Effect of dietary factors in pregnancy on risk of pregnancy complications: results from the Norwegian Mother and Child Cohort Study[1–4]

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ABSTRACT

There has been a thrilling development , as well as profound changes, in our understanding of the effect of fetal nutrition on the development and health of the child. The Norwegian Mother and Child Cohort Study (MoBa) is an ongoing nationwide population-based pregnancy cohort study that between 1999 and 2008 recruited 90,723 women with 106,981 pregnancies and 108,487 children. The objective of MoBa is to test specific etiologic hypotheses by estimating the association between exposures and diseases with a special focus on disorders that may originate in early life. An important aspect in this regard is maternal diet and nutritional status during pregnancy. Nutritional factors have long been considered to be important determinants of maternal and fetal health, and dietary information is currently being collected in a number of pregnancy cohorts in Europe and the United States. Thus far, pregnancy complications studied in MoBa are preterm birth, preeclampsia, and fetal growth; and the aim of this article is to report results of recently published studies of dietary factors in relation to these outcomes. Numerous studies are planned using MoBa data, and the aim is to add to the knowledge of the interplay between dietary factors, nonnutrients, and toxic dietary substances and epigenetic modulation on fetal development and health later in life. *Am J Clin Nutr* 2011;94(suppl):1970S–4S.

INTRODUCTION

There has been a thrilling development and profound changes in our understanding of the effect of fetal nutrition on the development and health of the child. Four decades ago, the consensus was that the fetus was protected and lived more or less as a parasite on the mother, only being affected by maternal nutrition if this was extremely unbalanced or insufficient. The mother would pay the nutritional price of a pregnancy, rarely the child (1). Subsequent research, not least connected to the emergence of epigenetics, has modified this picture toward a much more important role for a mother's diet during pregnancy. The diet has an effect on all systems of the body, including the fetus, and can modulate different functions far beyond the levels that are connected to malnutrition (eg, the expression of genes, hormone concentrations, the developing nervous system, and risk of diseases later in life) (2, 3). There has also been an accumulation of knowledge about the effects of nonnutrients and toxic dietary substances on fetal development and health later in life. As a consequence of this development in understanding, the monitoring of dietary intake has become an integral part of pregnancy and birth cohort studies.

THE NORWEGIAN MOTHER AND CHILD COHORT STUDY

The Norwegian Mother and Child Cohort Study (MoBa) is a long-term prospective pregnancy cohort that included >107,000 pregnancies in the years between 1999 and 2008 (4). Pregnant women were recruited for the study by postal invitation after they signed up for a routine ultrasound examination in their local hospital. Participants were asked to provide biological samples and answer questionnaires covering a wide range of information up to age 7 y for the child. The cohort database is linked to the Medical Birth Registry of Norway (5). In Norway, every citizen is given a unique personal 11-digit identification number at birth that follows the person throughout life. The identification number is also used to register diseases in a number of health registries, with one of the oldest being the Cancer Registry of Norway established in 1951. By connecting MoBa data with health registries through their identification number, it will be possible to follow MoBa participants from recruitment and decades into the future.

DIETARY ASSESSMENT IN MoBa

The objective of MoBa is to test specific etiologic hypotheses by estimating the association between exposures, including genetic, dietary, or lifestyle factors, and diseases with a special focus on disorders that may originate in early life. We were given the opportunity to develop and validate a dietary food-frequency questionnaire (FFQ) tailored for MoBa and to be answered during pregnancy. The basic planning of MoBa was not made on the

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basis of any single hypothesis or any set of hypotheses because the specific research questions that will emerge 10–50 y in the future cannot be foreseen. Therefore, the strategy was to collect data on as many relevant exposures and health outcomes as feasible. With regard to diet, this implied covering as many known aspects of the diet as possible on an individual level over a restricted time period during pregnancy. Our challenges in the development of dietary monitoring in MoBa have been described elsewhere (6). The MoBa FFQ is a semiquantitative questionnaire designed to capture dietary habits and intakes of dietary supplements during the first 4 mo of pregnancy. A database including >1000 dietary supplements with the nutrient content per portion has been created. For calculations of nutrient intake from supplements, we used brand names together with frequencies and amounts. Parallel to the implementation of the FFQ in March 2002, a validation study was undertaken that resulted in a number of publications and showed that the FFQ enabled a reasonable ranking of the participants' diets (7–10) and nutrient intakes through dietary supplements (11).

The aim of this article is to give an overview of results obtained thus far when the effect of diet during pregnancy on pregnancy complications was investigated (**Table 1**). One study investigated whether adherence to a Mediterranean-type diet (MD) was associated with preterm birth (12), and 2 studies investigated whether maternal dietary patterns or the use of vitamin D supplementation is associated with preeclampsia (13, 14). Furthermore, we report the results of a study that investigated maternal folate intake and status during the second trimester and infant growth measures (15).

MEDITERRANEAN DIET AND PRETERM BIRTH

A Mediterranean diet is characterized by abundant intakes of vegetables, fruit, whole grains, nuts, legumes, and fish and the use of olive oil as a source of fat. Furthermore, intakes of red meat, full-fat dairy products, and eggs are restricted (16). An intervention study showed that a Mediterranean diet reduced the incidence of preterm birth (17). This inspired us to investigate whether a MD could be associated with lower risk of preterm birth in MoBa (12). The 5 MD criteria in the current study were defined by the intake of ≥5 vegetables and fruit/d, ≥2 servings of fish/wk, the use of olive or canola oil for cooking and salad dressings, ≤2 servings of red meat/wk, and≤2 cups of coffee/d. The study population comprised 26,563 women who had answered the MoBa FFQ in the years 2002–2004 and were nonsmoking, had a body mass index (BMI; in kg/m^2) between 19–32, were between 21–38 y at the time of delivery, had a history of ≤3 spontaneous abortions before the current pregnancy, and had an acceptable energy intake. A total of 569 women (2.2%) met all MD criteria, 25,397 women (97.2%) met 1–4 MD criteria, and 159 women (0.01%) met none of the MD criteria. The number of preterm births in the MD group was 26 (4.6%), the number of preterm births in women who met 1–4 criteria was 1148 (4.5%), and the number of preterm births in women who met none of the criteria was 10 (6.3%). The women who met the MD criteria did not have reduced risk of preterm birth compared with the risk for women who met none of the MD criteria [odd ratio (OR) 0.73; 95% CI: 0.32, 1.68). However, an intake of fish ≥2 times/wk was associated with a lower risk of preterm birth (OR: 0.84; 95% CI: 0.74, 0.95) (12).

The women who fulfilled the MD criteria did not have a reduced risk of preterm birth. We had very few women who fulfilled the MD criteria. However, we did find that an intake of fish ≥2 times/wk reduced risk of preterm birth, which is in accordance with previous studies (18, 19). Fish intake in pregnancy has raised concerns because fish is a major source of polychlorinated biphenyls, polyfluorinated compounds, methyl mercury, and other environmental contaminants (20–22). Thus far, most of the studies on the effect of fish consumption on pregnancy outcomes are in favor of fish intake (23, 24). The influence of maternal fish and seafood intake on maternal and health outcomes will be further investigated in future studies.

DIETARY FACTORS AND PREECLAMPSIA

Preeclampsia is a major cause of maternal and fetal morbidity and mortality, but the cause is unknown. Several dietary substances have been hypothesized to influence risk of preeclampsia (25–28). We aimed to investigate the relation between dietary patterns and risk of developing preeclampsia (study a) (13) and the relation between vitamin D from diet and supplements and risk of developing preeclampsia (study b) (14). Both studies included 23,423 nulliparous women in MoBa in the years 2002–2006. Of these, 1267 (5.4%) women developed preeclampsia.

TABLE 1
Dietary factors in pregnancy and pregnancy complications in the Norwegian Mother and Child Cohort Study[1]

Dietary component	Pregnancy complication	Total no. of study sample	Association RR (95% CI)	Reference
Mediterranean diet according to 5 predefined criteria	Preterm birth	26,563	All criteria vs none: 0.73 (0.32, 1.68); intake of fish ≥2 times/wk vs less intake: 0.84 (0.74, 0.95)	Haugen et al, 2008 (12)
A vegetable pattern (vegetables, fruit, and vegetable oils)	Preeclampsia	23,423	Upper tertile vs lower tertile: 0.72 (0.62, 0.85);	Brantsæter et al, 2009 (13)
A processed pattern (meat products, snacks, and sweet beverages)			Upper tertile vs lower tertile: 1.21 (1.03, 1.42)	
Vitamin D from supplements	Preeclampsia	23,423	10–15 vs <5 μg: 0.73 (0.58, 0.92)	Haugen et al, 2009 (14)
Maternal folate intake and status	Fetal growth	2934	No association with gestational length, infant birth weight, head circumference, crown-heel length, or SGA	Nilsen et al, 2010 (15)

[1] RR, relative risk; SGA, small for gestational age.

Associations between dietary patterns and preeclampsia

In study a (13), exploratory factor analysis was used to identify underlying patterns in the dietary data. We extracted 4 dietary patterns. Each participant was assigned a score for each of the 4 patterns. The first pattern, which was denoted the vegetable pattern, was characterized by a high consumption of fresh and cooked vegetables, cooking oil, olive oil, fruit and berries, rice, poultry, and drinking water. The second pattern, which was denoted the processed pattern, was characterized by a high consumption of processed meat products, white bread, french fries, salty snacks, and sugar-sweetened drinks. These patterns correspond to the prudent and Western patterns seen in most populations and were correlated with maternal characteristics and other lifestyle behaviors. The vegetable-pattern factor scores increased with maternal age, length of education, and height, decreased with BMI, and were higher in nonsmokers than in smokers, whereas the processed-pattern factor scores decreased with increasing age, length of education, and height and increased with BMI and smoking. The other 2 patterns were not associated with maternal characteristics.

Women with preeclampsia had lower vegetable-pattern scores and higher processed food–pattern scores than did women who did not develop preeclampsia ($P < 0.001$). When confounders were adjusted for, the results showed that women with high scores on the vegetable pattern had significantly reduced risk of preeclampsia [relative risk (OR) for tertile 3 compared with tertile 1: 0.72; 95% CI: 0.62, 0.85], and women with high scores on the processed food pattern had increased risk (OR for tertile 3 compared with tertile 1: 1.21; 95% CI: 1.03, 1.42). The effects of the patterns were also examined according to different combinations of factor-score tertiles. The effect of having high scores on the vegetable pattern were strongest within the lowest tertile of the processed food pattern (35–40% risk reduction), whereas having high scores with the processed food pattern did not significantly increase risk in any of the vegetable-pattern tertiles (13).

Several mechanisms for a biological effect of dietary behavior on risk of preeclampsia may exist. Risk factors for preeclampsia include obesity, dyslipidemia, insulin resistance and other risk factors for atherosclerosis. Vegetables and plant foods are rich in micronutrients such as phytochemicals, antioxidants, vitamins, minerals, and dietary fiber, whereas many processed foods are made with the addition of sugar, salt, and saturated fats. In nonpregnant populations, dietary patterns characterized by a high consumption of vegetables and fruit and a low consumption of processed meats and foods rich in sugar and fats have been shown to reduce markers of the metabolic syndrome, inflammation, and cardiovascular disease.

The results of our study suggested that an adherence to dietary advice to consume a diet abundant in vegetables and fruit may also be beneficial with regard to preeclampsia. Pregnancy is a period when most women are highly motivated for dietary advice because changes toward a healthier diet may also benefit their children. Dietary changes have a low cost and low risk compared with medical interventions, and even a moderate increase in intakes of vegetables and plant foods may be of public health importance.

Associations between vitamin D intake and preeclampsia

In study b (14), the dietary intake of vitamin D from food and food supplements was calculated. The total intake from food and food supplements was categorized into 5 groups, and the intake from food supplements was categorized into 6 groups. The intake of vitamin D increased with age and length of education and was highest in the nonsmoking group. Prepregnancy BMI was not related to vitamin D intake.

Vitamin D intake from the diet was low (median: 3.0 μg vitamin D/d) and had no effect on risk of preeclampsia development. A total intake of 15–20 μg vitamin D/d (from diet plus supplements) reduced the risk of preeclampsia by 23%, and supplementation with 10–15 μg vitamin D/d reduced the risk by 27% after adjusting for confounders, which also included season. Supplementation with $\geq$15 μg vitamin D/d did not reduce the risk of preeclampsia further. Risk of preeclampsia with the use of food supplements without vitamin D was 1.37 (95% CI: 1.08, 1.73) (14).

Risk of preeclampsia was also estimated according to the timing of supplementary vitamin D use, and a protective effect of vitamin D supplement use was seen in early and late stages of pregnancy. Women who reported supplementary intake of vitamin D before pregnancy, in early pregnancy, and in late pregnancy had a 29% reduced risk of preeclampsia compared with that for women who never took vitamin D supplements (14).

Possible explanations for the biological effect of vitamin D status on risk of preeclampsia include the regulation of target genes associated with implantation and the effect on the maternal immune response to the fetus (29). Vitamin D intake through the diet is low, and the recommended intake of this vitamin is hard to reach by diet alone. In Norway, recommendations of supplementation with vitamin D are given to the general population as well as to pregnant women. Results from this study as well as from studies internationally have shown that recommendations might be too low for pregnant women, and an increased intake might reduce several pregnancy comorbidities (30). However, there is a need for more clinical studies before a consensus on the dose can be made.

MATERNAL FOLATE INTAKE AND INFANT BIRTH SIZE

Previous studies, including randomized trials, have reported inconsistent results regarding maternal folate status and infant birth size. However, most of these studies were small and often limited to a few folate indicators or a few markers of infant birth size. In a substudy of 2934 singleton pregnancies in MoBa during 2002–2003, we examined the relation between infant birth size and several maternal folate indicators that were measured during the second trimester (15). Folate indicators included food folate intake, folic acid supplement use and plasma folate and plasma total homocysteine concentrations. The birth-size markers included gestational age, infant birth weight, head circumference, crown-heel length, and small for gestational age. The mean total dietary folate intake was 456 μg folate/d, of which the food contribution was, on average, 268 μg folate/d and supplements contributed 188 μg folate/d. The results showed that food folate, supplemental folic acid, total dietary folate intake, plasma folate, and plasma total homocysteine were not significantly related to gestational age, infant birth weight, head circumference, or crown-heel length. There was a tendency for increased small-for-gestational-age risk at lower folate concentrations, but analyses yielded insignificant associations, possibly because of the low number of individuals with low folate intake. The results implied that dietary folate and plasma folate during the second

trimester are not essential predictors for infant birth size in well-nourished Norwegian pregnant women (15).

In Norway, food is not fortified with folic acid and pregnant women are recommended to take 400 mg folic acid/d as supplements 1 mo before and during the first 2–3 mo of pregnancy (31). Recent scientific developments have raised concerns regarding folic acid supplement use in pregnant women. A Norwegian study from 2009 using MoBa data provided some evidence that prenatal folic acid supplementation may increase the risk of certain infant respiratory diseases in early childhood (32). This finding was supported by a study from Australia (33), which showed that supplemental folic acid in late pregnancy was associated with an increased risk of childhood asthma at 3.5 y as well as persistent asthma. It is suggested that maternal folic acid supplementation may affect respiratory health in offspring via epigenetic mechanisms

SUMMARY AND PERSPECTIVES

MoBa is a relatively newly established pregnancy cohort, and few studies of dietary factors in relation to pregnancy complications have so far been published. However, many studies of dietary factors in relation to maternal and child health outcomes are planned. The influence of prenatal and early life exposures on health outcomes of offspring is of considerable scientific and public health interest. Food and dietary supplement intake data during pregnancy may help monitor protective and potential adverse effects. Dietary factors correlate with socioeconomic, genetic, and behavioral factors, and the sampling of DNA from the mother, father, and child (cord blood) has been vital in MoBa to better disentangle genetic and environmental pathways. However, the emerging field of epigenetics has added a whole new set of challenges to the study of dietary factors in relation to the complex pathologic process of pregnancy complications and offspring health. Pregnancy cohorts have been established in many countries, and networks have been established for a broad collaboration to meet future challenges.

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