

Delayed fatherhood

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ABSTRACT

Birth data from developed countries indicates that the average paternal age is increasing. As the trend to older fatherhood has become established, concerns have been raised that this may be linked to adverse outcomes, such as pregnancy complications, congenital anomalies, and long-term health implications for the child. Since the sperm of older fathers may be impaired due to the general effects of ageing, their offspring may be at risk due to defects in sperm quality at conception. A literature search was performed to identify pregnancy complications, fetal anomalies and health issues for the child when the father is in an older age bracket. Evidence for impairment in the sperm and genetic material of older fathers was reviewed. With an older father, there is evidence of an increase in stillbirths and a slightly increased risk of autism, bipolar disorder and schizophrenia in the offspring later in life. The increased risk of achondroplasia has long been recognised. For the mother, there is an increased rate of Caesarean section. Investigations of other possible adverse outcomes have produced mixed findings. Further robust and longitudinal studies are needed to clarify these issues.

BACKGROUND

Statistics from developed countries indicate that the average paternal age is increasing. In England and Wales, the mean age of fathers increased from 29.2 years in 1980 to 32.6 in 2011.¹ In Norway, the average age of first-time fathers was 26.2 years between 1966 and 1970; in 2009 it was 30.9 years.² Similar trends are reported from Germany³ and the USA.⁴

A confounding factor in many of the writings on this issue is the parallel increase in maternal age; older men having their first child are often partnered with a woman also of relatively advanced age. For example, in Australia, the average maternal age in 1971 was 25.4 years; by 2012 it was 30.7 years.⁵ However, not all studies on the paternal age effect make allowance for the

Key message points

- ▶ There is an increase in stillbirths when the father is older.
- ▶ There is an increased risk of autism, schizophrenia and bipolar disorder when the father is older.
- ▶ Despite the above mentioned concerns, the risk to the offspring is low.

increase in maternal age, or for other confounding factors such as sex of the child, the socioeconomic status of the parents, their alcohol and cigarette intake, and a family history of psychosis.

In addition, few studies look at the background health profile of the older father. A Norwegian study² examined this issue in 14 832 first-time fathers, and reported that the older men “were more likely to be overweight or obese, to be smokers, and to consume alcohol more frequently than a comparison group”.

METHODS

A search for publications in English dated between 1990 and 2013 was undertaken in the following databases: the Cochrane Library, PubMed, Embase, Scopus and the European Association of Grey Literature. The key words used were: ‘delayed paternity’, ‘paternal age effect’, ‘ageing sperm’, ‘pregnancy complications’ and ‘health issues for the child’. This is a rapidly expanding field. In PubMed alone, under ‘paternal age effect’ there were 57 new references recorded in 2013. References that were excluded were publications on infertility, reproduction success rates, multiple pregnancies, observational studies, case reports, post-birth paternal health issues, animal studies, and studies where no adjustment was made for maternal age.

A limitation was that complete information on paternal age was not always available. In a review of the 2007 US



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nationwide birth data⁴ it was found that 14% of the 4 316 233 deliveries did not have details on the paternal age.

SPERM QUALITY AND AGEING

The ageing process leads to changes in the cells in the testes that parallel changes in all other parts of the body. However, studies on semen characteristics in the ageing male, in particular sperm morphology, do not provide a uniform picture. A report on 792 American males⁶ undergoing *in vitro* fertilisation or intrauterine insemination in cases of female infertility only, compared the characteristics of semen in men aged 51–60 years to men aged 20–30 years. The authors reported that the mean percentage of normal sperm morphology in men aged 20–30 years was 69.7%, but this fell to 53.4% in the older age group. By contrast, a review of sperm characteristics⁷ from fertility units in five countries (USA, France, Spain, Brazil and Egypt) involved in assisted reproductive technology noted a decrease in the percentage of normal morphology with advancing age in only one of six units.

The quality of the genetic material carried in the sperm may also suffer the effects of ageing. Because male germ cells divide continuously, with many more mitotic divisions than the oocytes, the possibility of transcription errors among fathers is greater.⁸ Sperm are produced continuously throughout life. Sperm stem cells divide 30 times before puberty, and from then on every 16 days. By the age of 40 years, a sperm will have gone through 610 cell divisions; at age 50 years, it will have gone through 840 divisions, each time with the possibility of DNA errors in the process, with an increased likelihood of a mutation.

A recent study from Iceland⁹ provided evidence of increased mutations among older fathers. By sequencing the entire genome pattern of 78 parents and their children, the number of mutations passed on to their offspring by the mothers and fathers could be compared. Fathers passed on many times more new mutations than did mothers. The mutation rate was linked to the age of the father at conception, with an increase of about two mutations per year.

COMPLICATIONS IN THE PREGNANCY

A number of adverse outcomes such as miscarriages, stillbirths, preterm births and Caesarean sections have been studied to assess the paternal age effect.

The early loss of a fetus occurs in approximately 10–15% of pregnant women. Many of these pregnancy losses are thought to be due to chromosomal errors in the fetus. A study of 5121 pregnant Californian women¹⁰ found that the adjusted hazard ratio (HR) for miscarriage where the father was aged 35 years or more, compared with less than 35 years, was 1.27 [95% confidence interval (CI) 1.00–1.61], adjusted for maternal age. However, a different

experience was reported for European women,¹¹ where mixed outcomes were reported for three age brackets: “If the woman was 20–29 years old, the risk of miscarriage was not significantly high, whatever the age of the man. If the woman was 30–34 years old, the risk of miscarriage was higher if the man was greater than 40 years. If the woman was greater than 35 years, the risk of miscarriage increased, whatever the age of the man”. Accordingly, the authors argued that the risk of miscarriage was a “couple’s business”, rather than just attributable to the mother or father.

Stillbirths may also be linked to an older father, a possibility that was first raised in 1939.¹² More recently, a Missouri study¹³ reviewed the outcome of 755 334 deliveries between 1989 and 2005. There were 49 419 (6.5%) fathers aged 40 years or over. The authors reported that, after adjusting for maternal age, compared with infants born to younger fathers (25–29 years), those born to fathers aged 40–45 years had a 24% increased risk of stillbirth [odds ratio (OR) 1.24; 95% CI 1.04–1.47]. A Danish study¹⁴ analysed 23 821 pregnancies, of which 146 ended in stillbirth after 20 weeks’ gestation. It reported that pregnancies fathered by a man aged 50 years or older had almost twice the risk of ending in fetal loss, compared with pregnancies by younger fathers (HR 1.88; 95% CI 0.93–3.82), after adjustment for maternal age. An Italian study¹⁵ reviewed the outcome of 3 619 647 deliveries between 1990 and 1996, and analysed fetal deaths from 26 weeks. It found that paternal age over the age of 40 years increased the risk of stillbirth in mothers over 35 years of age, although this was modified if the mother had had a “high educational level”, thought to reflect better socioeconomic conditions. The consistency of these findings indicates a risk of increased stillbirth with an older father.

The evidence that advanced paternal age can be linked to a preterm birth is contradictory. An American study of 2 509 012 live births of married women aged 20–34 years from white, non-Hispanic first-time mothers¹⁶ did not identify a link between older paternal age and early preterm delivery. By contrast, the Missouri study quoted above¹³ claimed that with paternal age of 45 years or more, there was a 13% increased risk of preterm delivery between 33 and 37 weeks (OR 1.13; 95% CI 1.05–1.22), and a 29% risk of very preterm delivery, less than 33 weeks, compared to fathers aged 25–29 years (OR 1.29; 95% CI 1.15–1.44).

An increase in the Caesarean section rate with increasing paternal age has been consistently reported. A Taiwanese report¹⁷ indicated that for a mother aged 20–29 years, the Caesarean rate was 27.2% when the father was aged 20–29 years; but this increased to 35.8% if the father was over 40 years old. A study from New Jersey¹⁸ reported that, after adjusting for maternal age, the Caesarean section rate for infants of Caucasian fathers aged 20–29, 30–39 and 40+ years was 21.1%, 26.7% and 31.8%, respectively.

The prevalence of pre-eclampsia (or pregnancy-induced hypertension) was reported in an Israeli study¹⁹ as being lowest when the father was aged 25–34 years. There was an increased risk of the disorder with fathers aged over 34 years, but the risk was also slightly elevated in younger fathers, aged between 20 and 24 years. Nonetheless, the study found that the overall contribution to the disorder by the father was “modest” compared to the effect of maternal age. The Missouri study mentioned above¹³ also noted that it was both the young fathers aged under 20 years, and the older fathers over 45 years, who made a slight contribution to the incidence of pre-eclampsia.

CONGENITAL ANOMALIES IN THE OFFSPRING

Given the plausibility of increased mutations in the genetic material of older fathers, congenital birth defects would be expected to show a significant increase in line with paternal age. Since records of birth defects are available for large populations, links between paternal age and even rare congenital anomalies should be apparent.

An analysis of the 5 213 248 American deliveries between 1999 and 2000²⁰ noted that there were 77 514 (1.5%) offspring with birth defects. Compared to the father's age group of 25–29 years, infants born to fathers aged 50+ years had a 15% increase in defects (OR 1.15; 95% CI 1.06–1.24). However, infants born to mothers aged 45+ years had a 2.2-fold increase in defects. In other words, the mother's advancing age was a stronger factor in contributing to birth defects than the age of the father. However, the authors concluded that increased paternal age was associated with a slightly increased risk of a number of rare disorders, namely heart defects, tracheo-oesophageal fistula, oesophageal atresia and some chromosomal disorders.

A review of data from the American National Birth Defects Prevention Study²¹ concerning infants born between 1997 and 2004 looked at 50 types of congenital defect. It noted increased risk with increasing paternal age for diaphragmatic hernia, cleft palate, right heart ventricular outflow obstruction and pulmonary vein stenosis. Again, these are rare conditions.

By contrast, a Norwegian study²² of 1 869 388 births reported no “consistent evidence” of increased risk for either paternal or maternal age.

A Danish study²³ reported no association between paternal age and the overall prevalence of congenital malformations, but it did report an increase in some specific conditions, such as Down's syndrome, malformations of extremities, and syndromes of multiple systems.

A major congenital anomaly, Down's syndrome (trisomy 21), has been linked to increasing maternal age since it was first described by British geneticist Lionel Penrose in 1933,²⁴ but links with paternal age

have been unclear. The Danish study mentioned above²³ did report an increase in trisomy 21 with increased paternal age. However, an analysis of cases of trisomy 21 identified from the Texas Birth Defects Registry from 1999 to 2007²⁵ found an increased rate for fathers aged over 40 years, and also for fathers aged 20–24 years, but only when the mother was aged over 35 years. An examination of 3419 trisomy 21 cases from the New York congenital malformations registry from 1983 to 1997 claimed that there was a paternal contribution, but only if both the mother and the father were both aged over 35 years.²⁶

Contradictory results have also been reported for multiple sclerosis and retinoblastoma. An analysis of the Swedish Inpatient Register²⁷ identified 4443 patients with multiple sclerosis, and reported that the risk increased with the father's age, but not the mother's. For 51–55-year-old fathers, the OR was 2.0 (95% CI 1.35–2.96) compared to fathers aged 21–25 years. By contrast, a study from a Canadian database²⁸ found no such link in a review of 5681 multiple sclerosis cases.

Retinoblastoma is a condition that affects 1 in 15 000 births, and is the commonest inherited malignancy in childhood. A study of 187 cases of bilateral retinoblastomas in children aged under 6 years, identified from the Californian Cancer Registry,²⁹ reported that the disorder was associated with paternal age for fathers over 35 years (crude OR 1.73; 95% CI 1.20–2.47). However, a Swedish study,³⁰ reviewing 226 cases of retinoblastoma in children aged under 5 years, did not find such a link to paternal age.

LONG-TERM HEALTH COMPLICATIONS FOR THE CHILD

Increasing paternal age at conception has been considered as a possible contributor to a number of serious mental illnesses such as autism, bipolar disorder and schizophrenia. The aetiology of these conditions remains elusive, and there is no one single cause. A number of contributing factors have been identified, one of which appears to be an older father. Other risk factors are preterm birth, being the first-born child, a low birth weight less than 2500 g, being small for gestational age at birth, being born with a low Apgar score, and breech delivery. However, none of the known individual risk factors are present in the majority of cases, so our understanding of the causes of these conditions remains incomplete. It is postulated that *de novo* chromosome mutations in the sperm of older men may be a reason for their association with these disorders.³¹

The prevalence of autism has increased in recent decades. It is thought to occur in 10–20 per 10 000 individuals. Controversy remains as to whether this is a true rise or whether it is because of a change in diagnostic criteria, or a shift to diagnosis at an earlier age.

A report on 818 Danish children with autism born between 1984 and 1998³² found that the highest risk was for individuals who had a sibling diagnosed with autism. However, this study also reported that the risk of autism increased with paternal age, with the relative risk in the 40–44-year age bracket being 1.61 (95% CI 1.19–2.18) compared to fathers aged 25–29 years. A similar result was obtained in an analysis of data on Israelis with autism who were born in six consecutive years during the 1980s;³¹ the adjusted OR was 5.75 (95% CI 2.65–12.46) when the father was aged 40–49 years, compared to fathers aged under 30 years.

An examination of Californian birth records between 1990 and 1999³³ resulted in a more complicated picture of the connection between paternal age and autism. Out of 4 947 935 births, the researchers identified 12 159 individuals with autism (246 per 100 000). They reported that advancing maternal age increased the risk for autism, regardless of the paternal age. Compared with mothers aged 25–29 years, the adjusted OR for mothers aged 40 years and over was 1.51 (95% CI 1.35–1.70). In contrast, advancing paternal age was associated with the risk of autism only when the mother was under 30 years (OR 1.59; 95% CI 1.37–1.85). Other studies from the USA^{34 35} suggest that both increasing paternal and maternal age are independently associated with autism in the offspring. An Australian study³⁶ also found that autism cases had significantly older parents, though the paternal age factor was statistically weaker than the maternal age. By contrast, a study from Denmark³⁷ did not find a statistically significant association with either increasing maternal or paternal age.

Complicating the picture is that amongst the studies of autistic patients, there is “considerable variation in methods, sample size, variable selection, analyses, data quality and control groups”.³⁶ For example, the studies from the USA often include Caucasians, black Americans, Hispanics and Asians, whereas those from other countries generally assess more homogenous groups. Nonetheless, advancing paternal age appears to be one of several contributing factors in the development of autism.

Studies of bipolar disorder have also reported contradictory results. In Sweden since 1947, every citizen has had a personal identification number, allowing precise longitudinal data. From a population of 7 328 100, there were 13 428 patients identified with bipolar disorder.³⁸ The offspring of men aged 55 years and over were more likely to be diagnosed as having bipolar disorder than the offspring of men aged 20–24 years (OR 1.37; 95% CI 1.02–1.84). The maternal age effect was less pronounced. By contrast, a Californian study³⁹ comparing 94 bipolar disorder cases with 746 controls found no increased risk with paternal ageing.

Paternal age has been examined in studies of schizophrenia among Israeli, American and Swedish

populations. An Israeli study investigated the background of 658 persons admitted to psychiatric facilities in Jerusalem prior to 1998 with a diagnosis of schizophrenia.⁴⁰ The prevalence increased progressively with advancing paternal age. Compared with offspring of fathers aged less than 25 years, the relative risk of schizophrenia was 2.02 (95% CI 1.17–3.51) and 2.96 (95% CI 1.60–5.47) in offspring of men aged 45–49 and 50 years or more, respectively.

In a study of schizophrenia diagnosed in 25 025 children born in three American cities (Boston, Providence and Philadelphia) between 1959 and 1966,⁴¹ together with a literature review of nine other similar studies, the authors found that the fathers were slightly but not significantly older. They argued that compared with other risk factors for schizophrenia, advanced paternal age appears to be “intermediate in magnitude”, and only a risk factor among offspring of fathers aged 55 years and over.

A Swedish study⁴² reviewed the files of 754 330 children born between 1973 and 1980. It identified 639 (0.08%) individuals who had a diagnosis of schizophrenia. The authors reported that there was an increased risk with older fathers, and that the HR for each 10-year increase in paternal age was 1.47 (95% CI 1.23–1.76).

ACHONDROPLASIA

Achondroplasia is a rare condition that has been consistently linked with paternal ageing. It was the first disorder to be so identified by Wilhelm Weinberg in 1912.⁴³ The German physician noticed that it often presented in the last-born child of large families. His findings were confirmed by other studies in the mid-20th century by Mörch in 1941⁴⁴ and Penrose in 1955.⁴⁵

An American study in 1970 of 148 achondroplastic dwarfs⁴⁶ reported that the average paternal age for the disorder was 6.2 years older than fathers of normal children in the same population. A 1995 study⁴⁷ reported that the mean paternal age for Italian children with achondroplasia was 36.3 vs 31.7 years for matched controls; for Latin American children, the mean paternal age was reported as 37.19 vs 27.53 years for controls. The disorder is thought to be due to increased mutation frequency at the fibroblast growth factor receptor 3 (FGFR3) gene,⁴⁸ though a recent theory has suggested that it may be due to ‘selfish’ mutant spermatogonial stem cells.⁴⁹

DISCUSSION

As a man ages and his general physiological fitness declines, it seems reasonable to ask if the quality of the genetic material that he passes on to his children through the mother is compromised. Having clear evidence of adverse effects from an increase in paternal age would assist clinicians advising parents and help underpin public health approaches to support

children's healthy birth and development. However, the challenge in reversing the trend of ageing paternity is considerable. A Norwegian group² has suggested incentives, such as "facilitation of parental leave and improved financial conditions for couples to conceive a few years earlier than is usual in modern societies of today".

While there seems to be sufficient evidence to confirm that an older father's chromosomal material will carry increased mutations, the effects of these on his partner and on his children's future is much less clear. In the case of congenital anomalies, which represent the most immediate measure of impairment due to the father's genetic load, there is mixed evidence of an overall increase of such conditions linked to the father's age at conception. With the exception of achondroplasia, the evidence is inconsistent, or points to the effects of older fathers and older mothers combining to produce the negative outcome.

Studies of long-term serious outcomes for children, such as autism or schizophrenia, are suggestive but do not clearly demonstrate that the age of the father is a definitive factor. In the words of two German researchers,³ "even if the genetic risk for progeny from older fathers is slightly increased, the risk to the individual is low".

It should also be recognised that although there has been an increase in research on the paternal age effect, much of the research is correlational and few longitudinal studies specifically designed to answer questions relating to paternal age have been conducted. Obviously, further robust and longitudinal studies on these issues are needed, allowing for confounding factors such as the mother's age and the background of both parents.

It should also be acknowledged that there are significant benefits for a child born to an older father, in that the father may have become financially established, and be more emotionally mature to take on the role of fatherhood. Against this there is the possibility that the father may have his own health problems, and that he might die before the child reaches adulthood.

On a more philosophical note, the question of an optimum time to father a child has been addressed by Liu⁵⁰ who suggested that "it is not unreasonable to propose that the decade between 30 and 40 years of age is the optimal time for fathers to have a child, balancing both intelligence and health of the children".

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