



## Influence of Paternal Age on the Risk of Spontaneous Abortion

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The frequency of chromosomal anomalies in spermatozoa appears to increase with male age. Because these anomalies play a role in the etiology of spontaneous abortion, an influence of paternal age on risk of spontaneous abortion is plausible but not established. The aim was to characterize this influence in a prospective study among 5,121 California women, who as members of a prepaid health plan were interviewed in 1990 or 1991 when they were less than 13 weeks' pregnant and who were followed until the end of pregnancy. The risk of spontaneous abortion between weeks 6 and 20 of pregnancy was studied using a Cox model adjusted for maternal age. The adjusted hazard ratio of spontaneous abortion associated with paternal age of 35 years or more, compared with less than 35 years, was 1.27 (95% confidence interval: 1.00, 1.61), with no modification by maternal age. Among women aged less than 30 years, the hazard ratio of spontaneous abortion associated with paternal age of 35 years or more was 1.56 for first trimester spontaneous abortion and 0.87 for early second trimester spontaneous abortion (test of interaction,  $p = 0.25$ ). In conclusion, the risk of spontaneous abortion increased with increasing paternal age, with a suggestion that the association is stronger for first trimester losses.

abortion, spontaneous; confounding factors (epidemiology); maternal age; paternal age; pregnancy

Abbreviation: HR, hazard ratio.

About half of all spontaneous abortions occurring after the sixth gestational week carry a chromosomal anomaly (1, 2). The proportion of spontaneous abortions with chromosomal anomalies is likely to be higher for first trimester than for second trimester spontaneous abortions; it appears to peak around gestational week 11 (2, 3).

Chromosomal anomalies in the zygote may result from errors during gametogenesis in either parent, during fertilization, or during the first cellular divisions of the zygote (2). Thus, a male factor causing chromosomal anomalies in the spermatozoa may induce spontaneous abortion. Male age could be such a factor, as the frequency of sperm chromosomal anomalies, such as aneuploidy or DNA strand breaks, has been suggested to increase with age (4, 5). Similarly,

paternally inherited genetic mutations in the embryo, which may also cause spontaneous abortion, may be more frequent with increasing paternal age because of the continuous replication of male stem cells after puberty (6).

When examining the effect of paternal age, one must control for the effect of maternal age, because of its association with both spontaneous abortion risk (7, 8) and paternal age. Increases in the risk of spontaneous abortion with increasing paternal and maternal ages have been reported in a retrospective study (9). In another retrospective study spanning over a 15-year period, we reported that, after controlling for female age at conception, the risk of spontaneous abortion was increased when the male partner was aged 35 years or more, compared with less than 35 years. However, this was

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seen only among couples in which the woman was less than 30 years (10). An effect of paternal age for only a limited range of a woman's age did not agree with our a priori hypothesis. An a posteriori explanation of this result was that a weak effect of paternal age may be easier to identify in couples in which the woman is in her twenties than in couples in which the woman is in her thirties or forties. This is because younger women constitute a relatively homogeneous population as far as maternal biologic risk factors for spontaneous abortion are concerned, whereas among older women many biologic maternal factors, not all controlled for by an adjustment for female age, may influence the risk of spontaneous abortion and mask an effect of paternal age. Retrospective studies on spontaneous abortion are, moreover, potentially limited by recall bias. In a study comparing prospective records and data from a retrospective questionnaire spanning more than 20 years, women recalled only 80 percent of the spontaneous abortions that occurred in the 20 years prior to interview; for 20 percent of the recalled spontaneous abortions, the date of occurrence of the spontaneous abortion was recalled with an error greater than 1 year (11). For these reasons, it is important to have a prospective study confirming a possible paternal age effect on the risk of spontaneous abortion.

The main aims of this prospective study were to examine the effect of male age on the risk of spontaneous abortion and to test whether an effect exists independently of the age of the female partner. The secondary and more exploratory aim was to describe the relation between paternal age and risk of spontaneous abortion as a function of gestational age.

## MATERIALS AND METHODS

### Data collection

The Pregnancy Outcome Study was conducted between February 1990 and September 1991 in California among members of the Kaiser Permanente Medical Care Program, a large prepaid health plan (12–15). The women were interviewed as soon as possible after the detection of a pregnancy. When women called to make their first prenatal appointment, they were informed of the study and their eligibility was determined (12). To be eligible, the woman had to be older than 18 years, to be less than 13 weeks' pregnant, and to be Spanish or English speaking. Eligible women who agreed answered a computer-assisted telephone interview on average 8.5 weeks after the last menstrual period (5th–95th percentiles, 5.9–12.0 weeks). Women whose pregnancy had ended by the time of interview were not included; some information was collected on these pregnancies, including maternal age, but not paternal age.

### Pregnancy outcome

Only pregnancies ending with a livebirth, a stillbirth (fetal loss 21 weeks or more after the last menstrual period), or a spontaneous abortion (20 weeks or less after the last menstrual period) were included in this analysis. For consistency with other studies (10, 16) and because very early losses are detected less consistently than those occur-

ring later, we studied the risk of spontaneous abortion from gestational week 6 onward. Pregnancy outcome was ascertained for 99 percent of the participants, primarily from Kaiser medical records; 84 percent of the spontaneous abortions were identified by medical record review (12).

### Survival model

The length of the period at risk of spontaneous abortion varied according to the date of detection of the pregnancy; moreover, women who miscarried before the call for their first antenatal appointment or the planned date of interview were not included. To account for this left truncation and for variation in the risk of spontaneous abortion with gestational age (7), we used the Cox survival model (16) with delayed entry. The failure that we modeled was the occurrence of a spontaneous abortion, and the time variable was gestational age (weeks), defined as the number of days between the first day of the last menstrual period and the end of the pregnancy, divided by seven (without rounding). The period at risk of spontaneous abortion spanned from the gestational age at the time of interview or the end of the sixth gestational week, whichever came last, to the gestational age at the time of spontaneous abortion, or to the completion of gestational week 20, whichever came first. The gestational age at interview was missing for nine pregnancies, all ending with a livebirth or a stillbirth; for these pregnancies, the gestational age at interview was assumed to be 8.14 weeks, the median value observed among livebirths and stillbirths.

We plotted  $-\ln(-\ln(S))$ , where  $S$  is the probability of survival of the pregnancy adjusted for female age, against the logarithm of gestational age, for various values of paternal age. We examined these curves in order to check the proportional hazard assumption of the Cox model. This assumption was also tested by adding interaction terms to the model between the male age variable and the survival time (17). There was no evidence that this assumption was not valid (not shown). All the analyses were conducted using Stata version 8SE software (StataCorp LP, College Station, Texas).

### Coding of female and male ages

The woman's age at conception was defined as the number of days between her day of birth and the day of conception (assumed to have occurred 14 days after the last menstrual period), divided by 365.25 and not rounded. To limit any residual confounding bias by female age, we used the coding of female age with the best fit to the actual data, defined by using a fractional polynomial approach with two terms (18). The resulting terms were female age to the second and third powers.

The woman was asked about the age of the father of her current pregnancy. As defined in our earlier study (10), male age was first coded in two categories ( $<35$  or  $\geq 35$  years) in the survival model adjusted for maternal age. We also ran this model after exclusion of the pregnancies for which the woman declared that she was not living with the father, which yielded similar results (data not shown), and with paternal age coded into smaller categories. An interaction

**TABLE 1. Cumulative rates of spontaneous abortion from weeks 6–20 of gestation (as estimated by a survival model) and total number of pregnancies according to the ages of the male and female partners at conception among 5,121 California women prospectively followed in 1990–1991**

Female age (years)	Male age (years)														Total	
	<25		25–29		30–34		35–39		40–44		45–49		≥50		%	No.
	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.				
<20	15.3	174	21.1	23	0.0	5	0.0	4	0.0	1					15.1	207
20–24	6.9	513	10.8	529	6.6	129	4.0	27	0.0	6			0.0	1	8.5	1,205
25–29	16.1	73	12.3	931	10.4	649	17.2	150	12.2	48	8.3	12	40.0	5	12.4	1,868
30–34	0.0	21	10.5	175	9.7	652	13.8	332	12.9	86	21.3	25	7.7	14	11.1	1,305
35–39	0.0	2	24.3	31	14.8	100	17.4	216	18.1	95	21.9	24	33.3	8	18.1	476
≥40			33.3	3	43.8	6	57.7	14	34.6	25	33.3	9	33.3	3	40.6	60
Total	9.8	783	12.2	1,692	10.2	1,541	16.0	743	16.3	261	20.7	70	21.1	31	12.2	5,121

term between female and male ages was then introduced into the model, and the corresponding risks of spontaneous abortion were plotted. Finally, paternal age was also coded using a restricted cubic spline model to describe its effect without any strong assumptions about the shape of the association with the risk of spontaneous abortion (17).

#### Confounding factors other than female age

We adjusted for maternal tobacco use (0, 1–10, or more than 10 cigarettes/day), alcohol (yes/no), and caffeine consumption (total daily amount of caffeine estimated from coffee, tea, and sodas ingested (13)) during the week before interview and paternal tobacco smoking during the first trimester (yes/no). These factors were chosen because of their known or suspected influence on the risk of spontaneous abortion (13, 19–22). Missing values for these variables (<1 percent of the observations) were replaced by the median value observed for observations with no missing value. A previous spontaneous abortion was not considered a potential confounder, as a previous spontaneous abortion might have been caused by an elevated paternal age during the previous pregnancy (23). It has been debated whether maternal caffeine consumption is a potential cause of spontaneous abortion or a consequence of pregnancy symptoms such as nausea, which is in turn a possible marker of fetal viability (13, 21, 24). We therefore reran the main analysis without adjusting for caffeine consumption, which did not change the conclusions (data not shown).

#### Variations in the effect of male age according to gestational duration

According to our biologic hypothesis, the effect of male age on the risk of spontaneous abortion was expected to vary with gestational age (2). We therefore studied the influence of male age on the risk of spontaneous abortion in relation to gestational age. This was done by plotting the unadjusted hazards of spontaneous abortion by gestational age for male age greater than or equal to 35 years and less than 35 years. As the week-specific hazards of spontaneous abortion could

not be adjusted for any covariate, and as the risk of spontaneous abortion varies with female age from 30 years onward (8), this comparison was restricted to couples in which the woman was aged less than 30 years. Following this analysis, the association between paternal age and the risk of spontaneous abortion was estimated with the Cox model separately for weeks 6–12 and 13–20, and an interaction term between paternal age and gestational week (6–12 vs. ≥13 weeks) was added. The significance degree of this interaction term was taken as a test of variations with gestational week in the effect of paternal age on the risk of spontaneous abortion.

#### RESULTS

The eligible study pregnancies resulted in 4,645 livebirths or stillbirths and 491 spontaneous abortions that occurred after 6 completed gestational weeks. Male and female ages were known for 5,121 of the remaining pregnancies, 489 of which ended in a spontaneous abortion. The mean age of the women at conception was 28.3 years (5th–95th percentiles: 20.3–37.1 years). The mean male age at interview was 30.3 years (5th–95th percentiles: 21–41 years). The distribution of both ages is given in table 1. The correlation between maternal and paternal ages was 0.70 ( $p < 0.0001$ ). Among women still pregnant at 6 gestational weeks, the cumulative proportion of pregnancies ending in spontaneous abortion, as estimated by a survival model, was 12.2 percent.

After adjustment for maternal age, the risk of spontaneous abortion associated with a paternal age of 35 years or more was 1.26 times higher than when the father was aged less than 35 years (95 percent confidence interval: 1.00, 1.60). The result varied very little after further adjustment for female tobacco use and alcohol and caffeine consumption, as well as for paternal tobacco smoking (hazard ratio (HR) = 1.27, 95 percent confidence interval: 1.00, 1.61). Adjustment for a previous spontaneous abortion had little effect on the estimated hazard ratio (adjusted HR = 1.27, 95 percent confidence interval: 1.00, 1.61). The adjusted hazard ratio of spontaneous abortion associated with a maternal age of 40 years (referent, 25 years) when paternal age was not

**TABLE 2. Adjusted hazard ratios of spontaneous abortion by paternal and maternal ages for 5,121 pregnancies among California women in 1990–1991**

Age (years)	Estimation point (years)*	No. of pregnancies		Adjusted hazard ratio†	95% confidence interval	
		Total	Spontaneous abortions			
			No.			%
<b>Paternal age</b>						
<25		783	53	6.8	1	
25–29		1,692	156	9.2	1.47	
30–34		1,541	126	8.2	1.25	
35–39		743	98	13.2	1.74	
40–44		261	36	13.8	1.45	
≥45		101	20	19.8	1.87	
<b>Maternal age</b>						
<22.5	20	688	55	8.0	1.27	
22.5–27.4	25	1,622	134	8.3	1	
27.5–32.4	30	1,757	149	8.5	0.98	
32.5–37.4	35	848	97	11.4	1.30	
37.5–42.4	40	189	45	23.8	2.63	
≥42.5	45	17	9	52.9	8.80	

\* For maternal age, the hazard ratios of spontaneous abortion were estimated at the maternal age indicated as the estimation point. The numbers of pregnancies and spontaneous abortions represent all occurring in the specified maternal age range.

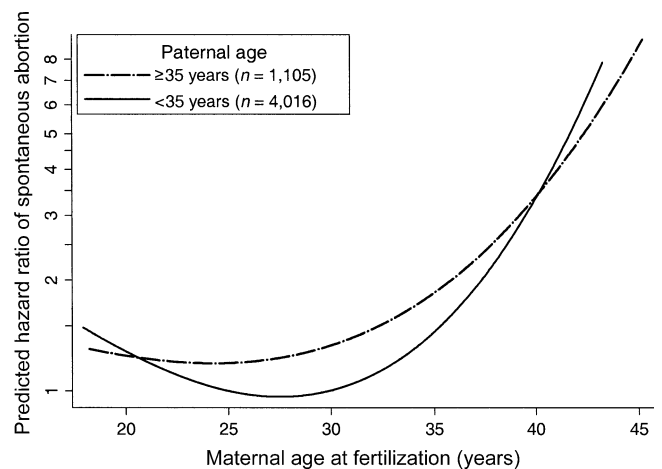
† Hazard ratios of spontaneous abortion adjusted for paternal age (categories), female age (coded by age at powers 2 and 3), paternal smoking during the first trimester of pregnancy (yes/no), and maternal tobacco use and alcohol and caffeine consumption during the week before interview.

adjusted for was 3.2 (95 percent confidence interval: 2.5, 4.1) and 2.6 (95 percent confidence interval: 1.9, 3.7) after adjustment for paternal age (table 2), a decrease of 19 percent.

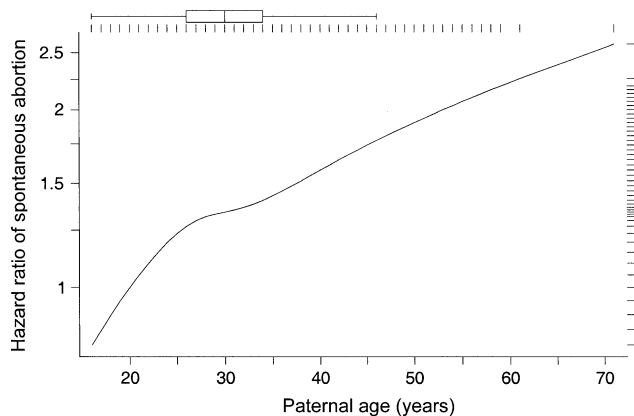
When allowing for a modification of the paternal age effect by maternal age, the hazard of spontaneous abortion was highest for older men when the woman was aged between 20 and 40 years. For women aged less than 20 years or more than 40 years, there was a tendency toward a reverse effect of older male age (figure 1). However, these more extreme age groups included few pregnancies, and a global test for interaction found little evidence that the effect of paternal age was modified by maternal age ( $p = 0.55$ ).

When male age was coded into smaller categories (table 2), the adjusted risk of spontaneous abortion was lowest when the man was aged less than 25 years and highest when the man was aged more than 45 years (for men aged 18–24 years as referent: HR = 1.87, 95 percent confidence interval: 1.01, 3.44). The adjusted influence of male age, as estimated by a smoothing approach, was consistent with a linear increase in the hazard of spontaneous abortion with male age between 20 years and 45 years (figure 2).

Changes in the hazard of spontaneous abortion with gestational age for women aged less than 30 years as a function of paternal age are given in figure 3. The increase in the hazard of spontaneous abortion with a male age of 35 or more years was greatest before weeks 13–14. We therefore considered the first trimester (6–12 completed weeks) and

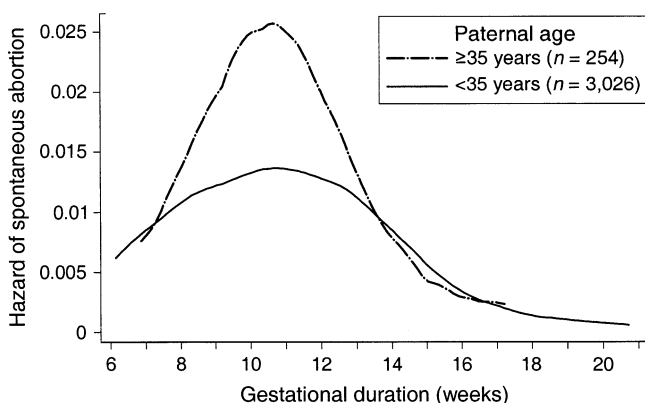


**FIGURE 1.** Adjusted hazard ratios of spontaneous abortion between 6 and 20 weeks of gestation according to maternal age and whether paternal age was less than 35 years or 35 years or more, California, 1990–1991 (5,121 women). The hazard ratio was predicted by a Cox model adjusted for female age, tobacco use (paternal and maternal), and alcohol and caffeine consumption, the referent value corresponding to women aged 25 years whose partner is aged less than 35 years, not exposed to tobacco, and not drinking alcohol or caffeinated beverages. The adjusted hazard ratio associated with male age greater than or equal to 35 years, compared with less than 35 years, was 1.19 for women aged 25 years (95% confidence interval: 0.73, 1.95), 1.33 for women aged 30 years (95% confidence interval: 1.01, 1.74), and 1.28 for women aged 35 years (95% confidence interval: 0.96, 1.69).



**FIGURE 2.** Hazard ratios of spontaneous abortion according to paternal age (referent, men aged 20 years), adjusted for maternal age, caffeine, alcohol consumption, and tobacco use, as well as paternal tobacco use, California, 1990–1991 (5,121 women). A restricted cubic spline model was used. Box plots, giving a lower adjacent value, 25th, 50th, and 75th percentile values, and upper adjacent values, are shown along the top and right side to indicate the distribution of the data according to each axis. The hazard ratios predicted for paternal ages of 35, 40, 45, and 50 years were, respectively, 1.43, 1.58, 1.74, and 1.90. Note that paternal age exceeded 62 years for only one observation.

the early second trimester (13–20 completed weeks) separately. Paternal age of 35 or more years had an adverse effect on the risk of first trimester spontaneous abortion (HR = 1.56, 95 percent confidence interval: 1.02, 2.39; 203 spontaneous abortions), which was not seen for gestational weeks 13–20, with a smaller number of pregnancies (HR = 0.87, 95 percent confidence interval: 0.35, 2.15; 76 spontaneous abortions) (test of interaction,  $p = 0.25$ ).



**FIGURE 3.** Raw weekly hazard of spontaneous abortion according to gestational age, when the man was either less than 35 years or 35 years or more, among 3,280 California women aged less than 30 years who were prospectively followed in 1990–1991.

## DISCUSSION

In this group of pregnant women followed prospectively, we found, after adjustment for female age, that the risk of spontaneous abortion was 27 percent higher among women with a male partner aged 35 or more years than among those whose partner was aged less than 35 years. The age of 35 or more years did not appear to be a clear threshold for the effect of male age. Instead, there was a steady increase in the risk of spontaneous abortion with paternal age, which was almost twice as high among men aged more than 45 years than among those aged less than 25 years. Results for men aged more than 45 years should be viewed with caution because of the small number of men in this age group.

The major strength of our study is its prospective design, allowing us to define the period at risk of spontaneous abortion accurately for each woman, to perform a survival analysis, and to minimize recall bias. This design also allowed us to study the variations in the hazard of spontaneous abortion with gestational age. Moreover, our statistical model, and in particular the cutpoint of 35 or more years used to categorize paternal age, had been defined in an earlier study conducted on a different population (10), thus reducing the likelihood that our current results represent chance findings (17).

One limitation of our study is that the only paternal exposure that could influence the risk of spontaneous abortion (25) taken into account was paternal smoking. Other paternal exposures such as paternal alcohol consumption at the time of conception (26), if correlated with paternal age, could have biased the estimated association between male age and the risk of spontaneous abortion.

Induced and therapeutic abortions are at risk of spontaneous abortion until the induction of the abortion (10, 27), but they were not taken into account in this study. We had information on a subset of 128 induced and therapeutic abortions that occurred after the time of interview (12). These are likely to correspond to a particular subgroup because we believe that many women who had an induced abortion during the study period did not schedule any appointment for prenatal care, which is the moment when women were asked to participate in the study, and were therefore not included.

Women who miscarried between the time they scheduled their first antenatal appointment and the phone contact for interview were not included. This was accounted for by using a model with delayed entry, allowing the period at risk of spontaneous abortion to start after the time of interview. Moreover, we could check that the age of the woman at interview of the 186 women who had miscarried before the time of interview (mean = 29.2, 5th–95th percentiles: 20–38 years) did not differ from that of the included women who had a spontaneous abortion who were included (mean = 29.2, 5th–95th percentiles: 20–39 years;  $p = 0.96$ ).

### Maternal age and paternal age

We used a fractional polynomial approach (18) because continuous variables like maternal age may be poorly controlled when a broad categorical coding is used (28). As an illustration, the use of binary coding for controlling

maternal age (<35 vs.  $\geq$ 35 years) with our data yielded an estimate of 1.37 for the adjusted hazard ratio associated with male age of 35 or more years, which overestimates the hazard ratio that we found using the polynomial coding (HR = 1.27). A linear coding for maternal age yielded a hazard ratio of 1.35, and, finally, for a categorical grouping with all women aged 35 or more years combined (<20, 20–24, 25–29, 30–34, and  $\geq$ 35 years), an adjusted hazard ratio of 1.39. The residual confounding occurring when maternal age is coded with such variables is, in part, due to the sizable increase in the risk of spontaneous abortion as women's age increases from 35 to 45 years (table 2) (8). By comparison, using a linear and a quadratic term for maternal age yielded a hazard ratio of 1.25 for paternal age, much closer to our estimate.

To our knowledge, most previous studies on this topic either did not adjust for female age or adjusted using broad age groups (e.g., grouping all women above 35 years). For instance, in a prospective study of 484 women, an odds ratio of spontaneous abortion of 2.3 was reported for male age above 35 years, but this was apparently not adjusted for female age (29). In a retrospective study (9), the point estimate of the odds ratio of spontaneous abortion among women aged 35–44 years was higher when paternal age was 40–64 years, compared with 35–39 years. The interpretation of this increase in the odds ratio in terms of the paternal age effect is uncertain, because the distribution of female age between 35 and 44 years may be shifted toward higher values when comparing partners of men aged 35–39 years with partners of men aged 40 or more years.

We found no evidence that the effect of male age on the risk of spontaneous abortion was modified by female age. This result differs from our previous observations (10), which were limited by the fact that our previous study was retrospective, spanned a 15-year period, and had a smaller sample size. We therefore tend to believe that the effect of male age on the risk of spontaneous abortion, as assessed by a multiplicative risk model, is unlikely to vary with female age between 20 and 40 years.

We treated maternal age as a confounding factor for the association between paternal age and the risk of spontaneous abortion. Symmetrically, the association between maternal age and spontaneous abortion is likely to be confounded by paternal age. We did, in fact, observe that the estimated influence of maternal age on the risk of spontaneous abortion decreased after adjustment for paternal age. Assuming that the reported effect of paternal age is not due to unmeasured maternal factors, earlier studies that did not control for paternal age may have overestimated the effect of maternal age on the risk of spontaneous abortion.

### Possible biologic mechanisms

We hypothesize that the increased risk of spontaneous abortion with male age is a consequence of an increasing frequency of chromosomal anomalies in the spermatozoa with male age, which in turn increases the risk of spontaneous abortion.

The influence of male age on the proportion of spermatozoa carrying a chromosomal anomaly or with damaged

DNA has been documented in several groups of men (4, 5, 30–33). It may well result, in part, from the continuous replication of stem cell chromosomes from puberty onward; indeed, male stem cells have undergone about 150 chromosomal replications at the age of 20 years and about 600 by the age of 40 years (6).

The chromosomal anomalies found in spontaneous abortions include autosomal trisomies, present in about 50 percent of abortuses with chromosomal anomalies, monosomy X (present in about 20 percent), and triploidy (16 percent). The remaining 12 percent correspond mainly to tetraploidy and structural anomalies of the chromosomes (2). The two most frequent anomalies sometimes have a paternal origin: Autosomal trisomies stem from non-disjunction during spermatogenesis in 10–20 percent or more of cases (2, 34, 35) and, in monosomy X, the missing chromosome is most often the paternal one (2, 36–38). Moreover, sperm chromosome aneuploidy may play a role in the etiology of recurrent pregnancy loss (39).

The association between paternal age and the risk of specific autosomal trisomies in spontaneous abortions was described in a case-control study (40). In comparison with controls, the mean paternal age was not increased for spontaneous abortions with trisomy 16 (142 cases;  $p = 0.74$ ), the most frequent autosomal trisomy; it was increased by 1.6 year for trisomy 21 (42 cases;  $p = 0.06$ ), the second most frequent autosomal trisomy. The study had 80 percent statistical power to detect a difference of 1 year in mean paternal age between spontaneous abortions with trisomy 16 and controls, but we question whether this large an effect would be expected (to give an order or magnitude, in our study, the mean difference in *maternal* age between spontaneous abortions and livebirths was only 1.4 year). The same study, also, reported no paternal age difference between chromosomally normal spontaneous abortions ( $n = 352$ ) and controls, with a statistical power of 80 percent to detect a mean difference of 0.5 year.

Specific genetic mutations in the embryo may also cause an abortion, and these may be more frequent with increasing male age because of the continuous replication of stem cells after puberty. A number of syndromes due to single base mutations, such as achondroplasia or Apert syndrome, have been shown to originate mostly from mutations in male stem cells and to be more frequent with increasing male age (6).

Our data suggesting that the effect of male age is stronger for first-trimester spontaneous abortions than for those occurring later must be interpreted with caution because of the small number of spontaneous abortions occurring after the first trimester ( $n = 76$ ), only five of which occurred among men aged 35 or more years. Moreover, the interaction test did not support the conclusion that gestational age modified the effect of paternal age as assessed on a multiplicative scale ( $p = 0.25$ ). There is some biologic evidence suggesting that the effect of male age on the risk of spontaneous abortion is stronger for first trimester than second trimester abortions, as supported by our data. Although cytogenetic studies must be viewed cautiously because of a possibly higher rate of failure of karyotyping or unavailability of abortus material for spontaneous abortions occurring at earlier gestational weeks, such studies on

karyotyped abortuses indicate that the proportion of abortuses with chromosomal anomalies is likely to be higher for first trimester than second trimester abortions (2, 3).

In summary, in a cohort study we observed an effect of male age on the risk of spontaneous abortion that was not explained by female age or female behavioral factors, such as consumption of alcohol or tobacco use during pregnancy.

*Note added in proof:* Another cohort study describing the influence of paternal age on the risk of spontaneous abortion and late fetal death was published since the acceptance of our manuscript (41).

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