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Use of Folic Acid Supplements in Early Pregnancy in Relation to Maternal Plasma Levels in Week 18 of Pregnancy

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Abstract

We compared plasma-folate at week 18 of gestation with self-reported use of supplements containing folic acid from before pregnancy to 17 weeks gestation. Birth cohorts typically measure plasma-folate in mid-gestation, but effects of folic acid supplementation are sometimes specific to the periconceptional period. The relationship between mid-gestation plasma-folate and periconceptional supplementation is not known.

The sample comprised 2911 women from The Norwegian Mother and Child Cohort Study. For women reporting continuous supplementation from gestational week -4-17 (N=238), median plasma-folate was 15.72 at week 18 (in nmol/L). This was about threefold higher than the median plasma-folate of 5.67 for women reporting no supplementation from week -4-17 (N=844), but only slightly higher than the median plasma-folate of 13.34 for all women reporting supplementation in week 13-17 (N=1158). Reported supplementation before week 8 was not associated with plasma-folate at week 18, in an analysis that adjusted for continued supplementation after week 8.

Overall we found a strong and coherent relationship between self-reported folic acid use and plasma-folate at week 18. We also found that plasma-folate at week 18 did not reflect self-

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reported supplementation before 8 weeks. For periconceptional supplementation *per se*, self-report data may offer a better measure.

Keywords

Folic acid; maternal report; periconceptional; plasma; pregnancy cohort

1 Introduction

Folate is involved in cell division, cell differentiation, nucleotide synthesis, and DNA methylation and is important for fetal development[1, 2]. Maternal use of folic acid supplements has been shown to reduce the risk of having a child with neural tube defects[3-9]. For the protective effect to occur, the folic acid supplement must be taken before the neural tube closure around day 28. The official guideline in Norway is to take a folic acid supplement of 400 μg a day, to start a month before conceiving, and to use the supplement through the second or third month of pregnancy[10, 11]. Norway has not implemented any policy of food supplementation with folate.

With data from the Norwegian Mother and Child Cohort Study (MoBa), we recently showed that maternal use of folic acid taken before 8 weeks gestation was related to reduced risk of the child having severe language delay at age three [12]. Folic acid supplementation after week eight, however, was not related to language delay in the child at age three. This suggests that the relation of folic acid intake to severe language delay could also be gestation specific.

It would have been useful to also have plasma folate levels for the period before eight weeks gestation. Supplementation intake may be imperfectly recalled and reported[13]. In MoBa, however, the earliest time at which plasma folate could be measured was in the samples taken around week 18 (17 weeks completed gestation). This is similar to other large prospective pregnancy cohorts; the first blood sample is often collected in the second trimester [14-16].

Nonetheless, available data from MoBa offer a unique opportunity to shed light on the validity of self-report data, and examine the utility of week 18 plasma folate as an indicator of supplementation in the periconceptional period. Plasma folate at week 18 has been measured for a randomly selected subsample of participating women in MoBa, and MoBa collects remarkably detailed self-report data about maternal supplement use from before pregnancy to 17 weeks gestation. Thus we could assess the strength and coherence of the relationship between self-reported folate supplementation and plasma folate at week 18. We could also examine the relation of maternal plasma folate at week 18 to self-reported periconceptional supplementation. We focused on supplementation use before eight weeks gestation, the interval implicated in our previous study of language delay.

2 Research design and method

2.1 Study population

This study is based in MoBa, which is a prospective pregnancy cohort that has been described in detail elsewhere[17]. 108 841 pregnant women enrolled in the study during the recruitment period between 1999 and 2008, with a participation rate of 38.5% (http://www.fhi.no/moba-en). Written informed consent was obtained from each participant and the study was approved by the Regional Committee for Medical Research and the Norwegian Data Inspectorate.

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The present analysis used a sub-study of 3045 women in MoBa that has also been described in detail elsewhere [18]. Briefly, these women were a random sample of pregnant women enrolled in MoBa who gave birth during the period July 2002 to December 2003, donated blood around week 18, returned the first pregnancy questionnaire and a Food Frequency Questionnaire, and were registered in the Medical Birth Registry of Norway. Since concurrent intake of antibiotics may interfere with microbiological assays and falsely reduce plasma levels of folate to extremely low levels [19], we excluded samples with plasma folate levels <2.33 nmol/L (n=30, i.e. the lower 1 percentile). We also excluded 106 samples from pregnancies that led to twins or triplets. The remaining 2911 pregnancies were used in this analysis.

2.2 Variables

Information on dietary supplement use was collected using the first pregnancy questionnaire. Women received this questionnaire, after they had signed up for a routine ultrasound examination offered freely to all pregnant women in week 17-18 of pregnancy. It included detailed questions about use of vitamins, minerals, and other dietary supplements in four week time windows from before pregnancy. They were asked to record use according to the ingredient list on the supplement container. Self-reported use of folic acid and other dietary supplements has been described previously in this cohort[18, 20, 21].

For the present analysis, we created six variables to examine timing of folic acid supplementation: (1) supplementation in week 13 to 17; (2) supplementation in week 9 to 12; (3) supplementation in week -4 to 8; (4) initiation of supplementation: no folic acid; week -4-0; week 0-4; week 5-8; week 9-12; week 13-17); (5) supplementation in every four week period from -4 to 17; (6) supplementation in every four week period from -4 to 12. For the first three of these six variables, we differentiated supplement use into four mutually exclusive categories: a) no use of dietary supplements; b) other supplements, but no folic acid; c) folic acid only; d) folic acid in combination with other supplements. For the other three of the six variables, we combined a) and b) to represent “no folic acid supplementation”, and combined c) and d) to represent “folic acid supplementation”.

As shown in Table 1, potential confounders were maternal education (<12y; 12y, 13-16y, 17+ y); maternal age (<25y, 25-29y, 30-34y, 35+y); planned pregnancy (no/yes); parity (0, 1, 2+); BMI (<25, 25-29, 30-34, 35+); smoking (no, sometimes, daily). Plasma folate values are presented as medians and interquartile ranges.

2.3 Laboratory measurements

Collection of biological samples and laboratory methods have been described previously[22]. Non-fasting blood samples were used for the preparation of plasma, collected into EDTA tubes, centrifuged within 30 minutes after collection, and placed in the hospital refrigerator (4°C). They were sent by ordinary postal service over night to the Biobank of MoBa at the Norwegian Institute of Public Health. On the day of receipt (usually 1-2 days after blood collection), EDTA plasma samples were aliquoted onto polypropylene microtiter plates (300μL in each well, 96-well format), sealed with heat-sealing foil sheets, and stored in a freezer at -80°C. Plasma folate was determined by microbiological assay, using a chloramphenicol resistant strain of *Lactobacillus casei*[23]. The assay determines biologically active folate species, predominantly 5-methyl-tetrahydrofolate, and has a CV that corresponds to 4% within-day and 5% between days, at a population median. The sample handling did not involve addition of ascorbic acid.

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2.4 Statistical analysis

To compute p-values for differences in plasma folate medians, we used the Kruskal Wallis test. To describe the relationship between supplement use (no supp; other supp; folic acid only; folic acid+) in the three windows of exposure (week 13-17; week 9-12; week -4-8) we used Spearman's rank correlation. To examine the relationship of self-reported supplement use within three specified time periods (weeks 13 to 17; 9 to 12; -4 to 8) to plasma folate at week 18, we used unadjusted and adjusted linear regression models with plasma folate as a continuous outcome. The predictor variables were dummy variables created from the four categories of supplement use (no supp; other supp; folic acid only; folic acid+) within each of these three time periods of exposure. The non-standardized regression coefficient (B) shows the expected difference in nmol/L plasma folate for the different exposure categories (type of supplement used) with no supplement use as the reference category. We further examined the relationship of folic acid use according to when folic acid was started (week -4-0; week 0-4; week 5-8; week 9-12; week 13-17) to plasma folate at week 18. Predictor variables were dummy variables created for folic acid use (no/yes) within each of the four week windows, with no folic acid use as the reference category. We also examined the relationship of continuous folic acid use (from week -4 to 17) to plasma folate at week 18. Since some women used folic acid before conception but stopped folic acid after week 12 we also examined continuous use through week 12.

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, Illinois). All P-values were 2-sided and values below 0.05 were considered statistically significant.

3 Results

The mean age of the pregnant women was 30 years, more than 40 % had 13-16 years of education, more than 40 % were pregnant with their first child, 77 % said the pregnancy was planned, 65 % had a BMI < 25 kg/m^2, and about 12 % reported smoking (Table 1).

The relationship between maternal report of supplement use and maternal plasma folate, respectively, with covariates (maternal age, BMI, education, pregnancy planning, parity and smoking) are presented in Table 1. All the covariates showed some association with either supplement use or plasma levels, or both.

Table 2 describes the patterns of reported folate supplementation for three time periods (weeks 13 to 17; 9 to 12; -4 to 8). The use of ‘folic acid only’ was higher (17-18%) for weeks -4 to 8 and weeks 9 to 12 than for weeks 13 to 17 (7.2%). Cessation of folic acid supplements after week 12 would be in accord with official Norwegian guidelines. By contrast, use of ‘folic acid in combination with other supplements’ was similar (32%) in all three periods.

Correlations between the three periods (weeks 13 to 17; 9 to 12; -4 to 8) of supplement use (no supplements; other supplements; folic acid only; folic acid+) are presented in Table 3 and ranged from 0.39 to 0.66 (all significant at p<.001).

In Table 4, plasma folate is shown for the six different combinations of timing and type of supplement reported. Median plasma folate at week 18 (in nmol/L) was 5.67 for 844 (28.9%) reporting no use of folic acid; 15.72 for 238 (11.5%) reporting continuous use from -4 weeks to 17 weeks; and 13.34 for 1158 (39.7%) reporting use in weeks 13-17. The highest folate levels are seen in women who reported use of folic acid in week 13 to 17 (combinations 1, 4 and 5 in Table 4). Women that reported continuous use through week 17

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had about threefold higher median plasma folate than women reporting no folic acid use at all in the same period.

Table 5 presents the relation between plasma folate and patterns of reported supplement use in three models, based on linear regression, for three different periods, with 'no supplement use' as the reference in each. Model 1 is unadjusted; Model 2 adjusted for all the covariates in Table 1; and Model 3 is further adjusted by including use of supplements in the other two periods. The non-standardized regression coefficient (B) shows the expected difference in nmol/L plasma folate for the different exposure categories (type of supplement used). In Model 3 reported use of folic acid only and folic acid+ in weeks 13 to 17 show a strong relationship with plasma folate levels in week 18. The same relationship is not evident for report of use in weeks 9 to 12 and weeks -4 to 8. This lack of association would be expected for two reasons related to change in pattern of supplement use. First, 50% of women report to use folic acid in weeks 9 to 12, while in weeks 13 to 17 the proportion of use is down to 40% (Table 2). Those women who discontinue use after week 12 are mainly women that used folic acid only. Secondly, as can be seen under (4) in Table 4 several women, that reported no use of folic acid in weeks -4 to 8, started to use folic acid in weeks 9 to 17.

When analysing the relationship according to start of folic acid use and plasma folate levels, week 13 to 17 again showed the strongest association. Continuous use of folic acid from week -4 to 17 showed a stronger association than continuous use that was discontinued by week 12 (Table 6).

4 Discussion

There were three main findings. First, we found intriguing differences in the patterns of use among those who reported using folic acid only, and those using folic acid in combination with other supplements. About 18 % of the women used 'folic acid only' in the period from before pregnancy to 12 weeks gestation, but after week 12, about 60 % of these stopped taking folic acid. They were most likely following the official Norwegian guidelines, i.e. they used a folic acid supplement of 400 μg and stopped after the third month of pregnancy. For those women who reported folic acid use in combination with other supplements, the proportion did not change; about 32 % took supplements in all three windows of exposure. This group probably contains women who only used a multivitamin, as well as those who used other vitamins or supplements with various amounts of folic acid.

Second, maternal report of timing and length of folic acid supplements was well reflected in maternal folate plasma levels in week 18. Plasma folate levels in week 18 were most strongly associated with maternal report of folic acid use in weeks 13 to 17. Women who reported use of folic acid in this period had higher plasma folate than women with no use of folic acid in the same period, regardless of whether a folic acid supplement had been used earlier in pregnancy. A small group of women reported continuous use of folic acid supplements from before pregnancy through week 17. These women had the highest plasma folate levels, likely reflecting that plasma folate is a function of accumulative folate intake. We did, however, observe that women who followed the official guidelines, to use folic acid from before pregnancy through the second or third month of pregnancy (but not after week 12), had lower plasma folate levels than women who reported folic acid use in weeks 13 to 17 only.

Third, we found no association between plasma folate levels in week 18 and maternal report of folic acid use during the period from before pregnancy to eight weeks gestation, absent continued use of folate after week eight. We suggest two main reasons for this finding. One is that, as noted above, some women took folic acid supplements in accord with official Norwegian guidelines, i.e. stopped taking folic acid supplements at week 12. The lower

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levels in this group may reflect the natural progression of pregnancy (increasing plasma volume and increasing utilization of available folate), which could lead to depleted folate levels between folic acid discontinuation (week 12) and blood sampling (week 18)[24, 25]. The other is that some of the women, who did not take folic acid supplements during the period before pregnancy to eight weeks gestation, started taking folic acid after week eight. This would increase their plasma folate levels at week 18, especially because of the strong influence of recent intake.

To our knowledge, this is the first prospective study where pregnant women responded to detailed questions regarding supplement use over four week periods, referring to ingredients lists on the supplement containers. The precision of these data made it possible to differentiate patterns of maternal report of supplement use with plasma folate levels in week 18 (also the median week for return of the questionnaire). The detailed data collection also made it possible to create four mutually exclusive categories of supplement use, and thereby separate women who used folic acid only from women who used folic acid together with other micronutrients. Strengths of our study include its prospective design, detailed assessment of supplement use, careful measurement of plasma folate in week 18, and detailed information about important covariates.

A potential weakness is that recall may be better for more recent supplement use. Another limitation is that we had no information on the dose of folic acid taken. We also acknowledge that the use of non-fasting plasma samples might have added preanalytical variation, potentially attenuating the associations. It should be noted that the optimal folic acid dose has not been established. Official guidelines for periconceptional supplement use and food fortification with folate, vary among countries. For example, the official guideline in the US recommends a higher daily intake (400-800 μg)[26], although the recommended time period for use is similar to Norway (from one month before conception through the first trimester). Also, by contrast with Norway, the US has a policy of food supplementation with folate. These and other differences (e.g. dietary patterns) need to be taken into account when considering the implications of these findings for studies in other countries. Finally, while this paper has focused primarily on periconceptional use of folic acid, it should be kept in mind that the use of folic may be beneficial throughout pregnancy and lactation. For example, folic acid use later in pregnancy has been associated in some studies with reduced risk of preterm birth and low-birth babies[27, 28]. In a previous publication from the MoBa cohort, however, we did not find maternal folate status in the second trimester to be associated with either birth weight or gestational age[18].

Concluding remarks

In conclusion, our results suggest that self-reported folic acid use had a strong and coherent relationship with plasma folate at week 18. But self-reported use from before pregnancy to eight weeks gestation was not associated with plasma folate at week 18, absent continued use after week eight. For periconceptional supplementation *per se*, self-report may offer a better measure than plasma folate at week 18.

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Abbreviations

MoBa	the Norwegian Mother and Child Cohort
CI	Confidence Interval

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Table 1

Maternal characteristics according to maternal use of supplements in week 13 to 17 of pregnancy and median folate in plasma from week 18 (25th and 75th percentile in parenthesis), N=2911.

		No supp		Other supp		Folic acid only		Folic acid plus		Plasma folate		P values
		n	%	n	%	n	%	n	%	nmol/L	25th and 75th	
Maternal education	<12	334	(29.8)	127	(20.0)	42	(19.9)	159	(16.8)	7.1	(5.1-11.5)	
	12	196	(17.5)	90	(14.2)	19	(9.0)	137	(14.5)	7.9	(5.2-12.9)	
	13-16	405	(36.2)	264	(41.6)	97	(46.0)	418	(44.1)	9.3	(6.3-16.0)	<0.000 *a)*
	17+	148	(13.2)	132	(20.8)	45	(21.3)	215	(22.7)	10.4	(7.2-17.6)	
	missing	36	(3.2)	21	(3.3)	8	(3.8)	18	(1.9)	8.1	(5.8-12.3)	
Maternal age	<25	168	(15.0)	83	(13.1)	19	(9.0)	95	(10.0)	6.7	(4.8-10.0)	
	25-29	403	(36.0)	206	(32.5)	75	(35.5)	311	(32.8)	8.2	(5.9-14.1)	<0.000 *a)*
	30-34	368	(32.9)	253	(39.9)	89	(42.2)	396	(41.8)	9.8	(6.4-16.3)	
	35+	180	(16.1)	92	(14.5)	28	(13.3)	145	(15.3)	9.9	(6.1-16.4)	
Pregnancy planning	No	260	(23.2)	125	(19.7)	32	(15.2)	185	(19.5)	7.7	(5.3-11.7)	
	Yes	838	(74.9)	496	(78.2)	177	(83.9)	747	(78.9)	9.1	(6.1-15.6)	<0.000 *a)*
	missing	21	(1.9)	13	(2.1)	2	(0.9)	15	(1.6)	9.1	(6.4-16.0)	
Maternal BMI	<25	680	(60.8)	435	(68.6)	141	(66.8)	652	(68.8)	9.2	(6.3-15.9)	
	25-29	239	(21.4)	133	(21.0)	42	(19.9)	172	(18.2)	8.0	(5.6-12.8)	
	30-34	96	(8.6)	35	(5.5)	16	(7.6)	66	(7.0)	7.3	(5.0-12.2)	<0.000 *a)*
	35+	42	(3.8)	13	(2.1)	7	(3.3)	28	(3.0)	7.2	(5.0-12.0)	
	missing	62	(5.5)	18	(2.8)	5	(2.4)	29	(3.1)	7.6	(5.3-11.5)	
Parity	0	395	(34.7)	285	(44.5)	87	(41.0)	457	(48.1)	9.8	(6.4-16.8)	
	1	448	(39.4)	232	(36.3)	88	(41.5)	330	(34.7)	8.6	(6.0-14.0)	<0.000 *a)*
	2+	294	(25.9)	123	(19.2)	37	(17.5)	163	(17.2)	7.6	(5.2-12.7)	
Maternal smoking	No	923	(82.5)	557	(87.9)	195	(92.4)	836	(88.3)	9.1	(6.1-15.5)	<0.000 *a)*

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	No supp		Other supp		Folic acid only		Folic acid plus		Plasma folate		P values
	n	%	n	%	n	%	n	%	nmol/L	25th and 75th	
Sometimes	52	(4.6)	29	(4.6)	4	(1.9)	39	(4.1)	7.4	(5.0-13.1)	
Daily	127	(11.3)	43	(6.8)	12	(5.7)	65	(6.9)	6.5	(4.3-9.8)	
missing	17	(1.5)	5	(0.8)	0	(0.0)	7	(0.7)	7.3	(5.5-13.7)	

a) Kruskal-Wallis test used for differences in plasma medians.

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Table 2

Number and percentage of maternal supplement use in the different periods of use (week 13 to 17; 9 to 12; -4 to 8). Supplement use categorized as no supplements; other supplements; folic acid only; folic acid plus, N=2911.

	No supplements		Other supplements		Folic acid only		Folic acid plus	
Supplement use in weeks:	n	%	n	%	n	%	n	%
13 to 17	1 119	38.4	634	21.8	211	7.2	947	32.5
9 to 12	1 223	42.0	234	8.0	512	17.6	942	32.4
-4 to 8	1 180	40.5	267	9.2	526	18.1	938	32.2

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Table 3

Spearman correlations between the three periods of supplements use: week 13 to 17; week 9 to 12; week -4 to 8 (supplement use in four categories: no supplements; other supplements; folic acid only; folic acid plus), N=2911.

	Week 13 to 17	Week 9 to 12	Week -4 to 8
Week 13 to 17	1		
Week 9 to 12	.459**	1	
Week -4 to 8	.395**	.660**	1

** $p<.001$

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Table 4

Mean and median plasma folate (nmol/L) in week 18 for the different patterns of maternal report of supplement use, n=2911.

	N	Mean	Median	Percentiles 25t/75th
(1) Use of supplements anytime in week 13 to 17				
No supplements	1 119	8.49	6.77	4.89-9.79
Other supplements only	634	9.41	7.96	5.86-10.95
Folic acid only	211	16.04	12.89	8.06-21.43
Folic acid+	947	15.92	13.80	8.63-21.72
(2) Use of supplements anytime in week 9 to 12				
No supplements	1 223	9.97	7.08	4.90-11.57
Other supplements only	234	9.99	7.08	5.16-12.35
Folic acid only	512	11.32	8.99	6.81-12.71
Folic acid+	942	14.43	11.77	7.90-19.03
(3) Use of supplements anytime in week -4 to 8				
No supplements	1 180	9.25	6.84	4.79-10.79
Other supplements only	267	12.02	8.21	5.36-14.83
Folic acid only	526	12.22	9.51	6.86-14.66
Folic acid+	938	14.25	11.41	7.89-18.95
(4) Initiation of folic acid week -4 to 17				
No folic acid	844	6.96	5.67	4.29-7.66
Start w -4-0	500	13.99	11.06	7.77-18.93
Start w 0-4	413	13.55	10.80	7.46-17.73
Start w 5-8	551	13.08	10.23	7.33-16.49
Start w 9-12	301	11.49	9.37	6.79-14.27
Start w 13-17	302	15.87	13.23	7.69-21.22
(5) Use of folic acid in every four week period				
-4 to 17	238	17.17	15.72	9.37-23.10
(6) Use of folic acid in every four week period				
-4 to 12	351	14.86	12.32	8.28-20.17

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Table 5

Crude and adjusted linear coefficients for maternal report of supplement use and plasma levels of folate, no supplement use as reference, N=2911.

		Model 1			Model 2[a)]			Model 3[b)]		
	N	B	95 % CI		B	95 % CI		B	95 % CI	
Week 13 to 17										
Other supplements only	634	.922	.14	1.69	0.335	-0.45	1.12	-.246	-1.08	0.59
Folic acid only	211	7.549	6.37	8.71	6.879	5.69	8.06	6.744	5.52	7.96
Folic acid plus	947	7.425	6.73	8.11	6.657	5.94	7.36	5.580	4.76	6.39
Week 9 to 12										
Other supplements only	234	0.015	-1.16	1.10	-0.115	-1.30	1.07	-1.209	-2.43	0.01
Folic acid only	512	1.348	.47	2.22	0.805	-0.08	1.69	-0.405	-1.34	0.53
Folic acid plus	942	4.459	3.74	5.17	3.686	2.93	4.43	0.238	-0.77	1.24
Week -4 to 8										
Other supplements only	267	2.772	1.65	3.89	2.491	1.36	3.61	2.309	1.15	3.45
Folic acid only	526	2.975	2.11	3.84	2.406	1.52	3.28	1.556	0.62	2.48
Folic acid plus	938	5.006	4.28	5.72	4.294	3.54	5.03	2.291	1.33	3.25

Supplement use pattern are included as dummies. Linear regression was used to determine the coefficients for folate plasma levels (subjects with no supplement use in the relevant period as reference, B=0). Missing was excluded pairwise.

a) Adjusted for education, age, planned pregnancy, BMI and smoking.

b) Adjusted for education, age, planned pregnancy, BMI, smoking, and the other windows of supplement use (w 9-12 and w -4-8; w 13-17 and w -4-8; w 13-17 and w 9-12).

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Table 6

Crude and adjusted linear coefficients for maternal report of folic acid use and plasma levels of folate, N=2911.

		Model 1			Model 2[a)]		
	N	B	95 % CI		B	95 % CI	
Folic acid no/yes							
Start w -4-0	500	7.032	6.13	7.51	6.038	5.09	6.98
Start w 0-4	413	6.589	5.63	7.92	5.820	4.83	6.80
Start w 5-8	551	6.123	5.25	7.54	5.495	4.59	6.39
Start w 9-12	301	4.525	3.46	6.99	3.845	2.74	4.93
Start w 13-17	302	8.906	7.84	9.97	8.013	6.91	9.10
Folic acid in every four week period							
w -4 to 17	238	6.005	4.87	7.13	5.104	3.95	6.24
Folic acid in every four week period							
w -4 to 12	351	3.647	2.68	4.60	2.760	1.78	3.73

Folic acid use dichotomized. Linear regression was used to determine the coefficients for folate plasma levels (subjects with no folic acid supplement use as reference, B=0).

[a)] Adjusted for education, age, planned pregnancy, BMI and smoking.