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Several studies have suggested that preterm delivery is related to a risk of subsequent ischaemic heart disease (IHD) in the mother. We conducted a nested case–control study in the E3N cohort to assess the association between preterm delivery of a first child and IHD, and the effect of major cardiovascular risk factors on this association. The study included 109 cases and 395 controls. Mothers who had preterm delivery were at an increased risk of IHD [multivariate hazard ratio 2.09 (95% confidence interval 1.07–4.09)]. This association was independent of major cardiovascular risk factors.

Keywords: case–control study, myocardial ischaemia, premature birth

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Introduction

Since Barker's workgroup [1] brought out the fetal origins of the coronary heart disease hypothesis, many studies have linked intrauterine growth restriction and an increased risk of ischaemic heart disease (IHD) in later life. Some workers have focused on the links between adverse pregnancy outcomes and the mother's risk of IHD, and there is growing evidence that events related to pregnancy might be risk factors for IHD [2]. Several observational studies have found that mothers who had a preterm delivery also had a two fold increased risk of death or admission as a result of IHD [3–5]. We conducted a nested case–control study in the E3N cohort [6], to assess the association between preterm delivery and IHD in a population sample of French women.

Methods

Data source

E3N is a French prospective study investigating cancer risk factors in 98 997 women born between 1925 and 1950. All women belong to the MGEN, a health insurance scheme primarily covering teachers. Since June 1990, after having given informed consent, participants have been asked at 24-month intervals to complete self-administered questionnaires including lifestyle characteristics. For each questionnaire, up to two reminders were sent to non-respondents. The response rate for each questionnaire was approximately 85%. Status regarding common risk factors for IHD was reported in the first questionnaire sent in 1990–1991, information on the length of the first pregnancy ending with the birth of a living baby was reported in the second questionnaire sent in 1992–1993. Each questionnaire included information on hospitalization for a myocardial infarction (MI).

Study design

We retrospectively identified in the whole E3N cohort women who self-reported having had a first MI between January 1990 and December 2000. Information on the definite diagnosis, electrocardiogram and enzymatic dosages was obtained by interviewing each case's general practitioner and scrutinizing information from hospital

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discharge records. On the basis of all available information, an independent committee of two cardiologists validated each event. There were 207 potential cases, of which 70 were excluded for a history of MI before recruitment to the main cohort study (*n*=14), angina pectoris (*n*=32), other cardiac diseases (*n*=13), psychiatric disorders (*n*=4) and other non-cardiac diseases (*n*=7). We also identified 32 deaths caused by IHD using data provided by the MGEN and the Information Department on the cause of death, (INSERM SC8) (International Classification of Diseases, ninth revision, codes 410–414). Of these 169 cases, 25 women who had never had a child and 32 women who did not complete the second questionnaire were excluded. A further three cases with incomplete data were also excluded. The study thus included 109 cases (92 non-fatal MI and 17 deaths as a result of IHD). For each case we randomly selected up to five controls, who were matched to the case on year of birth, year and month of inclusion in the E3N cohort, educational level (four classes) and area of residence at inclusion (21 regions). We checked for each control the living status and the absence of IHD at the time of diagnosis for the case. The study included 395 controls.

Exposures

Deliveries were classified as term or preterm according to the length of the pregnancy reported by the participants (in months). All women reporting a length of pregnancy of 8 months or less were considered to have had a preterm delivery. Only singleton first births of a live baby were considered in this study. Common baseline cardiovascular risk factors of IHD considered in the study were selfreported hypertension, diabetes mellitus, hypercholesterolemia, high body mass index, and smoking status (never, former, current).

Statistical analysis

All analyses were performed with the Statistical Analyses System (SAS Institute, USA). Univariate and multivariate conditional logistic regression models were used to estimate the hazard ratios (HR) of IHD linked to preterm delivery and cardiovascular risk factors. Covariates were included in the final model if the univariate *P* value was 10% or less. All statistical tests ware twotailed.

Results

The mean age at inclusion (SD) was 55.0 (7.6) years for cases, and 55.1 (7.6) years for controls. In cases, the mean time from inclusion to the occurrence of the event was 5.2 (3.1) years. As expected, cardiovascular risk factors were all significantly associated with the risk of IHD. Preterm delivery was reported in 21.1% of cases and 10.9% of controls. Preterm delivery was associated with an increased maternal subsequent risk of IHD [HR 2.12; 95% confidence interval (CI) 1.19–3.78]. Adjustment for cardiovascular risk factors did not affect this result (HR 2.09; 95% CI 1.07–4.09) (Table 1). When analysis was restricted to never smokers the HR was 2.2 (95% CI 0.91–5.33).

Table 1 **Cases and controls according to preterm delivery and ischaemic heart disease risk factors, adjusted hazard ratios (95% confidence intervals) and P value**

	Cases (%)	Controls (%)	Hazard ratio (95% CI)[a]	*P* value[b]
Preterm delivery	21.1	10.9	2.09 (1.07–4.09)	0.03
Hypertension	44.0	20.8	3.04 (1.74–5.32)	<0.001
Hypercholesterolemia	45.9	28.7	1.96 (1.16-3.29)	0.01
Diabetes	7.3	2.5	4.9 (1.45–16.40)	0.01
Former smoker	15.6	20.5	1.01 (0.52–1.90)	NS
Current smoker	25.6	8.6	3.95 (1.96–7.97)	<0.001

CI, Confidence interval. [a]Adjusted for all risk factors shown in the table. [b]*P* value for multivariate conditional logistic regression model.

Discussion

Women whose first child was born prematurely had a twofold increased risk of IHD. Adjustment for hypertension, diabetes mellitus, hypercholesterolemia, body mass index and smoking status had no influence on this association. Highly educated women composed the E3N cohort and we matched cases and controls on

educational level. Confounding by educational level is thus unlikely. We evaluated smoking status at inclusion in the study not during pregnancy. However, only 31% of the participants had ever smoked and adjustment on ex-smoking status was performed. Moreover, an analysis restricted to never smokers still found an association between preterm delivery and IHD of similar strength. The cause of premature delivery was not known, therefore we could not estimate the number with pre-eclampsia, which is a causal risk factor for premature delivery and was associated in several studies with thrombotic events including IHD [2,4,7–10]. Our study provides evidence that preterm delivery is a significant risk factor for IHD and major known cardiovascular risk factors cannot account for this association. Whether it is a causal risk factor remains to be proved.

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