Does age of the sperm donor influence live birth outcome in assisted reproduction?

N.K. Ghuman1,*, E. Mair2, K. Pearce3, and M. Choudhary1,2,*

1Department of Obstetrics and Gynaecology, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne NE1 4LP, UK
2Newcastle Fertility Centre, International Centre for Life, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne NE1 4EP, UK
3Haematological Sciences, Institute of Cellular Medicine, Medical School, William Leech Building, Newcastle University, Newcastle upon Tyne NE2 4HH, UK

*Correspondence address. Newcastle Fertility Centre, International Centre for Life, Newcastle upon Tyne NE1 4EP, UK (M.C.)/Department of Obstetrics and Gynaecology, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne NE1 4LP, UK (N.K.G.).
E-mail: meenakshi.choudhary@nuth.nhs.uk (M.C.)/drnavdeepghuman@gmail.com (N.K.G.)

Submitted on March 11, 2015; resubmitted on December 5, 2015; accepted on December 10, 2015

STUDY QUESTION: Does age of the sperm donor have an effect on reproductive outcomes (live birth rate and miscarriage occurrence) of donor insemination or in vitro fertilization treatment using donated sperm?

SUMMARY ANSWER: Live birth and miscarriage occurrence in assisted reproduction treatment using donor sperms was not found to be affected by the age of sperm donors up to 45 years old.

WHAT IS ALREADY KNOWN: Literature on the effect of sperm donor age on outcome of medically assisted reproduction is scarce. Most researchers agree that semen parameters deteriorate with increasing paternal age. However, there is no substantial evidence to suggest that this deterioration adversely affects the reproductive outcomes in couples undergoing medically assisted reproduction.

STUDY DESIGN, SIZE, DURATION: This retrospective cohort study analysed 46,078 first donor insemination treatments and fresh in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles using donated sperm from 1991 to 2012.

PARTICIPANTS/ DURATION/METHODS: The first fresh donor insemination and IVF/ICSI treatment cycles (46,078 treatment cycles) using donated sperm from the long-term anonymized data registry from 1991 to 2012 of the HFEA, the UK regulator, were analysed by the binary logistic modelling technique for association between sperm donor age and reproductive outcomes (live birth occurrence and miscarriage occurrence). The statistical package SPSS (version 21) was used for analysis and results were considered to be statistically significant if the P-value was <0.05.

MAIN RESULTS AND THE ROLE OF CHANCE: Of 46,078 women, 84.6% (N = 38,974) underwent donor insemination treatment and the remainder, 15.4% (N = 7104), had IVF/ICSI treatment with donor sperm. The live birth occurrence decreased with increasing female age in both treatment groups; In the donor insemination treatment group, it was 11.1% in 18–34 year old women, 8.3% in 35–37 year old women and 4.7% in 38–50 year old women. The corresponding figures in the IVF/ICSI treatment group were 28.9, 22.0 and 12.9% respectively. In each of these subgroups, no evidence of declining likelihood of live birth with increasing sperm donor age was found (P > 0.05). The miscarriage occurrence (i.e. number of miscarriages per 100 women commencing treatment) was 1.3% in 18–34 year old women, 1.9% in 35–37 year old women and 1.9% in 38–50 year old women undergoing donor insemination treatment. In the sperm donation IVF/ICSI treatment group, these figures were 5.7, 8.4 and 6.8% respectively. The results were not suggestive of any unfavourable effect of advancing sperm donor age on the odds of miscarriage occurrence (P > 0.05).

LIMITATIONS, REASONS FOR CAUTION: As sperm donors are a select population based on good semen indices, the generalization of results to the paternal population at large may not be possible. Although the study subgroups were controlled for female age, treatment modality and effect of previous treatment cycles, adjustments for certain potential confounding factors, such as smoking status, BMI of women and stimulation protocol used in IVF/ICSI treatment cycles, were not possible.

WIDER IMPLICATIONS OF THE FINDINGS: Live birth and miscarriage occurrence following assisted reproduction weren’t adversely affected by increasing sperm donor age up to 45 years. In view of the increasing demand for donor sperm, further studies may be required to ascertain the safe upper age limit for sperm donors.

© The Author 2016. Published by Oxford University Press on behalf of the European Society of Human Reproduction and Embryology. All rights reserved.
For Permissions, please email: journals.permissions@oup.com
Introduction

Infertility affects one in every seven couples in the UK and for approximately 25% of these couples, the infertility is due to factors in the male (National Institute of Clinical Excellence, 2013). Donated sperm may represent the only hope for some of these infertile couples to conceive. With ever-emerging societal changes in lifestyle and personal choices, single women and same sex female couples are also tapping into the resource of donor sperm to form a family. In the UK, 2013 saw a 30% rise of same sex female couples receiving treatment using donated sperm compared with 2012 (Human Fertilisation and Embryology Authority (HFEA), 2014). This increased demand for donated sperm has led to a steady increase in the number of imports of sperm from overseas sperm banks over the years. Overseas sperm donors constituted almost a third of newly registered sperm donors in 2013 (compared with 11% in 2005).

Although, as per current professional guidelines in the UK, men aged 41 years and over should not be accepted as sperm donors, the Human Fertilisation and Embryology Authority’s (HFEA) oocyte and sperm donation statistics report, published in 2014, reveals that the majority of newly registered sperm donors in 2012–2013 were 26 or older with a quarter over 40 years of age (HFEA, 2014). The HFEA long-term data registry (1991–2012) reveals that post anonymity removal (2005–2012), 60% of sperm donors were aged between 31 and 45 years whereas this figure was 28% before donor anonymity removal (1991–2004) (HFEA, 2013). In our fertility centre, a similar rising trend in sperm donor age was noted with mean ages (± SD) of 26.6 years (± 7.38) and 34.72 years (± 7.57) pre and post donor anonymity removal respectively (unpublished data).

This raises certain issues in the minds of clinicians and couples alike concerning the effect of sperm donor age on success rates of medically assisted reproduction and the upper age cut-off for these donors. There have been numerous studies (Schwartz and Mayaux, 1982; Noord-Zaadstra et al., 1991; Scott et al., 1995; Dunson et al., 2002) in published literature confirming the negative effect of increasing maternal age on female fertility and outcome of assisted reproduction, but the influence of paternal age on these outcomes is less well researched and contentious and literature on the effect of sperm donor age on the outcome of medically assisted reproduction is rare. Reports on the negative impact of increasing paternal age on fertility outcome and child health (de la Rochebrochard et al., 2003; Robertshaw et al., 2014) may cause anxiety for couples who are faced with limited donor choice and rising ages of sperm donors. The majority of published literature has considered the effect of paternal age in the general population or in IVF cases with oocyte donation. Questions concerning the effect of sperm donor age on success rates of assisted reproduction techniques have largely remained unanswered.

Hence it is vital that we provide information to couples based on evidence so as to help them make an informed decision. In the UK, all centres offering donor sperm treatments are registered with the HFEA and the HFEA dataset provides a rich mine of raw anonymized data to analyse these treatment outcomes. In this study, using the large, anonymized HFEA national database collected over two decades, we set out to determine the effect of sperm donor age on the chances of live birth occurrence in women undergoing medically assisted reproduction treatment. Our aim was to answer the question: does the age of sperm donor affect the chances of success in women undergoing medically assisted reproduction?

Materials and Methods

Study population and participants

In an attempt to find an answer to the above question, we looked at the freely available HFEA long-term anonymized data registry from 1991 to 2012 (HFEA, 2013).

The HFEA pipe delimited dataset was converted to an Excel spreadsheet format and was imported to MS Excel package 2007. Of the total 1 048 575 treatment cycles, the number of cycles using donated sperm was 237 852. Figure 1 depicts the breakdown of the number of the donor sperm treatment cycles analysed following exclusions. Restricting the analysis to first cycles enabled us to alleviate the compounding effect of previous cycles and to report results as per individual woman rather than per cycle. To adjust for women’s age, two groups were selected and separately analysed: women between 18 and 34 years with optimum reproductive potential and women >37 years (i.e. 38–50 years) which is taken as the conventional cut-off for decline of female fertility. An additional analysis was conducted to determine the influence of women at the farthest end of the age spectrum (45–50 years) whereby results for women in the 38–50 year and 38–44 year age brackets were compared (data provided upon request).

As the results were no different, the whole group (38–50 year old women) was included in the final analysis. For entirety, women aged 35–37 years were also studied as a third group. Within these three groups, donor insemination treatment cycles and IVF/ICSI treatment cycles were analysed separately. In all of the six groups, donor age categories were compared for live birth occurrence rates and occurrence of miscarriage. The categories chosen for sperm donor age (≤20, 21–25, 26–30, 31–35, 36–40 and 41–45) were similar to those used by the HFEA for data collection.

Live birth occurrence (where one live birth occurrence is one birth event in which at least one baby is born alive) rather than actual numbers of live births was used as the output measure. Likewise miscarriage occurrence rather than actual number of miscarriages was analysed. HFEA data were also searched for congenital abnormalities at birth in all of the study groups.

Exclusions

The cycles with missing data for the woman or sperm donor age were excluded from the analysis. Treatment cycles involving gamete or zygote intra-fallopian transfer (GIFT, ZIFT), cycles, oocyte donation, frozen embryos or surrogacy were excluded from the analysis. Out of 49 242 women undergoing first sperm donation treatment cycles, 46 078 women were finally included in the live birth analysis (the remaining 3164 women were excluded due to reasons explained in Fig. 1). For the miscarriage analysis, a further 2990 treatment cycles were excluded due to unrecorded data on early outcome (Supplementary Fig. S1).
Statistical analyses

Live birth occurrence was taken as the dependent variable and donor age, in categorical fashion, was used as a covariate. As the outcome could take one of two qualitative categories (e.g. live birth occurrence or no live birth occurrence), the binary logistic modelling technique was employed to establish the strength and pattern of association between outcome and sperm donor age (Lewis-Beck, 1980). This modelling technique requires few distributional assumptions and is applicable with either continuous or discrete explanatory variables, or both. The statistical package SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for analysis and results were considered to be statistically significant if the P-value was <0.05. In an effort to improve the transparency of the results, the odds ratio (OR) and 95% CI (confidence intervals) were also calculated. In this study, the binary logistic model expresses the odds of live birth occurrence as:

\[ \frac{p}{1-p} = \exp(\theta + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_s x_s) \]

where \( p \) is the probability of a live birth occurrence.

\( \beta_1, \beta_2, \ldots, \beta_s \) and \( \theta \) are unknown parameters that are estimated from the data.

For the categorical covariate, one category acts as the reference category; all other categories are compared with the reference category. In this study, donor age 41–45 years was taken as the reference level. As older sperm donor group acts as the reference category, the model enabled us to estimate the effect (on live birth occurrence) of being in a younger age group rather than the oldest age group. We hypothesize that a younger sperm donor would have an increased odds of live birth compared with an older donor assuming that increasing age has a similar effect on male fertility as on female fertility. Therefore, we decided to take older sperm donors as the reference category.

As the number of embryos transferred in each cycle may be an independent compounding factor, a one-way ANOVA test was used to compare mean embryos transferred and embryos created per cycle in each donor age category. This test was conducted in all three female age subgroups undergoing IVF/ICSI treatment. If the overall ANOVA test proved significant, it was decided to use the multiple comparisons Dunnett's test to establish if each of the younger sperm donor age categories had a higher mean number compared with oldest (41–45 year old) category.

Similarly the relationship between donor age and the binary response ‘occurrence of miscarriage’ was investigated. We investigated overall pregnancy loss combining biochemical pregnancy loss (after positive pregnancy test) and clinical pregnancy loss (after gestational sac has been demonstrated
by ultrasound scan). Ectopic pregnancies, pregnancy terminations and heterotropic pregnancies were excluded from the analysis. The binary logistic modelling technique was again used. A wealth of medical literature proves that the likelihood of miscarriage increases if the woman is aged \( \geq 35 \) years (Nybo Andersen et al., 2000; Heffner, 2004; Cleary-Goldman et al., 2005). Also there are studies in published literature (de La Rochebrochard and Thonneau, 2002; Kleinhaus et al., 2006) which indicate that increased paternal age is a risk factor for miscarriage therefore, as a corollary, we hypothesized that an older sperm donor would have an increased odds of miscarriage compared with a younger donor. Hence, here too the 41–45 years sperm donor age group was taken as the reference category for analysis.

HFEA data were also consulted for congenital abnormalities at birth in all six study groups.

**Ethical approval**

Formal ethical approval was not indicated as the freely available HFEA anonymized dataset was used for data procurement.

**Results**

Of 46,078 women, 84.58% \((N = 38,974)\) underwent donor insemination treatment and the remaining 15.42% \((N = 7,104)\) had IVF/ICSI treatment with donor sperm. In the donor insemination group, 66.51% \((N = 25,925)\) women were aged 18–34 years, 16.82% \((N = 6,559)\) were aged 35–37 years whilst the remaining 16.65% \((N = 6,490)\) were between 38 and 50 years of age. Similarly in the IVF/ICSI treatment group, 51.01% \((N = 3,624)\) of the women were in the 18–34 years age category, 19.10% \((N = 1,359)\) were aged 35–37 years and 29.85% \((N = 2,121)\) of the women belonged to the 38–50 years age category. The numbers of women in each sperm donor age category in all six study groups have been tabulated in Supplementary Table SI.

**Mean embryos transferred per cycle in IVF/ICSI treatment group**

The mean number of embryos transferred per women was 1.86, 1.88 and 1.81 for women aged 18–34, 35–37 and 38–50 years respectively. Single embryo transfer was recorded in 17.85, 17.44 and 16.78% women in these age brackets respectively. It was observed that the mean numbers of embryos transferred per cycle were higher in younger sperm donor categories than in the 41–45 years sperm donors (Supplementary Table SI). To assess whether number of embryos transferred were linked to number of embryos generated, we analysed the number of embryos created per cycle using a one-way ANOVA. For all three women’s age subgroups undergoing IVF/ICSI treatment, there was no evidence of a difference between the sperm donor age categories as regards the mean number of embryos created (Supplementary Table SII).

**Association of live birth occurrence and sperm donor age**

The overall live birth occurrence was 9.54% in the donor insemination treatment group and 22.76% in women undergoing IVF/ICSI treatments. In the donor insemination treatment group, the live birth occurrence was 11.07% in 18–34 year old women, 8.30% in 35–37 year old women and 4.70% in 38–50 year old women. The corresponding figures in the IVF/ICSI treatment group were 28.89, 22.00 and 12.91% respectively. Figures 2 and 3 compare odds of having a live birth occurrence in the different sperm donor age categories for donor insemination and IVF/ICSI treatment cycles for different women’s age brackets.

When applying binary logistic regression modelling, we hypothesized that the odds of having a live birth would increase as the sperm donor age decreased (compared with the oldest donor age group), however this pattern was not apparent. It was also observed that the differences in odds of live birth between each age category and the oldest donor age group was generally not statistically significant. Tables I and II show the odds ratio for live birth occurrence among all the donor age categories in the donor insemination and IVF/ICSI treatment groups respectively when taking the odds of having a live birth occurrence in the reference sperm donor category (41–45 years) as one. By including ‘number of embryos transferred per cycle’ as a covariate in the binary logistic regression model, we obtained adjusted estimates for the age categories: younger sperm donors were observed to have a lower odds ratio of live birth occurrence when compared with the oldest sperm donor age group and this was generally statistically significant in 18–34 year old...
between each sperm donor age category and the oldest group as the donor insemination group, no significant difference was observed in sperm donor age categories (vis-a-vis the oldest donor age group). For that the odds of having a miscarriage would be lower in the younger donor was explored using binary logistic regression. We hypothesized and 18.50% in older women (38–50 years).

The miscarriage rate (i.e. number of miscarriages per 100 women commencing treatment cycle). When adjusted for female age, the miscarriage occurrence was generally not significantly different for the various sperm donor age categories when compared with the oldest group (Table IV).

**Association of congenital abnormalities at birth and sperm donor age**

Upon examination of the HFEA long-term data registry, the congenital abnormalities if mentioned, were recorded in extremely low numbers, hence, a meaningful analysis was not feasible.

**Discussion**

There is no consensus amongst the key professional bodies about the upper sperm donor age limit, with the HFEA (UK) recommending <41 years (HFEA code of practice: guidance note 11), the ASRM (USA) recommending 40 years (Practice Committee of the American Society for Reproductive Medicine, and Practice Committee of the Society for Assisted Reproductive Technology, 2013), the Human Reproduction Act (Australia) recommending 45 years (Reproductive Technology Accreditation Committee, 2010) and ESHRE (Europe) recommending <50 years (ESHRE task force on ethics and law, 2010).

---

**Table I** Odds ratio for live birth occurrence among all the donor age categories in donor insemination treatment group, compared with the reference group (41–45 years).

<table>
<thead>
<tr>
<th>Sperm donor age categories</th>
<th>Live birth in donor insemination treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18–34 years old women</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>≤20 years</td>
<td>0.78 (0.64–0.95)</td>
</tr>
<tr>
<td>21–25 years</td>
<td>0.86 (0.73–1.02)</td>
</tr>
<tr>
<td>26–30 years</td>
<td>0.98 (0.82–1.16)</td>
</tr>
<tr>
<td>31–35 years</td>
<td>0.91 (0.76–1.10)</td>
</tr>
<tr>
<td>36–40 years</td>
<td>0.98 (0.81–1.19)</td>
</tr>
<tr>
<td>41–45 years</td>
<td>I</td>
</tr>
</tbody>
</table>

**Table II** Odds ratio for live birth occurrence among all the donor age categories in IVF/ICSI treatment groups, compared with the reference group (41–45 years).

<table>
<thead>
<tr>
<th>Sperm donor age categories</th>
<th>Live birth in IVF/ICSI treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18–34 years old women</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>≤20 years</td>
<td>0.85 (0.61–1.19)</td>
</tr>
<tr>
<td>21–25 years</td>
<td>0.76 (0.59–0.99)</td>
</tr>
<tr>
<td>26–30 years</td>
<td>0.87 (0.66–1.14)</td>
</tr>
<tr>
<td>31–35 years</td>
<td>0.79 (0.59–1.06)</td>
</tr>
<tr>
<td>36–40 years</td>
<td>0.92 (0.69–1.24)</td>
</tr>
<tr>
<td>41–45 years</td>
<td>I</td>
</tr>
</tbody>
</table>
2002). This lack of consensus demonstrates the paucity of evidence to show linkage of increasing male age and reproductive outcomes. In our study, we report that there is no evidence to showcase any decline in the likelihood of live birth with increasing sperm donor age. Adjusting for female age, treatment modality and removing the confounding effect of previous cycles, it was found that each donor age category was not significantly different when compared with the oldest donor age group (up to 45 years of age) with respect to live birth and miscarriage occurrence. Interestingly, we found a higher number of embryos transferred per cycle in younger sperm donor categories when compared with older sperm donor categories (which was generally statistically significant), even though the number of embryos created per cycle was comparable in all the donor age categories. After adjusting for number of embryos transferred per cycle, the odds of live birth occurrence was in general, lower for younger sperm donors compared with the older sperm donor age category in 18–34 year old women. A conceivable explanation for this observation (young sperm donors requiring more embryos to be transferred and lower live births compared with older sperm donors), may be attributed to the embryo quality or other unknown confounding factors unrecorded in the HFEA data. As data on embryo quality were not recorded in the HFEA dataset, further exploration into this subject was not feasible and hence we refrain from making concrete conclusions on this issue and suggest the need for further studies.

Most researchers agree that semen parameters especially semen volume (de La Rochebrochard and Thonneau, 2005; Neme et al., 2007) and frequent sperm motility (Whitcomb et al., 2011) deteriorate with increasing paternal age while sperm morphology and concentration largely remain unaffected (Frattarelli et al., 2008). However, published literature is not in consensus about whether this deterioration in semen parameters translates into decreased clinical pregnancy rate in couples undergoing medically assisted reproduction (Duran et al., 2010; Whitcomb et al., 2011).

Although there is paucity of published work evaluating association of sperm donor age and live birth rate, our study agrees with Paulson et al. (2001), Whitcomb et al. (2011) and Beguería et al. (2014) who observed no correlation between paternal age and pregnancy outcomes in oocyte donation models. Similar to our study, all the three studies have examined live birth rate in proportion to all treatment cycles. The results of the present study are also in consensus with a study by Luna and co-workers (Luna et al., 2009) who observed no significant decrease in clinical pregnancy rates in couples with paternal age below 60 years using oocyte donation models. Frattarelli et al. (2008) observed a decrease in live birth rate (among known pregnancies) after 50 years of paternal age in their study on donor oocyte treatment cycles although this study did not adjust for recipient female age. Our study findings were different from the results of a study undertaken by Robertshaw and colleagues (Robertshaw et al., 2014) which demonstrates 26% lower odds of

<table>
<thead>
<tr>
<th>Sperm donor age categories</th>
<th>Miscarriage in donor insemination treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18–34 years old women</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>≤20 years</td>
<td>1.15 (0.62–2.12)</td>
</tr>
<tr>
<td>21–25 years</td>
<td>1.36 (0.79–2.33)</td>
</tr>
<tr>
<td>26–30 years</td>
<td>1.24 (0.71–2.17)</td>
</tr>
<tr>
<td>31–35 years</td>
<td>1.48 (0.84–2.62)</td>
</tr>
<tr>
<td>36–40 years</td>
<td>1.49 (0.82–2.72)</td>
</tr>
<tr>
<td>41–45 years</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sperm donor age categories</th>
<th>Miscarriage in IVF/ICSI treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18–34 years old women</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>≤20 years</td>
<td>2.46 (0.77–7.82)</td>
</tr>
<tr>
<td>21–25 years</td>
<td>3.14 (1.20–8.23)</td>
</tr>
<tr>
<td>26–30 years</td>
<td>2.31 (0.86–6.22)</td>
</tr>
<tr>
<td>31–35 years</td>
<td>1.55 (0.52–4.59)</td>
</tr>
<tr>
<td>36–40 years</td>
<td>3.37 (1.26–9.02)</td>
</tr>
<tr>
<td>41–45 years</td>
<td>1</td>
</tr>
</tbody>
</table>
live birth rate with each 5-year increase in paternal age from 25 years of age, however a small sample size was their major limitation. Another key feature that we need to take into account is that the studies listed above look at effect of paternal age and live birth outcome but do not specifically address the effect of sperm donors’ age as sperm donors are likely to be a selective population based on their optimum sperm quality. Unpublished data from our centre show only 1 in 5 enquiries progress on to become sperm donors.

No evidence of an increase in odds of miscarriage among the older sperm donors was suggested by our study. In our study, we investigated miscarriage occurrence (miscarriages among all women undergoing treatment) rather than calculating miscarriage rate based on total number of pregnancies, as this approach is less prone to theoretical risk of over-estimation of miscarriage risk due to a decrease in the probability of a pregnancy by increasing age. Our study findings are in agreement with Beguería et al. (2014) who observed no difference in miscarriage occurrence among different male age groups using an oocyte donation model. Ferreira and colleagues (Ferreira et al., 2010) also observed no influence of paternal age on miscarriage outcome, after making adjustments for maternal age, in couples undergoing ICSI treatment. However, the majority of published medical literature examines miscarriage rate in proportion to all known pregnancies. Our findings are also in consensus with Luna and co-workers (Luna et al., 2009) who, in an oocyte donation model, reported no statistically significant correlation between clinical pregnancy loss and increasing paternal age, whereby estimating pregnancy loss in proportion to number of clinical pregnancies. Similar results were observed by Andersen and colleagues in a Danish population based cohort study of spontaneous pregnancies (Nybo Andersen et al., 2004). The study results differ from work by Rochebrochard and Thonneau who, in a population based study examining spontaneous conceptions, showed an OR of 6.73 (95% CI, 3.50–12.95) for miscarriage in couples where females were aged ≥35 years and male partners were aged 40–64 years, with couples having partners aged 20–29 years being used as the reference category (de La Rochebrochard et al., 2002). This study was not adjusted for the confounding effect of female age on miscarriage rate as couple age instead of male age was analysed. Likewise Slama et al. have shown a 1.26 times higher risk of spontaneous miscarriages (6–20 week pregnancy loss) if the paternal age was 35 years or above as compared with fathers aged less than 35 years (Slama et al., 2005). However, our findings suggest that a sperm donor aged 41–45 years does not have higher odds of miscarriage when compared with a younger sperm donor.

Zhu et al. (2005) in a population based cohort study on 71 937 couples found no association between paternal age and congenital malformations at birth. These findings are also supported by other studies (Polednak, 1976; Kazaura et al., 2004). Any positive relationship of trisomy 21 and advancing paternal age is conflict-ridden as it is observed by some (Stene et al., 1981) and refuted by others (Carothers et al., 1984; Hook and Regal, 1984; Martin and Rademaker, 1987). Martin and Rademaker demonstrated a significantly higher frequency of hyper-haploid sperm complement in younger men as compared with older men thus indirectly showing negative evidence for a relationship between paternal age and numerical chromosomal abnormalities (Martin and Rademaker, 1987). Autosomal dominant disorders such as achondroplasia, Apert syndrome, Marfan syndrome, etc. have been observed to be associated with increasing paternal age (Jones et al., 1975). Published literature has also linked increasing paternal age to neurocognitive disorders such as autism, schizophrenia and bipolar disorders (Wiener-Megnazi et al., 2012). Plas et al., in a review study has recommended that the sperm donor age should be less than 50 years in consideration of increased risk of structural chromosomal abnormalities with advancing paternal age (Plas et al., 2000). In the present study, as very few congenital abnormalities recorded were in the HFEA data (the number was nil in many subgroups), an evocative analysis in this regard was not possible. Exploration of association of autosomal dominant diseases and neurocognitive disorders is beyond the scope of this study.

Alio et al. (2012) observed an increased risk of stillbirth, preterm births and low birthweights in infants born to fathers older than 45 years of age and an elevated likelihood of small for gestational age, prematurity and low weight births in those born to fathers younger than 24 years in a population based study. The study does not look into these outcomes and concentrates on live birth as the key parameter of success of assisted reproduction and the outcome expected by couples seeking this treatment. Moreover, our study does not address reproductive outcomes for sperm donors older than 45 years and is based on the age of a selected population of sperm donors rather than paternal age of men undergoing fertility treatment.

One of the major strengths of this study lies in the fact that it analyses one of the largest and most comprehensive databases available on fertility and medically assisted reproduction outcomes. This greatly increases the power of the study and its internal validity. In an effort to reduce confounding variables, different study subgroups were controlled for female age, treatment modality and effect of previous treatment cycles. Subgroups were not adjusted for potential confounding factors such as smoking status, BMI of women and stimulation protocol used for stimulation in IVF/ICSI treatment cycles as no data were available on these factors in the anonymized HFEA data registry. However we presume that, given the large data set, any unknown confounding factors (and their confounding effect on results) will be randomly distributed among groups. Sperm donor age was analysed in a categorical fashion as the format of HFEA anonymized data precludes exploration of sperm donor age as a continuous variable. We were unable to analyse sperm donors beyond 45 years of age as sperm donor age is recorded only up to 45 years in the anonymized data. As sperm donors are a select population based on good semen indices, the generalization of results to the paternal population at large may not be possible. In addition, HFEA doesn’t collect or record paternal age in its database, precluding future studies using its database to assess the impact of paternal age rather than the ages of a select population of sperm donors on live birth outcome.

Conclusions

Limited and inconclusive medical literature on the effect of paternal age on success of medically assisted reproduction has prejudiced a firm ceiling on male or sperm donor age in relation to paternal reproductive potential. The study suggests that there is a lack of evidence for any adverse effect of advancing sperm donor age up to 45 years on live birth and miscarriage occurrence, which arguably are the most important measures of success of assisted reproduction. We postulate that, perhaps, moderation is required as regards the conservative limitation of the upper limit of age for semen donors, although this would require further studies to decide on an appropriate cut-off. In addition, we hope this study will provide reassurance to women limited by choice of available sperm donors regarding the impact of age of sperm donor on achieving a live birth.
Effect of sperm donor age on live birth outcomes

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

Authors’ roles
N.K.G. contributed to the conception of the study and was involved in data collection, statistical analysis, manuscript preparation and revision, construction of figures and tables and submission of manuscript. E.M. contributed to understanding of the sperm donor selection process, provision of local sperm donor data and critical appraisal of the manuscript. K.P. helped with statistical analyses, data interpretation and revising the manuscript. M.C. conceived the idea for the study, supervised the project and contributed to data collection, interpretation and critical appraisal of the manuscript including amendments and gave final approval.

Funding
This study received no funding from any individual or funding agency. N.K.G. was in receipt of a Commonwealth fellowship during the tenure of this study.

Conflict of interest
None declared.

References
de La Rochebrochard E, Thonneau P. Paternal age: are the risks of infecundity and miscarriage higher when the man in aged 40 years or over? Rev Epidemiol Sante Publique 2005;53:547–555.
Hook EB, Regal RR. A search for a paternal age effect upon cases of 47, + 21 in which the extra chromosome is of paternal origin. Am J Hum Genet 1984;36:413–421.


