

## SHORT REPORT

## Advanced paternal age: How old is too old?

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*J Epidemiol Community Health* 2006;60:851–853. doi: 10.1136/jech.2005.045179

Average paternal age in the UK is increasing. The public health implications of this trend have not been widely anticipated or debated. This commentary aims to contribute to such a debate. Accumulated chromosomal aberrations and mutations occurring during the maturation of male germ cells are thought to be responsible for the increased risk of certain conditions with older fathers. Growing evidence shows that the offspring of older fathers have reduced fertility and an increased risk of birth defects, some cancers, and schizophrenia. Adverse health outcomes should be weighed up against advantages for children born to older parents, mindful that these societal advantages are likely to change over time.

Changing patterns of education, employment, and marriage mean that the average age of childbearing for women is increasing, resulting in higher risks of adverse reproductive outcomes.<sup>1,2</sup> It has recently been suggested that the decade 25–35 years is the optimal age for women in Westernised societies to have their children balancing education, career, and family.<sup>3</sup> In England and Wales, the mean age at childbearing increased from 26.4 years in 1974 to 29.3 years in 2002.<sup>1</sup> Healthcare systems have responded to the increased risk associated with delaying maternity by offering screening for congenital abnormalities and treatment for infertility.<sup>4,5</sup> Meanwhile, the average paternal age is also increasing. The mean age of fathers in England and Wales increased from 29.2 years in 1980 to 32.1 in 2002.<sup>6</sup> The public health implications of this trend have not been widely anticipated or debated.

## TIME TRENDS IN PATERNAL AGE

## Births within marriage

In 1993, fathers aged <35 years accounted for 74% of live births within marriage in England and Wales, while only 25% of such births were to fathers aged 35–54 years. Ten years later, these percentages were 60% and 40%. Figure 1 illustrates these trends. If this trend continues, the proportion of fathers >35 years will further increase.

## ALL BIRTHS

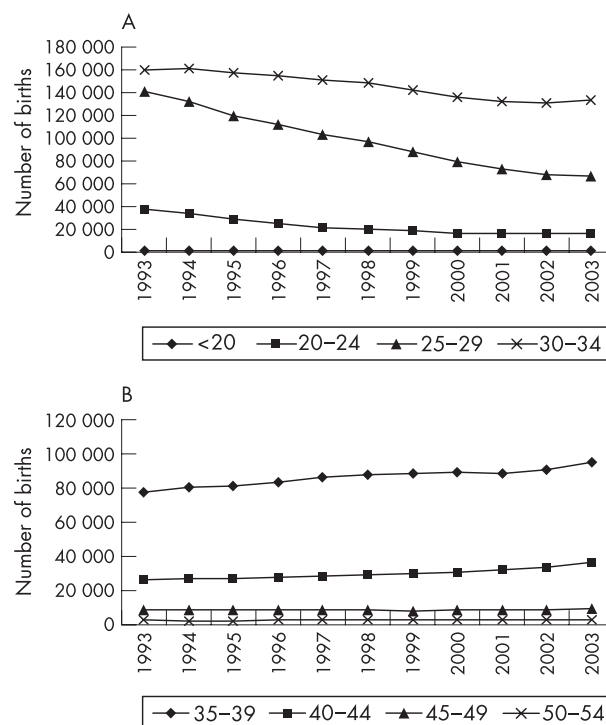
Data on time trends in paternal ages for all births in England and Wales are not available, and it could be argued that the increasing proportion of births occurring outside marriage will lead to declining paternal ages as the fathers of such children are younger than those for children born to married couples. Figure 2 shows the age distribution of fathers for all births in England and Wales in 2003, which reaches a maximum at age 32. While this approximately normal distribution is mirrored closely for the 60% of births that occurred within marriage, the paternal ages for births outside marriage is more uniform between the ages of 22 and 33 years, with a lower mean age at fatherhood. Between 1993 and 2003 the percentage of births occurring outside marriage

increased steadily from 32% to 41%. However, the demographic composition of the group having children outside marriage is changing.

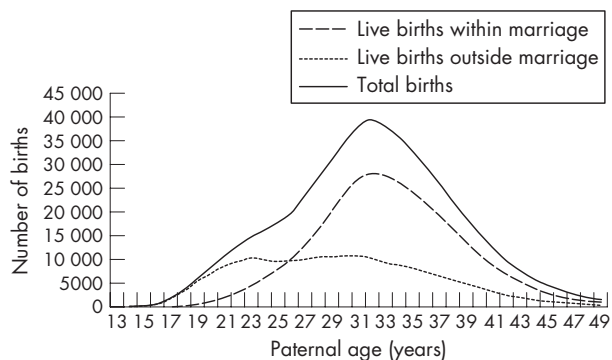
Maternal age data are available for all births (within and outside marriage) in England and Wales<sup>6</sup> and they show that the proportion and number of births to women of 30 and over are increasing.

## REASONS FOR INCREASING AGE AT PARENTHOOD

Changes in the population structure (different sizes of birth cohorts across the span of reproductive ages) explain the trend towards older parents to some extent,<sup>1</sup> but there is no doubt that societal changes have led to both men and women beginning families later. Advances in reproductive technologies are also contributing to this trend.<sup>7</sup> Some 3%–6% of births in most developed countries are now the result of assisted reproduction.<sup>8</sup> While the UK government directs substantial efforts towards reducing teenage pregnancy rates, little guidance is given on the risks of delaying childbearing until advanced maternal age, and less still on the risks of advanced paternal age. In the USA, the American Society for Reproductive Medicine has begun to publicise the risks of delaying childbearing, although their *Patient Guide on Age and*



**Figure 1** Trends in paternal age for live births within marriage in England and Wales, 1993–2003: (A) decreasing trends <35 years, (B) increasing trends 35–54 years. Source: Series FM1 no 32 (ONS, 2003). (Births to fathers over 54 years account for less than 0.5% of live births within marriages and are not shown).



**Figure 2** Distribution of paternal age for births in England and Wales in 2003: total births\* and live births within and outside marriage to fathers aged 13–49. Source: Series FM1 no 32 (ONS, 2003). \*All births within marriage, and those outside of marriage for which information about the father was provided at birth registration (82.5%).

*Fertility*<sup>9</sup> focuses mainly on the mechanisms and risks of maternal, rather than paternal, aging.

### RISKS ASSOCIATED WITH ADVANCED PATERNAL AGE

It is thought that accumulation of chromosomal aberrations and mutations during the maturation of male germ cells are responsible for increasing risks of certain conditions with advancing paternal age. The amount of DNA damage in sperm of men aged 36–57 is three times that of men <35 years.<sup>8</sup> There is a recent body of literature discussing the possible effects on reproductive outcomes, which has been summarised by Kühnert and Nieschlag.<sup>10</sup>

#### Fertility and birth

Regarding fertility, Kühnert and Nieschlag<sup>10</sup> conclude that men start to contribute to the reduced fertility of a couple in their late 30s, and to a reduced fecundity in their early 40s. For example, a descriptive study of birth rates in married couples in Ireland before the widespread use of contraception found that the probability of birth decreased for men from 42–43 years of age.<sup>11</sup> A more recent prospective cohort study of 5121 pregnant women in California concluded that the risk of spontaneous abortion increased with increasing paternal age, and found that the association was stronger for first trimester losses,<sup>12</sup> while another prospective cohort study of 23 821 pregnant women (based on the Danish national birth cohort) reported that the paternal age related risk of late fetal death was higher than the risk of early fetal death, and started to increase from age 45 years.<sup>13</sup> It has been suggested that advanced paternal age (>50 years) increases the risk of preterm delivery and low birth weight,<sup>14</sup> although others have found no such effect.<sup>15</sup> Although aneuploidy is the leading genetic cause of pregnancy loss, there is no substantial evidence for an effect of paternal age on the presence of extra or missing chromosomes<sup>10</sup> and the proportion of fetal deaths attributable to advanced paternal age is currently probably small.<sup>13</sup>

#### Birth defects, developmental illnesses, and childhood cancer

A Danish population based study of 1 489 014 live births concluded that paternal age is associated with cleft lip and cleft palate, independently of maternal age.<sup>16</sup> Single gene mutations are the suggested mechanism. Many autosomal dominant diseases (for example, achondroplasia) have been shown to be associated with increasing paternal age.<sup>10</sup> A population based study of childhood brain cancers reported to the Swedish Cancer

### What is already known on the topic

- The average paternal age in the UK is increasing, and the public health implications of this trend have not been widely anticipated or debated
- Accumulation of chromosomal aberrations and mutations during the maturation of male germ cells are thought to be responsible for increasing risks of certain conditions with advancing paternal age
- There is a growing literature on the effects for offspring of advanced paternal age. Risks include reduced fertility and increased risk of birth defects, schizophrenia, and cancer

### Policy implications

Adverse health outcomes should be weighed up against potential social advantages and disadvantages for children born to older parents, mindful that these societal effects are likely to change over time

Registry between 1960 and 1994 concluded that there is a paternal age effect, estimated to confer about 25% excess risk in fathers >35 years of age.<sup>17</sup> A case-control study of 10 162 matched pairs reported a threefold increase in risk of retinoblastoma for fathers  $\geq 45$  years<sup>18</sup> and a 50% increased risk of childhood acute lymphoblastic leukaemia for fathers aged 35 years or more was found in a historical cohort of 434 933 live births.<sup>19</sup> There is conflicting evidence regarding congenital heart defects, although it has been estimated that among offspring of men aged >35 years, about 5% of cases may be attributable to advanced paternal age.<sup>10</sup>

#### Illnesses in adulthood

Some diseases of complex aetiology such as schizophrenia are associated with advanced paternal age.<sup>10</sup> This may be because of an increase in mutations arising in paternal germ cells, although the possibility of confounding (for example, by schizoid personality traits) cannot be ruled out.<sup>16</sup> To illustrate the possible scale of the effects, results from a Swedish population based cohort study have been used to estimate that the increase in paternal age since 1980 could account for about 10% of new cases of schizophrenia diagnosed in the UK in 2002.<sup>20</sup> Advanced paternal age is associated with increased risk of cancers in offspring (for example, breast, prostate, nervous system).<sup>10</sup> There is less conclusive data regarding Alzheimer's disease.<sup>10</sup>

### CONCLUSIONS

A recent report concluded that “even if the genetic risk for progeny from older fathers is slightly increased, the risk to the individual is low”.<sup>9</sup> But as our appreciation of the genetic contribution to disease risk develops it seems probable that, if the current trends in timing of fatherhood continue, the consequences at a population level may nevertheless be worth considering further. The adverse health outcomes discussed here 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. For example, data from the national child development study show that young fathers are more likely to come from economically disadvantaged families and to

have lower educational attainment<sup>21</sup>; the labour force survey<sup>22</sup> found increasing income with age for men up to their early 40s. Socioeconomic factors such as educational level and occupation are currently associated with many health outcomes. For example people from less affluent backgrounds are less likely to use prenatal care services<sup>23</sup> but more likely to give birth to premature or low birthweight infants.<sup>24</sup> 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. Furthermore, as it becomes more common for men to become parents in later adulthood, the current (relatively affluent) socioeconomic composition of older fathers will change, and therefore the relative socioeconomic advantages of having an older father are likely to diminish. An evaluation of various scenarios may help to determine an optimal period of fatherhood balancing the social and economic advantages for the offspring of delayed paternity against the corresponding small, but increasingly well reported, genetic disadvantages. Such an evaluation would inform policy. Possible interventions might include health promotion advising people about the risk of delaying childbearing or changes at a societal level (for example, family benefits, flexible working) that encourage couples to have children earlier rather than later.

## CONTRIBUTORS AND SOURCES

All authors contributed to the conception of the article. IB wrote the initial draft of the paper and subsequent drafts including comments from DG and GDS. All authors have seen and approved the final version. The article arises from a review of the literature and analysis of data available from the Office for National Statistics. All authors are epidemiologists with an interest in public health applications. DG and GDS are members of the Faculty of Public Health.

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Competing interests: none.

Ethical approval: not needed.

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Accepted for publication 25 March 2006

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