Cumulative parenthood rates in 1735 couples: impact of male factor infertility

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Submitted on March 3, 2011; resubmitted on December 5, 2011; accepted on December 19, 2011

BACKGROUND: Most studies assessing the outcome of assisted reproductive technologies (ARTs) have reported live birth rates in couples by taking mainly the female factor into account. However, infertility is a couple’s concern, and the majority of publications do not take into consideration the true impact of male infertility on having the desired number of children.

METHODS: We carried out a follow-up study to evaluate the probability of having a child during treatments at the Toulouse Male Sterility Centre and after discontinuation from 2000 through 2008. Couples were followed for at least 4 years until discontinuation of treatment or delivery of a live infant.

RESULTS: We were able to contact 65% of the 1735 male partners by telephone. Of the 1131 respondents, 56% had become parents (60% if adoption is included), 28% after ART, 16% by natural pregnancy, 8% after non-ART treatment and 4% after ART in another centre. The cumulative rates of success reached 64% [95% confidence interval (CI), 60–67] for men ≤35 years and women ≤35 years after 9 years, and 31% (95% CI, 24–39) in older patients. With optimistic analysis, which assumes that patients for whom no information was available have the same chance of success in having a child as those whose reproductive outcome was known, the cumulative rate of success was 48% (95% CI, 45–50) in the 1735 couples.

CONCLUSIONS: More than half of couples consulting for male infertility succeeded in having a child. Male age over 35 years old appears as a key risk factor as well as the woman’s age, and these findings should encourage couples to attempt parenthood earlier.

Key words: male infertility / reproductive outcome / cumulative rates

Introduction

A couple’s ability to conceive is a major social concern and an important public health issue. In developed countries, it is estimated that between 9 and 14% of couples will have difficulties in conceiving, and in France one couple in seven will consult for infertility during their reproductive life, with the origin of the disorder being shared between the man and the woman (Thonneau et al., 1991; Boivin et al., 2007). Nevertheless, constant progress in assisted reproductive technologies (ARTs) has been observed within the last decades, and has given real hope to these infertile couples. Worldwide in 2005, in 53 countries, a total of 601 243 ART procedures were performed and resulted in live births (de Mouzon et al., 2009). A recent report from the European Society of Human Reproduction and Embryology (ESHRE) indicated that in the 20 European countries which keep ART registers, 58 199 ART cycles resulting in deliveries were performed in 2006 (de Mouzon et al., 2010).

So far, most studies assessing ART have reported live birth rates only in infertile couples treated with IVF/ICSI (Witsenburg et al., 2005; Elizur et al., 2006; Sutcliffe and Ludwig, 2007). However, the treatment of infertile couples is not limited to ART, as they may also become parents through natural pregnancy, non-ART treatment or adoption. Very little information is available on the desire for children in infertile couples during and after discontinuation of treatment in an infertility centre. In a study analysing long-term reproductive outcome in 946 couples visiting a fertility clinic, 28% succeeded in having children through spontaneous pregnancies, 11% after IVF and 21% after other treatments (Donckers et al., 2011). In a study of
123 women who discontinued unsuccessful IVF, 57 finally succeeded in becoming parents; 46% through adoption, 42% by natural pregnancy and 12% through further IVF treatment (de La Rochebrochard et al., 2009).

Another major limitation of the existing literature is the rarity of published papers on reproductive outcomes in couples consulting for male infertility. Although it is now well established that infertility is a couple’s concern, with the origin of the disorder being shared between male and female (Thonneau et al., 1993; Safarinejad, 2008), no information is given on men, as the very large majority of publications on ART outcomes focus on female infertility or on the fertility of both partners.

We conducted this study to provide evidence-based estimates of the long-term success rates in couples consulting for male infertility and who wish to have children.

Materials and Methods

Patients

In 2008, we performed a retrospective cohort study including all men consulting for male infertility between January 2000 and December 2004 at the Toulouse Male Sterility Centre (TMSC), Paule de Viguer University Hospital, Toulouse, France. Males were mainly referred to TMSC by a gynaecologist after evaluation of the female partner and/or an abnormal semen evaluation. Male infertility was defined as the inability of the couple to conceive after 12 months of contraceptive-free intercourse in the absence of female factors. Couples were included if we could verify that any identified causes of female infertility (tubal disorders, ovulation disorders, cervical disorders, endometriosis and hormonal disorders) had been treated at the date of inclusion.

Couples were followed at entry and during treatment by a specialist andrologist until either discontinuation of treatment or delivery of a live infant (duration of follow-up ranged between 4 and 9 years after the date of inclusion). The outcome assessment was based not only on delivery of a live infant obtained at TMSC but also on delivery of a live infant obtained at other ART centres after discontinuation at TMSC, as well as natural pregnancies and adoptions. The study received approval from the French Data Protection Authority in 2007 (N°07-290).

Data collection

In the first semester of 2008, a letter describing the study was sent to all the men who had consulted for infertility in our centre from 2000 through 2004, asking them to participate in the study by agreeing to a telephone interview. Short telephone interviews with the respondents were then conducted by trained interviewers. The interview covered male and female sociodemographic information relating to both partners, type of treatment and outcomes after discontinuation of treatment at TMSC, and final achievement or otherwise of their wish to have a child (including adoption). In the case of patients to whom the descriptive letter had not been delivered (patients who were ‘not known’ at the address they had given and letters that were returned to our research centre), we used the regional or national phone directory to contact them directly. Patients from whom no formal consent or refusal of consent was received after 2 months were recontacted by telephone and then by mail.

In a second step, the medical records of all respondents were analysed to obtain precise information on the main cause of infertility, type of treatments and reproductive outcomes. The grade of male infertility disorder was established from basic semen parameters, concentration and progressive motility according to the WHO criteria (World Health Organization, 2010). Only men who provided a semen sample at TMSC were included in order to avoid inter-laboratory variability. Semen samples were collected by masturbation after a recommended 3–5 days of sexual abstinence. Semen analyses were performed according to the WHO recommendations.

Four grades were defined:

(i) no identified semen factor: concentration ≥15 × 10⁶ spz/ml and motility ≥32%;
(ii) mild semen factor: concentration ≥5 × 10⁶ and <15 × 10⁶ spz/ml and motility ≥20% or concentration ≥15 × 10⁶ spz/ml and motility ≥20 and <32%;
(iii) severe semen factor: concentration >0 and <5 × 10⁶ spz/ml or motility >0 and <20%;
(iv) semen sterility: concentration = 0 or motility = 0.

At the TMSC, non-ART treatments (both medical and surgical, including pharmacological and hormonal treatment, varicocelectomy and vas deferens/epididymis surgery) could be proposed to infertile couples in the first instance. In addition, infertile couples, according to the grade of their infertility, could be offered six IUI and/or four IVF or ICSI treatment cycles using the partner’s sperm and/or IUI/IVF with donor sperm. Treatments of infertility were classified according to the last recorded treatment as ART treatments (IUI, IVF, ICSI using male sperm cells and ART with donor sperm) and non-ART treatments. Reproductive outcomes were classified as pregnancies through ART, pregnancies through non-ART treatments and natural pregnancies (i.e. without any treatment).

Statistical analysis

Data were first compared for respondents, those who refused to respond and non-respondents using the χ² test and Fisher’s exact test. Logistic regression was performed to describe factors associated with successful or unsuccessful parenthood outcome using crude and adjusted odds ratio (OR) and 95% confidence intervals (CIs).

The cumulative proportions of successful outcomes were calculated for the period studied after ART treatments (IUI, IVF, ICSI using male semen and ART with sperm donor), non-ART treatments and natural pregnancy were taken into account, using cumulative frequencies.

The Kaplan–Meier method was used to estimate the cumulative rates of successful parenthood outcomes and 95% CI. Censors were defined as couples who did not succeed in becoming parents. As information on reproductive outcome was not available for all men who had consulted for infertility (i.e. no information was obtained through various medical records for some patients who refused to respond and non-respondents), cumulative success rates were calculated according to two hypotheses. The ‘optimistic’ hypothesis assumes that patients for whom no information was available have the same chance of success in having a child as patients whose reproductive outcome was known. Therefore, we present the ‘pessimistic’ cumulative success rates calculated according to the assumption that none of the patients for whom no reproductive information was available succeeded in having a child.

Statistical analysis was performed using SAS software (9.0, SAS Institute, Inc.) and the significance level was defined as 5%.

Results

Study population

Of the 1735 couples consulting for male infertility at TMSC between 2000 and 2004, 1131 (65%) agreed to participate and completed the phone questionnaire (‘respondents group’) and 196 (11%) refused to participate (‘refusers group’). Of the remaining 408 (24%) patients
who were considered as non-respondents (‘non-respondents group’),
two-thirds were patients who could not be traced in telephone or
street directories.

There was a statistically significant difference in age at first visit of
male partners between respondents (mean ± standard deviation/
median = 34 ± 6/33 years) and non-respondents (33 ± 6/32
years) versus refusers (35 ± 7/34 years), as well as age at first visit
of female partners (31 ± 4/31 years for respondents and 30 ± 5/
30 for non-respondents versus 32 ± 5/32 for refusers; P < 0.05).

There were no essential differences between the three groups in dur-
ation of infertility for which the mean was 33 ± 25 (median = 24)
months in the 1735 couples (56% <24 months duration), for type
of infertility (63% of couples presented primary infertility) or for
semen grade. Mean follow-up was 1.6 ± 1.5 (median = 1) years.

Successful parenthood outcome in respondents (n = 1131)

Among the respondents, 56% finally succeeded in having a child, 28%
(311) by ART performed at TMSC, 4% (49) by ART performed in
another ART centre, 8% (94) through non-ART treatments and
16% (183) by natural pregnancy (Table I). Forty-nine couples (4%)
adopted children.

As shown in Fig. 1 and Table II, among the 637 couples who suc-
ceded in having a child, the greatest cumulative success rate was
observed in couples who conceived through ICSI or had a natural
pregnancy.

Using a multivariate model, we observed a negative relationship
for successful outcome in men aged >35 years (OR = 0.67 95%
CI, 0.50–0.91), in women aged >35 years (OR = 0.39 95%
CI, 0.27–0.56), in men with a middle education level (OR = 0.61 95%
CI, 0.42–0.89), in couples with a duration of infertility at inclusion
>24 months (OR = 0.57 95% CI, 0.44–0.74) and in men with a
semen infertility factor (OR = 0.52 95% CI, 0.35–0.76 for mild
factor, OR = 0.37 95% CI, 0.24–0.55 for severe factor and OR =
0.19 95% CI, 0.11–0.32 for semen sterility). Couples who had had
sperm donation (OR = 3.56, 95% CI, 1.73–7.31) had a higher chance
of achieving a pregnancy (Table III).

Regarding age, Kaplan–Meier estimates showed that cumulative
rates of success in having a child reached 64% (95% CI, 60–67) for
men aged ≤35 years and women aged ≤35 years, significantly
higher than success rates obtained in older patients [31% (95% CI,
24–39]. Stratified according to semen infertility grade, cumulative
success rate was 70% (95% CI, 64–76) if there was no identified
semen factor, and only 44% (95% CI, 37–51) in cases of semen ster-
ility (P < 0.05) (Fig. 2).

Successful parenthood outcome in the whole population (n = 1735)

In the refusers and non-respondents groups (196 refusers + 408
non-respondents = 604 couples), through various medical records
we finally obtained information on the outcome for 308 of these
604 couples, of whom 80 (26%) had been successful in having a
child. For the remaining 296 couples (80 refusers + 216 non-
respondents) for whom no information was available, the missing re-
productive outcome can be estimated according to two hypotheses.

According to the optimistic hypothesis, we assumed that among
these 296 couples whose outcome was unknown, the same
proportion were successful as among the 308 couples whose
outcome was known from the medical records. This yielded a cumu-
lative success rate of 48% (95% CI, 45–50), compared with 42% (95%
Table II  Cumulative percentages to conceive by year according to the method of conception for the 637 couples who succeeded in their desire to have children.

<table>
<thead>
<tr>
<th>Years from inclusion</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>After ART at TMSC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUI</td>
<td>6</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>IVF</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ICSI</td>
<td>3</td>
<td>12</td>
<td>21</td>
<td>24</td>
<td>25</td>
<td>25</td>
<td>25</td>
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<td>25</td>
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<tr>
<td>With sperm donor</td>
<td>—</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>By natural pregnancy</td>
<td>15</td>
<td>21</td>
<td>25</td>
<td>27</td>
<td>28</td>
<td>28</td>
<td>29</td>
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<td>29</td>
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<td>After non-ART pregnancy at TMSC</td>
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<td>13</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>15</td>
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<tr>
<td>After ART in another centre</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUI</td>
<td>0.16</td>
<td>0.31</td>
<td>0.31</td>
<td>0.47</td>
<td>0.47</td>
<td>0.47</td>
<td>0.47</td>
<td>0.47</td>
<td>0.47</td>
</tr>
<tr>
<td>IVF</td>
<td>0.47</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ICSI</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>With sperm donor</td>
<td>—</td>
<td>0.31</td>
<td>0.31</td>
<td>0.47</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*1-year interval before using ART with sperm donor at TMSC.

Table III  Factors associated with successful parenthood outcome among the 1131 respondents.

<table>
<thead>
<tr>
<th></th>
<th>Child (n = 637)</th>
<th>No child (n = 494)</th>
<th>Crude OR (95% CI) Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of the man at the first consultation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35 year</td>
<td>435 (68%)</td>
<td>274 (55%)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;35 year</td>
<td>202 (32%)</td>
<td>220 (45%)</td>
<td>0.57 (0.45–0.73)</td>
</tr>
<tr>
<td>Age of the woman at the first consultation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35 year</td>
<td>551 (87%)</td>
<td>345 (70%)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;35 year</td>
<td>86 (13%)</td>
<td>149 (30%)</td>
<td>0.36 (0.27–0.49)</td>
</tr>
<tr>
<td>Education level of the man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school (16 year)</td>
<td>257 (40%)</td>
<td>194 (39%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Secondary school (18 year)</td>
<td>89 (14%)</td>
<td>96 (20%)</td>
<td>0.70 (0.49–0.98)</td>
</tr>
<tr>
<td>University education</td>
<td>289 (46%)</td>
<td>203 (41%)</td>
<td>1.07 (0.83–1.39)</td>
</tr>
<tr>
<td>Education level of the woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school (16 year)</td>
<td>178 (28%)</td>
<td>146 (30%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Secondary school (18 year)</td>
<td>121 (19%)</td>
<td>94 (20%)</td>
<td>1.05 (0.74–1.49)</td>
</tr>
<tr>
<td>University education</td>
<td>330 (53%)</td>
<td>240 (50%)</td>
<td>1.12 (0.85–1.48)</td>
</tr>
<tr>
<td>Fecundity type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary infertility</td>
<td>421 (66%)</td>
<td>306 (62%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>216 (34%)</td>
<td>188 (38%)</td>
<td>0.83 (0.65–1.06)</td>
</tr>
<tr>
<td>Infertility duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 months</td>
<td>394 (62%)</td>
<td>247 (50%)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>243 (38%)</td>
<td>247 (50%)</td>
<td>0.61 (0.48–0.78)</td>
</tr>
<tr>
<td>Semen infertility grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No identified</td>
<td>174 (27%)</td>
<td>78 (16%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mild</td>
<td>170 (27%)</td>
<td>124 (25%)</td>
<td>0.61 (0.43–0.87)</td>
</tr>
<tr>
<td>Severe</td>
<td>209 (33%)</td>
<td>182 (37%)</td>
<td>0.51 (0.36–0.71)</td>
</tr>
<tr>
<td>Sterility</td>
<td>84 (13%)</td>
<td>110 (22%)</td>
<td>0.34 (0.23–0.50)</td>
</tr>
</tbody>
</table>

Continued
Table III  Continued

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Child (n = 637)</th>
<th>No child (n = 494)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>78</td>
<td>12</td>
<td>68</td>
<td>14</td>
</tr>
<tr>
<td>Non-ART treatment</td>
<td>137</td>
<td>22</td>
<td>132</td>
<td>27</td>
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<tr>
<td>IUI</td>
<td>124</td>
<td>19</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>IVF</td>
<td>46</td>
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<td>10</td>
</tr>
<tr>
<td>ICSI</td>
<td>214</td>
<td>34</td>
<td>170</td>
<td>34</td>
</tr>
<tr>
<td>Sperm donor</td>
<td>38</td>
<td>6</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>

*ORs were adjusted on age of the man, age of the woman, education level of the man, education level of the woman, fecundity type, infertility duration, semen infertility grade and type of treatment.

Bold values indicate that P-value <0.05 i.e. that OR obtained are significant.

Discussion

This first study including 1735 couples who consulted for mainly male infertility showed that in our cohort of 1131 respondents, 637 (56%) finally succeeded in having a child. After 9 years, 30% of these 637 live births were achieved through ICSI, 29% naturally, 15% after non-ART pregnancy, 14% through IUI, 6% through IVF and 6% after ART with sperm donor. Cumulative live birth success rates yielded 64% in young couples (men ≤35 years and women ≤35 years) and 70% if there was no identified semen factor. Based on the whole cohort, we estimated that between 42 and 48% of the 1735 couples consulting for male infertility will achieve their desire to have children. In our series of 1735 couples consulting for male infertility (2000–2004), 65% participated in the telephone interview, or 85% if we exclude the non-respondents who could not be contacted. Our participation rate was similar to the 83% obtained in a Swedish study which used telephone recruitment (Sydø et al., 2002) but was higher than that observed in studies using conventional postal questionnaires, varying from 29% (de La Rochebrochard et al., 2009) to 74% (Pinborg et al., 2009). Thus, telephone interviews may offer an interesting alternative for follow-up studies dealing with sensitive subjects thanks to the positive interactivity between interviewer and patient.

A potential bias leading to overestimation of our results could be due to loss to follow-up. But in our series, 24% of the 1735 couples were lost to follow-up, which is in fact a lower percentage than that of other studies (Filetto and Makuch, 2005; de La Rochebrochard et al., 2009; Fisher et al., 2010).

However, differences in male age and female age were observed in our recruitment population. The refusers were older than responders or non-responders. Assuming that most of the refusers were not successful in having a child, this difference can be explained by the impact of age on fecundity, as it is known that male and female ages play a considerable part in infertility (de La Rochebrochard and Thonneau, 2003; Marquard et al., 2009). This bias would imply overestimation of the probability of finally having a child.

In our series of 1735 couples consulting for male infertility, 56% of the 1131 male respondents had succeeded in having a child and 60% had succeeded if adoptions were included. Taking missing data into account, the cumulative success rates fell to 48% under the optimistic hypothesis and to 42% under the pessimistic hypothesis. As we assumed that none of the refusers and non-respondents with unknown reproductive outcomes had succeeded in having children, the hypothetical pessimistic cumulative success rate of 42% is probably underestimated. Consequently, it is also reasonable to estimate that, in our population, around one in two couples consulting for male infertility will succeed in having children within 4–9 years.

Interestingly, our results obtained in a large series of infertile men are in accordance with those observed in studies conducted in infertile couples undergoing IVF/ICSI, in which observed cumulative rates were 42 (Lintsen et al., 2007), 54.5 (Stolwijk et al., 2000), 63.1 (Olivius et al., 2002) and 66% ( Sharma et al., 2002), with a male factor being involved in 40, 33 and 33% of cases in the first three studies, respectively.

In our study, 16% of births resulted from natural pregnancies, which is lower than the 21% observed by Hennelly et al. (2000), than the 25% estimated in a prospective cohort study (Eijkemans et al., 2008) and than the 28% observed in a study including couples consulting in a fertility clinic (Donckers et al., 2011). This difference could be explained by the population, suggesting that couples consulting for male infertility have fewer births resulting from natural pregnancies than populations recruited during or after IVF/ICSI programmes. Interestingly, of the natural pregnancies which occurred in our series, two-thirds concerned couples with infertility of ≤24 months duration and three-quarters concerned couples with a diagnosis of ‘no identified semen factor’ or ‘mild semen factor’.

Ninety-four pregnancies (8%) were obtained in couples who received only medical and surgical treatments (non-ART treatments). These results, which are in agreement with those observed in the model developed by Collins and Van Steirteghem (2004), suggest that in some couples (depending on age, duration of infertility, and

Cl, 39–44) according to the pessimistic hypothesis where we assumed that none of these 296 couples succeeded in having a child (Fig. 3).
type of disorder) ART could be postponed and non-ART procedures proposed as first-line treatment.

The cumulative rates of success in having children in our population were higher (64%) for men aged ≤35 years and women aged ≤35 years, in agreement with previous papers showing an association between male age and female age in successful pregnancies (Dunson et al., 2002; de La Rochebrochard and Thonneau, 2003; Marquard et al., 2009). In multivariate analysis, male age ≤35 years remained significantly statistically associated with success in having children. Accordingly, it seems pertinent to take into consideration not only female age but also male age as important risk factors affecting reproductive outcomes (Elizur et al., 2005; Malizia et al., 2009; Yli-Kuha et al., 2009).

**Conclusion**

So far, this is the first study examining reproductive outcomes in a large series of couples consulting for male infertility with a 4–9-year follow-up. In this series of 1735 couples and whatever the cause of male infertility and the type of treatment, one in two couples finally succeeded in having children. This is a new, interesting and encouraging result for infertile men, and is similar to results observed in infertile women (Malizia et al., 2009).

Another key finding is the impact of male age, which like female age is an important and major factor to be taken into consideration. It should encourage couples to attempt to start planning to have children earlier.

**Acknowledgements**

The authors thanks to Nina Crowte for English language revision.

**Authors’ roles**

Data acquisition, analysis and interpretation, drafting and writing the manuscript and approval of the final manuscript—M.W. Conception and design of the study, obtention of financial support, data interpretation, writing the manuscript and approval of the final manuscript—

**Funding**

This study was supported by Agence de la Biomédecine (Saint-Denis La Plaine, France).

**Conflict of interest**

None declared.

**References**


