Prostaglandins, Leukotrienes and Essential Fatty Acids 100 (2015) 21–27

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Potential programming of selected cardiometabolic risk factors at childhood by maternal polyunsaturated fatty acid availability in the MEFAB cohort

Sylvia H.J. Jochems [a,*], Marij Gielen [a], Patrick Rump [b], Gerard Hornstra [c], Maurice P. Zeegers [a]

[a] NUTRIM School for Nutrition and Translational Research in Metabolism, Departments of Complex Genetics, Cluster of Genetics and Cell Biology, Maastricht University, The Netherlands
[b] Department of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands
[c] NUTRI-SEARCH, Brikkenoven 14, 6247 BG Gronsveld, The Netherlands

ARTICLE INFO

Article history:
Received 12 March 2015
Received in revised form
3 June 2015
Accepted 4 June 2015

Keywords:
Prenatal programming
Fetal origins
Polyunsaturated fatty acids
Cardiometabolic disease risk

ABSTRACT

Background: Increasing evidence suggests that long-chain polyunsaturated fatty acid (LCPUFA) availability *in utero* could program later health.
Objective: The objective of the study was to explore whether prenatal LCPUFA availability could be involved in programming cardiometabolic disease risk at childhood.
Methods: Data of 242 mother–child pairs from the Maastricht Essential Fatty Acid Birth (MEFAB) cohort were used. Multi-variable linear regression analysis was applied to identify associations between maternal LCPUFA concentrations around weeks 11, 22 and 32 of pregnancy and at time of delivery and cardiometabolic risk factors of their children (glucose metabolism, blood lipids, and blood pressure) at age 7.
Results: Maternal eicosapentaenoic acid (20:5$n-3$) at week 11 of pregnancy was negatively associated with children's glucose ($B=-0.34$ mmol/L; 95% CI: -0.56, -0.12). Positive associations were found between maternal linoleic acid (18:2$n-6$) at time of delivery and children's proinsulin ($B=0.25$ pmol/L; 95% CI: 0.08, 0.41); maternal 3-docosapentaenoic acid (22:5$n-3$) at week 11 and children's total cholesterol ($B=1.23$ mmol/L; 95% CI: 0.45, 2.01) and low-density-lipoprotein cholesterol ($B=1.12$ mmol/L; 95% CI: 0.42, 1.82); and maternal osbond acid (22:5$n-6$) at week 22 and tetracosadienoic acid (24:2$n-6$) at week 32 and children's diastolic blood pressure ($B=16.86$ mmHg; 95% CI: 7.63, 26.08 and $B=17.75$ mmHg; 95% CI: 6.37, 29.94, respectively).
Conclusion: Our findings suggest that maternal omega-6 ($n-6$) fatty acids may be of particular importance in relation to children's glucose metabolism and blood pressure, whereas omega-3 ($n-3$) fatty acids seem particularly related to blood lipids at childhood. In general, the strength of the associations appeared stronger with fatty acid concentrations in early pregnancy compared to late pregnancy.

1. Introduction

The 'Developmental Origins of Health and Disease' hypothesis states that the onset of cardiovascular disease [1] and type 2 diabetes [2] already starts *in utero* and could be the consequence of adaptation of the fetus to a limited nutrient and energy availability [3]. This phenomenon is referred to as 'developmental programming' and suggests that adverse intra-uterine environments could permanently alter metabolic pathways [3].

The nutritional status of the mother during pregnancy has been demonstrated to be essential in prenatal development and is suggested to play an important role in the fetal origins of adult disease [4]. In this respect, essential polyunsaturated fatty acids (PUFAs), together with their longer chain, more unsaturated fatty acid derivatives (LCPUFAs), could be of particular importance [5]. There are two essential LCPUFA families, the omega-6 ($n-6$) and omega-3 ($n-3$) family, and usually the $n-3$ fatty acids are considered most important for prenatal development [6]. However, adequate $n-6$ fatty acid availability is important as well [6]. Hence, the biological significance of both LCPUFA families deserves closer attention [7].

Prenatal LCPUFA supply strongly depends on the maternal diet and metabolism as well as on placental transport [8]. Therefore,

* Corresponding author.
E-mail address: s.jochems@maastrichtuniversity.nl (S.H.J. Jochems).

http://dx.doi.org/10.1016/j.plefa.2015.06.001
0952-3278/

the maternal LCPUFA status during pregnancy can be considered proxies for embryonic and fetal LCPUFA availability [9]. Although the LCPUFA concentrations of maternal plasma phospholipids (mg/L) increase during pregnancy, the proportional increase of the concentrations of Mead acid (20:3$n-9$) and Osbond acid (22:5$n-6$), shortage-indicators of arachidonic acid (20:4$n-6$) and docosahexaenoic acid (22:6$n-3$), respectively, is considerably stronger [5,9]. This suggests that the increased LCPUFA requirement during pregnancy may not be met adequately. There is increasing evidence that exposure to an unbalanced LCPUFA status during the perinatal period may result in impaired fetal growth [10], low birth weight [11] and adiposity at childhood [12].

Only limited research efforts have been made in investigating the impact of prenatal LCPUFA availability on cardiometabolic risk factors including the glucose metabolism, blood lipids and blood pressure [13,14]. Most studies have evaluated the nutritional status of pregnant women during the second or third trimester of pregnancy, whereas evidence suggests that prenatal development is especially vulnerable to maternal nutritional deficiencies during the first trimester [15]. Studies on the Dutch Hunger Winter seem to support the importance of nutrient timing [16]. Prenatal exposure to the Dutch famine in early pregnancy was associated with an increased risk of an atherogenic lipid profile, whereas exposure during late pregnancy was not [17].

Understanding the relationship between the maternal LCPUFA status at various points in time during pregnancy and at delivery and cardiometabolic risk in the offspring could identify specific LCPUFA requirements during critical periods of prenatal development. The 'Maastricht Essential Fatty Acid Birth' (MEFAB) cohort contains extensive fatty acid composition data of mothers at the first, second and third trimester of pregnancy and at the time of delivery, and on cardiometabolic risk factors of their children at age 7 (glucose metabolism, blood lipids, and blood pressure). Earlier results from the MEFAB cohort suggest that a higher availability of the $n-6$ fatty acids gamma linolenic acid (GLA, 18:3$n-6$) and dihomo gamma linolenic acid (DGLA, 20:3$n-6$) at birth was associated with reduced levels of plasma triacylglycerol (TAG), insulin resistance and body fatness [18] at childhood. Furthermore, insulin resistance at childhood was associated with leptin concentrations and aerobic capacity at age 7 [19]. Finally, maternal DGLA (20:3$n-6$) concentration throughout pregnancy was associated with an increased BMI at age 7 [20]. The MEFAB cohort provides a unique opportunity to explore whether prenatal availability of LCPUFAs during different gestational periods and at time of delivery, could be associated with cardiometabolic disease risk and may be involved in cardiometabolic risk programming.

2. Subjects and methods

2.1. Study design and population

The main purpose of the MEFAB cohort is to investigate whether prenatal availability of LCPUFAs may be involved in programming birth outcomes and later development. Between 1989 and 1995, 1238 pregnant women in the southern part of The Netherlands were recruited from antenatal clinics to participate in this observational study. Selection criteria for inclusion were a gestational age of less than 16 weeks, a diastolic blood pressure below 90 mmHg, and no apparent signs of cardiovascular, neurological, renal or metabolic disorders [5]. Between 1997 and 2000, a follow-up study was performed to explore the long-term associations of prenatal LCPUFA availability and cardiometabolic outcomes at childhood. All singleton babies born before 1994 and of whom an umbilical cord blood sample was available were candidates to be included. In total 750 children were eligible and 728 of them were successfully traced. Eventually 297 children around the age of 7 (age range 6.7–8.1 year) visited the outpatient clinic. A flowchart for study participation is given in Fig. 1.

2.2. Data collection at baseline

Between 1989 and 1995, maternal venous blood samples had been collected from 1238 women in EDTA-treated evacuated tubes during visits at four approximate time-points: at week 11 of pregnancy (median 10.9; IQR 8.7–12.9 weeks), at week 22 (median 22.1; IQR 21.3–23.0 weeks), at week 32 (median 32.1; IQR 31.4–33.0 weeks), and at delivery (median 40.0; IQR 39.1–41.0 weeks). Separation of the plasma from blood cells was performed by centrifugation (2000*g*, 4 °C, and 15 min) and aliquots were stored at −80 °C until analysis. Full LCPUFA profiles of the $n-6$ family (linoleic acid (LA, 18:2$n-6$), gamma linolenic acid (GLA, 18:3$n-6$), eicosadienoic acid (EDA, 20:2$n-6$), dihomo gamma linolenic acid (DGLA, 20:3$n-6$), arachidonic acid (ARA, 20:4$n-6$), docosadienoic acid (DDA, 22:2$n-6$), adrenic acid (AdrA 22:4$n-6$), osbond acid (× 22:5$n-6$), tetracosadienoic acid (TDA, 24:2$n-6$)) and the $n-3$ family (alpha-linolenic acid (ALA, 18:3$n-3$), eicosatrienoic acid (ETriA, 20:3$n-3$), eicosatetraenoic acid (ETA, 20:4$n-3$), eicosapentaenoic acid (EPA, 20:5$n-3$), 3-docosapentaenoic acid (3-DPA, 22:5$n-3$), docosahexaenoic acid (DHA, 22:6$n-3$)) of plasma phospholipids were determined by capillary gas–liquid chromatography as described by Al et al. [9]. The $n-3$ fatty acids stearidonic acid (SDA, 18:4$n-3$) and docosatrienoic acid (DTA, 22:3$n-3$) were not detected in measurable amounts. Individual fatty acid concentrations were expressed in % of the total fatty acids measured (% (w/w)). The LCPUFAs included in the present study are presented in Table 1. Medical record data was used for information on sex (male/female), parity (primipara/multipara), birth weight (grams) and gestational age (weeks). The gestational age was approximated from the first day of the last menstrual period till birth. If the last menstrual period was uncertain, gestational age was based on ultrasound measurements. All women provided written informed consent, and approval was obtained from the Medical Ethics Committee of the Academic Hospital Maastricht and the University of Maastricht.

2.3. Data collection at follow-up

Between 1997 and 2000, fasting venous blood samples had been collected in EDTA-treated evacuated tubes from 264 of the

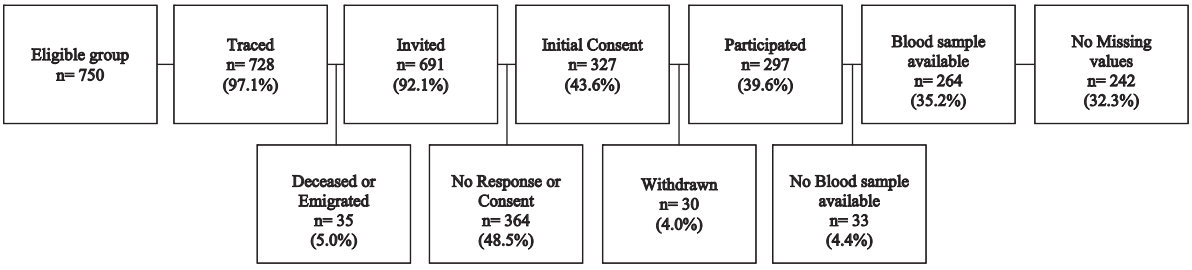

Fig. 1. Participation during follow-up study.