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Folic Acid and Risk of Preterm Birth, Preeclampsia, and Fetal Growth Restriction Among Women With Epilepsy

A Prospective Cohort Study

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Abstract

Background and Objectives

Women with epilepsy treated with antiseizure medication (ASM) have increased risk of pregnancy complications including preterm birth, fetal growth restriction, and preeclampsia. We aimed to investigate whether folic acid supplementation is associated with these pregnancy complications in women with epilepsy using ASM.

Methods

Singleton pregnancies in the prospective Norwegian Mother and Child Cohort Study (MoBa) (1999–2008) were included. Information on maternal epilepsy, ASM, folic acid supplementation, and pregnancy outcomes was obtained from the MoBa questionnaires and the Norwegian Medical Birth Registry. The main exposure, periconceptional folic acid supplementation, was defined as intake between 4 weeks before pregnancy and 12 weeks into pregnancy, retrospectively collected by recall of the mothers in weeks 17–19. The primary outcomes were preterm birth (gestational age <37 weeks at birth), small for gestational age (SGA), and preeclampsia.

Results

The study included 100,105 pregnancies: 99,431 without maternal epilepsy, 316 with maternal epilepsy and ASM exposure in pregnancy, and 358 with untreated maternal epilepsy. Among ASM-treated women with epilepsy, the risk of preterm birth was higher in those who did *not* use periconceptional folic acid (n = 64) compared with those who *did* (n = 245, the reference) (adjusted odds ratio [aOR] 3.3, 95% CI 1.2–9.2), while the risk of preterm birth among the reference was similar to the risk among women without epilepsy using folic acid periconceptionally (aOR 0.9, 95% CI 0.5–1.6). ASM-treated women with epilepsy starting folic acid after the first trimester had a higher risk compared with women without epilepsy with similar timing of folic acid (aOR 2.6, 95% CI 1.1–6.5), and even higher if not using folic acid (aOR 9.4, 95% CI 2.6–34.8). Folic acid was not associated with risk of preterm birth among women with epilepsy without ASM or among women without epilepsy. Folic acid was not associated with risk of preeclampsia or SGA among women with epilepsy.

Discussion

In women with epilepsy using ASM, periconceptional folic acid was associated with a lower risk of preterm birth. This finding supports the recommendation that ASM-treated women with epilepsy of childbearing potential should use folic acid supplementation on a regular basis.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Glossary

aOR = adjusted odds ratio; **ASM** = antiseizure medication; **BMI** = body mass index; **IQR** = interquartile range; **MBRN** = Medical Birth Registry; **MoBa** = Norwegian Mother and Child Cohort Study; **REC** = Regional Committees for Medical and Health Research Ethics.

Classification of Evidence

This study provides Class III evidence that for women with epilepsy using ASM, periconceptional folic acid supplementation decreases the risk of preterm birth.

Women with epilepsy, and especially those treated with antiseizure medication (ASM), have increased risk of pregnancy complications, such as preeclampsia, fetal growth restriction, and preterm birth.[1-7] These complications are leading causes of perinatal mortality and short-term and long-term morbidity for the mother and child.[8] Studies have suggested that folic acid supplementation may reduce pregnancy complications in women in general,[9-11] but findings are inconsistent.[12-15]

Folate is essential for DNA synthesis, and the demand for folate increases during pregnancy due to uterine, placental, and fetal growth.[16] Folate deficiency can lead to poor implantation and vascularization of the placenta and subsequently to preterm birth, preeclampsia, fetal growth restriction, and other placenta-related pregnancy complications.[17-19] Treatment with some ASMs is associated with reduced folate levels,[20,21] and many clinical guidelines recommend that ASM-treated women with epilepsy should take higher doses of folic acid supplements periconceptionally[22,23] than those recommended to pregnant women in general.[24] However, clinical practice varies internationally,[23,25] and the effect of folic acid supplementation on pregnancy complications has not been appropriately assessed.

Studies from the Norwegian Mother and Child Cohort Study (MoBa) have reported an association between periconceptional folic acid use and reduced risk of autistic traits and language delay in ASM-exposed children of women with epilepsy.[26,27] This prospective, nationwide observational study provides detailed information on timing of folic acid supplementation and plasma concentrations of folate in women with epilepsy. In this study, we used the same MoBa cohort to investigate whether folic acid supplementation is associated with the risk of preterm birth, preeclampsia, or restricted fetal growth, in women with and without epilepsy and ASM treatment.

Methods

Study Design

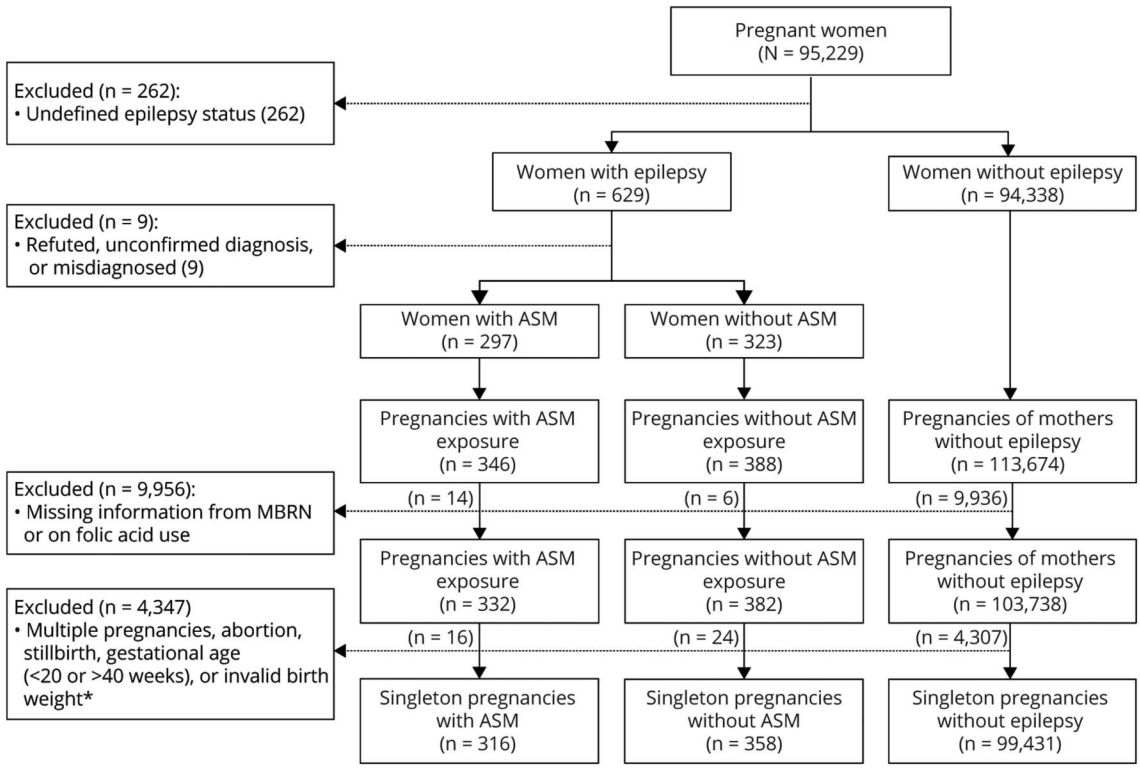
The MoBa is a prospective pregnancy cohort study conducted by the Norwegian Institute of Public Health.[28] Participants were recruited from all over Norway from 1999 to 2008. All pregnant women able to read and understand Norwegian were eligible for the study. The women consented to participation in 40.6% of the pregnancies. The cohort includes 114,500 children and 95,200 mothers. This study is based on version 10 of the quality-assured data files released for research in October 2017. The parents completed the questionnaires in pregnancy weeks 17–19 (Q1) and week 30 (Q2) regarding background, medical history, medication use, and use of folic acid supplements. In 2013, an additional questionnaire asking for more detailed information on epilepsy type, dose of folic acid supplement, and seizures during pregnancy was sent to 604 mothers with epilepsy in the MoBa database as part of a retrospective validation study (50% response rate).[29] Blood samples obtained from the mother during gestational weeks 17–19 and from mother and child (umbilical cord) at birth were stored in the MoBa Biobank.[30]

The Medical Birth Registry (MBRN) is a compulsory national health registry containing information on medication, maternal health before and during pregnancy including diagnoses such as epilepsy, and pregnancy outcomes such as gestational age, weight, and pregnancy complications.

Study Participants

The study population consisted of pregnancies of all women included in the MoBa cohort. We excluded pregnancies with missing information on pregnancy outcome (missing MBRN record), multiple pregnancy, gestational age at birth <20 or >44 weeks, stillbirths, spontaneous and late induced abortions, and pregnancies with missing information about folic acid supplementation (Figure 1). We further excluded children with unlikely birthweight, i.e., birthweight z-scores above +4 if gestational age <35 weeks or birthweight z-scores below −4.[31] The diagnosis of epilepsy and ASM use during pregnancy were self-reported in the MoBa questionnaire Q1 and/or reported by a doctor or midwife in MBRN and has been validated previously.[27-29] We excluded women with undefined epilepsy status in the MoBa database (Figure 1). The group "Epilepsy with ASM" consisted of women with epilepsy who were treated with any ASM during pregnancy (n = 316 pregnancies). Women with reported epilepsy in MoBa or MBRN, but without current ASM treatment, constituted the "Epilepsy without ASM" group (n = 358 pregnancies). A majority of these women (71%) had inactive epilepsy, defined as no seizures during the past 5 years or no ASMs during the

Figure 1 Flowchart of Included and Excluded Pregnancies



*Children with birthweight z-scores above +4 if gestational age <35 weeks and birthweight z-scores below −4. ASM = antiseizure medication; MBRN = Medical Birth Register of Norway; w = weeks.

past 2 years before pregnancy.[29] The "No epilepsy" group consisted of all pregnant women without epilepsy (n = 99,431 pregnancies).

Folic Acid Supplement Exposure

During gestational weeks 17–19 (Q1), the mothers registered the use of folic acid supplements (yes/no) for the following periods: earlier than 4 weeks before pregnancy, the past 4 weeks before pregnancy, and gestational weeks 0–4, 5–8, 9–12, and 13 or later. In gestational week 30 (Q2), the mothers reported the use of folic acid supplements for gestational weeks 13–16, 17–20, 21–24, 25–28, and 29 or later. Periconceptional use was defined as intake of any supplement during the period from 4 weeks before pregnancy to 12 weeks into pregnancy. Folic acid dose (0 mg, 0.4 mg, 1–2 mg, or ≥4 mg) was reported retrospectively in 286 of the 674 epilepsy pregnancies (135 of the 316 with ASM use) (eFigure 1, links.lww.com/WNL/C31). In 225 of the 316 ASM-exposed pregnancies, folate concentrations were measured in maternal plasma samples at gestational weeks 17–19. The concentration is given as the sum of 5-methyltetrahydrofolate and 4-alfa-hydroxy-5-methyltetrahydrofolate.[32,33] The reported dose of folic acid supplement used in the second and third trimester correlated with the maternal folate concentration measured in week 18 (eFigure 2, links.lww.com/WNL/C31).

ASM Exposure

ASM use during pregnancy was reported by the women in the MoBa questionnaires in gestational weeks 17–19 and week 30, and/or by a doctor or midwife in MBRN. In the previous validation study, there was a 100% agreement between self-reported ASM use in MoBa and ASM use registered in hospital case records.[29]

Pregnancy Outcome Variables

The primary outcome variables were obtained from MBRN: preterm birth (gestational age less than 37 weeks at birth), small for gestational age (SGA, as a proxy for fetal growth restriction, defined as an infant with birth weight below the 10th percentile for gestational age[31]), and preeclampsia. The composite variable *preeclampsia* included any of the following conditions: early preeclampsia (<34 weeks); mild, severe, or unspecified preeclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; and eclampsia.

A secondary outcome was gestational age at birth as a continuous variable. Gestational age was calculated from the ultrasound-based term date. If ultrasound term date was missing, the first day of the last menstrual period was used. Other pregnancy outcome variables used in descriptive analyses included cesarean section, 5-minute Apgar score, and birth weight.

Covariates

We selected potential confounders based on possible associations with the defined pregnancy outcomes and being exposed to ASM or folic acid supplement. The following covariates were included from MBRN: maternal age, pregestational diabetes, chronic hypertension, renal disease, induction of labor, and cesarean section. Covariates from the self-reported MoBa questionnaires included: parity, parental socioeconomic status (single mother, low educational attainment [≤9 years], low total household income [<400,000 NOK annually, equals around 41,000 EUR or 49,000 USD]), smoking or alcohol use during pregnancy, maternal pregestational body mass index (BMI), symptoms of depression or anxiety during pregnancy (mean score >1.75 on the Hopkins symptom checklist[34] at gestational week 17–19), ASM polytherapy (using 2 or more concomitant ASMs), any type of epileptic seizure during pregnancy, and tonic-clonic seizures during pregnancy.

Statistical Methods

In the main analysis, we estimated the odds of pregnancy complications (primary outcomes) in pregnancies of women *without* compared with women *with* periconceptional folic acid supplementation (primary exposure). Analyses were performed separately (stratified) for the 3 study groups: Epilepsy with ASM, Epilepsy without ASM, and No epilepsy (possible effect modifiers). In secondary analyses, we estimated the odds of pregnancy complications in women with epilepsy vs women without epilepsy (the groups Epilepsy with ASM vs No epilepsy and Epilepsy without ASM vs No epilepsy), stratified by the use of periconceptional folic acid supplementation. In another secondary analysis, the 2 groups of women with epilepsy were compared with the No epilepsy group, stratified by the timing of folic acid supplement: early use (periconceptionally), late start (second or third trimester), or no folic acid supplement use at all.

Groups were compared using the Pearson χ^2 test (χ^2) or Fisher exact test for categorical variables. For continuous variables, we used the Student *t* test or Wilcoxon rank sum (Mann-Whitney) for highly skewed or discrete variables. All tests were 2-sided, and statistical significance was assumed at $p < 0.05$. The associations between folic acid supplementation and/or ASM exposure and pregnancy complications were calculated as adjusted odds ratio (aOR) with 95% CI, using logistic regression analyses with adjustment for the predefined covariates (eMethods, links.lww.com/WNL/C31).

To assess interaction effects between folic acid supplementation and ASM use, we added an interaction term between these 2 variables in a logistic regression model. Sensitivity analyses were performed to assess the robustness of the findings by (1) excluding women who experienced tonic-clonic seizures during pregnancy, (2) excluding women who experienced any type of epileptic seizure during pregnancy, (3) excluding women treated with ASM polytherapy, and (4) including potential mediators of the effect on preterm birth as covariates in the regression models (planned cesarean section and induction of labor).

The analyses on folic acid duration included only pregnancies with gestational age ≥29 weeks at birth, because the latest reported period for the use of folic acid was "week 29 or later," to avoid that the calculated duration of folic acid use was restricted by premature births per se. The relationship between the different pregnancy complications and the folate concentration or folic acid supplement dose was investigated by multivariable linear regression and correlation analysis (for gestational age) and by logistic regression analysis (for dichotomous outcome variables). To account for clustering within mothers and thus lack of independence between siblings, we performed regression analyses with clustered robust standard errors.[35] Data were analyzed using Stata 16.0 (stata.com/).

Standard Protocol Approvals, Registrations, and Patient Consents

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and approval from The Regional Committees for Medical and Health Research Ethics (REC). This study was approved by REC (reference 2011/1616). Written informed consent was obtained from all participants in the study. The MoBa cohort is currently regulated by the Norwegian Health Registry Act.

Data Availability

The consent given by the participants does not allow storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply to datatilgang@fhi.no. Access to data sets requires approval from REC in Norway and a formal contract with MoBa.

Results

We included 100,105 singleton pregnancies in the analyses (Figure 1). In 674 of these, the mother had a diagnosis of epilepsy: 316 being exposed to ASM during pregnancy and 358 not exposed. Monotherapy was used in 255 of the 316 (81%) pregnancies with ASM exposure, polytherapy in 59 (19%), and 2 were not specified. The proportion of women using periconceptional folic acid supplement did not differ between women with epilepsy using ASM (245/309, 79%), women with epilepsy not using ASM (262/358, 73%), and women without epilepsy (74,282/98,394, 75%) ($p = 0.18$). The folic acid dose was significantly higher in women with epilepsy using ASM compared with women with epilepsy not using ASM throughout pregnancy (eFigure 1, links.lww.com/WNL/C31). Demographic and clinical characteristics are presented in Table 1.

Folic Acid Supplementation and Risk of Preterm Birth

In the Epilepsy with ASM group, the mean gestational age at birth was 279 days (SD = 11.8) in pregnancies *with*

Table 1 Demographic and Clinical Characteristics, Stratified by Epilepsy, ASM Use, and Use of Periconceptional Folic Acid

	Epilepsy with ASM		Epilepsy without ASM		No epilepsy	
	Periconceptional folic acid		Periconceptional folic acid		Periconceptional folic acid	
	No	Yes	No	Yes	No	Yes
	n = 64	n = 245	n = 96	n = 262	n = 24,112	n = 74,282
Maternal age, mean (SD), y	29.0 (5.3)	29.2 (4.8)	28.5 (5.4)	29.1 (4.8)	29.3 (5.1)	29.8 (4.4)
Parity, median (range)	2 (1–4)	1 (1–5)	2 (1–5)	1 (1–5)	2 (1–5)	2 (1–5)
Smoking during pregnancy, n (%)	11 (17)	23 (9)	20 (21)	11 (4)	3,221 (13)	3,934 (5)
Alcohol use during pregnancy, n (%)	5 (8)	6 (2)	4 (4)	5 (2)	769 (3)	1,805 (2)
No partner, n (%)	5 (8)	9 (4)	9 (10)	8 (3)	963 (4)	1,350 (2)
Low education, n (%)	4 (6)	7(3)	9 (9)	12 (5)	1,417 (6)	1,294 (2)
Low income, n (%)	8 (14)	26 (11)	17 (20)	18 (7)	2,242 (10)	3,959 (5)
Unplanned pregnancy, n (%)	23 (36)	49 (21)	33 (35)	55 (21)	6,512 (28)	12,531 (17)
Depression/anxiety in pregnancy, n (%)	9 (15)	48 (20)	17 (19)	36 (14)	2,918 (13)	7,381 (10)
Hypertension before pregnancy, n (%)	– (0)	3 (1)	1 (1)	2 (1)	123 (1)	387 (1)
Renal disease before pregnancy, n (%)	– (0)	2 (1)	1 (1)	2 (1)	128 (1)	404 (1)
Diabetes before pregnancy, n (%)	2 (3)	5 (2)	2 (2)	5 (2)	345 (1)	1,117 (2)
Any cesarean section, n (%)	17 (27)	63 (26)	19 (20)	53 (20)	3,413 (14)	10,345 (14)
Planned cesarean section, n (%)	7 (11)	26 (11)	7 (7)	18 (7)	1,327 (6)	3,722 (5)
Gestational age, mean (SD), d	272 (20)	279 (12)	278 (11)	278 (14)	279 (13)	279 (13)
Gestational age, mean (SD), wk	38.5 (2.9)	39.4 (1.7)	39.4 (1.6)	39.3 (1.9)	39.5 (1.8)	39.5 (1.8)
Apgar <7 at 5 min, n (%)	2 (3)	2 (1)	0 (0)	7 (3)	253 (1)	848 (1)
Birth weight, mean (SD), g	3,315 (713)	3,580 (590)	3,620 (563)	3,542 (576)	3,611 (575)	3,597 (556)
Seizure in pregnancy, n (%)[a]	5 (17)	35 (28)	5 (12)	8 (7)	NA	NA
Tonic-clonic seizure in pregnancy, n (%)	3 (10)	17 (13)	2 (5)	3 (2)	NA	NA
Folic acid high dose, n (%)[b]	NA	67/91 (74)	NA	16/54 (30)	NA	NA
Folate concentration, mean (SD)[c]	60.9 (33.7)	67.7 (28.1)	NA	NA	NA	NA
ASM polytherapy, n (%)	18 (28)	41 (17)	NA	NA	NA	NA
Lamotrigine, n (%)	26 (41)	102 (42)	NA	NA	NA	NA
Carbamazepine, n (%)	22 (34)	64 (26)	NA	NA	NA	NA
Valproate, n (%)	11 (17)	41 (17)	NA	NA	NA	NA
Levetiracetam, n (%)	5 (8)	29 (12)	NA	NA	NA	NA
Oxcarbazepine, n (%)	7 (11)	13 (5)	NA	NA	NA	NA
Topiramate, n (%)	3 (5)	14 (6)	NA	NA	NA	NA

Abbreviations: ASM = antiseizure medication; NA = not applicable.
Women with missing information on the use of folic acid supplement in the periconceptional period are not included in this table (n = 7 in the Epilepsy with ASM group, none in the Epilepsy without ASM group, and n = 1,037 in the No epilepsy group).
The ASMs listed were used in either monotherapy or polytherapy. Smoking: use in pregnancy; alcohol: ≥ 1 per month during pregnancy; and parity: parity 5 also includes >5.
[a] Any epileptic seizure during pregnancy, including tonic-clonic and other types of seizures.
[b] Proportion of women using high-dose folic acid supplement, that is, more than 0.4 mg daily. Only available for patients with epilepsy. n differs from the total group number because of 50% response rate on the questionnaire about dose.
[c] n = 219 total, measured in maternal plasma from women using ASM, between gestational week 17–19, given as nmol/L.

Table 2 Odds Ratios of Pregnancy Complications in Women Without Versus With Periconceptional Folic Acid Supplement, Stratified by Epilepsy and ASM Exposure

	Epilepsy with ASM		Epilepsy without ASM		No epilepsy	
	Periconceptional folic acid		Periconceptional folic acid		Periconceptional folic acid	
	No, n = 64	Yes, n = 245	No, n = 96	Yes, n = 262	No, n = 24,112	Yes, n = 74,282
Preterm birth, n (%)	9 (14)[a]	12 (5)	5 (5)	17 (6)	1,180 (5)	3,484 (5)
Crude OR	3.2 (1.3–7.9)[b]	1.0 (ref)	0.8 (0.3–2.2)	1.0 (ref)	1.0 (1.0–1.1)	1.0 (ref)
Adjusted OR	3.3 (1.2–9.2)[c]	1.0 (ref)	0.7 (0.2–2.3)	1.0 (ref)	1.0 (0.9–1.1)	1.0 (ref)
Small for gestational age, n (%)	9 (14)	21 (9)	7 (7)	19 (7)	1,606 (7)	4,776 (6)
Crude OR	1.7 (0.8–4.0)	1.0 (ref)	1.0 (0.4–2.4)	1.0 (ref)	1.0 (1.0–1.1)	1.0 (ref)
Adjusted OR	1.3 (0.5–3.6)	1.0 (ref)	0.9 (0.4–2.5)	1.0 (ref)	1.1 (1.0–1.2)[d]	1.0 (ref)
Preeclampsia, n (%)	3 (5)	15 (6)	0 (0)	17 (6)	910 (4)	2,804 (4)
Crude OR	0.8 (0.2–2.7)	1.0 (ref)	—	—	1.0 (0.9–1.1)	1.0 (ref)
Adjusted OR	0.8 (0.2–3.0)	1.0 (ref)	—	—	1.1 (1.0–1.1)	1.0 (ref)

Abbreviations: ASM = antiseizure medication; BMI = body mass index; OR = odds ratio; SGA = small for gestational age.
OR for placenta-related pregnancy complications in women *without* periconceptional folic acid supplement compared with women *with* periconceptional folic acid supplement, stratified by maternal epilepsy/ASM exposure. Logistic regression yielding ORs without adjustments (crude OR) and ORs adjusted for relevant covariates, with 95% CIs. The fully adjusted model includes the following covariates: maternal age, socioeconomic status, parity, anxiety/depression score, pregestational BMI, smoking during pregnancy, alcohol during pregnancy, unplanned pregnancy, pregestational diabetes, hypertension, and renal disease, plus polytherapy for the analyses with women on ASM. Some covariates were omitted in some analyses due to groups with zero or few observations (eMethods, links.lww.com/WNL/C31). Periconceptional folic acid: use of folic acid supplement 4 weeks before conception and/or during the first trimester. Preterm birth: gestational age <37 weeks. SGA: <10 percentile. Preeclampsia: preeclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; and eclampsia combined.
— =Statistical analyses not possible due to 0 or 1 observations in 1 or more of the variables.
[a] $p = 0.010$.
[b] $p = 0.013$.
[c] $p = 0.022$.
[d] $p = 0.008$.

periconceptional folic acid supplementation, compared with 272 days (SD = 19.8) *without* periconceptional folic acid ($p < 0.001$) (Table 1). In the Epilepsy without ASM and the No epilepsy group, the mean gestational age at birth was similar *with* and *without* folic acid supplement (Table 1).

In the Epilepsy with ASM group, 5% of the pregnancies (12 of 245) resulted in preterm birth if the mothers had used folic acid supplement periconceptionally, compared with 14% if they had not (9 of 64) (aOR 3.3, 95% CI 1.2–9.2) (Table 2). We found no association between folic acid supplement and preterm birth in the Epilepsy without ASM group or in the No epilepsy group (Table 2). Interaction analysis confirmed that the effect of folic acid differed between the 3 groups. Compared with the No epilepsy group, there was an interaction effect of folic acid supplement in the Epilepsy with ASM group ($p = 0.003$), but not in the Epilepsy without ASM group ($p = 0.619$). The aOR for preterm birth in the Epilepsy with ASM group did not change in sensitivity analyses neither when we excluded women with tonic-clonic seizures during pregnancy (n = 20), nor when we excluded women with any type of epileptic seizures during pregnancy (n = 40), nor when we included planned cesarean section (n = 33), induction of labor (n = 61), preeclampsia (n = 18), or type of ASM in the regression model (data not shown). When analyzing for each ASM separately, the association was not confined to any specific drugs (eTable 1, links.lww.com/WNL/C31).

Folic Acid Supplementation and Risk of SGA

In the Epilepsy with ASM group, the risk of SGA did not differ between women *without* periconceptional folic acid (14%) and women *with* periconceptional folic acid (9%) (aOR 1.3, 95% CI 0.5–3.6) (Table 2). In the Epilepsy without ASM group, the risk of SGA was the same *with* (7%) and *without* (7%) periconceptional folic acid (aOR 0.9, 95% CI 0.4–2.5) (Table 2).

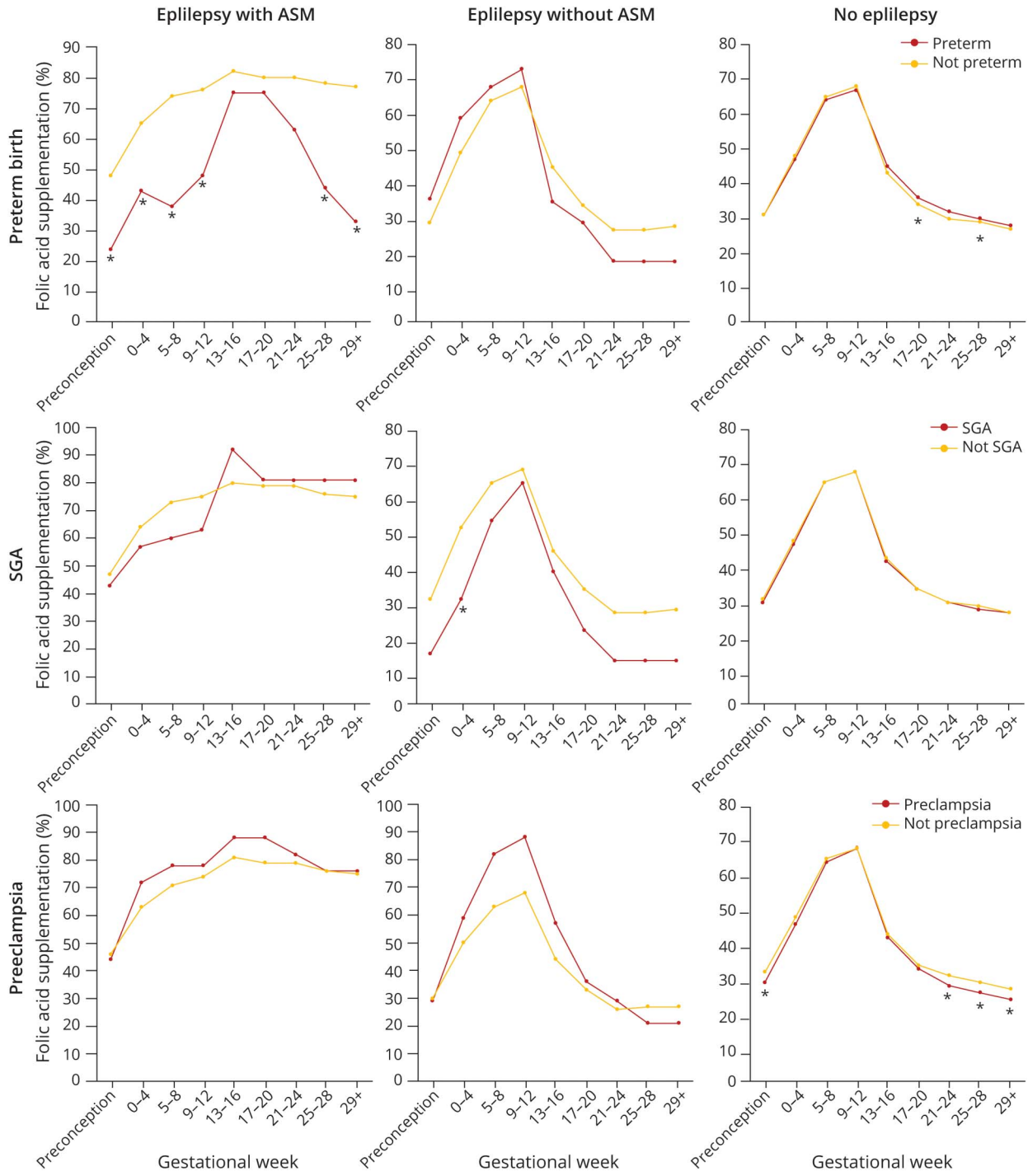
Folic Acid Supplementation and Risk of Preeclampsia

There was no association between periconceptional folic acid supplement and the risk of preeclampsia, neither in women with epilepsy using ASM, not using ASM, nor in the group without epilepsy (Table 2).

Timing of Folic Acid Supplementation

Among ASM-treated women with preterm birth, a lower proportion used folic acid supplement preconceptionally and during the first and third trimesters, compared with the ASM-treated women with no preterm birth (Figure 2). In the ASM-treated women who used folic acid supplementation already periconceptionally, the risk of preterm birth did not differ

Figure 2 Proportion (%) of Women Using Folic Acid Supplement at Different Time Points During Pregnancy



Red lines indicate women with the specified pregnancy complication. Orange lines indicate women without the specified pregnancy complication. Difference between the 2 groups was assessed by the Pearson χ^2 test ($\chi 2$) or Fisher exact test. Preterm birth: gestational age <37 weeks. SGA: <10 percentile. Preeclampsia: preeclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; and eclampsia combined. *p < 0.05. ASM = antiseizure medication; SGA = small for gestational age.

from women without epilepsy (aOR 0.9, 95% CI 0.5–1.6) (Table 3). By contrast, ASM-treated women who did not start the supplementation until the third or third trimester had an increased risk of preterm birth compared with women without epilepsy (aOR 2.6, 95% CI 1.1–6.5). ASM-treated women who did not take folic acid supplement at all during pregnancy (n = 16) had an even higher risk of preterm birth compared with women without epilepsy who did not take folic acid (aOR 9.4, 95% CI 2.6–34.8). The duration of folic acid supplementation was shorter among ASM-treated women with preterm birth (13.5 weeks, interquartile range [IQR] 10.5–26.0, n = 16) compared with ASM-treated women

Table 3 Odds Ratios (95% CIs) for Preterm Birth in Relation to Timing of Folic Acid Supplement

Timing of folic acid supplement	Epilepsy with ASM	Epilepsy without ASM	No epilepsy
Periconceptional use[d]	0.9 (0.5–1.6)	1.4 (0.9–2.3)	1.0 (ref)
	12 of 244 (5%)	17 of 260 (7%)	3,484 of 74,001 (5%)
Late start[e]	2.6 (1.1–6.5)[a]	0.6 (0.1–4.6)	1.0 (ref)
	5 of 48 (10%)	1 of 33 (3%)	368 of 7,752 (5%)
No use[f]	9.4 (2.6–34.8)[b]	1.3 (0.5–3.6)	1.0 (ref)
	4 of 16 (25%) [c]	4 of 63 (6%)	812 of 16,254 (5%)

Abbreviations: ASM = antiseizure medication; Ref = reference.
Adjusted odds ratios (OR) with 95% CIs for preterm birth in women *with* epilepsy compared with women *without* epilepsy. Analyses were stratified by timing of folic acid supplementation. Logistic regression analyses adjusted for maternal age, socioeconomic status, parity, anxiety/depression score, pregestational BMI, smoking during pregnancy, alcohol during pregnancy, pregestational diabetes, hypertension, and renal disease. Difference in proportions between groups was assessed by the Pearson χ^2 test (χ^2) or Fisher exact test.
Preterm birth: gestational week <37.
[a] $p = 0.046$.
[b] $p = 0.001$.
[c] $p < 0.0001$.
[d] Periconceptional use: folic acid supplement use during 4 weeks before conception or first trimester.
[e] Late start: start of folic acid supplement in second or third trimester.
[f] No use: no folic acid supplementation at any time during pregnancy.

without preterm birth (28 weeks, IQR 15.5–31.0, n = 275, $p = 0.008$). In the Epilepsy without ASM group and the No epilepsy group, the duration of folic acid use was similar among those *with* and those *without* preterm birth (data not shown).

Folic Acid Supplement Dose and Plasma Concentrations

Among ASM-treated women, higher doses of folic acid supplement in the third trimester correlated with increasing gestational age at birth (eFigure 3, links.lww.com/WNL/C31). For lamotrigine users, a lower folic acid dose in the second (n = 43) and third (n = 45) trimesters correlated moderately with low gestational age in their children, with Spearman rho 0.38, $p = 0.01$, and Spearman rho 0.36, $p = 0.02$, respectively (eFigure 4, links.lww.com/WNL/C31). An opposite pattern was seen for valproate, with Spearman rho −0.61 ($p = 0.03$) in the second trimester and −0.58 ($p = 0.02$) in the third trimester, but these groups were small (n = 13 and n = 16, respectively) (eFigure 5, links.lww.com/WNL/C31). There was no linear relationship between folate concentrations in week 18 and gestational age at birth (eFigure 6, links.lww.com/WNL/C31).

Classification of Evidence

This study provides Class III evidence that for women with epilepsy using ASM, periconceptional folic acid supplementation decreases the risk of preterm birth.

Discussion

In this prospective cohort study, women with epilepsy using ASM had a lower risk of preterm birth when they used periconceptional folic acid supplementation. The risk of preterm birth was 3 times higher in ASM-exposed women *without* periconceptional folic acid supplement compared with ASM-exposed women *with* folic acid supplement. Fourteen percent of the ASM-exposed women with epilepsy *without* periconceptional folic acid supplementation experienced preterm birth compared with only 5% in those *with* supplementation. Folic acid supplementation was not associated with risk of preterm birth among women with epilepsy *not* using ASM or in women without epilepsy. Folic acid supplementation did not influence the risk of SGA or preeclampsia in women with epilepsy.

A possible risk reduction of preterm birth by periconceptional folic acid supplementation is important because preterm birth is associated with short-term and long-term morbidity for both mother and child.[8] Two previous population-based cohort studies found an increased risk of preterm birth and pregnancy-related hypertensive disorders in women with epilepsy, but they could not identify any effect of folic acid supplement.[7,36] These studies did not have access to any detailed information on supplement use, whereas we were able to include specified and self-reported folic acid supplement data collected during pregnancy. We found that the association between folic acid supplement and risk of preterm birth was evident only if supplementation was used preconceptionally or in the first trimester. Thus, early start of folic acid supplement appears to be crucial. In the early stages of pregnancy, folate plays an important role in the development of the placenta, and it is also essential for growth and functioning of the placenta throughout pregnancy.[16] Although plasma folate concentrations decline with advancing pregnancy if intake is not adequate, it has been shown that folate stores in red blood cells increase slightly in midpregnancy and decrease during the third trimester.[37,38] Our study shows that ASM-treated women with epilepsy who experienced preterm birth were less likely to have used folic acid supplement before conception and during the first trimester, but also during the third trimester. They also had shorter duration of folic acid use than ASM-treated women with epilepsy with full term

pregnancies, suggesting that the continuous use of folic acid throughout pregnancy may be beneficial.

The importance of an early start of folic acid supplementation has previously been demonstrated for the general population.[9,11] The risk of preterm birth was lower if folic acid supplement was started before conception, and the risk decreased with the duration of supplementation preconceptionally. Two randomized controlled trials where high-dose folic acid supplement was started during the second trimester failed to show a preventive effect on the risk of preterm birth or preeclampsia in the general population.[12,15] We did not find any beneficial effect of folic acid during pregnancy on preterm birth in the large group of women without epilepsy. Other beneficial effects of periconceptional folic acid that have been reported in studies from the general population include reduced risk of neural tube defects[24] and improved cognitive function and neurodevelopment in the children.[39,40] In ASM-exposed children of women with epilepsy, studies have shown that maternal periconceptional folic acid supplementation improves their cognitive functions and verbal abilities and reduces their risk for autistic traits.[26,27,41,42]

There are several plausible mechanisms for a folic acid effect in ASM-treated women with epilepsy during pregnancy. Carbamazepine, valproate, phenytoin, barbiturates, lamotrigine, and possibly other ASMs interfere with folate metabolism.[20,21] Valproate, and to a lesser extent lamotrigine and levetiracetam, induces a downregulation of placental transporters involved in transfer of folate from the maternal to the fetal circulation.[43,44] Valproate and phenytoin also increase transporters that are involved in folate removal from cells.[44] Furthermore, the expression of folate transporters is reduced in preterm placentas.[45] Together, this suggests that women with epilepsy using ASM may need higher folic acid intake than others to ensure adequate transport of folate from mother to fetus. In line with this, many clinical guidelines recommend that ASM-treated women with epilepsy should take higher doses of folic acid supplements periconceptionally than the 0.4 mg daily, which is recommended to women in general when trying to conceive.[22,23] As unplanned pregnancies are common among women with epilepsy,[46] the International League Against Epilepsy Task Force on Women and Pregnancy recommends that all ASM-treated women with epilepsy having childbearing potential should take folic acid supplement of at least 0.4 mg daily.[47]

Strengths of this study include the nationwide cohort, the prospective design, the precise data concerning intake of folic acid supplement specified in 4-week periods, and the detailed information on a range of covariates that enabled us to adjust for important confounders. The validity of the epilepsy diagnosis in this cohort is high,[29] and the self-reported use of ASM has been confirmed by plasma concentrations.[29] Self-selection in MoBa may cause biased prevalence estimates but does not usually affect exposure-outcome associations.[48] The primary outcomes in this study were based on ultrasound assessments and medical birth records with minimal potential for information bias. Although the study is prospective, the first questionnaire was completed at pregnancy week 18, and folic acid intake at that time point might be more precisely reported than intake periconceptionally. This should, however, be nondifferential between groups and cause minimal recall bias. There is no mandatory folic acid food fortification in Norway, which could affect the generalizability of our findings to countries with such fortification.

Owing to the observational nature of this study, we cannot completely exclude that associations or lack of such are in part caused by confounding factors or the indication for treatment. We adjusted for a range of confounders, but there might still be unmeasured confounding related to differences in lifestyle or disease severity between women *with* and *without* folic acid supplementation. Women *with* and *without* supplementation did not differ in frequency of tonic-clonic seizures. Information on tonic-clonic seizures from the retrospective study of the MoBa cohort has been validated against hospital records, and the self-reported information was accurate.[29] Polytherapy was more frequent among women *without* than among women *with* periconceptional folic acid supplement. However, the association between folic acid supplementation and preterm birth was robust to adjustments for polytherapy and to the exclusion of women with tonic-clonic seizures or any type of seizure during pregnancy, showing that the increased risk of preterm birth was not confined to women with an uncontrolled seizure situation. We found no association between folic acid supplement and preterm birth when analyzing the ASMs separately. Since the statistical power was low for each individual ASM, weak associations would not be detected. We found that the retrospectively self-reported dose of folic acid supplement in the third trimester correlated with gestational age at birth among ASM users. When analyzing individual ASMs, the direction of this correlation differed between lamotrigine and valproate, but the number of women using valproate was low and the correlation among valproate users may be confounded by indication for high-dose folic acid supplement. Folate plasma concentrations in week 18 did not correlate with any of the pregnancy complications studied. However, folate concentrations in week 18 are not representative for folate concentrations during the periconceptional period when the placenta develops because plasma folate concentrations reflect folate intake over the past few weeks only.[49,50] As the women were enrolled in the study around pregnancy week 18, it was not possible to measure plasma folate concentrations in the periconceptional period.

We found that women with epilepsy using ASM who did *not* use folic acid supplements periconceptionally had a 3-fold increased risk of preterm birth compared with women with epilepsy using ASM who *did* use folic acid supplements. Our findings suggest a protective effect of folic acid supplementation on preterm birth if the supplement starts before pregnancy or in the first trimester. Our study supports the recommendation that ASM-treated women with epilepsy with a potential to become pregnant should use daily folic acid supplement.

The optimal dose of folic acid remains unknown and likely varies between different ASMs and between individual women. A broad scope of studies on even larger populations are essential to assess the risks and benefits of folic acid for individual ASMs, also taking genetic variations in folate metabolism into account.

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