Does Male Age Affect the Risk of Spontaneous Abortion? An Approach Using Semiparametric Regression

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Couples in industrialized countries tend to delay attempting to have children, which may lower their chances of livebirth. The authors assessed the association between male age and the risk of spontaneous abortion between weeks 5 and 20 of pregnancy, controlling for female age. They interviewed by telephone a random cross-sectional population of 1,151 French women who had been pregnant between 1985 and 2000 (participation rate, 73%). A total of 12.2% of the 2,414 pregnancies resulted in spontaneous abortion. Semiparametric regression was used to define a discrete time survival model with a random effect taking into account induced abortions, in which female age was coded by a third-degree polynomial. This final model predicted that the risk (rate ratio) of spontaneous abortion was 2.13-fold higher for women age 25 years whose partner was age 35 years or older than for women age 25 years whose partner was younger than age 35 years (95% confidence interval: 1.07, 4.26). No such increased risk of spontaneous abortion with male age was estimated when the woman was age 35 years (rate ratio = 0.61, 95% confidence interval: 0.35, 1.07). Thus, increasing male age could increase the risk of spontaneous abortion when the female partner is less than 30 years of age.

abortion, spontaneous; aging; fetal death; maternal age; men; paternal age; pregnancy; survival analysis

Abbreviations: CI, confidence interval; GPLM, generalized partial linear model.

Spontaneous abortion is the most frequent cause of fetal loss: 10–15 percent of all clinically detected pregnancies end with a spontaneous abortion between the second and fifth months of pregnancy (1, 2). About half correspond to chromosomal anomalies of the embryo (3).

The origin of these disorders is largely unknown. Bacterial infections of the female genital tract may play a role (4, 5). For women, exposures to a few physical or chemical compounds may be risk factors (6–16). The same is true for alcohol consumption (17), tobacco use (18), caffeine intake (19–21), and consumption of tap water from some areas (22–24); physical strain around the time of implantation (25); and psychological characteristics (26–28). Other factors that predict the risk of spontaneous abortion are a woman’s age at conception after age 35 years (29), parity, and previous history of spontaneous abortion (30). Very few potential male risk factors have been reported (31–35).

The association between the risk of spontaneous abortion and the age of the male partner at conception is of interest from a biologic and public health point of view, considering the increased birth rate among men older than age 35 years in western countries (refer to Kidd et al. (36)). Given the strong effect of female age on the risk of spontaneous abortion and its correlation with male age in western societies, it is essential to control efficiently for female age when the effect of male age is studied. One study suggested that, among women older than age 35 years, the risk of spontaneous abortion was higher when the partner was age 40 years or older than when he was age 35–39 years (37). In this study, female age was controlled for by using step functions. An alternative would be a contin-
uous modeling of female age, which could enable taking into consideration the sharp variations in the risk of spontaneous abortion among women age 35–45 years. With this perspective, non- and semiparametric models can complement parametric modeling (38, 39); they model the association between the outcome and the independent variables by using smoothing functions, making it possible to estimate the effects of male age with efficient control for female age and with few a priori hypotheses. Thus, they can be useful, for instance, in exploratory analyses.

By using semiparametric and parametric regression models, we studied the association between the risk of spontaneous abortion and the age of both partners at conception, carefully controlling for the effect of female age, in a cross-sectional sample of French women pregnant between 1985 and 2000.

MATERIALS AND METHODS

Study participants

The data were derived from a survey of the general population in France. This survey compared the occurrence of reproductive life events between two rural areas and studied the association between adverse reproductive life events and exposure to ionizing radiation (Slama et al., unpublished manuscript). The selected areas were the towns of Hillion, La Méaugon, Saint-Julien, and Yffiniac (Brittany, vicinity of Saint-Brieuc) and the canton of Beaumont-Hague (19 towns, Normandy), in which a nuclear waste reprocessing plant is situated.

We randomly selected 4,202 home telephone numbers from France Telecom telephone lists and managed to contact someone in 3,899 of these homes within 15 calls. A woman age 18–60 years was randomly selected from each household contacted. The inclusion criteria were occurrence of a pregnancy (whatever the outcome) or an attempt at becoming pregnant that lasted for at least 1 year between 1985 and the time of the interview. We estimated that 1,616 (38 percent) households included an eligible woman, and we obtained information about reproductive history for 1,183 of these women (73 percent of those eligible).

Questionnaires

Data were collected by means of a computer-assisted telephone interview between April and June 2000. Each woman was first asked general questions about herself and her current partner (occupation, month and year of birth) and to describe all of her pregnancies (outcome, duration, and date of termination) and to describe all attempts to become pregnant (whatever the outcome) or an attempt at becoming pregnant that lasted for at least 1 year between 1985 and the time of the interview. We estimated that 1,616 (38 percent) households included an eligible woman, and we obtained information about reproductive history for 1,183 of these women (73 percent of those eligible).

Partner’s age at the time of conception

For each pregnancy that ended with a livebirth, a spontaneous abortion, but not an induced abortion, the woman was asked whether her current partner was the father. If not, the father’s year of birth was asked. Age at conception was estimated as the number of days between the date (month and year) of conception and the birth date (month and year) of the woman or man, divided by 365.

Pregnancy outcome

We took into account only those pregnancies that started or ended between January 1, 1985, and spring 2000. Spontaneous abortion was defined as an unplanned termination of pregnancy between weeks 5 and 20 of the pregnancy. Some spontaneous abortions during the first 4 weeks of pregnancy were reported (18 pregnancies), but these were not considered because early pregnancy loss (41) is usually highly underreported. Pregnancies that the woman considered spontaneous abortions but lasting more than 20 weeks were not taken into account. Ectopic pregnancies were not considered either, because we assumed that these pregnancies were not at risk of spontaneous abortion. Most women (69 percent) described two pregnancies or more during the study period.

Missing data

When the month of conception or birth was unknown, it was assumed to be June 30. No missing years were replaced. When the duration of the pregnancy was unknown, it was considered to be 62 days for spontaneous abortions and 268 days for livebirths.

Statistical analyses

Analysis strategy. Our aim was to define a final model parametrically describing the effect of the ages of both partners on the risk of spontaneous abortion, that is, with a limited set of parameters and explicit functions of age. This final model was chosen from the family of discrete time survival models. To define this model, and in particular the shape of possible effect-measure modifications (42, 43) between the male and female ages, we first fitted a semiparametric binomial regression model in which the simultaneous effect of both ages was modeled as a nonparametric function. Semiparametric binomial regression model. We first considered a restricted data set, including only those pregnancies under way for more than 20 weeks at the time of the interview, spontaneous abortions, and livebirths. Our semiparametric model was a generalized partial linear model (GPLM) (44, 45), in which the nonparametric component was comprised of the two age variables and the parametric part consisted of the area from which the woman was recruited, as follows (equation 1):

\[
\text{logit}[P(Y_{ij} = 1)] = \ln \left( \frac{P_{ij}}{1 - P_{ij}} \right) = m(X_{ij}^F, X_{ij}^M) + \gamma \times T_i, \tag{1}
\]

where \(Y_{ij}\) is 1 in the case of a spontaneous abortion and 0 for other pregnancy outcomes; \(P_{ij} = P(Y_{ij} = 1)\) is the probability of spontaneous abortion for pregnancy \(j\) of couple \(i\); \(X_{ij}^F\) and \(X_{ij}^M\) are the ages at conception of the mother and father, respectively; and \(T_i\) is the time of the interview for couple \(i\).

For each pregnancy that ended with a livebirth, a spontaneous abortion, but not an induced abortion, the woman was...
Table 1. Characteristics of 2,414 pregnancies that occurred between 1985 and 2000 among 1,151 couples from Beaumont-Hague and the Saint-Brieuc area, France, according to outcome

<table>
<thead>
<tr>
<th>Area of recruitment of the woman</th>
<th>Livebirth (n = 1,991)</th>
<th>Spontaneous abortion (n = 272)</th>
<th>Induced abortion (n = 100)</th>
<th>Pregnancy under way (n = 51)</th>
<th>All pregnancies (n = 2,414)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Saint-Brieuc</td>
<td>537</td>
<td>27</td>
<td>87</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Beaumont-Hague</td>
<td>1,454</td>
<td>73</td>
<td>185</td>
<td>68</td>
<td>75</td>
</tr>
<tr>
<td>Duration of the pregnancy (5–95th percentiles) in weeks</td>
<td>38.4 (35.2–39.9)</td>
<td>9.3 (4.4–15.1)</td>
<td>8.0 (4.4–13.1)</td>
<td>24.3 (8.7–39.1)</td>
<td>33.5 (6.4–39.8)</td>
</tr>
<tr>
<td>Female age at conception</td>
<td>26.7 (24.1–29.7)</td>
<td>27.4 (24.6–31.5)</td>
<td>28.6 (22.5–34.7)</td>
<td>29.3 (26.8–31.8)</td>
<td>26.9 (24.2–30.1)</td>
</tr>
<tr>
<td>Male age at conception</td>
<td>26.7 (24.1–29.7)</td>
<td>27.4 (24.6–31.5)</td>
<td>28.6 (22.5–34.7)</td>
<td>29.3 (26.8–31.8)</td>
<td>26.9 (24.2–30.1)</td>
</tr>
<tr>
<td>Median (25–75th percentiles) in years</td>
<td>26.7 (24.1–29.7)</td>
<td>27.4 (24.6–31.5)</td>
<td>28.6 (22.5–34.7)</td>
<td>29.3 (26.8–31.8)</td>
<td>26.9 (24.2–30.1)</td>
</tr>
<tr>
<td>Age ≥35 years</td>
<td>101</td>
<td>5</td>
<td>32</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Male age at conception</td>
<td>251</td>
<td>13</td>
<td>51</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Median (25–75th percentiles) in years</td>
<td>26.7 (24.1–29.7)</td>
<td>27.4 (24.6–31.5)</td>
<td>28.6 (22.5–34.7)</td>
<td>29.3 (26.8–31.8)</td>
<td>26.9 (24.2–30.1)</td>
</tr>
<tr>
<td>Age ≥35 years</td>
<td>101</td>
<td>5</td>
<td>32</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Year of conception (excluding 1984 and 2000)</td>
<td>1985–1989</td>
<td>672</td>
<td>35</td>
<td>78</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1990–1994</td>
<td>666</td>
<td>35</td>
<td>101</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>1995–July 1999</td>
<td>557</td>
<td>29</td>
<td>81</td>
<td>31</td>
</tr>
<tr>
<td>Female parity (no. of livebirths)</td>
<td>0</td>
<td>803</td>
<td>40</td>
<td>113</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>772</td>
<td>39</td>
<td>97</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>416</td>
<td>21</td>
<td>62</td>
<td>23</td>
</tr>
<tr>
<td>No. of previous spontaneous abortions</td>
<td>0</td>
<td>1,659</td>
<td>83</td>
<td>196</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>270</td>
<td>14</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>62</td>
<td>3</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Female cigarette smoking during the first trimester (no./day)</td>
<td>0</td>
<td>1,797</td>
<td>93</td>
<td>236</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>≥10</td>
<td>134</td>
<td>7</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Female alcohol consumption during the first trimester (no. of drinks/week)</td>
<td>0</td>
<td>1,162</td>
<td>59</td>
<td>134</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>1–6</td>
<td>726</td>
<td>37</td>
<td>98</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>≥7</td>
<td>70</td>
<td>4</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Female urogenital disorder*</td>
<td>0</td>
<td>1,901</td>
<td>97</td>
<td>253</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>50</td>
<td>3</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Potential exposure to ionizing radiation‡</td>
<td>0</td>
<td>829</td>
<td>45</td>
<td>123</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1,002</td>
<td>55</td>
<td>122</td>
<td>50</td>
</tr>
<tr>
<td>Female body mass index at interview (kg/m²)</td>
<td>0</td>
<td>460</td>
<td>24</td>
<td>57</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>20–29</td>
<td>1,346</td>
<td>70</td>
<td>184</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>111</td>
<td>6</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>

* Before conception of the pregnancy studied.
† NA, not available.
‡ Previous or current work of the male or female partner at a site or company where radioactive elements were used, regardless of the reality and severity of the exposure and of the precedence of this work with respect to conception.

$X_M$ are the female and male ages at conception, respectively; and $T_i$ is the area from which the woman was recruited (Saint-Brieuc/Beaumont-Hague). The function $m$ and the parameter $\gamma$ were estimated by profile likelihood (39, 44, 46) using the glplmest quantlet in XploRe statistical software (47).

**Discrete time survival model.** Two features of the data were not taken into account by the GPLM model: 1) the lack
of independence between the outcomes of the various pregnancies of a given woman and 2) the fact that a woman who had an induced abortion was also at risk of spontaneous abortion until the date on which the abortion was induced. Excluding induced abortions may bias the age-specific rates of spontaneous abortion (48, 49), especially because the risk of induced abortion also varies strongly with female age (29). These points were addressed by using a survival model with a random effect. This approach is similar to that described by Rowland et al. (6), with a slightly different statistical model.

All pregnancies lasting more than 4 weeks and ending with livebirths, spontaneous abortions, or induced abortions (including for medical reasons), as well as all pregnancies under way at the time of the interview, were taken into account. The discrete survival duration was the number of weeks of gestation. Spontaneous abortions were treated as failure, and all other pregnancy outcomes were considered censoring events. Duration of all pregnancies was taken as the last complete week of pregnancy and was right-censored after 20 weeks. Pregnancies were entered in the risk set after the end of week 4 of pregnancy and remained so until termination of the pregnancy, time of the interview, or the end of week 20 of pregnancy, whichever occurred first. The unit of analysis was the (binary) issue of each week of pregnancy analyzed by using a binomial regression model (50), adjusted for the week of pregnancy. The link function of the regression model was the complementary log-log function (50). A woman-specific random effect enabled us to take into account the lack of independence between the various pregnancies of a given woman (51, 52). The parameters were estimated by maximizing the marginal likelihood function by means of Gaussian quadrature using the xtclog function of Stata 7.0 software (53); this software was used for all other statistical analyses. The statistical model has been described elsewhere (54). The exponentials of the estimated parameters are equivalent to the rate ratios estimated by using a Cox model (55), that is, to the ratio of the instantaneous rates of spontaneous abortion between the compared groups.

The specification of the variables was assessed by using a link test (53) achieved by fitting a survival model with a random effect in which the predicted values of the tested model and their squared values were used as covariates. The test corresponds to a test of the significance of the squared predicted value, a small p value indicating a possible lack of fit.

Coding of the couple’s age. We defined 5-year age groups of male and female ages and estimated the proportion of spontaneous abortion in each category of the couple’s age, cumulated over weeks 5–20 of pregnancy. We also estimated rate ratios of spontaneous abortion by use of our survival model, in which the age categories were coded as dummy variables. These rate ratios were adjusted for the area from which the women were recruited.

To define a parametric coding for woman’s age, we fitted a fractional polynomial regression model of degree 2 (56) in which male age was not taken into account (function fracpoly). The resulting coding for female age was used in the survival model in which male age was coded by using a discrete qualitative variable with five categories. We also allowed for an effect-measure modification between male and female ages. Thus, our most general survival model had 14 age variables. We retained all variables with a p value (as estimated by a likelihood-ratio test) of less than 0.25 (57).

We reduced the number of categories of the male age variable in two ways: 1) by visually comparing the graphs of the predicted risks of spontaneous abortion in each male age group and 2) by comparing the log likelihoods corresponding with the groupings of the five male age categories in two categories (15 models). Both methods led to the same coding for male age, which yielded our final model, as justified in the Results section of this paper. The final model was used to estimate the rate ratio of spontaneous abortion associated with male age for a given female age (57), together with a 95 percent confidence interval (lincom function). The

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**TABLE 2.** Rates (%) of spontaneous abortion between weeks 5 and 20 of pregnancy* according to the ages of the male and female partners at conception for 2,414 pregnancies occurring in 1985–2000 among 1,151 couples from Beaumont-Hague and the Saint-Brieuc area, France†

<table>
<thead>
<tr>
<th>Female age (years)</th>
<th>&lt;25</th>
<th>25–29</th>
<th>30–34</th>
<th>35–39</th>
<th>≥40</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td></td>
<td>No. of pregnancies‡</td>
<td>Rate</td>
<td>No. of pregnancies</td>
<td>Rate</td>
<td>No. of pregnancies</td>
</tr>
<tr>
<td>&lt;20</td>
<td>8.0</td>
<td>59</td>
<td>5.9</td>
<td>17</td>
<td>25.0</td>
<td>4</td>
</tr>
<tr>
<td>20–24</td>
<td>12.8</td>
<td>259</td>
<td>10.3</td>
<td>358</td>
<td>4.8</td>
<td>64</td>
</tr>
<tr>
<td>25–29</td>
<td>12.2</td>
<td>53</td>
<td>11.3</td>
<td>571</td>
<td>9.9</td>
<td>329</td>
</tr>
<tr>
<td>30–34</td>
<td>0.0</td>
<td>3</td>
<td>16.6</td>
<td>66</td>
<td>12.3</td>
<td>262</td>
</tr>
<tr>
<td>35–39</td>
<td>83.3</td>
<td>4</td>
<td>33.3</td>
<td>25</td>
<td>20.0</td>
<td>76</td>
</tr>
<tr>
<td>≥40</td>
<td>0.0</td>
<td>6</td>
<td>60.4</td>
<td>13</td>
<td>46.1</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>11.9</td>
<td>374</td>
<td>11.4</td>
<td>1,016</td>
<td>11.2</td>
<td>684</td>
</tr>
</tbody>
</table>

* Rates were estimated by using a fetal life table method, cumulating the week-specific proportions of spontaneous abortions occurring between weeks 5 and 20 of pregnancy.
† Empty cells correspond to age groups in which no pregnancies occurred.
‡ Number of pregnancies at risk of spontaneous abortion at the beginning of week 5 of gestation.
predicted values were displayed graphically with those of two (GPLM) semiparametric regression models for couples in which the male partner was younger than age 35 years or was age 35 years or older, adjusted for area of recruitment.

Our strategy of selecting the final model did not enable us to infer the first-type error from the reported $p$ values and confidence intervals because, among other reasons, multiple comparisons were performed between models.

Confounding factors. We considered the area from which the couples were recruited. Risk factors for spontaneous abortion specific to the first trimester of pregnancy were not available for induced abortions. By excluding induced abortions, we further adjusted our final model for female tobacco smoking (0–9 vs. 10 or more cigarettes/day), female alcohol consumption during the first trimester of pregnancy (continuous variable), and previous history of female urogenital disease (cancer of the uterus, salpingitis, chlamydia infection; coded as 1 if any of these occurred, 0 otherwise).

RESULTS

A total of 1,154 of the 1,183 women included (97.5 percent) in our study reported at least one pregnancy lasting 4 weeks or more during the previous 15 years. Of the 2,439 pregnancies that occurred between January 1985 and May 2000, we excluded 25 (1.0 percent) for which data concerning male or female age at conception were missing. Of the 2,414 remaining pregnancies (1,151 couples), 1,991 (82.5 percent) ended in a livebirth, 272 (11.3 percent) in a spontaneous abortion, and 100 (4.1 percent) in an induced abortion, and 51 (2.1 percent) were still under way at the time of the interview. The characteristics of these pregnancies are given in table 1.

The woman’s age at conception ranged from 14.3 to 45.6 years (median, 26.9 years), whereas the man’s age was 15.6–54.8 years (median, 29.1 years) at the time of conception (tables 1 and 2). The coefficient of correlation between female and male ages was 0.73. The mean difference between the man’s age and the woman’s age was 2.4 years (5th, 50th, and 95th percentiles: −2.4, 2.0, and 8.8 years, respectively). The rate of spontaneous abortion was 12.2 percent (table 2).

<table>
<thead>
<tr>
<th>Female age (years)</th>
<th>&lt;25</th>
<th>25–29</th>
<th>30–34</th>
<th>35–39</th>
<th>≥40</th>
<th>All men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate ratio</td>
<td>0.8</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.61</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.64</td>
<td>0.71</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.61</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>1.2</td>
<td>1.1</td>
<td>1.5</td>
<td>7.0</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.52</td>
<td>0.81</td>
<td>0.27</td>
<td>0.03</td>
<td>0.60</td>
<td>0.68</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>0.23</td>
<td>0.90</td>
<td>0.51</td>
<td>0.01</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>$p$ value</td>
<td>5.3</td>
<td>0.77</td>
<td>0.28</td>
<td>0.91</td>
<td>0.62</td>
<td>0.90</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>0.006</td>
<td>0.9</td>
<td>0.28</td>
<td>0.9</td>
<td>0.62</td>
<td>0.9</td>
</tr>
<tr>
<td>$p$ value</td>
<td>1 (referent)</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>1.0</td>
<td>1.6</td>
<td>1.5</td>
<td>5.7</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.80</td>
<td>0.03</td>
<td>0.005</td>
<td>&lt;0.0005</td>
<td>0.07</td>
<td>0.07</td>
</tr>
</tbody>
</table>

a Rate ratios in the last row and column were estimated by using models in which the only age variable was male age or female age, respectively.

b Discrete time survival model with a random effect.

§ Because of small sample sizes, for couples in which the woman was less than age 20 years, all men age 30–40 years were grouped together.

¶ Because of small sample sizes, couples in which the man was younger than age 25 years and the female partner was age 30–34 years were grouped together with couples in which the man was age 25–29 years and the female partner was age 35–39 years.
The GPLM semiparametric model showed no trend in the risk of spontaneous abortion with male age that could be observed for all age groups of the female partner (figure 1). For a given female age, the risk of spontaneous abortion was highest in relation to the oldest men only when the female partner was younger than age 25 years. This finding supported an effect-measure modification between the two age variables.

The life table estimates of the risk of spontaneous abortion (table 2) and the survival model (table 3) exhibited trends similar to those shown in figure 1.

Nonparametric coding of the age variables

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Parametric coding of the age variables

From the estimates described above, we decided to code male age as a categorical variable with five classes, including terms of effect-measure modification with female age. Female age was coded by using a polynomial of degree 3, which resulted from the fractional polynomial estimation, including an interaction term with male age (model 1, table 4). The male age variable was reduced from five categories to two categories (refer to the Materials and Methods section) corresponding to men younger than age 35 years and those age 35 years or older (model 2, table 4 and figure 2a).

For this model, the degree of significance of the variables coding female age, male age, and their interaction terms was less than 0.25 (table 4), which was also the case for the random effect ($p < 0.0005$). The link test provided no sign of a poor specification of the variables ($p = 0.82$). Therefore, model 2 was chosen as our final model. Figure 2a gives its predicted values and figure 2b those of a semiparametric GPLM model.

According to this model (figure 2a), the rate ratio of spontaneous abortion in women age 25 years whose partner was age 35 years or older compared with women age 25 years whose partner was younger than age 35 years was 2.13 (95 percent confidence interval (CI): 1.07, 4.26). When the female partner was age 35 years, this rate ratio was 0.61 (95 percent CI: 0.35, 1.07). When we adjusted the results for female tobacco smoking, alcohol consumption, and previous history of female urogenital disease (table 5), the rate ratio of spontaneous abortion in women age 25 years whose partner was age 35 years or older compared with women age 25 years whose partner was younger than age 35 years was 1.95 (95 percent CI: 0.97, 3.92).

DISCUSSION

In a population of 1,151 couples who described 2,414 pregnancies between 1985 and 2000, we observed an increased risk of spontaneous abortion when the man was age 35 years or older compared with younger than age 35 years at the time of conception, but only when his female partner was in her twenties (rate ratio = 2.13 for women age 25 years). Because of the small number of pregnancies in which there was a big difference between female and male ages (table 2), this potential effect of male age after 35 years should be interpreted with caution.

For women age 35 years, the risk of spontaneous abortion associated with the male partner being age 35 years or older...
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was lower than in couples in which the male partner was younger than age 35 years (figure 2a). This result does not match our a priori hypothesis. One could explain the modification of the effect of male age with female age by the fact that a weak effect of male age is more likely to be highlighted among couples in which female age is low and therefore unlikely to influence the risk of spontaneous abortion.

One study of the last planned pregnancy of 3,174 couples reported that, among those in which the female partner was older than age 35 years, the risk of spontaneous abortion was greater when the male partner was age 40 years or older compared with younger than age 40 years (37). Among the couples that included a female partner age 35 years or older or age 30–34 years, the risk of spontaneous abortion seemed to decrease and then increase with male age. Among couples in which the female partner was age 20–29 years, the odds ratio of spontaneous abortion ranged from 1.0 when the male partner was age 20–29 years to 1.8 when he was age 40–64 years (95 percent CI: 0.5, 6.2). Thus, this study (37) also favored an effect of male age on the risk of spontaneous abortion, but a residual confounding effect by female age cannot be excluded because a discrete variable with broad categories was used to adjust for female age.

Pregnancy outcome

Spontaneous abortions. Occurrence of spontaneous abortion was assessed retrospectively on the basis of the woman’s declaration. The overall rate of spontaneous abortion between weeks 5 and 20 of gestation was 12.2 percent. This rate is similar to that reported in France and elsewhere when various methods were used (1, 29, 58).

Induced abortions. Induced abortions are a major point of concern when the risk of spontaneous abortion (48, 49) is studied. We chose to take them into account by use of a survival model. This model assumes that the probability of induced abortion is independent of the probability of spontaneous abortion. This assumption may be difficult to justify (49). In our study, the proportion of induced abortion was low (4.9 percent of all pregnancies excluding ectopic pregnancies). In the Beaumont-Hague area, the rate of induced abortion is about half the average rate of approximately 20 per 100 pregnancies observed in France (59). We may therefore have missed about 50 percent of the induced abortions likely to have occurred in the study population. It is also plausible that some of the pregnancies we considered spontaneous abortions were actually induced abortions, an issue of pregnancy that some women may be reluctant to declare. If the rate of underreporting of induced abortion varies with male age, this occurrence might have led to a spurious effect of male age on spontaneous abortions. Considering that our finding of effect was essentially based on a subgroup of 14 pregnancies (males age 35 years or older, women younger than age 25 years; tables 2 and 3), these points constitute important limitations of our study.

Potential confounding factors

Female age. The continuous coding of female age in our final model (by use of two variables: age squared and age cubed), defined by a fractional polynomial (56), makes it unlikely that the effect of male age on the risk of spontaneous abortion was due to residual confounding by female age.

FIGURE 2. Predicted probability of spontaneous abortion as a function of the woman’s age when the male partner was younger than age 35 years (solid line, 2,074 pregnancies) or age 35 years or older (dashed line, 340 pregnancies) for 2,414 pregnancies that occurred in Beaumont-Hague and the Saint-Brieuc area, France, between 1985 and 2000. The data were fitted by using a) a final survival model with a random effect (model 2, table 4) and b) a semiparametric (generalized partial linear model (GPLM)) model, in which 100 induced abortions and 20 current pregnancies under way for less than 20 weeks were excluded. Both models were adjusted for the area from which the women were recruited; for reading convenience, only the values predicted for the Beaumont-Hague area were plotted.
Adjustment of our final model for female tobacco smoking and alcohol consumption during the first trimester of pregnancy and for a previous history of female urogenital disease did not change much the estimated effect of male age (table 5), but we had to exclude induced abortions from this analysis. We did not collect information on caffeine consumption (20, 21).

Some of the women or men we included were potentially exposed to ionizing radiation at work, which may affect the occurrence of fetal loss (16, 60). We excluded these persons and again estimated our final model. Among the 977 remaining pregnancies, the rate ratio of spontaneous abortion quantifying the effect of male age was 4.27 (95 percent CI: 1.75, 10.42), a value similar to the rate ratio of 2.13 estimated for the whole population.

**Time since conception.** The risk of a woman forgetting about a spontaneous abortion may increase with time since the spontaneous abortion occurred (61). We applied our final model to the 1,544 pregnancies conceived between 1990 and 2000. Among women age 25 years, the rate ratio of spontaneous abortion associated with the male partner being age 35 years or older was 1.83 (95 percent CI: 0.76, 4.41), lower but similar to the overall rate ratio of 2.13.

**Previous reproductive history.** We did not adjust for the number of previous pregnancies, livebirths, or spontaneous abortions since they are not potential confounding factors (62). All pregnancies that occurred after 1985 were included in the model and were accounted for in the random effect, which models the heterogeneity between couples in their propensity to undergo a spontaneous abortion (51, 52). However, the random effect does not model sequence effects in pregnancy history: the tendency to stop seeking a pregnancy after reaching the desired family size and to attempt another pregnancy after a spontaneous abortion.

**Possible biologic mechanisms**

A possible biologic pathway through which male age could affect the probability of spontaneous abortion implies alteration of semen quality. Although the function of Leydig and Sertoli cells may decrease with age (63, 64), it is still debatable whether sperm quality changes with age. Semen volume, sperm motility (36), and the proportion of morphologically normal sperm (65) may indeed decrease with age. It is not known to what extent these semen parameters affect the probability of spontaneous abortion. Some genetic muta-
tions (66) and sperm aneuploidy (a number of chromosomes other than a multiple of 23) may also be more frequent with age. The latter may be associated with an increased risk of fetal loss (36). If true, these sperm-mediated effects of age should mainly concern spontaneous abortions with chromosome anomalies.

Other potential mechanisms exist. For example, age-related sociologic or psychological factors, such as the quality of the couple’s relationship, may be associated with psychological stress in the woman and thus affect the occurrence of spontaneous abortion (26, 27, 67).

Conclusion

In our study, the finding of an increased risk of spontaneous abortion when the man was age 35 years or older compared with younger than age 35 years is consistent with male age affecting the risk of spontaneous abortion. These preliminary results should be interpreted with caution because of a limited sample size and retrospective data collection. The statistical model we used could be tested in other populations or be enlarged to study other risk factors. More generally, in studies concerning the risk of spontaneous abortion in which female age needs to be controlled for, this adjustment should be made by using a coding similar to that used here, not by merely entering female age with a single linear term or by a step function corresponding to broad age groups. Because a possible biologic pathway by which male age could influence the risk of spontaneous abortion is an increase with age in the importance of chromosomal defects of the spermatozoa, the effect of male age could be studied in pregnancies for which the karyotype of the embryo is known.

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