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Brief report

Folic Acid Supplementation and Interpregnancy Interval

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Abstract

Background: Maternal folic acid supplementation between subsequent pregnancies may be important to reduce the risk of low folate status associated with short interpregnancy intervals. We examined how the prevalence of preconception folic acid use for a given pregnancy in Norwegian women varied according to the time interval from the previous pregnancy.

Methods: Analysis was based on 48 855 pairs of pregnancies with the second pregnancy included in the Norwegian Mother and Child Cohort Study (birth years 1999–2009). Interpregnancy interval was defined as the time from birth of a child to the conception of the subsequent sibling. Preconception folic acid use was defined as any use of folic acid-containing supplements within the last 4 weeks before the second pregnancy.

Results: The prevalence of preconception folic acid use was 31%. Among women with a term birth (≥37 weeks) in the previous pregnancy (92%), those with interpregnancy intervals ≤12 and ≥49 months were associated with up to 35% lower prevalence of preconception folic acid use for the second pregnancy, relative to the reference group (13–24 months). The low use in short intervals was mainly attributable to lower proportion of planned pregnancies and fewer women with higher education. Among women with a preterm birth (<37 weeks) in the previous pregnancy (8%), preconception folic acid use significantly decreased with increasing pregnancy spacing.

Conclusions: Our finding of a lower preconception folic acid use in women with both short and long interpregnancy intervals might help identifying those with higher risk of folate deficiency and preventing unwanted pregnancy outcomes.

Keywords: *cohort, folate, interpregnancy interval, pregnancy, vitamins.*

Background

Periconceptional maternal use of folic acid supplements is the single most important factor that has been identified for reducing the risk of having a baby with a neural tube defect (NTD).[1,2] Depending on the background prevalence of NTDs, it has been demonstrated that a daily intake of 400 µg or more before and early in pregnancy can prevent as much as 85% of NTDs.[3–5] Despite compelling evidence on reduced NTD risk from existing studies, maternal folic acid supplementation during the periconceptional period is still low in many countries.[1,2]

Higher parity has been identified as a strong independent predictor for not taking folic acid supplements.[6,7] This is an important finding because women who have undergone a recent viable pregnancy may be at increased risk of folate depletion in the next pregnancy, especially if the interval between pregnancies is short.[8–10] Such depletion may not only contribute to an excess risk of NTDs in the subsequent

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pregnancy, but possibly also to excess risk of other adverse health outcomes associated with folate status.[10–12] Increased maternal folic acid supplementation between subsequent pregnancies, therefore, might be particularly important.[10–12]

Despite the relevance of maternal folic acid supplementation between closely spaced pregnancies, there is limited knowledge on how the prevalence of preconception folic acid supplementation for a given pregnancy varies according to the time interval from the previous pregnancy. Particularly, a low use in the shortest interpregnancy intervals (IPIs) would suggest a need of public health actions to increase supplementation. To examine this, we analysed data from 48 855 participating women in the Norwegian Mother and Child Cohort Study (MoBa) giving birth in 1999–2009.

Methods

MoBa is a prospective population-based pregnancy cohort study that in the years from 1999 to 2009 included more than 107 000 mothers and their children.[13] Mothers were recruited to the study through a postal invitation after they had signed up for the routine ultrasound examination at their local hospital, usually scheduled around gestational week 18. Informed consent was obtained from each participant prior to study enrolment, and the study has been approved by the Regional Committee for Medical and Health Research Ethics.

The MoBa participation rate was 38.5%. Although low participation in MoBa influences prevalence estimates, such non-representativeness does not necessary affect exposure–outcome associations.[14,15]

Our study comprised 58 392 pairs of subsequent pregnancies where the second pregnancy was a singleton included in MoBa. If a woman was registered with two or more pregnancies in the cohort study, we included only the sibling pair connected to her last registered cohort pregnancy ($n = 53\,882$). We further excluded 1719 pairs of pregnancies with missing birth date or gestational age in at least one of the two siblings and another 3308 pairs with missing baseline cohort questionnaire, leaving a total of 48 855 pregnancy pairs for analyses.

The IPI was defined as the time from birth of a child to the estimated conception of the subsequent child of the same mother. The estimated date of conception of the second child was calculated as the date of birth minus the length of gestation.[16] Gestational age was based on second trimester ultrasound measurements or, if missing, the first day of the last reported menstrual period. Length of the IPI was rounded off to whole months and analysed as a categorical variable, with the category 13–24 months as the reference.

Preconception folic acid use was defined as any use of folic acid-containing supplements within the last 4 weeks before onset of the second pregnancy. Information on use for the second pregnancy was obtained from the cohort baseline questionnaire filled in by the mothers around gestational week 18.[7] The most commonly used folic acid supplements for pregnant women in Norway contain 400 μg of folic acid, while the most commonly used multivitamin supplements contain 200 μg of folic acid.

Associations between IPIs and preconception folic acid use were estimated by prevalence ratios with 95% confidence intervals using log-binomial regression models with the log-link function, and were analysed separately for women with and without a previous preterm birth (<37 weeks). Analyses were performed with and without adjustment for year of birth, maternal age at delivery, marital status, number of previous births (parity), maternal education, maternal smoking at gestational week 18, and pregnancy planning. All covariates were abstracted at the time of the second pregnancy and they have previously been related to maternal folic acid use in the same cohort.[7] Women with missing data on covariates were excluded from the adjusted analyses.

Results

Being a smoker during the second pregnancy, being a single mother, having lower educational level, and having higher parity were generally more frequent in women with both short and long IPIs (Table 1). Shorter intervals were particularly associated with a lower proportion of pregnancy planning and a higher proportion of women having a preterm birth in the previous pregnancy.

The overall prevalence of preconception folic acid use before onset of the second pregnancy was 31% (15 297/48 855). Among women with a term birth in the previous pregnancy (92%), those with IPIs ≤12 and ≥49 months were associated with a 35–22% lower prevalence of preconception folic acid use for the second pregnancy, relative to the reference group (Table 2). After adjustment of potential confounders, only weak associations with IPIs were observed, some

Table 1. Maternal characteristics according to interpregnancy interval in the Norwegian Mother and Child Cohort Study, 1999–2009

Characteristics[a]	All women[b]	Interpregnancy interval (months)						*P*-value[c]
		≤6	7–9	10–12	13–24	25–48	≥49	
No. of women	48 855	1230	1815	2833	14 321	16 640	12 016	
Maternal age (years)								<0.001
Mean ± SD	31.8 ± 4.13	30.2 ± 4.75	30.4 ± 4.50	30.9 ± 4.21	31.1 ± 3.93	31.6 ± 3.85	33.5 ± 4.07	
Median (range)	32 (16–47)	30 (18–43)	30 (19–44)	31 (16–44)	31 (19–47)	32 (19–47)	34 (21–47)	
Marital status (%)								<0.001
Single/other	2.8	3.6	2.1	2.0	1.9	2.1	5.1	
Married/cohabitant	97.2	96.4	97.9	98.0	98.1	97.9	94.9	
Educational level (%)								<0.001
Primary school	2.8	4.8	3.0	2.3	1.8	2.2	4.5	
Secondary school	33.2	38.7	32.3	29.7	25.6	31.7	44.8	
University/college	62.0	54.6	62.8	65.8	70.8	64.2	48.3	
Other	1.5	1.6	1.2	1.7	1.3	1.4	1.8	
Previous births (no.)								<0.001
Mean ± SD	1.47 ± 0.70	1.61 ± 0.83	1.45 ± 0.74	1.41 ± 0.71	1.35 ± 0.64	1.45 ± 0.66	1.66 ± 0.74	
Median (range)	1 (1–4)	1 (1–4)	1 (1–4)	1 (1–4)	1 (1–4)	1 (1–4)	2 (1–4)	
Maternal smoking (%)								<0.001
Yes	8.8	11.6	7.8	6.3	5.3	7.5	15.3	
Pregnancy planning (%)								<0.001
Yes	80.3	56.5	56.4	67.1	81.9	86.2	79.2	
Previous preterm birth (%)								<0.001
Yes	8.0	23.1	8.0	6.6	5.7	6.6	11.5	

[a]Characteristics at the time of the second pregnancy.
[b]Information was missing for 231 women on education, 322 women on smoking, and 599 women on pregnancy planning.
[c]*P* value for difference: chi-square test for categorical variables, one-way analysis of variance for continuous variables.
SD, standard deviation.

of which were statistically significant. The attenuated associations were mainly attributable to adjustment of pregnancy planning and maternal educational level.

Among women with a preterm birth in the previous pregnancy (8%), supplemental folic acid use before the second pregnancy decreased with increasing pregnancy spacing and was significantly higher when the IPI was shorter (Table 2). This association remained unchanged after adjustment of potential confounders. In this group, also substantially higher proportions of women with IPIs ≤6 months had planned their pregnancies (82%; not shown in tables).

Comment

This study showed that maternal use of folic acid supplements before a given pregnancy was generally lower in women with both short and long time intervals from the previous pregnancy. In the subgroup of women with a preterm birth in the previous pregnancy (8%), supplemental folic acid use was more frequent in mothers with shorter IPIs, suggesting alternated motives for preconception folic acid use in women with and without a previous preterm birth.

There are strong arguments for increasing use of folic acid supplements in women with closely spaced pregnancies. During pregnancy, there is an increased need of folate because of the increase in the red cell mass, enlargement of the uterus, and growth of the placenta and fetus.[17] This may result in lower maternal blood folate concentrations late in pregnancy, which may take several months to restore to normal concentrations after pregnancy.[10,18] Consequently, women who become pregnant shortly after a previous birth may be more depleted than other women.[8–10] Unless corrected, such depletion may contribute to an excess risk of NTDs in the subsequent pregnancy[10] as well as increased risk of maternal morbidity.[12]

It has been hypothesized that low folate status may also be the explanation of excess risk of other adverse pregnancy outcomes associated with short IPIs, e.g. small size for gestational age,[10] autistic disorders,[16] general birth defects,[19] and schizophrenia.[20] However, few studies have actually evaluated the

Table 2. Association between interpregnancy interval and preconception folic acid use in the Norwegian Mother and Child Cohort Study, 1999–2009

Group[a]	Interpregnancy interval (months)	No. of women	Supplement use (%)[b]	Model 1, prevalence ratio [95% CI][c]	Model 2, prevalence ratio [95% CI][d]	Model 3, prevalence ratio [95% CI][e]
Term birth	≤6	946	222 (23.5)	0.65 [0.58, 0.73]	0.92 [0.82, 1.02]	0.96 [0.86, 1.07]
	7–9	1669	398 (23.8)	0.66 [0.60, 0.72]	0.85 [0.78, 0.93]	0.87 [0.80, 0.94]
	10–12	2647	747 (28.2)	0.78 [0.73, 0.83]	0.90 [0.85, 0.96]	0.89 [0.84, 0.95]
	13–24[f]	13 499	4871 (36.1)	1	1	1
	25–48	15 541	5320 (34.2)	0.95 [0.92, 0.98]	0.94 [0.91, 0.97]	0.97 [0.95, 1.00]
	≥49	10 638	2620 (24.6)	0.68 [0.66, 0.71]	0.77 [0.74, 0.80]	0.81 [0.78, 0.84]
	Overall	44 940	14 178 (31.5)			
Preterm birth	≤6	284	120 (42.3)	1.24 [1.05, 1.46]	1.27 [1.09, 1.49]	1.29 [1.11, 1.49]
	7–9	146	48 (32.9)	0.96 [0.75, 1.24]	1.11 [0.88, 1.40]	1.09 [0.88, 1.35]
	10–12	186	57 (30.6)	0.90 [0.71, 1.14]	0.95 [0.76, 1.18]	0.98 [0.79, 1.22]
	13–24[f]	822	281 (34.2)	1	1	1
	25–48	1099	314 (28.6)	0.84 [0.73, 0.95]	0.84 [0.74, 0.96]	0.89 [0.79, 1.01]
	≥49	1378	299 (21.7)	0.63 [0.55, 0.73]	0.74 [0.64, 0.85]	0.79 [0.69, 0.91]
	Overall	3915	1119 (28.6)			

[a]Women with or without a preterm birth (<37 weeks) in the first pregnancy.
[b]Preconception folic acid use for the second pregnancy.
[c]Prevalence ratio was estimated by unadjusted log-binomial regression models.
[d]Prevalence ratio was adjusted for pregnancy planning (no, yes) and maternal education (primary school, secondary school, university/college, other).
[e]Additional adjustments for year of birth, maternal age at delivery, marital status (single/other, cohabitant/married), parity (1, 2, 3, 4 previous births), and maternal smoking at gestational week 18 (no, yes).
[f]Reference category.
CI, confidence interval.

folate depletion hypothesis in relation to these outcomes. In a study of fetal growth restriction,[11] initiation of folic acid supplementation between two consecutive pregnancies was shown to attenuate the adverse association of short IPI with small size for gestational age and low birthweight in the subsequent child.

Strong predictors for not following public health recommendations for supplement use are unplanned pregnancies, low educational level, and lack of awareness of the recommended timing of folic acid use.[6,7,21,22] Still, even for these women, there should be a large potential in improving preconception folic acid use from one pregnancy to another. One plausible strategy could be to recommend postpartum supplementation at the time of the first postpartum health care visits.[10–12] Such recommendation could be particularly relevant in countries where food fortification with folic acid has not yet been implemented.

The results of the present study may be generalizable to other populations of women of reproductive age. It should, however, be noted that participants in MoBa report higher prevalence of folic acid use than what is seen in the general population of women giving birth in Norway.[14] The problem with low folic acid use and folate depletion in women with short IPIs, therefore, may be more common in more representative populations.

In conclusion, in this large population-based cohort of pregnant women, we found a lower prevalence of preconception folic acid supplement use in women with both short and long IPI. The low use in short IPIs was mainly attributable to lower proportion of planned pregnancies and fewer women with higher education. More focus on assuring folic acid supplementation in these groups may have substantial disease preventive effects in a public health perspective. Also women with long IPI should increase their preconception folic acid intake to reduce the risk of having a baby with a NTD in the next pregnancy.

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