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Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study

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ABSTRACT

Objective: Periconceptional folic acid or multivitamin supplementation is recommended for prospective pregnant women to prevent neural-tube defects. The question is whether it is worth continuing these supplementations after the first trimester of pregnancy or not. Thus the possible fetal growth promoting and/or preterm birth reducing effect of vitamin supplements in the second and mainly in the third trimester was studied.

Study design: Comparison of birth outcomes of singletons born to primiparous pregnant women with prospectively and medically recorded vitamin supplement in the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA), 1980–1996 contained 6293, 169, and 311 primiparae with folic acid alone, multivitamins and folic acid + multivitamin supplementation, respectively, and their data were compared to the data of 7319 pregnant women without folic acid and folic acid-containing multivitamin supplementation as reference.

Results: Mean gestational age was 0.3 week longer and mean birth weight was by 37 g higher in the group of folic acid alone, than in the reference group (39.2 weeks; 3216 g). The rate of preterm births (7.6%) was significantly lower compared with the reference sample (11.8%), but the rate of low birth weight newborns did not show significant reduction. Folic acid alone in the third trimester associated with 0.6 week longer gestational age and a more significant reduction in the rate of preterm births (4.8%).

Conclusions: Minor increase in mean birth weight after high dose of folic acid supplementation during pregnancy would not be expected to result in too large babies; however, the significant reduction in the rate of preterm births may have great public health benefit.

1. Introduction

Periconceptional folic acid or folic acid containing multivitamin supplementation has been shown to have a clear preventive effect on the recurrence [1,2] and first occurrence [3,4] of neural-tube defects, therefore this primary preventive method is recommended for prospective pregnant women.

In Hungary most pregnant women use high doses of folic acid during pregnancy mainly after the first visit in the antenatal care clinics [5,6]. However, the question is frequently raised whether it is worth continuing this supplement after the first trimester of pregnancy or not. Meta-analyses of supplementation studies recommended further researches to measure the effect of dietary folate or folic acid intake during pregnancy on reducing the rate of preterm delivery and low birth weight as an "urgent priority" [7,8]. On the other hand recently the fetal weight promoting effect of folic acid and/or multivitamins has been stated by some medical doctors as an argument against this preventive method, because the large birth weight may associate with a higher risk for birth complications of newborns.

The population-based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [9] was appropriate to test the hypothesis regarding the possible fetal growth promoting and/or preterm birth reduction effect of folic acid and/or folic acid containing multivitamin supplementation during pregnancy, particularly in the third trimester, i.e. during the time of the most intensive fetal growth. Thus the objective of the study was to compare the length of gestation at delivery and birth weight, in addition the rate of preterm births and low birth weight of singletons as main outcome measures in primiparae who used prospectively and medically recorded folic acid alone or folic acid-containing multivitamins or folic acid plus a multivitamin and in pregnant women who did not take these supplements during their pregnancy as reference.

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2. Materials and methods

2.1. Subjects

The HCCSCA is based on the comparative analysis of cases affected with congenital abnormalities and their matched controls without any defect. However, here only controls are evaluated because congenital abnormalities in cases may have a more drastic effect for birth weight and gestational age than folic acid and/or multivitamins.

Controls (henceforth *newborns*) were selected from the National Birth Registry of the Central Statistical Office. In general two newborns were matched to every case with congenital abnormalities selected from the Hungarian Congenital Abnormality Registry [10] according to sex, birth week, and district of parents' residence. Newborns from multiple pregnancies were excluded from this analysis.

2.2. Collection of exposure data and confounding factors

Data of maternal variables and exposures were obtained from three sources.

2.2.1. Prospective medically recorded data

An explanatory letter was mailed to mothers immediately after the selection of newborns asking them to send us the *prenatal maternity logbook* and other *medical records* regarding the study pregnancy and these medical documents were sent back within 3 weeks. Prenatal care was mandatory for pregnant women in Hungary (if somebody did not visit prenatal care clinic, she did not receive a maternity grant and leave), thus nearly 100% of pregnant women visited prenatal care clinics, on average 7 times, in their pregnancies. The first visit was between the 6th and 12th gestational week, and obstetricians recorded, among other information, vitamin supplements in the prenatal maternity logbook.

2.2.2. Retrospective self-reported maternal information

A structured *questionnaire* with a list of medicinal products (drugs and pregnancy supplements) and diseases, plus a printed informed consent form were also mailed to the mothers. Mothers were asked to read these enclosed lists as a memory aid before they filled in the questionnaire and to send back it with the signed informed consent.

The mean ± S.D. time elapsed between the birth and the return of the "information package" (questionnaire, logbook, discharge summary, signed informed consent) in our prepaid envelope was 5.2 ± 2.9 months.

2.2.3. Supplementary data collection

Regional nurses were asked to visit 200 non-respondent and 600 respondent mothers as a part of two validation studies [11,6] and they helped mothers to fill in the questionnaire, evaluated the data of available medical documents (mainly prenatal maternity logbooks) and collected some other (mainly lifestyle) data by cross-interview of mothers and their close relatives living together.

Overall, the necessary information was available in 83.0% of controls (81.3% from reply, 1.7% from visit). The data set of the HCCSCA between 1980 and 1996 is used here because after 1996 the collection of data was changed and recent data have not been validated until now.

2.3. Definition of study groups

(1) Folic acid (FA) alone was used. Only one type of 3 mg FA tablet was available in Hungary during the study period.
(2) FA containing micronutrient combinations, the so-called multivitamins (MV). The three most frequently used micronutrient combinations were Elevit prenatal® (55.3%; containing 0.8 mg FA), Materna® (39.0%, containing 1.0 mg FA) and Polyvitaplex-10® (2.9%; containing 0.1 mg FA) during the study period.
(3) Micronutrient combinations without FA in very heterogeneous products used mainly for body building and other purposes, these pregnant women were excluded from the study.
(4) MV + FA together. The proportion of Elevit prenatal®, Materna® and Polyvitaplex-10® use was 42.6%, 31.9% and 24.3% in this group, respectively.
(5) The reference group included pregnant women without FA and MV supplementation before conception (at least 3 months) and during the study pregnancy.

Gestational age was calculated from the first day of the last menstrual period, and was evaluated with birth weight on the basis of discharge summaries of inpatient obstetric clinics. The rate of low birth weight (<2500 g) and preterm births (<37 weeks) were estimated on the gestational age at delivery and birth weight of newborns.

Among confounders, we evaluated maternal age, birth order (parity), maternal employment status which showed a correlation with education and income thus was used as indicator of socioeconomic status of pregnant women [12]. The occurrence of smokers and drinkers was evaluated only in two subsamples of the data set including 800 pregnant women [6,11].

2.4. Statistical analysis

We used the software package SAS version 8.02 (SAS Institute Ins., Cary, North Caroline, USA): Birth outcomes and maternal variables of vitamin supplemented groups and unsupplemented group as reference were analyzed in contingency tables. At comparison of mean birth weight and gestational age at delivery adjusted Student *t*-test while rate of preterm births and low birth weight adjusted odds ratios (OR) with 95% confidence interval (95% CI) were used in unconditional logistic regression model.

3. Results

There were 2,146,574 births in Hungary during the study period. Our sample included 38,151 newborns, thus represented 1.8% of Hungarian births, however, 403 twins and 374 newborn infants born to mothers supplemented with micronutrient combinations without FA were excluded from the study, respectively.

Table 1 shows the number pregnant women with different vitamin supplements in the total data set. In the group of FA alone women used 1–3 tablets per day, but the intake was 2 tablets in 69% of pregnant women, thus the estimated daily dose was 5.6 mg. In the group of MV most pregnant women (about 98%) used one tablet; the estimated daily dose of FA was 0.85 mg. In the group of MV + FA nearly all women consumed one tablet from each of MV and FA, but the proportion of different MV was different than in the MV group therefore the estimated daily intake of FA was 3.7 mg.

According to maternal variables, the user of FA alone was the youngest (25.4 ± 4.8 years), while the user of MV was the eldest (27.0 ± 5.1 years) with a somewhat lower mean birth order (1.6 ± 0.8). The mean birth order was 1.7 in other groups. The proportion of high socioeconomic status was larger in the MV (42.0%), FA alone (41.2%) and MV + FA (41.2%) supplemented groups than in the reference sample without supplementation (38.2%). Of 200 pregnant women in the first validation study, 88 used FA alone while the second validation study included 600 pregnant women with FA