Late paternity and stillbirth risk

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BACKGROUND: The role of paternal ageing on the incidence of some genetic diseases in offspring depends on the hypothesis that spontaneous mutations accumulate due to continuous cell divisions during spermatogenesis. We examined the effect of paternal age on the complex multifactorial character, stillbirth. METHODS: In 3619647 Italian singletons born in 1990–1996 we evaluated stillbirth risk as a function of paternal ageing by means of multiple logistic regression models, which included maternal age and family education, as categorical covariates and interactions. The categorical risk was estimated for mothers and fathers beyond threshold ages of 35 and 40 years, respectively. RESULTS: Stillbirth risk increases with paternal ageing in mothers $\geq$ 30 years old, and maternal age and family education modify the impact. In families with low education, the risk accounts for odds ratio (OR) 1.015 [95% confidence interval (CI) 1.01–1.02] in mothers aged 30–34 years, and for OR 1.032 (95% CI 1.02–1.04) in mothers aged $\geq$ 35 years; in families with higher education the risk accounts for OR 1.008 (95% CI 1.00–1.02) and OR 1.025 (95% CI 1.01–1.04), respectively, in mothers aged 30–34 and $\geq$ 35 years. In these latter families, for mothers aged <35 and fathers $\geq$ 40 years the risk accounts for OR 1.12 (95% CI 1.00–1.25).

CONCLUSIONS: The effect of paternal ageing on stillbirth risk is revealed in mothers aged $\geq$ 30 years and is modified by family education. In mothers aged 30–34 years from families with high education, the increase imputable to paternal ageing might be indicative of a genetic component.

Key words: delayed childbearing/paternal age/maternal age/pregnancy outcome/risk at birth

Introduction

The role of maternal age on pregnancy outcome has been widely examined from a medical and epidemiological point of view, both in general and in relation with specific pathologies, in so far as that female ageing per se induces an overall reduction in the chance of bearing a child, and in particular a healthy child (Cnattingius et al., 1992; Fretts et al., 1995; Bianco et al., 1996; Dollberg et al., 1996; Breart, 1997; Faden et al., 1997; Horta et al., 1997; Tarin et al., 1997; Gilbert et al., 1999; Pattenden et al., 1999; Astolfi and Zonta, 2002). The role of paternal age has been less extensively studied, although as early as 1912 a genetic component in the effect of advanced age was hypothesized by Weinberg (1912), who suggested that sporadic cases of achondroplasia could be associated with paternal ageing, and subsequently by Haldane (1947), who inferred a higher mutation rate in males than in females.

Sporadic cases of some monogenic diseases due to single base substitutions, like achondroplasia, osteogenesis imperfecta, and Apert, Crouzon and Pfeiffer syndromes, have been found to be prevalently of paternal origin, and in some cases a sharply increased incidence with increasing paternal age has been observed (Risch et al., 1987; Carlson et al., 1994; Moloney et al., 1996; Bunin et al., 1997; Wilkin et al., 1998; Blumsohn et al., 2001).

The association between paternal ageing and the increase in the incidence of genetic diseases may be explained by the high number of germ cell duplications: if 23 duplications per year are assumed, divisions increase from 150 at the age of 20 years, to 610 at 40 years and to 840 at 50 years (Vogel and Ratnerberg, 1975; Drost and Lee, 1995). In consequence, genetic load in the male germ line is expected to increase for the accumulation of point mutations owing to replication errors and reduced activity of repair enzymes (Crow, 1997; 2000), length mutations, strand mispairing in short tandem repeats (Leeflang et al., 1999; Cummings and Zoghbi, 2000) and a longer exposure to environmental mutagens (Allen et al., 1995; Thomas, 1996).

Harmful mutations, even with mild deleterious effects, might influence monogenic as well as complex polygenic traits so as to affect progeny survival and health. Recently, it has been observed that paternal ageing enhanced the risk of some complex multifactorial pathologies, such as schizophrenia, preeclampsia, Alzheimer’s disease and miscarriage (Bertram et al., 1998; Esplin et al., 2001; Malaspina et al., 2001; 2002; de La Rochebrochard and Thonneau, 2002; Harlap et al., 2002; Slama et al., 2003).

The problem of late reproduction has become especially important during the last decade, when socioeconomic and cultural changes have driven Western populations to very...
low levels of fertility and led to postponement of child bearing to advanced age (Fretts et al., 1995; Gosden and Rutledge, 1995; Breart, 1997). Consequently, the evaluation of neonate mortality and morbidity risk in relation to parental ageing has assumed greater relevance from a biological, as well as a sociodemographic and personal, point of view. The importance of delaying childbearing to an advanced age has previously been examined in the Italian population, and the risk of unfavourable pregnancy outcomes has been estimated as a function of maternal ageing (Astolfi et al., 1999; Astolfi and Zonta, 2002).

The aim of this paper was to examine the effect of paternal ageing on a complex multifactorial character, stillbirth, after adjustment for maternal age and family education. It is expected that among young mothers who live in highly educated families, where the role of biological and environmental factors on pregnancy impairment may be greatly reduced, the stillbirth risk, possibly associated with late paternity, calculated factors on pregnancy impairment may be greatly reduced, the stillbirth risk, possibly associated with late paternity, could be indicative of a genetic component linked to ageing.

Materials and methods

Data are derived from the birth records of the Italian Istituto di Statistica (ISTAT) and cover the period 1990–1996. In order to avoid possible confounding factors, from the 3,854,450 births that occurred in Italy during this period, we selected 3,619,627 singletons born to parents aged ≥20 years. Babies with a gestational age <26 weeks were excluded since, according to the ISTAT definition, only fetal deaths that occur after completion of the 26th week of gestation are recorded as stillbirths.

Family educational level was coded in two classes: low, corresponding to the present Italian compulsory education of both parents (≤8 years schooling); and high, corresponding to the secondary school diploma or university degree of at least one parent. It should be noted that a low educational level is usually assumed to be a reliable indicator of unfavourable socioeconomic conditions.

Maternal age was grouped in four classes of 5-year intervals, with the last class grouping mothers ≥35 years; paternal age was considered in 1-year interval classes, ranging from 20 to 86 years.

Through multiple logistic regression analyses the response variable stillbirth risk [Prob(stillbirth)/Prob(livebirth)] was studied as a linear function of the quantitative variable paternal age (F_i; i = 20, 86), the categorical variables maternal age (M_j; j = 1, 4) and family education (E_k; k = 1, 2), and the interactions F*M, F*E, M*E and F*M*E. Models that included paternal age as the explanatory factor. The expected stillbirth rates are reported in Table I, evaluated by paternal and maternal age classes, after stratification by educational level, since the impact of ageing is expected to be modified by the recourse to medical care, which family education can modulate.

The role of paternal ageing on stillbirth risk was evaluated by means of multiple logistic regression models, which included maternal age and family education, as categorical covariates and interactions. The simplest model that best fitted the data included the linear effect of paternal ageing, maternal age and education, and the M*E and F*M interactions (Table II). Maternal age ≥30 years and low education are per se significant risk factors, and moreover, education modifies the effect of the mother, as shown by the E*M interaction. Paternal ageing per se does not show a significant effect, but, as is shown by the F*M interaction, changes by maternal age class, so that the risk increases slightly in mothers aged 30–34 years and more clearly in mothers ≥35 years.

After stratification by educational level and maternal age class, the quantitative effect of paternal ageing was evaluated through logistic regression applied to a linear model with paternal age as the explanatory factor. The expected stillbirth rates are reported in Figure 1. Better education always reduces mortality at birth, but in both education levels paternal ageing does not significantly change the risk in young mothers (<30 years). In mothers aged 30–34 years case (Risch et al., 1987; Crow, 1997; 2000). Interactions were tested by fitting models with and without each single interaction, and the simplest model was chosen (Clayton and Hills, 1995).

The critical ages, 35 years for mothers and 40 years for fathers, were used as threshold values to estimate the relative stillbirth risk [odds ratio (OR) (95% CI) after stratification by family education (low versus high).

Statistical analyses were performed using the programs SPSS 12 and SAS version 6.12.

Results

During the period 1990–1996, the average age at childbirth was 29.1 years for mothers and 32.5 years for fathers. Late paternity, at or beyond 40 years, was not a rare event: it occurred in ~11% of the births, which is over 386,000 neonates, of which ~40% were born to mothers <35 years old. During this period, the overall stillbirth rate accounted for 0.44%, corresponding to ~16,000 babies. The frequencies and rates are reported in Table I, evaluated by paternal and maternal age classes, after stratification by educational level, since the impact of ageing is expected to be modified by the recourse to medical care, which family education can modulate.

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the risk increases slightly with paternal ageing, and accounts for OR 1.008 (1.00–1.02) in highly educated families and for OR 1.015 (1.01–1.02) in the poorly educated ones. In mothers aged $\geq 35$ years, the effect is OR 1.025 (1.01–1.04) and OR 1.032 (1.02–1.04) in highly and poorly educated families, respectively.

When the age effect was categorically investigated and the threshold ages of 40 years for the fathers and 35 years for the mothers were considered, we observed that fathers aged $\geq 40$ years always contribute to increase stillbirth risk compared with their younger counterparts (Table III). However, the lowest risk, at the significance limit [OR 1.12 (1.00–1.25)], occurs in young mothers ($< 35$ years) of highly educated families, while in the older mothers ($\geq 35$ years) and/or in poorly educated families, a similar increase in the risk is observed, ranging from 23% to 29%.

**Discussion**

Paternity at advanced age is not a rare event, and it has been increasing during the last two decades, at least partly driven by the tendency of the woman to delay childbearing. In Italy during the recent period under study (1990–1996), the percentage of fathers aged at least 40 years old has increased from 9.5% to 12.4%, and the percentage of fathers $\geq 45$ years old from 2.4% to 3.3%. However, only the role of paternal age has been widely examined. It has been found to increase the incidence of adverse pregnancy outcomes, although its relative weight can be highly modified by some pathologies, such as preeclampsia and subfertility status, life style (e.g. smoking or alcoholism), and/or fetus and family conditions (e.g. birth order and socioeconomic level) (Faden et al., 1997; Horta et al., 1997; Pattenden et al., 1999; Jolly et al., 2000; Alfirevic et al., 2002; Astolfi and Zonta, 2002; Goldenberg and Thompson, 2003).

Stillbirth is a complex event with multiple aetiologies, even after the exclusion of complications during pregnancy and labour, like defective placental maturation and asphyxia, and maternal pathologies, like diabetes, hypertension, thrombophilia and acquired infections (Stallmach et al., 2001; Alfirevic et al., 2002; Kramer et al., 2002; Kupferminc et al., 2002; Goldenberg and Thompson, 2003; Kunzel and Misselwitz, 2003; Rai, 2003). When, for the large amount of the examined data coming from the National Vital Statistics, the weight of pathological factors can be ignored and some relevant covariates (maternal age and education) are controlled for, a genetic component may be hypothesized in the defective growth and maturation of the fetus, in addition to congenital anomalies.
which are continuously increasing in importance (Kramer et al., 2002; Kunzel and Misselwitz, 2003).

We studied the stillbirth risk as a quantitative linear function of paternal ageing. A quantitative effect, continuously cumulating with ageing, can be expected on the basis of the underlying genetic hypothesis, although slight and therefore difficult to reveal. Unlike what has been reported for specific genetic diseases (Risch et al., 1987; Crow, 1997; 2000), the linear model showed the best fit in comparison with exponential or power models. The effect of paternal ageing was found to be modified by maternal age and family education (Table II; Figure 1). Even when mothers live in highly educated families, where consciousness in facing pregnancy and recourse to antenatal care can be assumed, paternal ageing gradually increases the risk (OR 1.02; \( P < 0.001 \)). However, the effect is restricted to mothers aged \( \geq 30 \) years, being OR 1.01 in mothers aged 30–34 years and OR 1.03 in mothers aged \( \geq 35 \) years (Figure 1). The effect of paternal ageing was not revealed among young mothers <30 years old. The finding should be supported by further investigations aimed at excluding a possible artefact due to the low frequency (5.8%) of babies born to mothers aged <30 years and to fathers \( \geq 35 \) years. However, when the threshold ages of 35 and 40 years for mothers and fathers, respectively, are considered, even in young mothers (<35 years) the relative risk for fathers \( \geq 40 \) years accounts for OR 1.12 (Table III).

We are conscious that one of the limits of the analysis resides, in addition to the reduced number of the considered explanatory covariates, in their coding criteria. Although maternal education is widely considered to be among the most reliable predictors of the fetal health, we considered the education of the family on the assumption that awareness of problems during pregnancy and the consequent recourse to advanced prenatal care can be enhanced by a high level of education in at least one parent. Ageing was assumed to impair fetal health, and the paternal and maternal effects were examined in 1- and 5-year intervals, respectively. The risk was also evaluated contrasting mothers \( > 35 \) years old and fathers \( > 40 \) years old with their younger counterparts. Such ages are generally accepted as critical thresholds, because of the strong increase in the risk of specific neonatal and maternal pathologies, miscarriage and problems during delivery (Risch et al., 1987; Cnattingius et al., 1992; Fretts et al., 1995; Tarin et al., 1997; de La Rochefrochard and Thonneau, 2002; Slama et al., 2003).

The aim of this study was to find a possible cumulative effect of paternal ageing on stillbirth risk, and the hypothesis appears to be supported in mothers aged \( \geq 30 \) years. When the most favourable conditions are present, i.e. in mothers aged 30–34 years living in highly educated families, the 5% increase of the stillbirth risk every 5 years of paternal ageing might be indicative of a genetic paternal contribution, associated with an accumulation of harmful mutations.

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References


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