ELSEVIER

Atherosclerosis 196 (2008) 42–48

ATHEROSCLEROSIS

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Maternal smoking in pregnancy is associated with cholesterol development in the offspring: A 27-years follow-up study

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Received 24 September 2006; received in revised form 21 January 2007; accepted 29 January 2007
Available online 2 March 2007

Abstract

Objective: To examine the associations of maternal smoking in pregnancy with development of cholesterol levels from childhood to adulthood.
Methods: Total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were measured annually from 1975 to 1993 and in 2002 in 350 subjects aged 5–19 years at baseline who participate in a prospective cohort study. Pregnancy and birth data were obtained through questionnaires sent to the parents.
Results: Children of mothers who smoked in pregnancy showed a higher annual change in total cholesterol of 0.12 mmol/l per 10 years (95% confidence interval (CI): 0, 0.23) compared to children whose mothers did not smoke in pregnancy. Larger effect estimates were found in children with moderate overweight (0.39 mmol/l per 10 years (95% CI: 0.14, 0.63). HDL-cholesterol and LDL-cholesterol showed tendencies towards a decrease and increase, respectively, in children of mothers who smoked in pregnancy compared to children whose mothers did not smoke in pregnancy. Adjustment for potential confounders did not materially change the effect estimates.
Conclusion: This study suggests for the first time that maternal smoking in pregnancy is associated with an increased rise in total cholesterol levels and a tendency towards an adverse lipoprotein profile in the offspring.

Keywords: Cohort study; Smoking; Pregnancy; Birth weight; Lipids; Cholesterol

1. Introduction

The fetal origins hypothesis postulates that an adverse fetal environment, especially fetal undernutrition, leads to developmental adaptations that permanently program the fetus' structure, physiology and metabolism [1]. This programming would be in favour of short-term survival and would lead to fetal growth retardation and low birth weight. Long-term effects of this programming would be detrimental and lead to cardiovascular diseases and their risk factors. This hypothesis has gradually modified into a more general developmental plasticity model in which various fetal and postnatal exposures lead to programming responses [2].

Recent systematic reviews of epidemiological studies suggested only small effects of low birth weight on both blood pressure and blood cholesterol in later life [3,4]. An explanation for these small effect sizes and the discrepancy with findings from animal studies may be that low birth weight is not an appropriate measure of an adverse fetal environment. Studies examining the effect of directly measured adverse fetal exposures instead of only birth weight on diseases in later life may reveal stronger associations. Maternal smoking in pregnancy is the most important determinant of low birth weight in Western countries and leads to persistent adverse developmental changes due to direct fetal exposure to

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doi:10.1016/j.atherosclerosis.2007.01.032

nicotine and the associated maternal life style and dietary habits [5]. It has been demonstrated previously that maternal smoking in pregnancy is associated with obesity and higher blood pressure in childhood [6,7]. These effects were independent of birth weight and may predispose the individual to the development of cardiovascular disease. To our best knowledge, it is currently unknown whether maternal smoking in pregnancy is associated with cholesterol levels in the offspring.

Therefore, we studied the associations between maternal smoking in pregnancy with development of total cholesterol, high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol levels in a prospective cohort study from childhood to adulthood.

2. Methods

2.1. Design and study population

All subjects aged 5 years and older living in two districts in Zoetermeer, a suburban town in the Netherlands, were invited to participate in the Epidemiological Preventive Organization Zoetermeer (EPOZ) Study between 1975 and 1978 [8]. This is a population-based study on risk indicators for chronic disease. Of the 5670 eligible children aged 5–19 years, 4649 (response 81%) were included. From this group, a random sample of 596 children was selected for an annual follow-up study on the natural history of cardiovascular risk factors and their determinants. Complete data were available for 425 fathers and 454 mothers at baseline. The children visited the research center annually in the same month of the year, preferably at the same time of the day, between 1975 and 1993 and again in 2002. The response for these annual visits gradually declined to 81% ($n = 483$) in 1993 and 61% ($n = 362$) in 2002. The median number of visits for the present analysis is 15 (range 2–19) and the median follow-up time is 23.6 (95% range 3.1–26.9) years.

2.2. Measurements

The annual measurements were performed in the same month of the year for each individual. Blood samples were drawn by antecubital venipuncture for cholesterol measurements from the start of the study. Measurements of HDL-cholesterol were started in 1979 and of LDL-cholesterol were started in 1984. Height and weight were measured without shoes and heavy clothing and body mass index was calculated (weight/height^2 (kg/m^2)). Information on life style factors including smoking habits and alcohol consumption was obtained through questionnaires at each visit. The same methods were used in both parents at baseline.

2.3. Laboratory analysis

The laboratory analyses of lipoprotein-cholesterol concentrations for this study are described in detail elsewhere [9]. Briefly, serum total cholesterol was measured with an automated enzymatic method at baseline and from 1983 to 1993 with a modified reagent (CHOD/PAP High Performance, Boehringer Mannheim, FRG) [10]. The standard deviation of duplicate serum cholesterol measurements stored at −20 °C for up to 4 years did not exceed 3.0% and did not show a significant drift. Measurements of HDL-cholesterol (from 1979) and LDL-cholesterol (from 1984) were performed by the same method after precipitation. A phosphotungstate method with a minor modification was used for HDL-cholesterol measurements and polyvinylsulphate (Boehringer Mannheim, FRG) was used for LDL-cholesterol measurements [11,12]. From 1989, automated analyses were carried out on a Technicon Auto Analyser-II system (Technicon Instruments, Tarrytown, NY, USA) initially and on a Kone Specific Analyzer (Kone Instruments, Espoo, Finland) using frozen (−20 °C) serum samples. In 2002, total cholesterol was measured by an automated enzymatic procedure using Roche CHOD-PAP reagent kit. HDL-cholesterol was measured with the Roche CHOD-PAP direct HDL-cholesterol assay using PEG-modified enzymes and dextran sulphate. All measurements were carried out at the Department of Epidemiology & Biostatistics at the Erasmus Medical Center, Rotterdam, the Netherlands. This department participated in the Dutch National Cholesterol standardization program (KCA foundation) from 1977 and in the lipid standardization program of the World Health Organization (WHO) Regional Lipid Reference Center in Prague, Czechoslovakia from 1978. During the baseline period, quality control was indirectly checked on the CDC protocol by monthly comparison with cholesterol determination using the Abell-Kendall method [13]. Accuracy and precision of total cholesterol and HDL-cholesterol measurement were within acceptable limits (CDC/WHO) over the entire period.

Age-specific total cholesterol levels measured in 1975–1982 were similar to those measured in 1983–1990. For instance, comparing the first with the second period, in 15 years old the levels were 4.54 (standard deviation (S.D.) 0.84) mmol/l ($n = 210$) and 4.51 (S.D. 0.71) mmol/l ($n = 101$), respectively; in 16 years old levels were 4.52 (S.D. 0.89) mmol/l ($n = 203$) and 4.51 (S.D. 0.75) mmol/l ($n = 127$), respectively. In 20 years old levels were 4.81 (S.D. 0.85) mmol/l ($n = 168$) and 4.92 (S.D. 0.90) mmol/l ($n = 189$), respectively [9].

2.4. Pregnancy and birth data

A questionnaire to obtain pregnancy and birth data was sent to the parents of the children in 1993. This questionnaire included questions about birth weight (g) and maternal smoking in pregnancy (no, yes). Of the 483 subjects in the study in 1993, the addresses of 33 parents could not be found and 2 children had died during follow-up. Of the 448 questionnaires sent, 353 were completed and returned to the investigators (response 79%). Information about maternal smoking in pregnancy was known in 350 subjects.