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Original Contribution

Folic Acid and Multivitamin Supplement Use and Risk of Placental Abruption: A Population-based Registry Study

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The authors investigated a possible association of supplemental folic acid and multivitamin use with placental abruption by using data on 280,127 singleton deliveries recorded in 1999–2004 in the population-based Medical Birth Registry of Norway. Odds ratios, adjusted for maternal age, marital status, parity, smoking, pregestational diabetes, and chronic hypertension, were estimated with generalized estimating equations for logistic regression models. Use of folic acid and/or multivitamin supplements before or any time during pregnancy was reported for 36.4% of the abruptions (0.38% of deliveries) and 44.4% of the nonabruptions. Compared with no use, any supplement use was associated with a 26% risk reduction of placental abruption (adjusted odds ratio = 0.74, 95% confidence interval: 0.65, 0.84). Women who had taken folic acid alone had an adjusted odds ratio of 0.81 (95% confidence interval: 0.68, 0.98) for abruption, whereas multivitamin users had an adjusted odds ratio of 0.72 (95% confidence interval: 0.57, 0.91), relative to supplement nonusers. The strongest risk reduction was found for those who had taken both folic acid and multivitamin supplements (adjusted odds ratio = 0.68, 95% confidence interval: 0.56, 0.83). These data suggest that folic acid and other vitamin supplementation during pregnancy may be associated with reduced risk of placental abruption.

abruptio placentae; dietary supplements; folic acid; Norway; pregnancy; risk factors; vitamins

Abbreviations: CI, confidence interval; OR, odds ratio.

Periconceptional intake of folic acid supplements improves maternal folate status and reduces the risk of delivering a baby with neural tube defects (1, 2). Increasing evidence suggests that prenatal use of vitamins including folic acid may also have a protective effect on other adverse pregnancy outcomes and complications as well (3–8).

Maternal folate status has long been hypothesized to have a role in placental abruption. In the 1960s and 1970s, results from several observational studies suggested that low folate intake or low circulating folate increased the risk of placental abruption (9–11). In the 1980s, a possible link between other vitamins and placental abruption was also reported (12). However, a relation between vitamins and placental abruption is uncertain. Several studies are inconclusive (13–15), and the need for further research has been emphasized (16).

More recently, a consistent association between placental abruption and elevated plasma homocysteine concentrations was reported (17–20). Elevated homocysteine is a responsive marker of impaired folate status and has been shown to be an

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independent risk factor for premature vascular disease (21, 22). Homocysteine levels can be lowered by folic acid and vitamin B_{12} supplementation (23). However, we know of no available evidence as to whether homocysteine-lowering therapy can result in a reduced risk of placental abruption or any other homocysteine-related adverse pregnancy outcome.

Despite the proposed role of folate in placental abruption, few epidemiologic studies have addressed whether supplemental folic acid or multivitamin use during pregnancy can reduce occurrence of the complication. In the present study, we tested this hypothesis by using data from a large population-based registry in Norway, where both folic acid and multivitamin use before and during pregnancy, as well as placental abruption, have been recorded since December 1998.

MATERIALS AND METHODS

Study population

This study was based on all livebirths and stillbirths recorded in the Medical Birth Registry of Norway from 1999 through 2004. It was approved by the Norwegian Data Inspectorate.

The Medical Birth Registry of Norway is a large perinatal database in which registration of all births in Norway has been compulsory since 1967 (24). It comprises extensive medical information on the mother's health before and during pregnancy, on delivery, and on the newborn (since 1998, from gestational week 12). In brief, medical data are collected by using a standardized notification form for each birth. The form is completed at the time of birth (during hospitalization) by the attending health personnel and is sent to the registry within a few weeks postpartum. In December 1998, a revised version of the notification form was introduced to include new variables, such as maternal dietary supplement intake and smoking. The present study was based on data from only the revised form during the period 1999–2004.

Initially, our study comprised a total of 349,043 births. We excluded 12,944 (3.7 percent) multiple births, because they might involve complex confounding mechanisms that differ from those in singleton gestations (25), and an additional 55,972 (16.0 percent) deliveries for which information on vitamin use was missing, leaving data on 280,127 singleton deliveries (representing 226,724 women) for analyses.

Vitamin supplementation

Information on dietary supplement intake (collected during hospitalization) was recorded on the notification form by using check boxes and included questions on regular use of folic acid supplements before or during pregnancy and regular use of multivitamin supplements before or during pregnancy. Information on dose, frequency, or exact duration of folic acid use was not recorded. However, prenatal folic acid tablets used in Norway during the study period contained 0.4 mg of folic acid, while most multivitamin supplements contained 0.1–0.4 mg of folic acid. Furthermore, official 1998 guidelines state that all women who may become pregnant should take a daily folic acid supplement of 0.4 mg from 1 month before pregnancy through the first 2–3 months of pregnancy to reduce the risk of neural tube defects (26).

In this study, vitamin supplement use was classified as use of folic acid and/or multivitamin supplements before or any time during pregnancy. We also categorized the women by time period of vitamin use (i.e., both before and during pregnancy, during pregnancy only, and before pregnancy only) and by supplement type (i.e., multivitamin alone, folic acid alone, and both folic acid and multivitamin).

Placental abruption

Placental abruption was defined as the premature separation of a normally situated placenta and was recorded by a check box or open text coded according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision. Placental abruption is usually a clinical diagnosis based on prenatal signs and symptoms, such as antepartum hemorrhage, uterine pain or tenderness, or fetal distress. However, according to current practice in Norwegian hospitals, the diagnostic criteria are extended to include retro-placental impression or blood clot behind the placenta. Because delivery nearly always takes place on the same day as abruption, we used gestational age at delivery as an approximation of the time of the abruption. If a woman experienced an abruption and delivered before gestational week 37, we defined her abruption as preterm abruption.

Other variables

Gestational age, in weeks, was based on second-trimester ultrasound measurements (96.5 percent). If the ultrasound measurement was missing, gestational age was estimated on the basis of the last reported menstrual period (2.8 percent). Gestational age information was missing for 1,984 (0.7 percent) of the deliveries. We also abstracted data on maternal age (<25, 25–34, >34 years), marital status (married, cohabiting, single, or other), parity (0, 1, 2, >2 births), smoking habits (nonsmoker, smoker), pregestational diabetes (no/yes), chronic hypertension (no/yes), and preeclampsia (no/yes). Maternal smoking was recorded by check boxes for daily and occasionally smoking at the beginning of and at the end of pregnancy. Maternal diseases and preeclampsia were recorded by check boxes or open text coded according to *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision codes.

Statistical analyses

All statistical analyses were carried out by using SAS (Statistical Analysis System) version 9.1 software for Windows (SAS Institute, Inc., Cary, North Carolina). All p values were two sided, and values below 0.05 were considered statistically significant. The associations between vitamin supplement use and placental abruption were examined by using logistic regression models. Supplement use was incorporated in the models as a binary variable (no vitamin

TABLE 1. Vitamin supplement use by mothers delivering 280,127 singletons recorded in the Medical Birth Registry of Norway, 1999–2004, according to maternal characteristics

Maternal characteristic	No.	Vitamin supplement use (%)*			
		Any	Before and during pregnancy	During pregnancy only	Before pregnancy only
All mothers	280,127	44.4	15.9	27.3	1.3
Age at delivery (years)†					
<25	49,920	36.9	7.9	28.0	1.0
25–34	188,468	45.9	17.2	27.5	1.3
>34	41,738	46.6	19.7	25.4	1.5
Marital status‡					
Single	17,873	34.3	8.2	25.2	0.9
Cohabiting	121,453	44.5	14.7	28.6	1.2
Married	136,957	45.7	18.1	26.2	1.3
Parity§					
0	112,251	49.8	16.9	31.6	1.3
1	100,880	43.3	16.6	25.4	1.3
2	47,434	38.5	13.9	23.5	1.2
>2	19,473	33.2	11.3	20.8	1.1
Smoking¶					
No	194,318	47.6	18.1	28.2	1.3
Yes	58,029	40.1	10.8	28.2	1.1
Pregestational diabetes					
No	278,389	44.4	15.9	27.3	1.3
Yes	1,738	40.7	15.7	23.5	1.6
Chronic hypertension					
No	278,310	44.4	15.9	27.3	1.3
Yes	1,817	38.3	16.3	20.7	1.3
Preeclampsia					
No	269,217	44.5	15.9	27.3	1.3
Yes	10,910	42.6	14.6	26.7	1.3
Placental abruption					
No	279,057	44.4	15.9	27.3	1.3
Yes	1,070	36.4	13.2	22.1	1.1

* Refers to folic acid and/or multivitamin supplement use.
† Information on maternal age was missing for 1 delivery.
‡ Information on marital status was missing for 3,844 deliveries.
§ Information on parity was missing for 89 deliveries.
¶ Information on smoking was missing for 27,780 deliveries.

use/vitamin use), or as a categorical variable (i.e., no vitamin use, use both before and during pregnancy, use during pregnancy only, use before pregnancy only), or as an ordered categorical variable according to four increasing folic acid doses (i.e., no vitamin use, multivitamin use alone, folic acid use alone, both folic acid and multivitamin use), with no use of folic acid or multivitamin supplements as the reference category. We calculated both crude and adjusted odds ratios with 95 percent confidence intervals. Adjustment variables were maternal age, marital status, parity, smoking, pregestational diabetes, and chronic hypertension. In addition, correlation between pregnancy outcomes for the same woman was taken into account by using generalized estimating equations methodology, assuming an exchangeable working correlation structure (27).

A test for trend over folic acid intake was obtained by including the ordered categorical variable with combinations of folic acid and multivitamin use as a continuous variable, using the chi-square test in simple models and the z test in generalized estimating equations models. A test for effect modification of the vitamin-abruption association by smoking and preeclampsia was obtained by including product

terms for vitamin use and the two variables in adjusted generalized estimating equations models, using the Wald test. Preterm abruption (<37 weeks of gestation) was analyzed as a separate outcome in addition to the overall analysis. We used Cox regression analysis with a binary time-varying covariate (<37, ≥37 weeks) to test whether hazard ratios for vitamin use were significantly stronger for preterm than for term abruption.

RESULTS

Maternal characteristics among the 280,127 singleton deliveries recorded from 1999 through 2004 are shown in table 1. Mean maternal age at delivery was 29.2 (standard deviation, 5.0) years (range: 13–53 years). Almost 95 percent of the mothers were married or cohabiting, and 40 percent delivered for the first time. Twenty-three percent of the pregnant women smoked daily or occasionally during the pregnancy. About 1 percent of the women had pregestational diabetes or chronic hypertension, and almost 4 percent developed preeclampsia.

The overall reported use of folic acid and/or multivitamin supplements was 44.4 percent; 15.9 percent of the women used the vitamin supplements both before and during pregnancy, 27.3 percent used the supplements during pregnancy only, and 1.3 percent used them before pregnancy only (table 1). Supplement use was generally more frequent among older women and among mothers who were married or cohabiting, had lower parity, did not smoke, and did not have pregestational diabetes or chronic hypertension (table 1).

Placental abruption was reported for 0.38 percent of the deliveries ($n = 1{,}070$; table 1). About one half of the abruptions were preterm (<37 weeks of gestation, $n = 501$). A crude comparison of gestation-specific abruption rates showed that placental abruption was less common among women reporting folic acid and/or multivitamin use than among nonusers, especially when the abruption occurred before 37 weeks of gestation (figure 1).

Multiple logistic regression analyses showed that those who had taken folic acid and/or multivitamin supplements before or any time during the pregnancy had a 26 percent reduction in the risk of overall placental abruption (adjusted odds ratio (OR) = 0.74, 95 percent confidence interval (CI): 0.65, 0.84) and a 40 percent reduction in the risk of preterm abruption (adjusted OR = 0.60, 95 percent CI: 0.49, 0.73), after adjustment for maternal age, marital status, parity, smoking, pregestational diabetes, and chronic hypertension (table 2). Exclusion of women who developed preeclampsia did not alter the overall effect estimates (OR = 0.75, 95 percent CI: 0.65, 0.86). Further analyses showed that the association between vitamin use and placental abruption was slightly stronger for women who smoked during pregnancy (OR = 0.67, 95 percent CI: 0.53, 0.85) than for those who did not (OR = 0.78, 95 percent CI: 0.67, 0.92). Tests for effect modification of the vitamin-abruption association by smoking and preeclampsia were not statistically significant ($p = 0.17$ and $p = 0.69$, respectively).

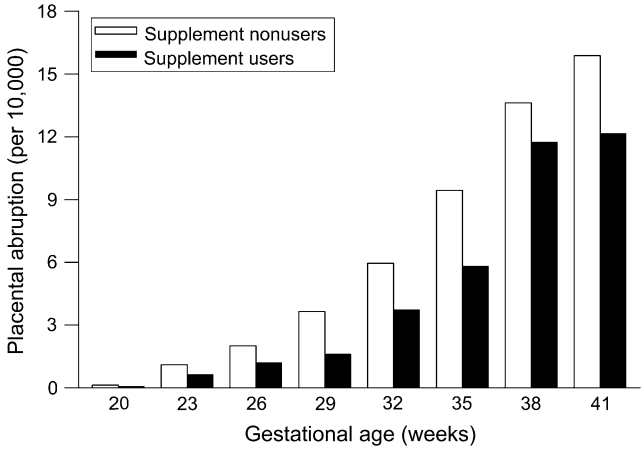

FIGURE 1. Gestation-specific occurrence of placental abruption ($n = 1{,}070$) among singleton births to vitamin supplement users ($n = 124{,}399$) and nonusers ($n = 155{,}728$), the Medical Birth Registry of Norway, 1999–2004. The *x*-axis represents ongoing pregnancies in 3-week intervals from 19 through 42 weeks of gestation. Vitamin supplement use refers to use of folic acid and/or multivitamin supplements before or any time during pregnancy.

Examining effects of potential confounders revealed that smoking was a strong determinant of placental abruption (OR = 1.82, 95 percent CI: 1.58, 2.09). However, in the present study, smoking or other adjustment variables had little or no impact on the association between vitamin supplement use and placental abruption.

We also investigated placental abruption in relation to time period of folic acid and/or multivitamin supplement intake: before and during pregnancy, during pregnancy only, and before pregnancy only (table 2). The odds ratios did not change by time period of use for either placental abruption overall or preterm abruption.

The relation of combinations of folic acid and multivitamin supplement use with placental abruption are presented in table 3. Because the strength of the associations did not change markedly by time period of supplement use and the number of cases in subgroups was limited, results for overall use are presented for each of the vitamin combinations. Adjusted regression analyses showed that the risk of overall placental abruption was reduced with the use of multivitamin and folic acid supplements (adjusted OR = 0.72 and adjusted OR = 0.81, respectively). The strongest risk reduction was found for women using both multivitamin and folic acid supplements (adjusted OR = 0.68, 95 percent CI: 0.56, 0.83), although confidence intervals overlapped across the subgroups.

Finally, we examined whether any use of folic acid and/or multivitamin supplements was more protective against preterm abruption than against term abruption. We found that both crude and adjusted relative risks of vitamin use for preterm and term abruption were significantly different (test for nonproportional hazards: $p = 0.009$ and $p = 0.015$, respectively).

TABLE 2. Odds ratios, with 95% confidence intervals, for placental abruption among 280,127 singleton deliveries in the Medical Birth Registry of Norway, 1999–2004, according to maternal vitamin supplement use

Vitamin supplement use*	No.	Placental abruption ($n = 1,070$)						Preterm abruption (<37 weeks of gestation) ($n = 501$)†					
		No.	%	Crude OR‡,§	95% CI‡	Adjusted OR¶	95% CI	No.	%	Crude OR	95% CI	Adjusted OR	95% CI
No use#	155,728	681	0.44	1		1		340	0.22			1	
Any use	124,399	389	0.31	0.71	0.63, 0.81	0.74	0.65, 0.84	161	0.13	0.59	0.49, 0.71	0.60	0.49, 0.73
Use before and during pregnancy	44,523	141	0.32	0.72	0.60, 0.87	0.76	0.62, 0.92	56	0.13	0.58	0.43, 0.76	0.59	0.43, 0.79
Use during pregnancy only	76,350	236	0.31	0.71	0.61, 0.82	0.73	0.63, 0.86	100	0.13	0.60	0.48, 0.75	0.61	0.48, 0.77
Use before pregnancy only	3,526	12	0.34	0.78	0.44, 1.38	0.73	0.39, 1.36	5	0.14	0.65	0.27, 1.57	0.57	0.21, 1.55

* Refers to folic acid and/or multivitamin supplement use.
† Excluded were 1,984 births (1,968 nonabruptions and 16 abruptions) because data on gestational age were missing.
‡ OR, odds ratio; CI, confidence interval.
§ Calculated by using simple logistic regression models.
¶ Calculated by using generalized estimating equations for logistic regression models, adjusted for maternal age, marital status, parity, smoking, pregestational diabetes, and chronic hypertension.
# Reference category.

DISCUSSION

We examined the effects of vitamin supplement use on placental abruption among 280,127 singleton deliveries in Norway during a 6-year period. Our data showed that women who had used folic acid or multivitamin supplements during pregnancy had a significantly lower risk of developing placental abruption than women who had not used such supplements. Our data also showed that this association was stronger when the abruption was preterm (<37 weeks of gestation).

The present study was based on data from a population-based registry and comprised separate information on folic acid and multivitamin supplement intake. The large sample size and the standardized collection of data allowed precise effect estimates overall as well as in subgroups. Furthermore, there was no mandatory fortification of foods with folic acid in Norway at the time of this study that could have affected our results. Nevertheless, findings from the present study should be interpreted with some caution. Information on vitamin supplement use for women with and without abruption was collected during hospitalization at the time of birth and not during the earlier stages of pregnancy. In addition, some hospitals may have underreported or provided incorrect information on the supplement type or on the timing of supplement use. Furthermore, our study did

TABLE 3. Odds ratios, with 95% confidence intervals, for placental abruption among 280,127 singleton deliveries in the Medical Birth Registry of Norway, 1999–2004, according to combinations of maternal folic acid and multivitamin supplement use

Vitamin supplement use*	No.	Placental abruption ($n = 1,070$)						Preterm abruption (<37 weeks of gestation) ($n = 501$)†					
		No.	%	Crude OR‡,§	95% CI‡	Adjusted OR¶	95% CI	No.	%	Crude OR	95% CI	Adjusted OR	95% CI
No use#	155,728	681	0.44	1	1	1		340	0.22	1	1	1	
Multivitamins alone	27,345	87	0.32	0.73	0.58, 0.91	0.72	0.57, 0.91	31	0.11	0.52	0.36, 0.75	0.48	0.32, 0.71
Folic acid alone	47,070	157	0.33	0.76	0.64, 0.91	0.81	0.68, 0.98	73	0.16	0.71	0.55, 0.91	0.75	0.57, 0.98
Folic acid and multivitamins	49,984	145	0.29	0.66	0.55, 0.79	0.68	0.56, 0.83	57	0.11	0.52	0.39, 0.69	0.53	0.39, 0.72
p for trend**				<0.001		<0.001				<0.001		<0.001	

* Refers to use before or any time during pregnancy.
† Excluded were 1,984 births (1,968 nonabruptions and 16 abruptions) because data on gestational age were missing.
‡ OR, odds ratio; CI, confidence interval.
§ Calculated by using simple logistic regression models.
¶ Calculated by using generalized estimating equations for logistic regression models, adjusted for maternal age, marital status, parity, smoking, pregestational diabetes, and chronic hypertension.
# Reference category.
** *p* for trend (chi-square test in simple models and *z* test in generalized estimating equations models).

TABLE 4. Characteristics of women with and without data on vitamin use for those with or without abruption for singleton births recorded in the Medical Birth Registry of Norway, 1999–2004

Characteristic	Nonabruption				Abruption			
	Vitamin data missing		Vitamin data provided		Vitamin data missing		Vitamin data provided	
	No.	%	No.	%	No.	%	No.	%
Total	55,569	100.0	279,057	100.0	403	100.0	1,070	100.0
Age at delivery (years)*								
<25	9,412	16.9	49,758	17.8	63	15.6	162	15.1
25–34	36,828	66.3	187,755	67.3	271	67.2	713	66.6
>34	9,327	16.8	41,543	14.9	69	17.1	195	18.2
Marital status†								
Single	3,579	6.8	17,795	6.5	44	11.5	78	7.4
Cohabiting	20,505	39.0	120,978	44.0	144	37.8	475	44.8
Married	28,534	54.2	136,449	49.6	193	50.7	508	47.9
Parity‡								
0	23,123	41.6	111,842	40.1	160	39.8	409	38.3
1	18,604	33.5	100,535	36.0	136	33.8	345	32.3
2	9,220	16.6	47,241	16.9	64	15.9	193	18.1
>2	4,590	8.3	19,352	6.9	42	10.4	121	11.3
Smoking§								
No	29,366	79.2	193,697	77.1	184	72.2	621	64.6
Yes	7,697	20.8	57,689	22.9	71	27.8	340	35.4
Pregestational diabetes								
No	55,177	99.3	277,334	99.4	396	98.3	1,055	98.6
Yes	392	0.7	1,723	0.6	7	1.7	15	1.4
Chronic hypertension								
No	55,395	99.7	277,256	99.4	398	98.8	1,054	98.5
Yes	174	0.3	1,801	0.6	5	1.2	16	1.5
Preeclampsia								
No	53,113	95.6	268,263	96.1	364	90.3	954	89.2
Yes	2,456	4.4	10,794	3.9	39	9.7	116	10.8

* Information on maternal age was missing for 3 nonabruptions.
† Information on marital status was missing for 6,786 nonabruptions and 31 abruptions.
‡ Information on parity was missing for 119 nonabruptions and 3 abruptions.
§ Information on smoking habits was missing for 46,177 nonabruptions and 257 abruptions.

not include information on dose, frequency, or exact duration of folic acid and multivitamin use. Such data would have led to more complete analysis and added value to the interpretation of the results.

The prevalence of placental abruption in our study (0.38 percent) is lower than that reported in the United States and Canada (28, 29) but is similar to that found in Sweden and Finland (30–32). A lower abruption rate found in the Nordic countries compared with that observed in North America could reflect a variation in the diagnostic criteria used, characteristics of the study population, or variation in the coding of placental abruption. Unfortunately, information on placental abruption in the Medical Birth Registry of Norway was not validated against clinical charts at the time of this study. Thus, we do not know whether the report of placental abruption was subject to some underreporting or other misclassification. In any case, we do not suspect that such misclassification differed between vitamin groups.

Deliveries for which vitamin use information was missing were excluded from our study. This exclusion may be a problem, because subjects who were included may differ in some systematic way from those who were not. We evaluated the possibility of bias due to missing data by comparing distributions of maternal age, marital status, parity, smoking, pregestational diabetes, chronic hypertension, and preeclampsia for women with and without abruption (table 4). We found essentially no differences between the subjects included and excluded regarding either the abruption or nonabruption group, suggesting that a systematic difference was not present.

Another concern in observational studies is unmeasured confounding. Although we adjusted for several potential

confounders, including smoking, the observed associations could be partially explained by intake of other dietary micronutrients, socioeconomic factors, or other health behaviors related to supplement use. However, adjustment had little impact on the association between vitamin supplement use and placental abruption, suggesting that unknown or unmeasured confounding factors would have to be strongly related to both vitamin use and placental abruption to produce the observed results.

Body mass index has been shown to be an important effect modifier of the association between periconceptional multivitamin use and preeclampsia (6). Unfortunately, we did not have information on maternal prepregnancy weight or body mass index to examine this possibility with respect to abruption.

To our knowledge, ours is the first large study to assess the association between supplemental vitamin intake and placental abruption. Although some intervention trials involving folic acid or other micronutrients have been conducted for placental abruption, they were small and provided no conclusive evidence (15, 33, 34). Nevertheless, our finding of a risk reduction with folic acid supplement use is consistent with results from a meta-analysis (35) and other reports (17–20) showing that maternal folate deficiency and elevated plasma homocysteine are associated with increased risk of placental abruption. Our results, however, disagree with those from a recent report from Canada, which showed that food fortification with folic acid had no impact on the prevalence of placental abruption (29). Some (van der Molen et al. (36), Nurk et al. 37)), but not all (Jaaskelainen et al. (38)), studies have also reported an association between decidual vasculopathy, including placental abruption, and a *C*-to-*T* substitution (*677C→T* polymorphism) in the methylenetetrahydrofolate reductase gene. A relation with the *677C→T* polymorphism may support our findings, because *TT* carriers tend to have lower serum folate and higher homocysteine concentrations than those with the *CT* or *CC* genotype (39).

In our study, associations between vitamin supplement use and placental abruption were strongest for women using both folic acid and multivitamin supplements (OR = 0.68), followed by multivitamins alone (OR = 0.72) and folic acid alone (OR = 0.81). Because confidence intervals were overlapping, we could not draw any firm conclusion from these estimates, although they suggest that vitamins other than folic acid may provide additional benefit. Earlier findings of significantly lower concentrations of vitamins A, B_6, B_{12}, and E in women with abruption support this possibility (12, 17, 18).

Surprisingly, effect estimates were similar for women who reported vitamin use both before and during pregnancy, during pregnancy only, or before pregnancy only. An explanation for this finding may be that the time categories of vitamin supplement use largely overlapped. The analysis of use before pregnancy only was based on a limited number of abruption events ($n = 12$), however, and results from this subgroup analysis should therefore not be emphasized.

Effects of vitamin use on placental abruption appeared to be stronger for preterm abruption than for overall abruption. One could argue that women who delivered early did not have the opportunity to take vitamins in time, thus resulting in an artificially larger reduction in the risk of preterm abruption compared with that of term abruption (40). However, in Norway, nearly all users of folic-acid-containing supplements start supplementation during the first 4 months of pregnancy (26), which is before any abruption was recognized in our study. In addition, we found that women who started use even before pregnancy and continued use during pregnancy had the same risk of preterm abruption as those who started supplementation during pregnancy. Our results of a stronger association of vitamin use with preterm abruption may therefore suggest a different etiology and a different pathogenesis of abruptions before term in comparison with those at term.

In conclusion, this is the first large study known to examine an association of supplemental folic acid and multivitamin use with placental abruption, comprising 1,070 abruptions among 280,127 singleton deliveries. Our study suggests that women who use folic acid and multivitamins during pregnancy are significantly less likely than nonusers to develop placental abruption. Our findings also suggest that vitamins other than folic acid may have a role in the etiology of abruption.

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