Does male age have an influence on the risk of spontaneous abortion? An approach combining semiparametric and parametric regression.

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Running title:
Male age and spontaneous abortion.

ABSTRACT

Couples from Western countries tend to delay their pregnancies, which may affect their ability to obtain a live birth. We assessed the association between male age and the risk of spontaneous abortion taking into account woman's age. We performed telephone interviews on a cross-sectional random population sample of 1124 French women who had been pregnant between 1985 and 2000, who described 2281 pregnancies, among which 290 (12.7%) ended by a spontaneous abortion. We used logistic regression and generalised partial linear models, a class of semiparametric regression models. Our final random effect logistic regression model predicted that, among women aged 25 years, the odds-ratio (OR) of spontaneous abortion associated with the male partner being older than 35 years, as compared to men younger than 35 years, was 2.48 (95% Confidence Interval (CI): [1.13-5.41]). No such effect of male age was observed when the woman was 35 years (OR=0.53, CI: [0.27-1.01]). Male age had on the whole no strong influence on the risk of spontaneous abortion, but exhibited an increased risk after 35 years, only among younger women. This possible effect should be further investigated, possibly in studies with assessment of the presence of chromosomal abnormalities in the abortus. *(196 words)*

Key words: Spontaneous abortion / foetal loss / man's age / semiparametric models/ logistic / random effect

TEXT

INTRODUCTION

Spontaneous abortion is the most frequent cause of foetal loss, with 10 to 15% of the clinically detected pregnancies ending with a spontaneous abortion [1].About half of them correspond to chromosomal anomalies of the embryo[2].

The aetiology of those disorders remains mostly unknown. A few behavioural, physical or chemical risk factors have been reported (for instance smoking or exposure to heavy metals[1,3]). Psychological and immunological factors in the woman may also play a role on the occurrence of spontaneous abortion [4-7]. Other identified factors which showed to be good predictors of the risk of spontaneous abortion are woman's age at conception, parity or gravidity, and previous history of spontaneous abortion [8].

The association between the risk of spontaneous abortion and the age of the male partner at conception has so far little been described in the literature. This question is of interest as far as public health is concerned, given the increase in the birth rate for men over age 35 in the USA (quoted in [9]) and other Western countries. One study about the last pregnancy of a cross-sectional population sample reported an increased risk associated with the male partner being older than 40 years, observed only when the female partner was more than 35 years old[10].

Given the strong influence of female age on the risk of spontaneous abortion, the fact the ages of a couple's partners are quite strongly correlated makes it necessary to control efficiently for female age. Otherwise, residual confounding by female age may induce an association between male age and the risk of spontaneous abortion. In this regard, non- and semiparametric modelling offer a complement to parametric modelling [11,12]; they model the association between the dependent variable and quantitative independent variables by very general smooth functions, allowing to define finely the influence of female age to adjust for it, and to help defining the shape of possible effect modifications between both age variables.

We studied the association between the risk of spontaneous abortion and the age of both partners at conception, among a cross-sectional sample of French couples who conceived a pregnancy between 1985 and 2000.

STUDY POPULATION AND STATISTICAL METHODS

Population sample

The data used for this study come from an epidemiological survey among the general population of two French rural areas aiming at comparing the occurrence of reproductive life events in those areas, and at studying the association between adverse reproductive life events and exposure to ionising

radiation (Slama et al., *manuscript*). The selected areas are the towns of Hillion, La Méaugon, Saint-Julien and Yffiniac (Bretagne), and the canton of Beaumont-Hague (Normandie), where a nuclear waste reprocessing plant is situated.

Inclusion criteria and pregnancies under study

The couples were selected at random from (France Telecom) telephone lists of the study areas. We randomly selected among the people living in each home a woman aged between 18 and 60. The inclusion criteria were the occurrence of a pregnancy (whatever the issue) between 1985 and the time of interview, or an attempt at pregnancy lasting at least one year. The interviews took place between April and June, 2000.

We randomly selected 4202 homes, reached a person by telephone in 3899 homes. We estimated the number of homes with an eligible woman to be 1616 (38.5%). Among those, we obtained information about reproductive history for 1183 women (73.2% of the eligible women). There were 2290 pregnancies occurring between 1985 and may 2000 among 1126 couples and ending by a live birth or a spontaneous abortion; for 9 of these pregnancies, male age at conception was unknown and the analyses presented here were therefore conducted on 2281 pregnancies among 1124 couples, ending with either a spontaneous abortion or a live birth.

Questionnaires

The data were collected through a computer assisted telephone interview.

The woman was first asked to give some general information about herself and her current partner (occupation, month and year of birth), to describe in chronological order all of her pregnancies (issue, duration and date of termination), and attempts at pregnancy. For each pregnancy, the woman was asked if the partner with which the pregnancy occurred was her current partner, and for his year of birth if necessary. The woman answered then questions about her health and occupational exposures (mainly to ionising radiation), and so did her current partner.

The women's questionnaires lasted on average 45 minutes.

Spontaneous abortion

We defined spontaneous abortion as an unplanned termination of the pregnancy during the first twenty weeks of pregnancy. Some pregnancies considered by the woman as spontaneous abortions but lasting more than 20 weeks were excluded. All the pregnancies that ended during the study period with either a live birth or a spontaneous abortion were taken into account in the analyses, yielding a total of 2290 pregnancies, 290 of which were spontaneous abortion (12.7%) with defined ages of both partners at conception. This value corresponds to an average of 2.0 pregnancies per woman. The age at conception was estimated from the date (month and year) of termination of the pregnancy, and its duration.

Missing data

When missing, the date of occurrence of the pregnancy was assumed to be the June 30th, and duration of the pregnancy was supposed to be 62 days for spontaneous abortion (72 missing

values, corresponding to 24.8% of the spontaneous abortions) and 268 days for live birth (7 missing values, 0.4%).

STATISTICAL ANALYSES

Strategy of analysis

We first conducted separately logistic regression and semiparametric regression analyses, in order to define a parametric final model including not too many variables, which could later be enlarged to other risk factors for spontaneous abortion. This strategy leads to a final parametric model that may fit the data rather well, but the estimated p-values cannot be interpreted as the value of the first type error, since multiple comparisons between models are performed, and the model is tested on the same data that were used to define it. Another *a priori* choice was the selection of age as unique behavioural and socio-physiological risk factors of spontaneous abortion. This choice implies that we considered age as a proxy indicator of various risk factors for spontaneous abortion, and that we did not intend to explain the biological or sociological mechanisms underlying the observed associations. We still took into account the area of inclusion of the couples, which is a possible confounding factor [13] for the association under study.

We first defined 5 years age groups for male and female ages, and estimated the proportion of spontaneous abortion (number of spontaneous abortion divided by the number of pregnancies ending with either spontaneous abortion or live birth) in each category of the couple’s age. We also defined for women an age group below 20 years; all men older than 40

were gathered in one group due to the small sample size for those ages.

Logistic regression models:

There were 6 age groups for women, 5 for men, defining 30 age groups for the couple. These age categories were coded as dummy variables in a logistic regression model with a random effect[14,15], motivated by the fact that each woman contributed for two pregnancies on average. This random effect accounts for the dependence between successive pregnancies of a given woman. This model can be written:

$$\text{logit}[P(Y_{ij}=1)] = \alpha + u_i + \sum_{k,l=1,\ldots,5} \beta_{kl} . I_{(X_{ij}^F \in G_k)} . I_{(X_{ij}^M \in G_l)} + \delta . T_i \quad (1)$$

where $P(Y_{ij}=1)$ is the probability of spontaneous abortion for the pregnancy j of couple i, X^F, X^M stand for the female and male age at the conception of the pregnancy ij, and $I_{(X_{ij}^F \in Gk)}$ is 1 if the female age variable corresponding to the pregnancy ij is in the age group $G_{k,\ k\leq 30}$, and 0 otherwise. T_i indicates the geographical area where the woman i lived at the time of interview (Normandie or Bretagne). The random effect variables (u_i) are supposed to be mutually independent, with a common underlying normal distribution with mean 0, and variance to be estimated. The parameters α, (β_{kl}) and γ were estimated by the maximum likelihood method (function xtlogit, Stata statistical software: release 6.0, College Station, TX, USA, Stata Corporation). The value exp(β_{kl}) constitutes our estimate of the

odds-ratio (OR) of spontaneous abortion for couples with woman being in the age group G_k and man in age group G_l, compared to the reference category. The OR varies like the ratio of the proportion of spontaneous abortion between the compared categories, but is more distant from 1[13].

Semiparametric regression models:

We fitted a semiparametric model including both age variables. The model was a generalised partial linear model [16,17], in which the nonparametric component was constituted of the two age variables. It was adjusted for the city of recruitment of the woman and was written as follows:

$$\text{logit}\left[P\left(Y_{ij}=1\right)\right] = m\left(X^{F}_{ij}, X^{M}_{ij}\right) + \delta . T_i \qquad (2)$$

The association between the logit of the probability of spontaneous abortion and the age variables is this time modelled nonparametrically by the function *m*, which, together with the parameter γ, was estimated by profile likelihood [16,18] (gplm quantlet, XploRe statistical software, MD Tech, Berlin, Germany). The bandwidths that we have chosen (that is, the broadness of the age-interval taken into account around a given point to estimate the probability of spontaneous abortion at this point) were somewhat greater for man's than for woman's age because of a greater span of the men's ages distribution.

Selection of the final model:

From the estimations provided by the models (1) and (2) above (cf. results section), we inferred our final logistic regression model among the following class of parametric logistic regression models with random effect: woman's age was coded by a polynomial of degree 3, and man's age by a discrete variable with 5 categories coded by dummy variables; moreover, we allowed for an effect modification between the 2 variables. Our most general model had thus 19 age variables (model 3, table 4).

We first simplified woman's age coding by trying to remove the terms containing X_F, X_F^2 or X_F^3. A variable was taken out of the model only if the corresponding p value obtained by a likelihood-ratio test [19] was smaller than 0.25. We then reduced the number of categories of the male age variable, by a qualitative examination of the predicted risks of spontaneous abortion for the 5 age groups. We also compared the log-likelihood values of the 10 models corresponding to all possible groupings of the male age variable in 2 categories. Both methods yielded the same coding of male age, which constituted our final model (model 6, table 4). This model was compared to a model without any variable representing male age, a comparison which was meant to indicate us if the introduction of man's age in the model really brought information on the risk of spontaneous abortion. The predicted values of our final model were also graphically compared to those of a quadratic spline regression model, also adjusted on the city of recruitment[11].

We estimated OR of spontaneous abortion associated with man's age, for a given age of the woman partner, from our

final model [19], together with a 95% confidence interval (CI) (lincom function, Stata 6.0).

RESULTS

Among the 2281 pregnancies under study, the woman's age at conception ranged from 14 to 46 years, with a mean and a median of 27 years, whereas men were between 16 and 54 years old at the time of conception (mean: 30, median 29 years, cf. table 2). The female and male ages had a coefficient of correlation of 0.72 ($p<5.10^{-5}$). The men were on average 2.4 years older than their partner at the time of conception, the 5^{th} and 95^{th} percentiles of the difference being –9 and 21 years, respectively. The characteristics of the pregnancies under study are given in table 1.

Tab. 1

Considering each age variable separately

The average rate of spontaneous abortion was 12.7%, and it ranged from 10.1% among women under 20 years to 43.8% among women older than 40 years at the time of conception. The raw association between the woman's age and the risk of spontaneous abortion showed an increase from approximately 25-30 years upward (table 2, last column).

Tab. 2

Considering both age variables simultaneously

The stratified analysis showed no trend in the risk of spontaneous abortion with male age that could be observed for all age groups of the female partner (table 2). A monotonous increase in the risk of spontaneous abortion with woman's age was observed when the man was younger than 30 years. For older men, the risk of spontaneous abortion started to decrease and then increased with female age, the minimum risk being

observed for women close to 30 years. The logistic regression estimations (table 3) and the semiparametric regression estimates (figure 1), adjusted for the area of recruitment of the couples, exhibited similar trends.

Fig. 1

Tab. 3

Thus, only for younger women did we observe an increased risk of spontaneous abortion with male age, for men older than approximately 35 years, compared to men younger than 35 years. This increased risk was not obvious when the female partner was older than 30-35 years, indicating a potential effect modification between the two age variables.

Selection of the final model

From these results, we wanted our final model to allow for an effect modification between the two age variables, and we decided to code man's age as a categorical variable, as no clear trend had been observed. We started from model (3), in which the woman's age was coded by a polynomial, with an effect modification with male age coded in 5 age groups. The coding of female age was first simplified, which constituted our model 4 (table 4 and figure 2).

Fig. 2

We further grouped all couples whose male partner was younger than 35 years, on the one hand, and all couples whose male partner was older than 35 years on the other. This grouping was motivated by the predicted probabilities of pregnancies of model 4 (figure 2), and it also corresponded to the model with the best fit (measured by the log-likelihood of the model) among all possible models in which the male age variable was coded by a binary variable. It constituted our model 5 (table 4).

We tested the elimination of the variables coding male age (model 6, table 4), but the likelihood ratio test led us to keep it in the model (p=0.05). This value tends to indicate that the introduction of the variables coding male age increased the goodness-of-fit of the model to the data, which led us consider model 5 as our final model to predict the risk of spontaneous abortion according to male and female ages. This p-value should, still, not be interpreted like a first-type error, and is likely to underestimate it, since we defined our final model in order to maximize our chance to observe an effect of male age.

Fig. 3

According to our final model (5), when the woman was 25 years, the OR of spontaneous abortion associated with the male partner being older than 35 years, adjusted for city and woman’s age, was 2.48 (95% CI: 1.13-5.41), couples with men younger than 35 years being taken as a reference. When the female partner was 35 years, the OR of spontaneous abortion estimated by model (5) associated with the man being 35 years or more, was 0.53 (95% CI: 0.27-1.01).

The figure 3b gives a spline estimate of the association between woman’s age and risk of spontaneous abortion for the two male age groups and yielded conclusions qualitatively similar to those of our final parametric model shown in figure 3a.

DISCUSSION

In a population of 1124 couples who conceived 2281 pregnancies between 1985 and 2000, we observed an increased risk of spontaneous abortion when the man was older than 35 years at the time of conception, compared to couples with a man younger than 35 years, but only when the female partner was in her twenties (0R=2.48 for women aged 25 years). Due to a small number of pregnancies with a big difference between female and male ages, this potential effect of man age after 35 years should be taken cautiously. For women older than 30 years, the risk of spontaneous abortion associated with the male partner being older than 35 years was decreased, compared to couples with a male partner younger than 35 years; this observation does not match our a priori hypotheses and is therefore more likely to be a chance finding.

Measure of the occurrence of spontaneous abortion

The occurrence of spontaneous abortion was retrospectively assessed, on the basis of the woman's declaration, without any verification in medical files. This procedure of data collection may entail classification biases, and underreporting of the occurrence of spontaneous abortion.

The overall rate of spontaneous abortion was 12.7% when all other issues of pregnancy but live birth were neglected. This rate corresponds to 14.5 spontaneous abortion for 100 live births. It is similar to what has been reported in France and elsewhere with various methodologies [20]. From a study using hospital registers from Denmark for the years 1978-1992, and supposing that only 80% of women with spontaneous abortions

were hospitalised [21], one can estimate the following rates of spontaneous abortion according to maternal age: 13.2% for 12-19 years (compared to 10.1% in our study), 11.1% for 20-24 years (11.4%), 11.9% for 25-29 years (11.2%), 15.1% for 30-34 years (15.0%), 24.6 for 35-39 years (20.7%) and 49.3% for 40-45 years (43.8%). This relatively good agreement with the Danish study indicates no major under or over-reporting of spontaneous abortions in our data.

Classification biases: It is plausible that some of the pregnancies that we considered as spontaneous abortion corresponded to other issues of pregnancy (ectopic pregnancy for example). If, for a given age of the woman, the man's age had an influence on the probability of induced abortion or of occurrence of ectopic pregnancy, then this could bias our estimates of the effect of male age. We have no information on such a point, that we cannot test on our data, and can therefore not discard this potential bias.

A possible issue of pregnancy that may entail such declaration biases is induced abortion. Some women may indeed be reluctant to admit that they underwent an induced abortion, and therefore may have described as spontaneous an induced abortion; they may also simply not describe the corresponding pregnancy. The rate of induced abortion in our population sample was 7.2 for 100 live births, which is about the half of what is observed at the level of the Manche département where Beaumont-Hague is located, where the incidence of abortion is itself about half of what is observed in France as a whole[22]. An underreporting of induced abortion (of about 7 for 100 live birth) is thus very likely in our data, if we suppose that the

situation in Beaumont-Hague is similar to that of the whole département, and that the situation is similar around Saint-Brieuc. It is possible that some of the induced abortions be described as spontaneous. Since induced abortions occur most often in women below 20, in their early twenties, or older than 35 years, this may distort our estimates of the association between occurrence of spontaneous abortion and age. Assuming that this reporting bias was smaller among women who have a regular partner, we estimated our final model only for pregnancies which occurred after that the interrogated woman started her relation with her current partner (if she had any at the time of interview). This restriction left the OR of spontaneous abortion associated with male age virtually unchanged (data not shown).

Potential confounding factors

Time since conception as a source of bias

The risk for a woman to forget or to make an error on the date of occurrence of a spontaneous abortion may be increasing with the delay since the spontaneous abortion. Indeed, the date corresponding to the 10^{th} percentile of the distribution of the date of termination of pregnancy was 5 months later for spontaneous abortions than for live birth in our dataset. This difference may correspond to a tendency to underreport the most ancient spontaneous abortions, which could artificially increase the effect of male age if the proportions of men older than 35 years were not the same for pregnancies that began at different periods. Among women aged 25 to 29 years at the conception of the studied pregnancy, the proportion of men

older than 35 years was slightly more important for the pregnancies ending in 1997-1999 than for those ending in 1985-1987 (8.7% versus 6.5%). We estimated our final models separately in two calendar periods. Among women aged 25 years, the OR of spontaneous abortion associated with a male age greater than 35 years was 3.02 (95% CI: 0.95-9.57) for pregnancies conceived before 1990, and 2.06 (95% CI: 0.71-5.93) for pregnancies conceived between 1990 and 2000. This similarity with the overall OR of 2.48 tends to indicate that the effect of male age is not due to differential reporting between most ancient and more recent spontaneous abortions.

Previous reproductive history

Various factors may influence the risk of spontaneous abortion. Our results were adjusted for the area of inclusion of the subjects because this factor was likely to be independently associated with age and risk of spontaneous and act as a confounding factor. Our aim was to test a possible influence of man’s age on the risk of spontaneous abortion, without trying to explain in terms of biological or psycho-sociological mechanisms the observed associations. Moreover, the small number of pregnancies with an important difference between the partners’ ages (for instance, only 10 pregnancies occurred among women aged 20-24 years who had a partner aged 35 years or more, table 2) was in our eyes the main limitation of our study, and was not likely to be overcome by adjustment.

We did not adjust, notably, for the previous number of pregnancies, of live birth (parity) or of spontaneous abortion. Since all the pregnancies that occurred after 1985 are included in the model, previous history of spontaneous

abortion (occurring after 1985) is to some extent accounted for, since the random effect allows couples with a high propensity to undergo a spontaneous abortion (whatever the age) to have a higher basal risk of spontaneous abortion than other couples, provided they attempted to obtain pregnancies.

Parity may be on the causal pathway between age and the risk of spontaneous abortion, which justifies not to adjust for this factor [13]. Indeed, when our final model was applied separately to nulliparous and non-nulliparous women (those who had had a live birth before the pregnancy under study), the OR of spontaneous abortion associated with the male partner being older than 35 years, predicted for a 25 years-old woman, was 4.81 (95% CI: 1.52-15.21) for nulliparous women, and 1.01 (95% CI: 0.29-3.54) for parous women. This difference between the OR for nulliparous and non-nulliparous women justifies not to adjust for parity, and indicates that the estimated increased risk associated with male age is in our population restricted to couples with a nulliparous woman.

Some of the included subjects (mainly men) were occupationally exposed to ionising radiation, which may influence the occurrence of adverse reproductive health outcomes [23]. We conducted analyses restricted to the couples for which the man and the woman declared to have never been followed up for exposure to ionising radiation, and never to have worked in the vicinity of sources of ionising radiation. This restriction left 932 pregnancies among 452 couples, i.e. 48.5% of the pregnancies). In this population sub-sample, we observed qualitatively similar patterns for the influence of male age as in the whole population, the OR for spontaneous abortion associated with the male partner being older than 35

years being 5.19 (95% CI: 1.77-15.18) among women aged 25 years.

We tried to check that all the above-mentioned potential sources of bias taken as a whole (and not only separately) could not explain the observed associations. To do so, we estimated our final model on the pregnancies that responded to all restriction criteria quoted above (conception occurring in 1990 or later, obtained with the same partner as at the time of interview, none of the partner having been followed for exposure to ionising radiation before termination of pregnancy). There were 538 such pregnancies among 307 couples. For women aged 25 years, the estimated OR of spontaneous abortion associated with a male age greater than 35 years, was 3.65 (95% CI: 0.64-20.89), which is consistent with the value of 2.48 obtained on the whole population sample. This finding is coherent with the estimated association not being artificially induced by the potential biases mentioned above and taken as a whole.

Biological plausibility of an effect of man's age on the probability of spontaneous abortion

The relation between age and ability to conceive is not as well documented for men as for women, which was one of the motivation of our study. The probability to obtain a pregnancy without any medical assistance is very reduced for women above 45 years. This higher risk of spontaneous abortion among older women seems to be explained by a poorer oocyte quality with increasing woman's age, rather than by a reduced ability of the uterus to sustain a pregnancy [24,25,26].

The association between man's age and ability to conceive (either assessed by waiting time to pregnancy or risk of spontaneous abortion) was little documented in the literature, but it is known that men are likely to conceive up till 60 or 70 years old. From a biological point of view, although there is a decrease in Leydig cells and Sertoli cells function with age [27,28], the question of the evolution of sperm quality with age is debated. A review [9] concluded on a plausible decrease in semen volume, sperm motility and proportion of morphologically normal sperm. It is not known whether these semen parameters are likely to have an influence on the probability of spontaneous abortion. Sperm aneuploidy -that is, a number of chromosomes other than a multiple of 23- may also be more frequent with age, and is possibly associated with an increased risk of foetal loss [9].

If these biological hypotheses concerning an increase in sperm aneuploidy and a decrease in sperm concentration, motility, and proportion of morphologically normal sperm with age are true, one could expect that such sperm-mediated effects on the risk of spontaneous abortion mainly concern chromosomally abnormal spontaneous abortions. In other words, the association between male age and the risk of spontaneous abortion may be different for chromosomally abnormal and normal foetal losses. This could not be tested with our data.

Other potential mechanisms exist. An influence of man's age on the risk of spontaneous abortion could for instance also be explained by sociological or psychological mechanisms like the quality of the human relationship inside the couple, which could be associated with psychological stress and could thus affect the occurrence of spontaneous abortion [4,5,29].

Parametric and semiparametric models

Our logistic parametric regression model and semiparametric regression model yielded very similar results, although they used different estimation procedures, and are not really adapted to correlated data. They mainly allowed us to propose a realistic family of models for our final parametric model.

The increased risk of spontaneous abortion observed in this study when the man was older than 35 years, compared to men younger than 35 years, is coherent with an influence of man’s age on the risk of spontaneous abortion. These preliminary results should be taken with care and tested in other populations. Since a possible biological pathway by which male age could influence the risk of spontaneous abortion is an increase with age in the importance or amount of defects of the spermatozoa, the potential effect of male age could be studied among pregnancies for which the karyotype of the embryo is known.

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TABLES

Table 1: Characteristics of the pregnancies under study according to their issue (2281 pregnancies among 1124 couples).

	Live birth (%) n=1991	Spontaneous abortion (%), n=290
Area of recruitment		
Bretagne	537 (85)	95 (15)
Normandie	1454 (88)	195 (11)
Gestational age, in weeks from the last menstrual period (5-95th percentiles)	38.4 (35-40)	8.9 (3-15)
Number of missing values	7 (0.4)	72 (24.8)
Mean age at conception (standard deviation)		
Female	27.1 (4)	28.1 (5)
Male	29.6 (5)	30.2 (5)
Parity before pregnancy		
0 live births	803 (87)	121 (13)
1-2 live births	772 (88)	103 (12)
≥ 3 live births	416 (86)	66 (14)
Number of previous spontaneous abortions		
0	1666 (89)	215 (11)
1	271 (85)	48 (15)
≥ 2	62 (65)	33 (35)
Female 1st term tobacco consumption (cigarettes/day)		
0	1504 (88)	215 (13)
1-5	133 (86)	22 (14)
5-9	167 (92)	15 (8)
≥10	135 (83)	28 (17)
Potential male exposure to ionising radiation before conception		
No	945 (86)	154 (14)

Yes	1046 (89)	136 (12)
Potential female exposure to ionising radiation before conception		
No	1439 (87)	207 (13)
Yes	552 (87)	83 (13)
Female body mass index at interview (kg/m^2)		
< 20	462 (88)	64 (12)
20-24	1067 (87)	161 (13)
25-29	281 (88)	38 (12)
≥ 30	114 (87)	17 (13)

Table 2: Observed rates of spontaneous abortion [number of spontaneous abortions/(number of spontaneous abortion and live birth)] according to the ages of male and female partners at conception. The number of pregnancies is indicated between parentheses.

	Man's age (years)					
Woman's age	**<25**	**25-29**	**30-34**	**35-39**	**≥ 40**	Total
<20	10.4 (48)	6.3 (16)	50.0 (2)	0.0 (3)	(0)	**10.1 (69)**
20-24	13.2 (242)	10.5 (343)	6.5 (62)	40.0 (10)	(0)	**11.4 (657)**
25-29	13.7 (51)	11.5 (550)	10.1 (316)	13.2 (53)	6.7 (15)	**11.2 (985)**
30-34	0.0 (1)	16.7 (66)	14.5 (249)	14.7 (102)	20.0 (15)	**15.0 (433)**
35-39	(0)	66.7 (3)	28.0 (25)	20.0 (65)	10.7 (28)	**20.7 (121)**
≥ 40	(0)	(0)	(0)	20.0 (5)	54.6 (11)	**43.8 (16)**
Total	**12.6 (342)**	**11.6 (978)**	**12.2 (654)**	**16.8 (238)**	**18.8 (69)**	**12.7 (2281)**

Table 3: Estimated odds-ratio (OR) and p values (in parentheses) for spontaneous abortion according to male and female age at the time of conception (years). The OR from the last line and column were estimated by model in which the only age variable was male age and female age, respectively. Adjusted for city (Bretagne=0, Normandie=1). Empty cells correspond to empty age groups.

Woman's age	**Man's age**					**All men**
	<25	25-29	30-34	35-39	≥ 40	
<20	1.0 (.99)	0.6 (.61)	2.3 (.52)			**0.8 (.69)**
20-24	1.2 (.45)	1 (ref)	0.4 (.17)	10.4 (.004)		**1 (ref)**
25-29	1.1 (.80)	1.0 (.85)	0.9 (.79)	1.2 (.74)	1.1 (.85)	**0.9 (.57)**
30-34	14.9 .03	1.6 (.27)	1.4 (.27)	1.5 (.28)		**1.3 (.18)**
35-39			4.3 (.01)	2.3 (.05)	1.0 (.99)	**2.2 (.008)**
≥ 40				1.9 (.63)	14.0 (.001)	**6.9 (.002)**
All women	**1.1 (.64)**	**1 (ref)**	**1.1 (.77)**	**1.7 (.02)**	**1.9 (.10)**	

Highlighting indicates cell size ≤ 15 pregnancies.

Table 4: Description of the various logistic regression model used to define the final model, together with the p-value of some variables (2281 pregnancies among 1124 couples). Model 5 corresponds to the final model.

Model	Linear term: logit(P_{ij})=[§]	p-value[*]	Deviance	Likelihood-ratio test (degrees of freedom)[#]
(3)	$\alpha + u_i + [\gamma^{(1)} + \beta^{(1)}_1 X_F + \beta^{(1)}_2 (X_F)^2 + \beta^{(1)}_3 (X_F)^3] I^{(1)}_M + \ldots$	$(\beta^{(1)}_1, \ldots, \beta^{(5)}_1)$:0.45	1659.6	
	$+[\gamma^{(4)} + \beta^{(4)}_1 X_F + \beta^{(4)}_2 (X_F)^2 + \beta^{(4)}_3 (X_F)^3] I^{(4)}_M$	$(\beta^{(1)}_2, \ldots, \beta^{(5)}_2)$:0.44		
	$+ [\beta^{(5)}_1 X_F + \beta^{(5)}_2 (X_F)^2 + \beta^{(5)}_3 (X_F)^5] I^{(5)}_M + \delta . T_i$	$(\beta^{(1)}_3, \ldots, \beta^{(5)}_3)$:0.42		
(4)	$\alpha + u_i + [\gamma^{(1)} + \beta^{(1)}_2 (X_F)^2 + \beta^{(1)}_3 (X_F)^3] I^{(1)}_M + \ldots + [\gamma^{(4)} + \beta^{(4)}_2 (X_F)^2 +$	$(\beta^{(1)}_2, \ldots, \beta^{(5)}_2)$:0.03	1664.3	0.45 (5)
	$\beta^{(4)}_3 (X_F)^3] I^{(4)}_M + [\beta^{(5)}_2 (X_F)^2 + \beta^{(5)}_3 (X_F)^5] I^{(5)}_M + \delta . T_i$	$(\beta^{(1)}_3, \ldots, \beta^{(5)}_3)$:0.02		
(5)	$\alpha + u_i + [\gamma + \beta_2 (X_F)^2 + \beta_3 (X_F)^3] I_{M<35} + [\beta'_2 (X_F)^2 + \beta'_3 (X_F)^5] I_{M \geq 35} + \delta . T_i$	(β_2, β'_2): 0.001	1671.9	0.58 (9)
		(β_3, β'_3): 0.0003		
(6)	$\alpha + u_i + \beta_2 (X_F)^2 + \beta_3 (X_F)^3 + \delta . T_i$	β_2: 0.01	1679.8	0.05 (3)
		β_3: 0.003		

[§] Linear term of the logistic regression model for the pregnancy j of couple i. The parameters are written with greek letters. X_F stands for female age at conception, $I^{(k)}_M$ indicates that male age is in group k, T stands for the city of recruitment, u_i is the random effect. For variables X_F, I_M, the index ij was omitted.

[*] Degree of significance of the indicated parameters, as estimated by a likelihood ratio test. Parentheses indicate parameters whose significance was tested simultaneously.

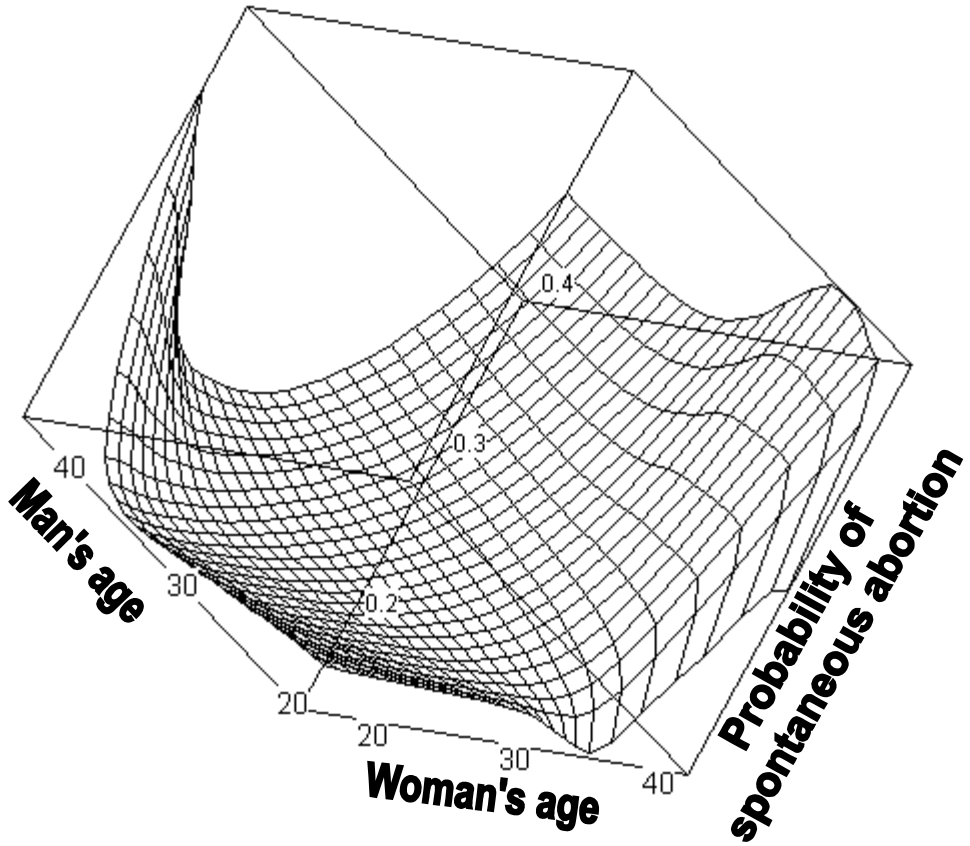
Degree of significance of the likelihood ratio test between the model in the corresponding line, and the model from the line above.

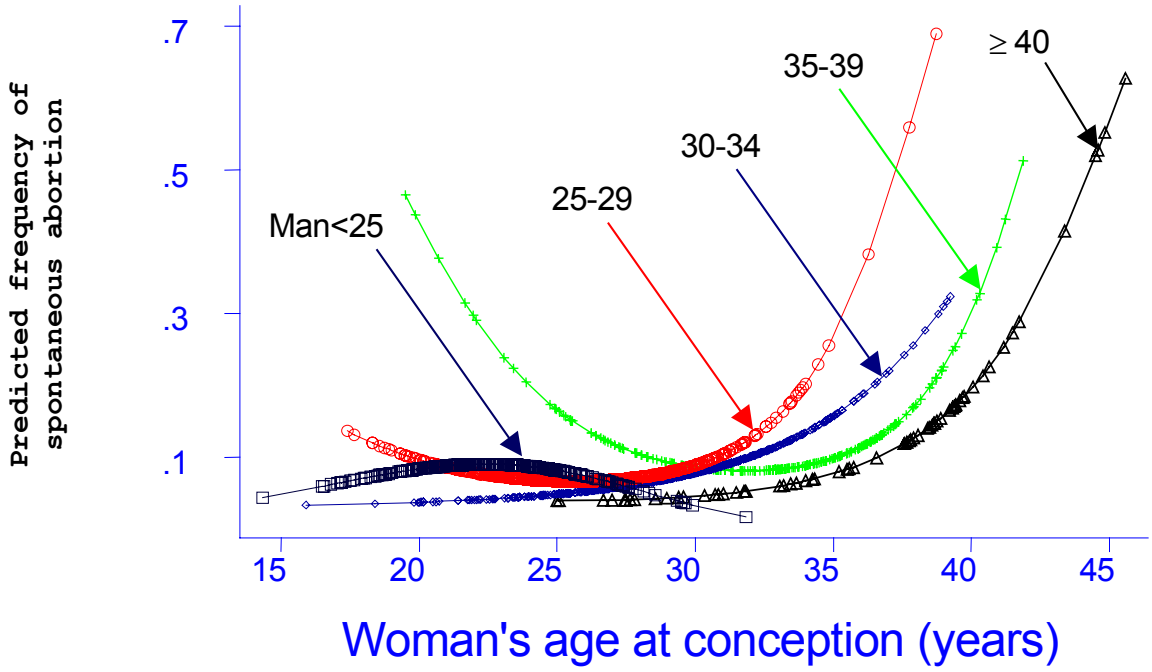
FIGURES

Figure 1: Probability of spontaneous abortion according to the age of both partners at the time of conception (in years), adjusted for the city of recruitment. Semiparametric regression (generalised partial linear model), 2281 pregnancies among 1224 couples. The probability of spontaneous abortion (vertical axis) is given on the natural scale. Value of Akaike's criterion: 1726

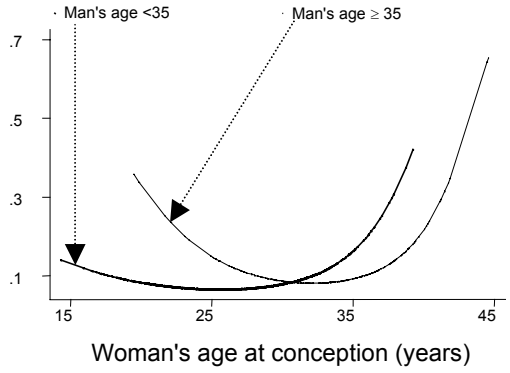
Figure 2: Predicted probability of spontaneous abortion in function of the woman's age, for 5 age groups of the male partners. The arrows indicate male age. The data were fitted by a logistic regression model with random effect in which female age was coded by a polynomial of degree 3 (model 4, table 4). Although the models were adjusted for the city of recruitment, the predicted values are shown only for the Beaumont-Hague area, for reading convenience. In each male age group, the predicted values for the Saint-Brieuc area were very similar to those estimated for Beaumont-Hague, but very slightly higher.

Figure 3: Predicted probability of spontaneous abortion in function of the woman's age, when the male partner is younger (1980 pregnancies) or older than 35 years (301 pregnancies). The arrows indicate male age. The data were fitted by a) a logistic regression model with random effect in which female age was coded by a polynomial of degree 3 (model 5, table 4), corresponding to our final model and b) by a quadratic spline model. Both models were adjusted on the city of recruitment of the couples. Same remark as in the legend of figure 2 concerning the city.


0.4
0.3
0.2
40
30
20
Man's age
20
30
40
Woman's age
Probability of
spontaneous abortion


Predicted frequency of spontaneous abortion
.7
.5
.3
.1
Man<25
25-29
30-34
35-39
≥ 40
15
20
25
30
35
40
45
Woman's age at conception (years)

(a): Final parametric model



(b): Spline model