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Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study

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BACKGROUND: It is well known that miscarriage risk increases with age. However, studies usually investigate only maternal age effects. We investigated both maternal age and paternal age effects on miscarriage risk to provide insight into this frequent reproductive failure. METHODS: The last planned pregnancies (n = 3174) that ended in a birth or miscarriage were analysed in a retrospective population-based study on women aged 25–44 years in Denmark, Germany, Italy and Spain. Maternal and paternal ages were analysed together, using a single variable 'couple age' in a multivariate logistic regression analysis, with couples composed of a woman and a man both aged 20–29 years forming the reference group. RESULTS: After adjustment for various factors (e.g. reproductive history, country), we found that the risk of miscarriage was higher if the woman was aged ⩾35 years, as has already been reported in a number of studies. However, the increase in risk was much greater for couples composed of a woman aged ⩾35 years and of a man aged ⩾40 years. Potential source of bias (especially 'reproductive compensation') are discussed. CONCLUSIONS: The risk of an adverse pregnancy outcome is highest if both partners are advanced in age.

Key words: ageing/fetal death/maternal age/paternal age/spontaneous abortion

Introduction

The proportion of women giving birth after 35 years of age has risen considerably in industrialized countries. In the USA, the birth rate (per 1000) of women aged 35–39 years increased from 19.0 in 1976 to 37.4 in 1998 (Ventura *et al*., 1988; Guyer *et al*., 1999). Over the same period, several studies have concluded that women aged ⩾35 years have a higher frequency of various adverse reproductive events: infertility, spontaneous abortion, pregnancy complications (such as Caesarean section, pre-eclampsia), congenital abnormalities, maternal mortality and perinatal mortality, than do younger women (Schwartz and Mayaux, 1982; Newcomb *et al*., 1991; Nybo Andersen *et al*., 2000).

One of the most frequent adverse reproductive events is spontaneous abortion, with up to 10% of recognized conceptions lost during the pregnancy (Nybo Andersen *et al*., 2000). Most studies concerning the risk factors for spontaneous abortion have concluded that the predominant negative effects are those of advanced maternal age (with a clear increase in risk after 35 years) and previous spontaneous abortion (Leridon, 1976; Regan *et al*., 1989; Coste *et al*., 1991; Fretts *et al*., 1995; Nybo Andersen *et al*., 2000; Osborn *et al*., 2000). Conflicting results have been obtained for other spontaneous abortion risk factors such as maternal consumption of tobacco, maternal psychological problems, interval between pregnancies, or previous use of the contraceptive pill (Risch *et al*., 1988; Coste *et al*., 1991; Dominguez *et al*., 1991). Thus most of these studies analysed the effect of female factors on spontaneous abortion. Male factors may also affect spontaneous abortion risk, but have been little analysed. Most studies on male factors have focused on the effect of professional exposure of the man to toxic substances (such as ethylene oxide, rubber chemicals, solvents, thiocarbamates, carbaryl) on spontaneous abortion risk in his partner (Lindbohm *et al*., 1991; Savitz *et al*., 1997). Paternal age has only rarely been considered: only five studies (published before 1980) have investigated the risk of spontaneous abortion according to both maternal and paternal age (Yerushalmy, 1939; Warburton and Fraser, 1964; Woolf, 1965; Resseguie, 1976; Selvin and Garfinkel, 1976). Four of these studies analysed medical certificates for fetal deaths occurring after 20 weeks gestation (Yerushalmy, 1939; Woolf, 1965; Resseguie, 1976; Selvin and Garfinkel, 1976). Three of these four studies concluded that paternal age had an effect, after adjusting for maternal age (Yerushalmy, 1939; Woolf, 1965; Selvin and Garfinkel, 1976); the fourth did not (Resseguie, 1976). However, only one of these studies used a multivariate model to take

confounding effects into account but, unfortunately, in this model, the effect of age was assumed to be linear (Selvin and Garfinkel, 1976). A fifth study analysed the risk of spontaneous abortion in mothers with a child presenting a possible genetic defect (Warburton and Fraser, 1964). Using a multiple regression model, the authors were unable to assess the relative effects of paternal and maternal age. However, they suggested that paternal age had a greater effect than maternal age.

We addressed the question of an effect of paternal age on the risk of miscarriage by studying data recorded in the European Multicenter Study on Infertility and Subfecundity conducted between 1991 and 1993, which took the couple as the unit of analysis although only the women were interviewed. We studied maternal and paternal ages together, using a single categorical variable, 'couple age', in a multivariate model of miscarriage risk.

Materials and methods

The data used in this study are from the retrospective European Study of Infertility and Subfecundity, conducted between August 1991 and February 1993. Fourteen population-based samples of women aged 25–44 years were randomly selected from census registers and electoral rolls in towns in Denmark, Germany, Italy and Spain. The same protocol and questionnaire were applied to all samples. The questionnaire was developed in English, translated into national languages and then translated back into English to check the translations. The aim of the European Study of Infertility and Subfecundity was to evaluate the frequency of, and risk factors for, subfecundity and infertility in these countries. The 'unit of analysis' was the couple, although only women were questioned, by trained women, in a personal interview lasting 30–90 min. Questions concerned sociodemographic characteristics (male and female), reproductive history, time taken to achieve the first and last pregnancies other than those ending in induced abortion, use of contraception, the seeking of medical advice by couples with fertility problems, recent occupational exposures and working conditions of the man and woman and the lifestyle (alcohol and coffee consumption) of the man and woman.

We analysed last planned pregnancies ending in miscarriage or birth. We excluded other causes of death (induced abortion, ectopic pregnancy, stillbirth and death within 7 days following the birth), which may have aetiologies other than miscarriage. We also excluded pregnancies that were not completed at the time of interview. We restricted our analysis to planned pregnancies, as unplanned pregnancies ending in induced abortion may be declared by the woman as a miscarriage. Moreover, in the case of unplanned pregnancy, the notion of 'time to pregnancy' is meaningless.

Constitution of age classes

Previous studies (Coste *et al*., 1991; Nybo Andersen *et al*., 2000; Osborn *et al*., 2000) have shown no significant effect of maternal age on spontaneous abortion between the ages of 20 and of 29 years. We therefore used the 20–29 year age group as the reference for both women and men. As we had very few couples including a woman or man aged <20 years and as we were interested in the effects of ageing, we decided to exclude these younger couples. For couples aged ⩾30 years, we stratified data into 5 year classes. As we found only 20 women aged ⩾40 years and 61 men aged ⩾45 years, we pooled these 'older' individuals with the previous age group and so the oldest age group was 35–44 years for women and 40–64 years for men. Thus, maternal age was divided into three age classes: 20–29 (reference age group), 30–34 and 35–44 years; and paternal age was divided into four age classes: 20–29 (reference age group), 30–34, 35–39 and 40–64 years. Maternal and paternal ages were significantly correlated ($r = 0.64$, $P < 0.0001$). As a result of this correlation, analysis of maternal age and paternal age in the same multivariate model posed problems of colinearity. To deal with this, we defined a new variable, 'couple age', combining the three maternal age groups with the four paternal age groups. We defined a total of 12 classes for this variable 'couple age' (presented in Figure 1a). The 'couple age' variable made it possible to study maternal and paternal ages.

The potential confounding factors considered included the country (Denmark, Germany, Spain, and Italy); the time to pregnancy (TTP, classed as 'TTP <6 months', '6 to <12 months' and 'TTP ⩾12 months'); the smoking habits of the woman and of the man (recorded as 'yes/no' responses: the woman/the man smoked/did not smoke at the time they started having intercourse without using birth control); the past reproductive history of the woman recorded by four dichotomous variables: number of the pregnancy (= 1/>1), history of miscarriage (yes/no), history of ectopic pregnancy (yes/no), history of induced abortion (yes/no).

We carried out unadjusted and adjusted logistic regression analyses (using SAS®) according to the various risk factors for miscarriage. We tested goodness of fit by the Hosmer–Lemeshow test (Hosmer and Lemeshow, 1989).

Results

The European Study of Infertility and Subfecundity included 6188 women. Of these, we first excluded 2958 subjects because they did not satisfy analysis inclusion criteria: women who had never been pregnant ($n = 1518$); women whose pregnancies had all ended in induced abortion ($n = 226$); women whose last pregnancy was not a miscarriage or a live birth, i.e. the last pregnancy was ectopic ($n = 55$), a stillbirth ($n = 16$), a death within 7 days ($n = 8$), or was not yet completed ($n = 204$); the last pregnancy was unplanned ($n = 879$); the woman or her partner was <20 years of age ($n = 52$). Another 56 subjects were excluded because of missing data. The remaining 3174 pregnancies constituted the study population, for which 4.9% ended in a miscarriage. The characteristics of the study population [number/percentage/unadjusted odds ratio (OR)] are shown in Table I: this population consisted predominantly of couples composed of a woman and a man both aged 20–29 years (32.0%) who took <6 months (70.2%) to achieve a pregnancy that was not the first (69.3%).

We analysed age effect by estimating OR with logistic regression and assessed the goodness of fit of our model by the Hosmer–Lemeshow test ($P = 0.76$). Table II shows the adjusted miscarriage OR for the 12 couple-age classes (taking couples of women and men both 20–29 years old as the reference group), country, number of the pregnancy, TTP, female and male smoking, history of miscarriage, history of ectopic pregnancy and history of induced abortion. The results for the couple-age classes of Table II are also

(a) Number of couples in the twelve classes

Paternal age	Maternal age 20-29 years	30-34 years	35-44 years
20-29 years	1016	77	10
30-34 years	719	474	32
35-39 years	169	302	150
40-64 years	46	82	97

(b) Adjusted odds ratios and 95% confidence intervals of the twelve couple-age classes

Paternal age	Maternal age 20-29 years	30-34 years	35-44 years
20-29 years	1.00 (reference)	1.72 (0.62, 4.74)	9.18 (1.80, 46.66)
30-34 years	1.06 (0.61, 1.86)	1.62 (0.93, 2.82)	3.87 (1.24, 12.02)
35-39 years	1.31 (0.56, 3.07)	1.06 (0.52, 2.17)	3.38 (1.76, 6.47)
40-64 years	1.80 (0.52, 6.24)	2.90 (1.26, 6.67)	6.73 (3.50, 12.95)

(c) Adjusted odds ratio and 95% confidence intervals of the three couple-age zones

Paternal age	Maternal age 20-29 years	30-34 years	35-44 years
20-29 years	*standard risk zone*		*high risk zone*
30-34 years	**1.00 (reference)**		**2.87 (1.86, 4.45)**
35-39 years			
40-64 years		*high risk zone*	*highest risk zone* 5.65 (3.20, 9.98)

Logistic-regression analyses were adjusted for country, number of the pregnancy, time to pregnancy, female smoking, male smoking, history of miscarriage, history of ectopic pregnancy, history of induced abortion

Figure 1. Couple age in the study of miscarriage risk, European Study on Infertility and Subfecundity, 1991–1993 (n = 3174).

presented visually in Figure 1a. There was a significant increase in the risk of miscarriage if the woman was 30–34 years of age and the man was 40–64 years of age, or if the woman was 35–44 years of age, whatever the age of the man. This increase was much more marked for couples composed of a woman aged ⩾35 years and of a man aged ⩾40 years: for these couples the OR was 6.73 [95% confidence interval (CI): 3.50–12.95], versus 3.38 (95% CI: 1.76–6.47) for couples composed of a woman aged ⩾35 years and of a man aged 35–39 years. The OR for couples composed of a woman aged ⩾35 years and of a man aged 20–29 years was also high (OR = 9.18) but this was probably due to the small number of couples in this group (n = 10), the confidence interval being very large (95% CI: 1.80–46.66). To summarize these trends, we regrouped couple-age classes according to the OR obtained in Table II (and reported in Figure 1b) into three 'zones' (Figure 1c): 'standard zone' (no significant increase in miscarriage risk), 'high zone' (significant increase in miscarriage risk), and 'highest zone' (major increase in miscarriage risk). Figure 1c shows the adjusted miscarriage OR for these three couple-age zones: the risk of miscarriage was significantly higher in the zones of 'high' (OR: 2.87; 95% CI: 1.86–4.45) and 'highest' (5.65; 3.20–9.98) risk than in the 'standard risk' zone (Figure 1c). The OR was also significantly higher in the 'highest risk' zone (1.97; 1.03–3.77) than in the 'high risk' zone.

The frequency of miscarriage (Table II) was also significantly higher if TTP was between 6 and 12 months (OR: 2.27; 95% CI: 1.44–3.60) or >12 months (2.33; 1.58–3.43). A history of miscarriage (2.29; 1.53–3.42) and a history of ectopic pregnancy (3.98; 1.42–11.18) were also linked to miscarriage. No increase in miscarriage risk was associated with country, number of the pregnancy, female and male smoking and history of induced abortion.

Discussion

Analysis of the last pregnancy outcome for 3174 women interviewed in a large European study showed a clear effect

Table I. Characteristics of the study population used for analysis of miscarriage risk, European Study on Infertility and Subfecundity, 1991–1993 (n = 3174)

Variable		No.	%	Crude OR (95% CI)
Couple age (years)				
Maternal	Paternal			
20–29	20–29[a]	1016	32.0	
20–29	30–34	719	22.7	1.05 (0.61, 1.82)
20–29	35–39	169	5.3	1.37 (0.60, 3.17)
20–29	40–64	46	1.5	2.22 (0.65, 7.54)
30–34	20–29	77	2.4	2.21 (0.83, 5.85)
30–34	30–34	474	14.9	1.77 (1.03, 3.03)
30–34	35–39	302	9.5	1.20 (0.60, 2.42)
30–34	40–64	82	2.6	3.44 (1.53, 7.74)
35–44	20–29	10	0.3	7.94 (1.62, 38.96)
35–44	30–34	32	1.0	4.54 (1.50, 13.73)
35–44	35–39	150	4.7	4.06 (2.19, 7.54)
35–44	40–64	97	3.1	7.74 (4.18, 14.33)
Country				
Denmark[a]		527	16.6	
Germany		858	27.0	1.13 (0.68, 1.84)
Spain		471	14.9	0.88 (0.48, 1.63)
Italy		1318	41.5	1.14 (0.71, 1.84)
Pregnancy rank				
1[a]		974	30.7	
>1		2200	69.3	1.33 (0.92, 1.93)
Time to pregnancy				
<6 months[a]		2227	70.2	
6 to <12 months		375	11.8	2.37 (1.52, 3.69)
⩾12 months		572	18.0	2.71 (1.87, 3.92)
Woman smoking				
No[a]		1879	59.2	
Yes		1295	40.8	1.27 (0.92, 1.76)
Man smoking				
No[a]		1318	41.5	
Yes		1856	58.5	1.10 (0.79, 1.53)
History of miscarriage				
No[a]		2671	84.2	
Yes		503	15.8	2.37 (1.65, 3.39)
History of ectopic pregnancy				
No[a]		3142	99.0	
Yes		32	1.0	3.69 (1.40, 9.73)
History of induced abortion				
No[a]		2879	90.7	
Yes		295	9.3	1.76 (1.11, 2.79)

[a]Reference group.
OR = odds ratio; CI = confidence interval.

of maternal age and paternal age on the risk of miscarriage, with three trends, as shown in Figure 1c. If the woman was 20–29 years old, the risk of miscarriage was not significantly high whatever the age of the man. If the woman was 30–34 years old, the risk of miscarriage was higher if the man was aged ⩾40 years. If the woman was aged ⩾35 years, the risk of miscarriage increased whatever the age of the man. However, if the woman was aged ⩾35 years and the man was aged ⩾40 years, the risk of miscarriage was substantially higher with an OR of 1.97 (1.03, 3.77) when comparing the 'highest' and the 'high' risk zones (Figure 1c). We checked that our results were not due to the inclusion of the oldest individuals (⩾40 years old for women and ⩾45 years old for men) by restricting our analysis to women aged 20–39 years and to men aged 20–44 years. When doing this, similar results were obtained. In addition, there may be a residual confounding effect between maternal and paternal ages: in one age class, the women were 1 year older on average if the man was 40–64 years old than if the man was 20–29 years old. For example, in the class in which the women were 35–44 years old and the men were 20–29 years old, the mean age of the women was 36.4 years whereas in the class in which the women were 35–44 years old and the men were 40–64 years old, the mean age of the women was 37.1 years. However, we estimated that this residual confounding effect could not account for the large increase in miscarriage risk for couples composed of a woman aged ⩾35 years and of a man aged ⩾40 years. We recognize that studying age in large classes (⩾5 years) limits the analysis to threshold effects only (Figure 1) and that age probably has a much less clear-cut effect, having a gradual deleterious impact. Our analysis was also limited by the small numbers in some age groups (especially for couples composed of a

Table II. Adjusted associations of couple-age classes with pregnancy outcome (miscarriage/live-birth), European Study on Infertility and Subfecundity 1991–1993 (n = 3174)

Variable		Adjusted OR (95% CI)
Couple age (years)		
Maternal	Paternal	
20–29	20–29[a]	
20–29	30–34	1.06 (0.61, 1.86)
20–29	35–39	1.31 (0.56, 3.07)
20–29	40–64	1.80 (0.52, 6.24)
30–34	20–29	1.72 (0.62, 4.74)
30–34	30–34	1.62 (0.93, 2.82)
30–34	35–39	1.06 (0.52, 2.17)
30–34	40–64	2.90 (1.26, 6.67)
35–44	20–29	9.18 (1.80, 46.66)
35–44	30–34	3.87 (1.24, 12.02)
35–44	35–39	3.38 (1.76, 6.47)
35–44	40–64	6.73 (3.50, 12.95)
Country		
Denmark[a]		
Germany		1.22 (0.71, 2.09)
Spain		1.18 (0.61, 2.27)
Italy		1.35 (0.81, 2.26)
Pregnancy rank		
1[a]		
>1		0.84 (0.54, 1.31)
Time to pregnancy		
<6 months[a]		
6 to <12 months		2.27 (1.44, 3.60)
⩾12 months		2.33 (1.58, 3.43)
Woman smoking		
No[a]		
Yes		1.27 (0.90, 1.79)
Man smoking		
No[a]		
Yes		1.09 (0.77, 1.56)
History of miscarriage		
No[a]		
Yes		2.29 (1.53, 3.42)
History of ectopic pregnancy		
No[a]		
Yes		3.98 (1.42, 11.18)
History of induced abortion		
No[a]		
Yes		1.56 (0.93, 2.63)

[a]Reference group.
OR = odds ratio; CI = confidence interval.

woman aged ⩾35 years and of a man aged 20–29 years or 30–34 years).

Several studies have shown an increase in the risk of spontaneous abortion in women aged ⩾35 years (Dominguez *et al*., 1991; Nybo Andersen *et al*., 2000; Osborn *et al*., 2000). Multiple regression analysis in a cross-sectional unmatched case–control study (Dominguez *et al*., 1991) has shown that maternal age begins to have an effect only after the age of 35 years. Our results are consistent with this conclusion but, taking paternal age into account, we found that (i) if the man was ⩾40 years of age, maternal age began to have a negative effect earlier, from the age of 30 years; (ii) if the man was ⩾40 years of age, the increase in miscarriage risk was much higher if the woman was aged ⩾35 years. In previous studies, the effect of paternal age has rarely been analysed. The most relevant study (Selvin and Garfinkel, 1976) assessed, in a multivariate logistic model, the risk of spontaneous abortion based on $>1.5\times10^6$ birth and fetal death certificates recorded in New York State from 1959 to 1967. The authors concluded that maternal and paternal ages have effects of similar significance. However, in their logistic model, they considered that maternal and paternal age effects were linear, a controversial assumption: reproductive age patterns are usually represented as J- or U-shaped curves (Nybo Andersen *et al*., 2000). We used a more appropriate methodological approach and found a clear negative effect of paternal age after 40 years.

Various hypotheses have been put forward to account for the increase in adverse reproductive outcomes with age. In women, a link between increasing age and a higher incidence of chromosomal abnormality has been established (Boue *et al*., 1975; Cowchock *et al*., 1993). However, conflicting conclusions have been drawn concerning the possible effect of age on oocyte quality and uterus senescence (Levran *et al*., 1991; Abdalla *et al*., 1993; Cano *et al*., 1995). In men, studies using a fluorescence in-situ hybridization approach have suggested that the probability of producing aneuploid offspring is higher for older fathers (⩾50 years old) than for younger fathers (<30 years old) (Griffin *et al*., 1995). A recent paper comparing men aged 23–39 years with men aged 59–74 years also concluded that there was a higher frequency of sperm chromosome aberrations in older men (Sartorelli *et al*., 2001). These results are presumably related to the higher risk of birth defects in the offspring of older fathers, especially for those linked to new dominant mutations (Penrose, 1955; Savitz *et al*., 1991; McIntosh *et al*., 1995), giving a general pattern of increasing relative risk of adverse reproductive outcomes with paternal age. This paternal age effect led to fixing of the upper age limit for semen donors at 40 years (Bordson and Leonardo, 1991). In addition, if sexual activity declines with male age, this may lead to an increase in the risk of miscarriage linked to fertilization of an 'old' (time elapsed between ovulation and fertilization) oocyte (Guerrero and Rojas, 1975). However, this hypothesis is controversial (Gray *et al*., 1995).

Our study confirmed the importance of a history of miscarriage, a well-documented miscarriage risk factor (Leridon, 1976; Risch *et al*., 1988; Regan *et al*., 1989; Coste *et al*., 1991). In this study, a history of ectopic pregnancy was also a risk factor for miscarriage, consistent with the results of other studies (Honore, 1979; Coulam *et al*., 1989; Fedele *et al*., 1989). We also found that the risk of miscarriage was significantly higher for couples taking ⩾6 months to conceive. This association between a long time being required for conception and a higher risk of miscarriage is less well documented, and has been reported in some studies (Tietze *et al*., 1950; Rachootin and Olsen, 1982; Strobino *et al*., 1986; Schaumburg and Boldsen, 1992; Baird *et al*., 1993; Joffe and Li, 1994; Hakim *et al*., 1995; Gray and Wu, 2000). In retrospective studies, reproductive outcome observations depend on the statement of the woman, and subclinical abortions are completely omitted. As estimates of the subclinical abortion rate range from 8 to 78% (Wilcox *et al*., 1988; Modvig *et al*., 1990;

Zinaman *et al*., 1996), these unnoticed spontaneous abortions may be an important factor in the time to conception declared by women. The observed higher miscarriage risk in couples taking longer to conceive may be due partly to an association with subclinical abortions. The three risk factors found in our analysis suggest that there may be a common cause for such different adverse reproductive events: delay in conception, ectopic pregnancy, miscarriage, and perhaps also infertility. This notion of the same 'key reproductive disorder' giving 'various adverse reproductive outcomes' requires further investigation.

Bias and limits

The data were collected from retrospective declarations by the women, so two limitations must be considered concerning pregnancy outcomes. First, it has been estimated that only three-quarters of spontaneous abortions are recalled in this type of study (Wilcox and Horney, 1984), but, as our analysis concerned the outcome of the last pregnancy, women were probably less likely to have forgotten. Second, the notion of miscarriage was not precisely defined, as it would have been in medical data. Women may have been confused to some extent concerning the type of death. However, data were collected by means of interviews by trained women who could help women to differentiate between the types of deaths if needed. Induced abortion may also have been declared as miscarriage (Simonds *et al*., 1998; Houzard *et al*., 2000). We restricted our analysis to planned pregnancies to limit this possible bias. Furthermore, the frequency of miscarriage observed in our study (4.9%) is consistent with that of ~5–6% reported in other studies of last pregnancy outcomes (Weinberg *et al*., 1994). This is about half that for first pregnancies, which is 10–15% (Weinberg *et al*., 1994). As suggested by Weinberg *et al*., such a low rate for last pregnancies may reduce the statistical power of the study (Weinberg *et al*., 1994). The low miscarriage rate for last pregnancy outcomes is due to the couple's attitude: couples tend to 'replace' a miscarriage by another pregnancy until they achieve a live birth (a phenomenon called 'reproductive compensation'). The chance of succeeding in replacing a miscarriage depends on the time required to conceive. It had been concluded that this time could increase with maternal age and paternal age (Ford *et al*., 2000) but this age effect was later called into question (Sallmen and Luukkonen, 2001). Such factors may result in overestimation of the couple-age effect in our analyses. However, our results on age effect in the 'high-risk zone' (OR = 2.87) are consistent with those of other studies on maternal age. For example, an OR of 3.13 (95% CI: 1.56, 6.26) was found for women aged ⩾35 years in a cross-sectional case–control study (Dominguez *et al*., 1991). We thus observed no major age overestimation for these ages linked to the analysis of last pregnancies. We planned to adjust for the effect of a possible 'replacement attitude' by studying first pregnancy outcomes; 10.5% of first pregnancies ended in miscarriage in the European Study of Infertility and Subfecundity. However, first pregnancy outcomes were not suitable for analysing the age effect because nearly all the couples concerned were young (for first pregnancies, 96.5% of couples were in the 'standard risk' zone in Figure 1c, 2.6% in the 'high risk' zone and 0.9% in the 'highest risk' zone).

Finally, the multicentre European study was carried out in urban areas. However, in our opinion, there is little or no difference between rural and urban areas because no conclusive results have been produced concerning this issue (Hemminki and Forssas, 1999).

In summary, we demonstrate here the importance of taking into account both maternal and paternal age to measure miscarriage risk: if the woman is ⩾35 years of age and the man is ⩾40 years of age, the risk of miscarriage is substantially higher than for couples of other age combinations. The idea of major reproductive risk for couples combining negative male and female factors has already emerged in studies of couples seeking medical advice (Emperaire *et al*., 1982; Spira, 1986; Thonneau *et al*., 1991). Thus, a French multicentre survey conducted in 1988–1989 on couples who consulted a doctor for infertility showed that in 39% of cases, both the man and the woman presented reproductive disorders and concluded that 'infertility is essentially a 'couple's business'' (Thonneau *et al*., 1991). More generally, this work raises questions concerning the level of miscarriage risk for couples in assisted reproduction programmes: the decline in assisted reproduction success rate with the age of the woman is well known (Rosenwaks *et al*., 1995). In Australia, 26% of the women who became pregnant by IVF procedures during the 1979–1986 period were ⩾35 years of age. Among these women, the rate of spontaneous abortion was 34.8 versus 21.5% among women aged <35 years (Saunders and Lancaster, 1989). In the USA, 8.4% of the women who became pregnant by IVF procedures during 1991 were ⩾40 years of age. For these women, the rate of spontaneous abortion was 33.9 versus 18.6% among women aged <40 years (American Fertility Society, 1993).

In conclusion, older couples (and especially those asking for assisted reproduction), i.e. couples composed of a woman aged ⩾35 years and of a man aged ⩾40 years, should be informed that they have a high risk of miscarriage. The importance of investigating the paternal age effect was pointed out by R.Jeffrey Chang, MD, President of ASRM at the 2000 annual meeting: ''The impact of age on reproductive health is a vital issue for the 21st Century. We have known that age was an important factor for women's reproductive health. The question of declining fertility as men age is an important one that needs additional research to resolve''.

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