death certificates recorded from 1959 to 1967 in New York State, the

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**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 Homey, 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 (Caughhey 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 Cesarean 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).

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, polyhydramnios, 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; Leitch, 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 in 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., 2007).
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; Lamberti 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 (Vahaly 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, 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, pre-eclampsia, 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 paternal 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/.

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