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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 MoBa questionnaires and the Norwegian Medical Birth Registry. The main exposure, periconceptual 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 week 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 to those who *did* (n=245, the reference) (adjusted odds ratio (aOR) 3.3, 95% confidence interval (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 to 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.

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.

ACCEPTED

Introduction:

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 birth¹⁻⁷. These complications are leading causes of perinatal mortality and short- and long-term morbidity for the mother and child⁸. Studies have suggested that folic acid supplementation may reduce pregnancy complications in women in general⁹⁻¹¹, but findings are inconsistent¹²⁻¹⁵.

Folate is essential for DNA synthesis, and the demand for folate increases during pregnancy due to uterine, placental and fetal growth¹⁶. 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 complications¹⁷⁻¹⁹. 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 general²⁴. However, clinical practice varies internationally^{23,25}, and the impact 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 the present study, we used the same MoBa cohort to investigate whether folic acid supplementation is associated with the risk of preterm birth, pre-eclampsia or restricted fetal growth, in women with and without epilepsy and ASM treatment.

Methods

Study design

The MoBa Study is a prospective pregnancy cohort study conducted by the Norwegian Institute of Public Health²⁸. 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. The current study is based on version 10 of the quality-assured data files released for research in October 2017. The parents completed questionnaires in pregnancy week 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 week 17-19 and from mother and child (umbilical cord) at birth were stored in the MoBa Biobank³⁰.

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 -4³¹. 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 previously²⁷⁻²⁹. 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 last five years or no ASMs during the last two years prior to pregnancy²⁹. 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 use of folic acid supplements (yes/no) for the following time periods: earlier than 4 weeks before pregnancy, the last 4 weeks before pregnancy, gestational weeks 0-4, 5-8, 9-12, and 13 or later. In gestational week 30 (Q2), the mothers reported use of folic acid supplements for gestational weeks 13-16, 17-20, 21-24, 25-28, and 29 or later. Periconceptual 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 in the Supplement). In 225 of the 316 ASM-exposed pregnancies, folate concentrations were measured in maternal plasma samples at gestational week 17-19. The concentration is given as the sum of 5-methyltetrahydrofolate and 4- α -hydroxy-5-methyltetrahydrofolate^{32,33}. The reported dose of folic acid supplement used in the 2nd and 3rd trimester correlated with the maternal folate concentration measured in week 18 (eFigure 2 in the Supplement).

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 records²⁹.

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 age³¹), and preeclampsia. The composite variable *preeclampsia* included any of the following conditions: early preeclampsia (<34 weeks), mild, severe, or unspecified preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), 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 caesarean 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 caesarean 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 checklist³⁴ at gestational week 17-19), ASM polytherapy (using two 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 to women *with* periconceptual folic acid supplementation (primary exposure). Analyses were performed separately (stratified) for the three 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 versus women without epilepsy (the group “Epilepsy

with ASM” vs. “No epilepsy”, as well as “Epilepsy without ASM” vs. “No epilepsy”), stratified by the use of periconceptual folic acid supplementation. In another secondary analysis, the two groups of women with epilepsy were compared to the “No epilepsy” group, stratified by the timing of folic acid supplement: early use (periconceptually), late start (2nd or 3rd trimester), or no folic acid supplement use at all.

Groups were compared using the Pearson's chi-squared test (χ^2) or Fisher's exact test for categorical variables. For continuous variables, we used the Student's t-test or Wilcoxon rank-sum (Mann-Whitney) for highly skewed or discrete variables. All tests were two-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% confidence interval (CI), using logistic regression analyses with adjustment for the predefined covariates (eMethods in the Supplement).

To assess interaction effects between folic acid supplementation and ASM use, we added an interaction term between these two 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 caesarean section and induction of labor).

The analyses on folic acid duration included only pregnancies with gestational age ≥ 29 weeks at birth, since the latest reported period for 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 errors³⁵. Data were analyzed using Stata 16.0 (<https://www.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). The current 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 two 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 to women with epilepsy not using ASM throughout pregnancy (eFigure 1). 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* periconceptional folic acid supplementation, compared to 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 to 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 three groups. Compared to 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 caesarean 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 in the Supplement).

Folic acid supplementation and risk of SGA

In the 'Epilepsy with ASM' group, the risk of SGA did not differ between women *without* periconceptual folic acid (14%) and women *with* periconceptual 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%) periconceptual 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 periconceptual 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 1st and 3rd trimesters, compared to the ASM-treated women with no preterm birth (Figure 2). In the ASM-treated women who used folic acid supplementation already preconceptionally, the risk of preterm birth did not differ from

women without epilepsy (aOR 0.9, 95% CI 0.5–1.6) (Table 3). In contrast, ASM-treated women who did not start the supplementation until the 2nd or 3rd trimester had an increased risk of preterm birth compared to 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 to 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 to ASM-treated women 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 3rd trimester correlated with increasing gestational age at birth (eFigure 3 in the Supplement). For lamotrigine users, a lower folic acid dose in the second (n=43) and third (n=45) trimester correlated moderately with low gestational age in their children, with Spearman’s rho 0.38, p=0.01, and Spearman’s rho 0.36, p=0.02, respectively (eFigure 4 in the Supplement). An opposite pattern was seen for valproate, with Spearman’s rho -0.61 (p=0.03) in the second and -0.58 (p=0.02) in the third trimester, but these groups were small (n=13 and n=16, respectively) (eFigure 5 in the Supplement). There was no linear relationship between folate concentrations in week 18 and gestational age at birth (eFigure 6 in the Supplement).

Classification of Evidence: This study provides Class III evidence that for women with epilepsy using ASM, periconceptual 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 periconceptual folic acid supplementation. The risk of preterm birth was three times higher in ASM-exposed women *without* periconceptual folic acid supplement compared to ASM-exposed women *with* folic acid supplement. Fourteen percent of the ASM-exposed women with epilepsy *without* periconceptual folic acid supplementation experienced preterm birth compared to only five percent 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 periconceptual folic acid supplementation is important as preterm birth is associated with short- and long-term morbidity both for mother and child⁸. 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 pregnancy¹⁶. While 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 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 defects²⁴ 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, induce a down-regulation 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 cells⁴⁴. Furthermore, the expression of folate transporters is reduced in preterm placentas⁴⁵. 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 epilepsy⁴⁶, 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 daily⁴⁷.

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 high²⁹, and the self-reported use of ASM has been confirmed by plasma concentrations²⁹. Self-selection in MoBa may cause biased prevalence estimates but does not usually affect exposure-outcome associations⁴⁸. 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 non-differential 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.

Due to the observational nature of this study, we can not 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 accurate²⁹. 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 seizures 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 3rd 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, since 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 three-fold increased risk of preterm birth compared to 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.

Appendix 1: Authors

Name	Location	Contribution
Silje Alvestad, MD PhD	University of Bergen, Norway; National Center for Epilepsy, Oslo University Hospital, Norway	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Elisabeth Husebye, MD	University of Bergen, Norway; Haukeland University Hospital, Norway	Acquisition of data; interpreted the data; revised the manuscript for intellectual content
Jakob Christensen, Dr.Med.Sci.	Aarhus University Hospital, Denmark	Interpreted the data; revised the manuscript for intellectual content
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Nils Erik Gilhus, MD Dr.Med	University of Bergen, Norway; Haukeland University Hospital, Norway	Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content
Torbjörn Tomson, MD PhD	Karolinska Institutet, Sweden; Karolinska University Hospital, Sweden	Interpreted the data; revised the manuscript for intellectual content
Marte Bjørk, MD PhD	University of Bergen, Norway; Haukeland University Hospital, Norway	Design and conceptualized study; acquisition of data; interpreted the data; revised the manuscript for intellectual content

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Bibliography

1. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet* 2015;386:1845-1852.
2. MacDonald SC, Bateman BT, McElrath TF, Hernandez-Diaz S. Mortality and Morbidity During Delivery Hospitalization Among Pregnant Women With Epilepsy in the United States. *JAMA Neurol* 2015;72:981-988.
3. Kilic D, Pedersen H, Kjaersgaard MI, et al. Birth outcomes after prenatal exposure to antiepileptic drugs--a population-based study. *Epilepsia* 2014;55:1714-1721.
4. Razaz N, Tomson T, Wikstrom AK, Cnattingius S. Association Between Pregnancy and Perinatal Outcomes Among Women With Epilepsy. *JAMA Neurol* 2017;74:983-991.
5. Hernandez-Diaz S, McElrath TF, Pennell PB, et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. *Ann Neurol* 2017;82:457-465.
6. Artama M, Braumann J, Raitanen J, et al. Women treated for epilepsy during pregnancy: outcomes from a nationwide population-based cohort study. *Acta Obstet Gynecol Scand* 2017;96:812-820.
7. Borthen I, Eide MG, Veiby G, Daltveit AK, Gilhus NE. Complications during pregnancy in women with epilepsy: population-based cohort study. *BJOG* 2009;116:1736-1742.
8. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016;388:3027-3035.

9. Bukowski R, Malone FD, Porter FT, et al. Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study. *PLoS Med* 2009;6:e1000061.
10. Catov JM, Bodnar LM, Olsen J, Olsen S, Nohr EA. Periconceptional multivitamin use and risk of preterm or small-for-gestational-age births in the Danish National Birth Cohort. *Am J Clin Nutr* 2011;94:906-912.
11. Li B, Zhang X, Peng X, Zhang S, Wang X, Zhu C. Folic Acid and Risk of Preterm Birth: A Meta-Analysis. *Front Neurosci* 2019;13:1284.
12. Saccone G, Berghella V. Folic acid supplementation in pregnancy to prevent preterm birth: a systematic review and meta-analysis of randomized controlled trials. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2016;199:76-81.
13. Martinussen MP, Bracken MB, Triche EW, Jacobsen GW, Risnes KR. Folic acid supplementation in early pregnancy and the risk of preeclampsia, small for gestational age offspring and preterm delivery. *Eur J Obstet Gynecol Reprod Biol* 2015;195:94-99.
14. Sengpiel V, Bacelis J, Myhre R, et al. Folic acid supplementation, dietary folate intake during pregnancy and risk for spontaneous preterm delivery: a prospective observational cohort study. *BMC Pregnancy Childbirth* 2014;14:375.
15. Wen SW, White RR, Rybak N, et al. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. *BMJ* 2018;362:k3478.
16. Warzyszynska JE, Kim Y-IJ. *Folate in Human Health and Disease*. eLS John Wiley & Sons, Ltd: Chichester 2014.
17. Baker BC, Mackie FL, Lean SC, et al. Placental dysfunction is associated with altered microRNA expression in pregnant women with low folate status. *Mol Nutr Food Res* 2017;61.

18. Bergen NE, Jaddoe VW, Timmermans S, et al. Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: the Generation R Study. *BJOG* 2012;119:739-751.
19. Jongbloet PH, Verbeek AL, den Heijer M, Roeleveld N. Methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms resulting in suboptimal oocyte maturation: a discussion of folate status, neural tube defects, schizophrenia, and vasculopathy. *J Exp Clin Assist Reprod* 2008;5:5.
20. Linnebank M, Moskau S, Semmler A, et al. Antiepileptic drugs interact with folate and vitamin B12 serum levels. *Ann Neurol* 2011;69:352-359.
21. Ni G, Qin J, Li H, et al. Effects of antiepileptic drug monotherapy on one-carbon metabolism and DNA methylation in patients with epilepsy. *PLoS One* 2015;10:e0125656.
22. NICE. Epilepsies: diagnosis and management (CG137). Guideline from the National Institute for Health and Care Excellence (<https://www.nice.org.uk/guidance/cg137>) 2012; Updated 12 May 2021, access date 30 Nov 2021.
23. Tomson T, Battino D, Bromley R, et al. Global Survey of Guidelines for the Management of Epilepsy in Pregnancy: A report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epilepsia Open* 2020;5:366-370.
24. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;338:131-137.
25. George IC, Bartolini L, Ney J, Singhal D. Differences in treatment of epilepsy in pregnancy: A worldwide survey. *Neurol Clin Pract* 2019;9:201-207.
26. Bjork M, Riedel B, Spigset O, et al. Association of Folic Acid Supplementation During Pregnancy With the Risk of Autistic Traits in Children Exposed to Antiepileptic Drugs In Utero. *JAMA Neurol* 2018;75:160-168.

27. Husebye ESN, Gilhus NE, Riedel B, Spigset O, Daltveit AK, Bjork MH. Verbal abilities in children of mothers with epilepsy: Association to maternal folate status. *Neurology* 2018;91:e811-e821.
28. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol* 2016;45:382-388.
29. Bjørk MH, Veiby G, Spigset O, Gilhus N. Using the Norwegian Mother and Child Cohort Study to determine risk factors for delayed development and neuro-psychiatric symptoms in the offspring of parents with epilepsy. *Norsk Epidemiologi* 2014;24:79-89.
30. Paltiel L, Anita H, Skjerden T, et al. The biobank of the Norwegian Mother and Child Cohort Study – present status. *Norsk Epidemiologi* 2014;24.
31. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000;79:440-449.
32. Hannisdal R, Ueland PM, Eussen SJ, Svardal A, Hustad S. Analytical recovery of folate degradation products formed in human serum and plasma at room temperature. *J Nutr* 2009;139:1415-1418.
33. Hannisdal R, Ueland PM, Svardal A. Liquid chromatography-tandem mass spectrometry analysis of folate and folate catabolites in human serum. *Clin Chem* 2009;55:1147-1154.
34. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic journal of psychiatry* 2003;57:113-118.
35. Rogers WH. Regression standard errors in clustered samples. *Stata Technical Bulletin* 1993;13: .

36. Danielsson KC, Borthen I, Morken NH, Gilhus NE. Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway. *BMJ Open* 2018;8:e020998.
37. Qvist I, Abdulla M, Jagerstad M, Svensson S. Iron, zinc and folate status during pregnancy and two months after delivery. *Acta Obstet Gynecol Scand* 1986;65:15-22.
38. Bates CJ, Fuller NJ, Prentice AM. Folate status during pregnancy and lactation in a West African rural community. *Hum Nutr Clin Nutr* 1986;40:3-13.
39. Roth C, Magnus P, Schjolberg S, et al. Folic acid supplements in pregnancy and severe language delay in children. *JAMA* 2011;306:1566-1573.
40. Gao Y, Sheng C, Xie RH, et al. New Perspective on Impact of Folic Acid Supplementation during Pregnancy on Neurodevelopment/Autism in the Offspring Children - A Systematic Review. *PLoS One* 2016;11:e0165626.
41. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013;12:244-252.
42. Meador KJ, Pennell PB, May RC, et al. Effects of periconceptual folate on cognition in children of women with epilepsy: NEAD study. *Neurology* 2020;94:e729-e740.
43. Meir M, Bishara A, Mann A, et al. Effects of valproic acid on the placental barrier in the pregnant mouse: Optical imaging and transporter expression studies. *Epilepsia* 2016;57:e108-112.
44. Rubinchik-Stern M, Shmuel M, Eyal S. Antiepileptic drugs alter the expression of placental carriers: An in vitro study in a human placental cell line. *Epilepsia* 2015;56:1023-1032.

45. Castano E, Caviedes L, Hirsch S, Llanos M, Iniguez G, Ronco AM. Folate Transporters in Placentas from Preterm Newborns and Their Relation to Cord Blood Folate and Vitamin B12 Levels. *PLoS One* 2017;12:e0170389.
46. Herzog AG, Mandle HB, Cahill KE, Fowler KM, Hauser WA. Predictors of unintended pregnancy in women with epilepsy. *Neurology* 2017;88:728-733.
47. Tomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epileptic Disord* 2019;21:497-517.
48. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol* 2009;23:597-608.
49. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, OBV, and Choline. . *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington (DC): National Academies Press (US) 1998;8, Folate. .
50. Roth C, Bjorke-Monsen AL, Reichborn-Kjennerud T, et al. Use of folic acid supplements in early pregnancy in relation to maternal plasma levels in week 18 of pregnancy. *Mol Nutr Food Res* 2013;57:653-660.

Table 1. Demographic and clinical characteristics, stratified by epilepsy, ASM use and use of periconceptual folic acid.

	Epilepsy with ASM		Epilepsy without ASM		No epilepsy	
	Periconceptual folic acid		Periconceptual folic acid		Periconceptual 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 caesarean section, n (%)	17 (27)	63 (26)	19 (20)	53 (20)	3,413 (14)	10,345 (14)
Planned caesarean section, n (%)	7 (11)	26 (11)	7 (7)	18 (7)	1,327 (6)	3,722 (5)
Gestational age, mean (SD), days	272 (20)	279 (12)	278 (11)	278 (14)	279 (13)	279 (13)
Gestational age, mean (SD), weeks	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), grams	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
TC 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

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=1037 in the “No epilepsy” group).

ASM: antiseizure medication. The ASMs listed were used either in monotherapy or polytherapy. Smoking: use in pregnancy. Alcohol: ≥ 1 per month during pregnancy. Parity: parity 5 also includes >5 . TC: tonic-clonic. SD, standard deviation. NA, not applicable.

- a) Any epileptic seizure during pregnancy, including TC and other types of seizures
- b) Proportion of women using high dose folic acid supplement, i.e. more than 0.4 mg daily. Only available for epilepsy patients. *n* differs from 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

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Table 2. Odds ratios of pregnancy complications in women *without* versus *with* periconceptual folic acid supplement, stratified by epilepsy and ASM exposure

	Epilepsy with ASM		Epilepsy without ASM		No epilepsy	
	Periconceptual folic acid		Periconceptual folic acid		Periconceptual 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 (<i>ref</i>)	0.8 (0.3–2.2)	1.0 (<i>ref</i>)	1.0 (1.0–1.1)	1.0 (<i>ref</i>)
Adjusted OR	3.3 (1.2–9.2) ^c	1.0 (<i>ref</i>)	0.7 (0.2–2.3)	1.0 (<i>ref</i>)	1.0 (0.9–1.1)	1.0 (<i>ref</i>)
SMALL FOR GESTATIONAL AGE,	9 (14)	21 (9)	7 (7)	19 (7)	1,606 (7)	4,776 (6)

n (%)						
Crude OR	1.7 (0.8–4.0)	1.0 (<i>ref</i>)	1.0 (0.4–2.4)	1.0 (<i>ref</i>)	1.0 (1.0–1.1)	1.0 (<i>ref</i>)
Adjusted OR	1.3 (0.5–3.6)	1.0 (<i>ref</i>)	0.9 (0.4–2.5)	1.0 (<i>ref</i>)	1.1 (1.0–1.2) ^d	1.0 (<i>ref</i>)
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 (<i>ref</i>)	-	-	1.0 (0.9–1.1)	1.0 (<i>ref</i>)
Adjusted OR	0.8 (0.2–3.0)	1.0 (<i>ref</i>)	-	-	1.1 (1.0–1.1)	1.0 (<i>ref</i>)

Odds ratio (OR) for placenta-related pregnancy complications in women *without* periconceptional folic acid supplement compared to 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% confidence intervals. 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 (see eMethods in the Supplement). ASM: anti-seizure medication. 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, small for gestational age: <10 percentile. Preeclampsia: preeclampsia, HELLP, and eclampsia combined.

a) $p=0.010$, b) $p=0.013$, c) $p=0.022$, d) $p=0.008$, -) statistical analyses not possible due to 0 or 1 observations in one or more of the variables.

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Table 3 Odds ratios (95% confidence intervals) for preterm birth in relation to timing of folic acid supplement

	Epilepsy with ASM	Epilepsy without ASM	No epilepsy
Timing of folic acid supplement			
Periconceptual use¹	0.9 (0.5–1.6)	1.4 (0.9–2.3)	1.0 (ref)
	<i>12 of 244 (5%)</i>	<i>17 of 260 (7%)</i>	<i>3,484 of 74,001 (5%)</i>
Late start²	2.6 (1.1–6.5) ^a	0.6 (0.1–4.6)	1.0 (ref)
	<i>5 of 48 (10%)</i>	<i>1 of 33 (3%)</i>	<i>368 of 7,752 (5%)</i>
No use³	9.4 (2.6–34.8) ^b	1.3 (0.5–3.6)	1.0 (ref)
	<i>4 of 16 (25%)^c</i>	<i>4 of 63 (6%)</i>	<i>812 of 16,254 (5%)</i>

Adjusted odds ratios (OR) with 95% confidence intervals for preterm birth in women *with* epilepsy compared to 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 Pearson's chi-squared test (χ^2) or Fisher's exact test.

Preterm birth: gestational week <37. ASM: antiseizure medication. Ref: reference. 1) Periconceptional use: folic acid supplement use during the 4 weeks before conception or 1st trimester. 2) Late start: start of folic acid supplement in 2nd or 3rd trimester. 3) No use: no folic acid supplementation at any time during pregnancy.

a) p=0.046, b) p=0.001, c) p<0.0001.

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Figure legends:

Figure 1. Flowchart of included and excluded pregnancies.

ASM: anti-seizure medication. MBRN: Medical Birth Register of Norway. w: weeks. *

children with birthweight z-scores above +4 if gestational age <35 weeks and birthweight z-scores below -4.

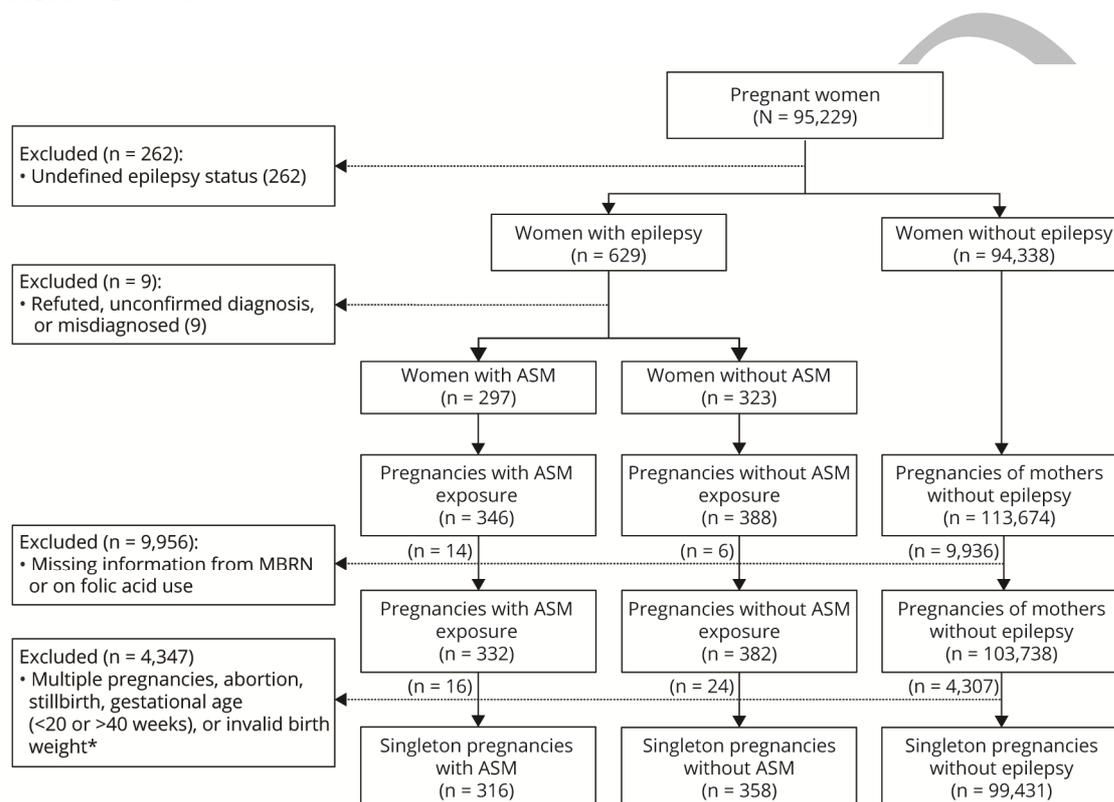


Figure 2. Proportion (%) of women using folic acid supplement at different time points during pregnancy.

Red lines indicate women with the specified pregnancy complication. Orange lines indicate women without the specified pregnancy complication. Difference between the two groups was assessed by Pearson's chi-squared test (χ^2) or Fisher's exact test. ASM: anti-seizure medication. Preconc: preconception. Preterm birth: gestational age <37 weeks. SGA, small for gestational age: <10 percentile. Preeclampsia: preeclampsia, HELLP, and eclampsia combined. *p<0.05

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