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RESEARCH ARTICLE

Prescribing patterns for higher dose folic acid in pregnant women with epilepsy treated with antiseizure medication

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Abstract

Objective: This study was undertaken to characterize the use of higher doses of folic acid (≥1 mg daily) in relation to pregnancy in Denmark, Norway, and Sweden in women with epilepsy treated with antiseizure medication (ASM).

Methods: In this observational study, we used data from national medical birth, patient, and prescription registers in Denmark, Norway, and Sweden to retrospectively identify pregnancies in women with epilepsy treated with ASM from 2006 to 2017. The proportion of higher dose folic acid supplementation in pregnancies among women receiving ASM for epilepsy was calculated according to country of origin, time period, and type of ASM. Logistic regression with restricted cubic splines was used to model country-specific time trends.

Results: Among a total of 2 748 882 pregnancies, we identified 8695 (.3%) pregnancies after restricting the population to women with ASM-treated epilepsy. A

prescription for higher dose folic acid was filled in 4719 (54.3%) of these pregnancies. The proportion supplemented with higher dose folic acid was highest in Sweden (74.3%) and lower in Norway (41.4%) and Denmark (34.3%). Furthermore, we observed a decreasing trend of higher dose folic acid use in Denmark and Norway from year 2012 to 2017. Among those who used higher dose folic acid, 42% did not start preconception supplementation with higher dose folic acid.

Significance: Supplementation with higher dose folic acid occurred in approximately half of pregnancies in women with ASM-treated epilepsy, with many not starting supplementation until after becoming pregnant. Considerable variability was observed in the use of higher dose folic acid across the countries, despite similar population characteristics and health care systems. Future guidelines should be simplified with clear recommendations developed in a collaborative manner by relevant specialists including neurologists, obstetricians, pediatricians, and public health specialists to enhance real-world applicability.

KEYWORDS

antiseizure medication, epilepsy, folic acid, pregnancy, prenatal care

1 | INTRODUCTION

Epilepsy is a common neurological disease affecting millions of women of childbearing age.[1,2] Women with epilepsy planning to become pregnant face various challenges, including balancing the benefits and adverse effects of antiseizure medication (ASM) and folic acid supplements during pregnancy.[3] Clinical guidelines widely recommend using higher dose folic acid (≥1 mg daily) in conjunction with ASM treatment in relation to pregnancy, as ASM is associated with teratogenic risks and lowered folate concentrations in blood.[4–6] Despite strong evidence demonstrating the protective effects of folic acid supplementation against neural tube defects in the general population,[7–9] similar evidence is lacking regarding protectiveness against congenital anomalies in women with epilepsy on ASM treatment during pregnancy. Nevertheless, association studies addressing health outcomes in children exposed to ASM prenatally have reported other benefits from higher dose folic acid use, such as a lowered risk of autistic traits,[10] better intelligence quotient outcomes (except for valproate),[11] and a lowered risk of language impairment in some[12] but not all studies.[13,14] Conversely, use of higher dose folic acid in pregnancy has been associated with an increased risk of childhood cancer in children born to women with epilepsy.[15]

Current clinical guidelines for pregnant women with ASM-treated epilepsy pose a challenge to both patients and clinicians, as the optimal timing and dosage of folic acid supplementation before and during pregnancy for achieving potential benefits remain uncertain. Current recommendations vary widely from .4 to 5 mg of daily supplementation, with inconsistent guidance on whether to maintain or adjust the doses throughout pregnancy (Table S1, Supplementary Material).[16–28] Varying guidelines for pregnant women with ASM-treated epilepsy exist in Denmark, Norway, and Sweden, despite their similar demographics and health care systems.

To better understand recent practices and pinpoint areas for improving folic acid supplementation guidelines for women with epilepsy during their pregnancy, we conducted a study in Denmark, Norway, and Sweden. Our objective was to explore and describe whether the use of

Key points

- Only half of the pregnancies in women treated with an ASM for their epilepsy were supplemented with higher doses of folic acid (≥1 mg daily).
- Whereas most pregnancies in women with ASM-treated epilepsy were supplemented with higher dose folic acid in Sweden (74.3%), a lower proportion received such supplementation in Norway (41.4%) and Denmark (34.3%).
- Among pregnancies in women with ASM-treated epilepsy supplemented with higher dose folic acid, supplementation was not initiated in >40% of the pregnancies until after the patient became pregnant.

higher doses of folic acid resonated with the national clinical guidelines and whether the use differed across these different ASM therapies during pregnancy, and to compare the use between the included countries.

2 | MATERIALS AND METHODS

2.1 | Study population

First, we retrospectively identified the pregnancies in the national medical birth registers. We were able to link information in the medical birth registers with information on filled prescriptions in the national prescription registers by using the unique personal identification number assigned to each citizen at birth or immigration in each of the three participating countries. Our data source was the SCAN-AED study, a Nordic multiregistry study with full data coverage from all countries and registers from year 2006 to 2017 (www.scanaed.org).[29,30] The registers and variables used are described in further detail in the Supplementary Materials and Table S2. The total number of pregnancies identified was 2 748 882 (Figure 1). We restricted the study population to pregnancies in women with epilepsy corresponding to the 10th version of International Statistical Classification of Diseases and Related Health Problems code G40 or G41 registered in patient records at any time before the date of delivery and where these individuals also had at least one ASM prescription fill between the date of the last menstrual period and the date of delivery.

To accurately determine the time elapsed between the last menstrual period and the date of delivery in relation to the date of filling of higher dose folic acid and ASM prescriptions, we excluded women with improbable pregnancy durations of <154 days or >314 days, and those with missing pregnancy length (Figure 1; $n = 15$, .2% of all pregnant women with ASM-treated epilepsy).

2.2 | Higher dose folic acid

We defined higher dose folic acid use as having filled at least one prescription for folic acid tablets with a dosage strength of either 1 mg or 5 mg, which are the two available prescription-based dose strengths. These prescriptions were filled between 90 days before the last menstrual period and the date of delivery. The medications

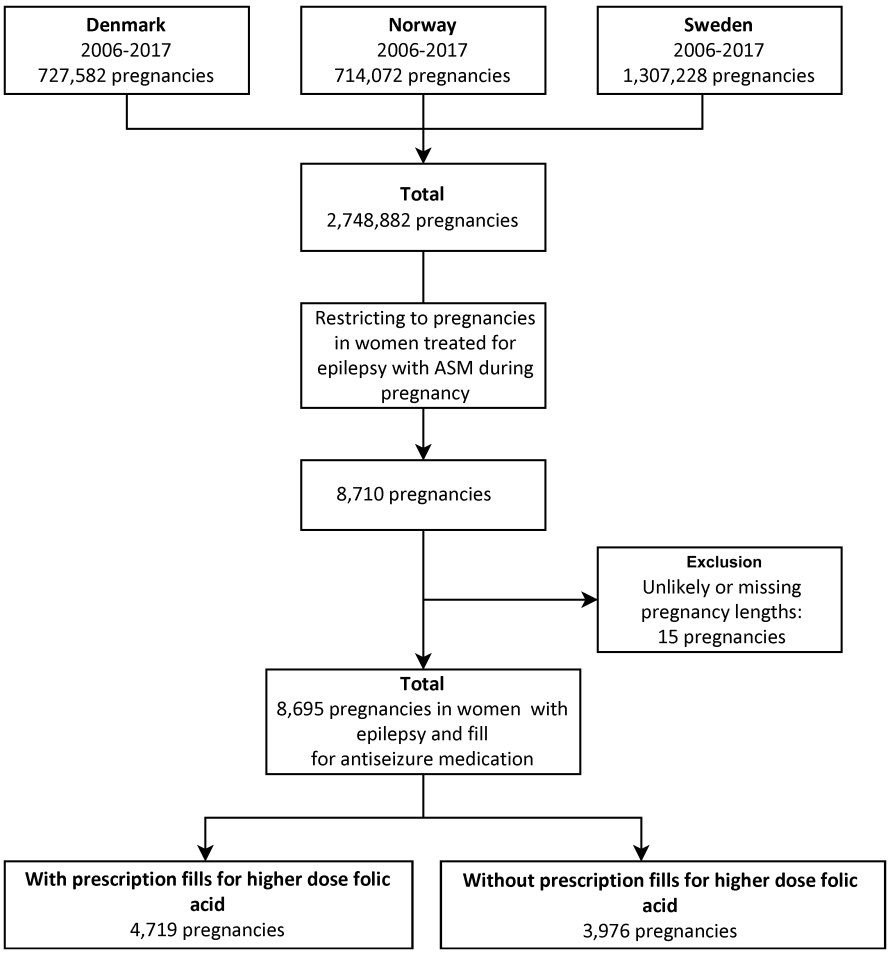

FIGURE 1 Flowchart showing study population selection. Flowchart shows pregnancies in Denmark, Norway, and Sweden from 2006 to 2017 and identification of women diagnosed with epilepsy and fill for antiseizure medication (ASM), grouped into those with and without filled prescriptions for higher dose folic acid.

were identified in the prescription registers by using the Anatomical Therapeutic Chemical (ATC) code of B03BB01. One drug dispensing may cover a period exceeding 90 days, as a prescription for higher dose folic acid typically contains between 250 and 1000 pills per package.

2.3 | Antiseizure medication

We defined use of ASM as filled prescriptions assigned with either of the ATC codes S01EC01, N05BA09, or N03 that were filled between the last menstrual period and the date of delivery. Use of ASM was categorized into any ASM use and stratified into ASM polytherapy or ASM monotherapy. ASM monotherapy was defined as prescription fills for no more than one type of ASM between the last menstrual period and the date of delivery. We focused on the eight most frequently used monotherapies in our population.[31] Other monotherapies were pooled into a single category coined "other ASM monotherapy." ASM polytherapy was defined as use of at least two different types of ASM between the last menstrual period and the date of delivery.

2.3.1 | Statistical analyses

We calculated the proportion of pregnancies in women with ASM-treated epilepsy who used higher dose folic acid in each country separately and combined. To illustrate changes in the proportion of higher dose folic acid use, we applied logistic regression with restricted cubic splines with calendar year as an independent variable and stratified data on country. This method allowed for a flexible and nonlinear representation of the relationship between year of delivery, country, and the proportion of pregnancies supplemented with higher dose folic acid with corresponding 95% confidence intervals. Changes in the proportion of higher dose folic acid use were similarly illustrated stratified for any ASM use, and then stratified for ASM monotherapy and ASM polytherapy. To enhance our understanding of higher dose folic acid supplementation in relation to differences in ASM treatments between the countries, we calculated the proportion of pregnancies receiving any ASM use, and then for ASM monotherapy and ASM polytherapy, regardless of concomitant higher dose folic acid use.

We estimated the use of over-the-counter folic acid (typically .4 or .8 mg daily) in pregnancies with ASM-treated epilepsy in Norway. This calculation was done by subtracting the number of pregnant women with filled prescriptions for 1 mg and/or 5 mg folic acid from all pregnant women self-reporting use of any folic acid before or during pregnancy and recorded in the Medical Birth Registry of Norway. Information of self-reported usage of folic acid in relation to pregnancy was not available for pregnancies in Denmark or Sweden.

The timing of the initial higher dose folic acid use in relation to pregnancy was assessed by producing country-specific histograms, allowing for a 1-year lookback prior to the last menstrual period.

Stata version 17 was used for all analyses.[32]

3 | RESULTS

From a total of 2 748 882 pregnancies in the general population in Denmark, Norway, and Sweden, we identified 8695 pregnancies (.3%) in women with ASM-treated epilepsy (Figure 1). Among these, 4719 (54.3%) pregnancies were supplemented with higher dose folic acid, whereas 3975 pregnancies (45.7%) were not (Table 1).

3.1 | Higher dose folic acid supplementation by country and ASM type

The proportion of pregnancies supplemented with higher dose folic acid was highest in Sweden, with 74.3% ($n = 2936$ of 3954 pregnancies) compared with 41.4% in Norway ($n = 917$ of 2215 pregnancies) and 34.3% in Denmark ($n = 866$ of 2526 pregnancies; Table 2). Whereas the proportion of pregnancies supplemented with higher dose folic acid did not change during the time of follow-up in Sweden, we observed a decreasing trend in Denmark and Norway from 2012 onward by using logistic regression with cubic splines as illustrated in Figure 2 (point estimates of proportions provided in Table S3, Supplementary Material).

The proportion of pregnancies in women with epilepsy using higher dose folic acid and being treated with carbamazepine or valproate monotherapy was equally high in all countries (Figure 3). For lamotrigine, levetiracetam, oxcarbazepine, and topiramate monotherapy, fewer pregnancies in Denmark and Norway were supplemented with higher dose folic acid than in Sweden. In the composite group "other ASM monotherapies," <60% of pregnancies were supplemented with higher dose folic acid from 2012 and onward in all countries (Figure 3).

Regardless of higher dose folic acid use, we observed that a higher proportion used carbamazepine and valproate in relation to pregnancy in Sweden (23.1% and 12.1%, respectively) than in Norway (13.0% and 9.0%, respectively) and in Denmark (4.6% and 7.0%, respectively; Table S4, Supplementary Material). Overall, women with ASM-treated epilepsy most frequently

TABLE 1 Population characteristics in pregnancies in women receiving ASM for epilepsy, with and without higher dose folic acid supplementation.

Characteristics	Number of pregnancies in women with ASM-treated epilepsy	
	Higher dose folic acid	No higher dose folic acid
Total, *n* (%)[a]	4719 (54.3)	3976 (45.7)
Country, *n* (%)[a]		
Denmark	866 (34.3)	1660 (65.7)
Norway	917 (41.4)	1298 (58.6)
Sweden	2936 (74.3)	1018 (25.7)
Year of delivery, *n* (%)[b]		
2006–2009	1450 (30.7)	1257 (31.6)
2010–2013	1690 (35.8)	1256 (31.6)
2014–2017	1579 (33.5)	1463 (36.8)
ASM, *n* (%)[b]		
Any ASM monotherapy	4719 (100.0)	3976 (100.0)
Carbamazepine	884 (18.7)	385 (9.7)
Levetiracetam	433 (9.2)	523 (13.2)
Lamotrigine	2008 (42.6)	2097 (52.7)
Oxcarbazepine	155 (3.3)	148 (3.7)
Topiramate	158 (3.3)	129 (3.2)
Valproate	610 (12.9)	246 (6.2)
Other ASM monotherapy[c]	282 (6.0)	356 (9.0)
ASM polytherapy[d]	189 (4.0)	92 (2.3)

Note: Use of higher dose folic acid was defined as prescription fills of a drug associated with an ATC code of B03BB01 with dose strengths or 1 mg or 5 mg in the 90 days leading up to the last menstrual period and until the date of delivery. ASM was defined as prescription fills of drugs associated with ATC code S01EC01, N05BA09, or N03 between the last menstrual period and date of delivery.

Abbreviations: ASM, antiseizure medication; ATC, Anatomical Therapeutic Chemical.

[a]Rowwise percentage.

[b]Columnwise percentage.

[c]Other antiseizure monotherapy reimbursed corresponding to ATC code S01EC01, N05BA09, or N03.

[d]ASM polytherapy was defined as prescription of at least two different ASMs.

used lamotrigine (47.2%) and levetiracetam (11.0%) during pregnancy, although the proportions were lower in Sweden (43.2% and 9.1%, respectively; Table S4, Supplementary Material).

3.2 | Use of over-the-counter folic acid during pregnancy

Out of 2215 pregnancies to mothers with ASM-treated epilepsy in Norway, we found that 1077 (48.6%) reported folic acid use but did not fill prescriptions for higher doses of folic acid, suggesting that these mothers likely supplemented with lower doses of folic acid, which are available over the counter (Table S5, Supplementary Material). Only 221 (10.0%) were registered with no use of any folic acid supplementation before or during pregnancy and with no recorded prescription fills for higher doses of folic acid. Across different types of ASMs used in relation to pregnancy, the percentage with no folic acid supplementation varied from 15% to 27%. It was least common not to use any folic acid supplementation in mothers treated with valproate (15%; Table S6, Supplementary Material).

3.3 | Timing of first use of higher dose folic acid prescription in relation to pregnancy

By extending the lookback from 90 days to 1 year prior to the last menstrual period, a total of 4988 pregnancies were identified and included when we assessed the timing for the first use of higher doses of folic acid in relation to pregnancy. We observed that 42% (2097 of 4988 pregnancies) of pregnancies in women with ASM-treated epilepsy were not supplemented with higher dose folic acid until after the pregnancy had started (Figure 4; Table S7, Supplementary Material). Periconceptional higher dose folic acid supplementation

TABLE 2 Use of higher dose folic acid prescriptions during pregnancy in women with epilepsy treated with ASM, by country.

Higher dose folic acid characteristics	Country			
	Denmark	Norway	Sweden	Combined
Total pregnancies, *n* (%)[a]	2526 (29.1)	2215 (25.5)	3954 (45.5)	8695 (100)
Any higher dose folic acid, *n* (%)[b]	866 (34.3)	917 (41.4)	2936 (74.3)	4719 (54.3)
Total who used 5 mg folic acid, *n* (%)[c]	825 (95.3)	20 (2.2)	2717 (92.5)	3562 (75.4)
Total who used 1 mg folic acid, *n* (%)[c]	33 (3.8)	892 (97.3)	149 (5.1)	1074 (22.8)
Total who used 1 mg and 5 mg folic acid, *n* (%)[c]	8 (.9)	5 (.5)	70 (2.4)	83 (1.8)

Note: Use of higher dose folic acid was defined as prescription fills of a drug associated with an ATC code of B03BB01 with dose strengths or 1 mg or 5 mg in the 90 days leading up to the last menstrual period and until date of delivery. ASM was defined as prescription fills of drugs associated with ATC code S01EC01, N05BA09, or N03 between the last menstrual period and date of delivery.Abbreviations: ASM, antiseizure medication; ATC, Anatomical Therapeutic Chemical.

[a]Percentage of recorded pregnancies in women with epilepsy and fill for ASM.

[b]Columnwise percentage of total pregnancies per country or of all countries combined (total).

[c]Columnwise percentage of total amount of folic acid prescription fills.

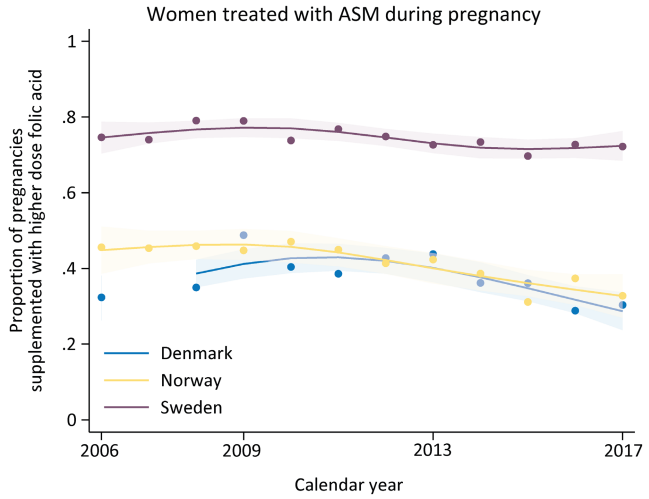

FIGURE 2 Proportion of pregnancies in women with epilepsy on antiseizure medication (ASM) using higher dose folic acid during pregnancy. Trends in proportion of pregnancies in women on ASM for epilepsy filling a prescription for higher dose folic acid (≥1 mg) are shown. Lines with corresponding confidence intervals were produced using restricted cubic splines with observed proportions added as scatterplot. Splines were not added for Denmark in 2007 due to missing information on higher dose folic acid prescriptions fills. Specific point estimates with corresponding confidence intervals are available in Table S3 in the Supplementary Material.

was most common in Sweden (60%) and Denmark (59%), and least common in Norway (52%).

4 | DISCUSSION

In this large, multinational study describing supplementation of higher dose folic acid in relation to pregnancy in women with ASM-treated epilepsy, we observed that only half of the pregnancies were supplemented with higher dose folic acid. Among those who used higher dose folic acid, more than one third did not start using it before becoming pregnant.

We observed that it was most common to supplement pregnancies with higher dose folic acid in Sweden, regardless of the type of ASM used. The proportion of pregnancies in Sweden supplemented with higher dose folic acid remained stable from 2006 to 2017. This aligns with the guidelines in effect in Sweden during the study period. Swedish health authorities issued clear recommendations for 5 mg of folic acid daily for persons using valproate and carbamazepine, starting in 1997 and, subsequently, recommending 5 mg daily during pregnancy for any type of ASM used from 2011 to 2019.[23,24] Whereas we were unable to assess folic supplementation practices for women treated with ASM in relation to pregnancy after 2017, it is worth noting that in 2019 the Swedish health authorities changed the recommendations to .4 mg folic acid daily regardless of whether the person is being treated with an ASM.[25] The Swedish health authorities have consistently emphasized the absence of conclusive evidence regarding the optimal dose and timing of folic acid to achieve potential benefits from higher dose folic acid in the various clinical guidelines.

In contrast to pregnancies in Sweden, less than half of pregnancies in women with ASM-treated epilepsy were supplemented with higher dose folic acid in Norway (41.4%) and Denmark (34.3%). In both countries, we observed a decreasing proportion of pregnancies supplemented with higher dose folic acid in relation to pregnancy from 2012 to 2017. Plausible explanation for declining use of higher dose folic acid is reduced usage of valproate and carbamazepine, two ASMs for which higher doses of folic acid particularly were recommended during the study period.[33,34] Also, it is possible

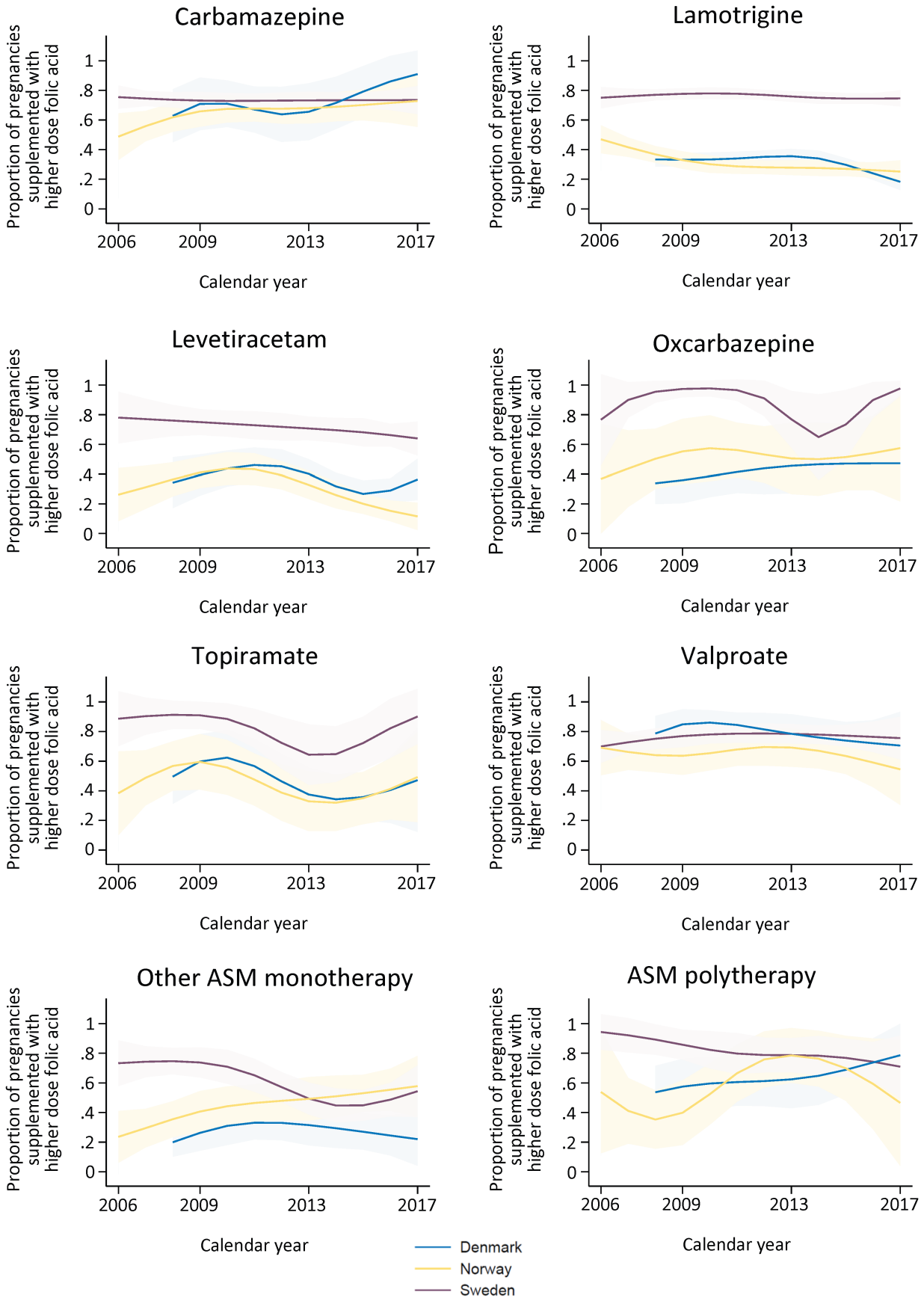

FIGURE 3 Higher dose folic acid utilization during pregnancy among women across different antiseizure medication (ASM) therapies. Graphs show trends in the proportion of pregnancies in women with ASM-treated epilepsy supplemented with higher dose folic acid (>1 mg). Lines with corresponding confidence intervals were produced using restricted cubic splines.

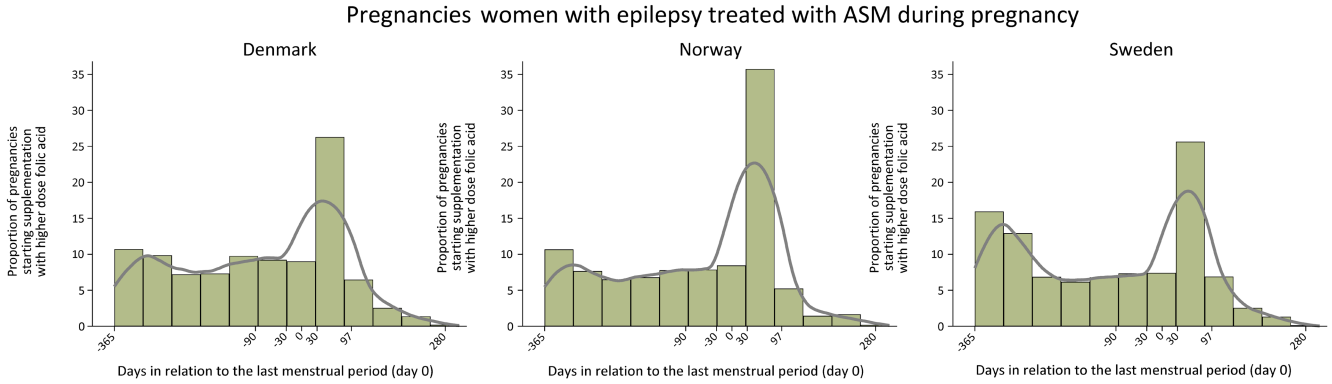

FIGURE 4 Timing of the first usage of higher dose folic acid in relation to the start of pregnancy. Individual histograms from each of the included countries showing the timing of higher dose folic acid (≥1 mg) prescription fills in relation to last menstrual period for pregnancies in women diagnosed with epilepsy and treated with antiseizure medication (ASM). In this analysis, we allowed for 1-year lookback prior to the last menstrual period. Gray lines illustrate the kernel density plot of the histograms. Bar graphs in each histogram are equal to a proportion of 55.0 days in relation to the last menstrual period (pregnancy start), reflecting 1 year prior to pregnancy start (−365 days); 3 months prior to pregnancy start, at which point supplementation is recommended to be initiated (−90); the time immediately before and after pregnancy start (−30 and 30 days); the end of the first trimester (79 days); and the mean pregnancy length (280 days).

that clinicians have been increasingly aware that the evidence does not support higher dose folic acid being protective against neural tube defects associated with ASM and have changed their prescribing practice already before the national guidelines changed.[35] However, most pregnancies involving valproate monotherapy, carbamazepine monotherapy, or ASM polytherapy were supplemented with higher dose folic acid. This observation aligns well with the recommendations in two of three current clinical guidelines in Norway, which recommend higher dose folic acid for pregnant women with epilepsy on carbamazepine, valproate, or ASMs of "unknown teratogenic potential."[18,21,22] Additionally, the Danish clinical guideline for folic acid supplementation also recommends a daily 5-mg dosage for older types of ASM, including valproate and carbamazepine.[16]

One explanation for the higher proportion of pregnancies consistently receiving higher dose folic acid supplementation may be the simplicity of Swedish guidelines, which did not distinguish between specific ASM types. Furthermore, unlike Norway, Sweden has only one available set of clinical recommendations for folic acid supplementation for those treated with ASM during pregnancy, and compared to Denmark, the recommendations have been updated more frequently. For valproate and carbamazepine, both of which had higher dose folic acid supplementation recommendations in Denmark (at least valproate) and Norway, we noticed that the proportion of pregnancies supplemented with higher dose folic acid was more similar to what we observed in Sweden for these two ASM types. For other ASM therapies in Denmark and Norway, we observed more variability in the proportion of pregnancies receiving higher dose folic acid supplementation during pregnancy.

We observed that among pregnancies to women with ASM-treated epilepsy in Norway, the use of over-the-counter folic acid by those who did not fill prescriptions for higher doses of folic acid included approximately half of all pregnancies. No use of any folic acid before or during pregnancy occurred in only 10% of all the included pregnancies in Norway. No folic acid use was least common in women who were treated with valproate during pregnancy. In contrast, only 27% were supplemented with folic acid doses <1 mg daily in a recent US study including 302 pregnant women with epilepsy enrolled between 2012 and 2016 studying behavioral outcomes and neurodevelopmental disorders in children born of women with epilepsy.[36] Higher doses of folic acid (≥1 mg daily) were used in 60%, whereas 11% did not use any folic acid during pregnancy. Nearly all were treated with an ASM during their pregnancy, and the study population was recruited from specialist health care centers and was not population-based.

In our study, we observed that >40% of the pregnancies in women with ASM-treated epilepsy were not started on preconception higher dose folic acid supplementation. Moreover, preconceptional supplementation of higher dose folic acid was more common in Sweden than in Denmark and Norway. This finding is in line with results in neurodevelopment of children born to women with epilepsy conducted in the UK showing that only 46% initiated folic supplements prior to conception, in which 70% of the population used ≥5 mg folic acid daily.[14] The late initiation of folic acid supplementation underscores the need for enhanced prepregnancy planning protocols for women

of childbearing age with epilepsy, given that pregnancies in this population are commonly unplanned.[37]

This study has some limitations. The results may not be generalizable to other regions or countries with different clinical guidelines. We did not have detailed information on actual consumption of higher dose folic acid and ASM or biological levels reflecting the use of these two medications and therefore mainly relied on information about filled prescriptions as the best available surrogate.[38] We did not have information on self-reported use of folic acid in Denmark or Sweden, which for Norway could be used to estimate the use of over-the-counter low-dose folic acid. Because a folic acid prescription may contain as many as 1000 pills per package and we did not have exact information concerning prescribed daily dose, we were unable to report the exact daily average exposure for folic acid. Although it could be of interest to compare the timing of the first folic acid prescription in the first pregnancy to that of subsequent pregnancies, this comparison was not feasible due to limited observations in several key time intervals during pregnancy when stratifying for the first, second, and third pregnancy. We lacked exact information regarding the absence of data on higher dose folic acid use in Denmark for the year of 2007, but this finding is in line with publicly available data on Danish data use and is unlikely to impact the study results.[39] The results may not be generalizable to pregnancies with other indications for higher dose folic acid supplementation than ASM.

5 | CONCLUSIONS

We observed that only half of pregnancies in women with ASM-treated epilepsy received higher dose folic acid supplementation. Overall, Sweden had a higher rate of such supplementation than Denmark and Norway. Nevertheless, higher dose folic acid supplementation was common in all countries for individuals on valproate monotherapy or carbamazepine monotherapy. For other types of ASM therapies, we found considerable variations in higher dose folic acid usage between the countries. Among those who used higher dose folic acid supplementation during pregnancy, >40% did not begin until after pregnancy onset.

Our results emphasize a need for improved practice patterns to better reflect clinical guidelines. Future guidelines should be simplified and with clear recommendations, and they should be developed in cooperation between neurologists, obstetricians, pediatricians, and public health specialist. This should contribute to a better translation into real-world practice.

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CONFLICT OF INTEREST STATEMENT

S.A. reports speaker honoraria from Eisai. M.-H.B. reports receiving funding from the Norwegian Research Council and the Norwegian Epilepsy Association; honoraria from giving lectures or serving on advisory boards from Teva, Eisai, AbbVie, Lilly, Jazz Pharmaceuticals, Angelini Pharma, Lundbeck, Pfizer, and Eisai; consultancy honoraria from Novartis; and institutional grants from Sanofi outside of the submitted work. J.C. has received honoraria from serving on the scientific advisory board of UCB Nordic and Eisai; honoraria for giving lectures from UCB Nordic and Eisai; and funding for a trip from UCB Nordic. J.C. was also supported by the Novo Nordisk Foundation (NNF16OC0019126 and NNF22OC0075033), the Central Denmark Region, and the Danish Epilepsy Association. J.W.D. was supported by the Independent Research Fund Denmark (1133-00026B). N.E.G. has received financial support from UCB, Argenx, Janssen, Merck, Roche, Alexion, Immunovant, Octapharma, Huma, Denka, and Dianthus. M.G. and M.K.L. report that their institution has received funding from pharmaceutical companies to conduct postmarketing drug safety research outside the submitted work. J.I. reports that the core facility for biostatistics and data analysis led by her has received funding from Sanofi and Novartis to conduct postmarketing drug safety research outside the submitted work. T.T. reports funding from Accord, Glenmark, GSK, UCB, Eisai, Ecu Pharma, Bial, Teva, Sanofi, SF Group, GW Pharma, Zentiva, and Angelini as donations to the EURAP pregnancy registry; and speaker honoraria to his institution from Eisai, Angelini, GSK, and UCB. Y.S. was supported by the Independent Research Fund Denmark, project number 9039-00296B. H.Z. was supported by a University of New South Wales Scientia Program Award. H.M.V. reports no relevant disclosures. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

In accordance with the Danish Data Protection Act, the SCAN AED dataset is maintained at Statistics Denmark and cannot be exported or be made available outside of Statistics Denmark. However, the primary sources of data for the SCAN-AED project, derived from nationwide registers in the Nordic countries, may be obtained through the appropriate national authorities upon application.

PATIENT CONSENT STATEMENT

Because this study relies solely on mandatory and anonymized data obtained from registries, there was no requirement for individual patient consent. The need for informed consent has been exempted by the relevant ethical and data protection authorities, or it is legally waived in all the countries included in this research.

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REFERENCES

1. Tomson T, Battino D, Bromley R, Kochen S, Meador K, Pennell P, 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(6):497–517.
2. Global Burden of Disease Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol. 2019;18(4):357–75.
3. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol. 2011;10(7):609–17.
4. Dwyer ER, Filion KB, MacFarlane AJ, Platt RW, Mehrabadi A. Who should consume high-dose folic acid supplements before and during early pregnancy for the prevention of neural tube defects? BMJ. 2022;377:e067728.
5. Kishi T, Fujita N, Eguchi T, Ueda K. Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. J Neurol Sci. 1997;145(1):109–12.
6. Linnebank M, Moskau S, Semmler A, Widman G, Stoffel-Wagner B, Weller M, et al. Antiepileptic drugs interact with folate and vitamin B12 serum levels. Ann Neurol. 2011;69(2):352–9.
7. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26):1832–5.
8. Prevention of neural tube defects: results of the Medical Research Council vitamin study MRC Vitamin Study Research Group. Lancet. 1991;338(8760):131–7.
9. Wilson RD, O'Connor DL. Guideline No. 427: folic acid and multivitamin supplementation for prevention of folic acid-sensitive congenital anomalies. J Obstet Gynaecol Can. 2022;44(6):707–719.e1.
10. Bjork M, Riedel B, Spigset O, Veiby G, Kolstad E, Daltveit AK, 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(2):160–8.
11. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244–52.
12. Husebye ESN, Gilhus NE, Spigset O, Daltveit AK, Bjork MH. Language impairment in children aged 5 and 8 years after antiepileptic drug exposure in utero – the Norwegian mother and child cohort study. Eur J Neurol. 2020;27(4):667–75.
13. Meador KJ, Cohen MJ, Loring DW, Matthews AG, Brown C, Robalino CP, et al. Cognitive outcomes at age 3 years in children with fetal exposure to antiseizure medications (MONEAD study) in the USA: a prospective, observational cohort study. Lancet Neurol. 2023;22(8):712–22.
14. Bromley RL, Bullen P, Campbell E, Craig J, Ingham A, Irwin B, et al. Neurodevelopment of babies born to mothers with epilepsy: a prospective observational cohort study. Epilepsia. 2023;64(9):2454–71.
15. Vegrim HM, Dreier JW, Alvestad S, Gilhus NE, Gissler M, Igland J, et al. Cancer risk in children of mothers with epilepsy and high-dose folic acid use during pregnancy. JAMA Neurol. 2022;79:1130–8.
16. Sundhedsstyrelsen. Referenceprogram for epilepsi (Reference Programme for Epilepsy, in Danish): Sundhedsstyrelsen, Center for Evaluering og Medicinsk Teknologivurdering. 2005. https://www.sst.dk/~/media/BE8541443FC8498BBF2B92746F9061A4.ashx
17. Norwegian Society of Gynecology and Obstetrics. Veileder i fødselshjelp 1998: The Norwegian Medical Association. 1998. https://www.nb.no/items/2a69d2ca4258928a8e29f822ceee4487?page=0&searchText=veileder%20f%C3%B8dselshjelp
18. Norwegian Society of Gynecology and Obstetrics. Archived and outdated clinicial recommendations during pregnancy: The Norwegian Medical Association. 2014. https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/arkiv-utgatte-veiledere/#Veileder%20arkiv-%20utg%C3%A5tte%20versjoner
19. The Norwegian Medical Association. Retningslinjer for behandling av kvinner med epilepsi. Konsensusrapport 2011. The Norwegian Medical Association: The Norwegian Medical Association. 2011. https://www.legeforeningen.no/contentassets/85c53bc045db433bbde37c0490558838/retningslinjer-for-behandling-av-kvinner-med-epilepsi.doc
20. The Norwegian Medical Association. Retningslinjer for behandling av kvinner med epilepsi: The Norwegian Medical Association. 2018. https://www.legeforeningen.no/contentassets/f3dde659c8e147e59b47eda62d02a621/retningslinjer-for-behandling-av-kvinner-med-epilepsi-2018.pdf

21. Danielsson K. Norsk gynekologisk forening Veileder i fødselshjelp (2020) (Guideline in birthing services (2020), in Norwegian). Norwegian Society of Gynecology and Obstetrics. 2020. https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/veileder-i-fodselshjelp/nevrologiske-sykdommer-i-svangerskapet/
22. National Centre for Epilepsy. Planlegging av svangerskap og fødsel (Planning of pregnancy and birth, in Norwegian): Spesialsykehuset for epilepsi (SSE) og Oslo Universitetssykehus (OUS). 2022. https://epilepsibehandling.no/index.php?action=topic&item=JhraRspk
23. Swedish Medical Products Agency. Behandling av epilepsi – Rekommendationer. Info från Läkemedelsverket (Treatment of epilepsy – Recommendations, in Swedish). Läkemedelsverket. 1997.
24. Swedish Medical Products Agency. Läkemedelsbehandling av epilepsi – ny rekommendation. Information från Läkemedelsverket (treatment of epilepsy - new recommendation, in Swedish). Läkemedelsverket. 2011.
25. Swedish Medical Products Agency. Läkemedel vid epilepsi – behandlingsrekommendation (medication for epilepsy - treatment recommendation, in Swedish). 2019. https://www.lakemedelsverket.se/sv/behandling-och-forskrivning/behandlingsrekommendationer/sok-behandlingsrekommendationer/lakemedel-vid-epilepsi--behandlingsrekommendation
26. SIGN. Diagnosis and management of epilepsy in adults: A national clinical guideline: Scottish Intercollegiate Guidelines Network. 2015. https://www.sign.ac.uk/media/1079/sign143_2018.pdf
27. NICE. Epilepsies in children, young people and adults: National Institute for Health and Care Excellence. 2022. https://www.nice.org.uk/guidance/ng217/resources/epilepsies-in-children-young-people-and-adults-pdf-66143780239813
28. Tomson T, Battino D, Bromley R, Kochen S, Meador KJ, Pennell PB, 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(3):366–70.
29. Cohen JM, Cesta CE, Kjerpeseth L, Leinonen MK, Hálfdánarson Ó, Karlstad Ø, et al. A common data model for harmonization in the Nordic pregnancy drug safety studies (NorPreSS). Norsk Epidemiologi. 2021;29:1–19.
30. Laugesen K, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdottir UA, Lunde A, et al. Nordic health registry-based research: a review of health care systems and key registries. Clin Epidemiol. 2021;13:533–54.
31. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 2018;17(6):530–8.
32. StataCorp. Stata statistical software: release 17. College Station, TX: StataCorp LLC; 2021.
33. Daugaard CA, Sun Y, Dreier JW, Christensen J. Use of antiepileptic drugs in women of fertile age. Dan Med J. 2019;66(8):1–5.
34. Cohen JM, Cesta CE, Furu K, Einarsdottir K, Gissler M, Havard A, et al. Prevalence trends and individual patterns of antiepileptic drug use in pregnancy 2006-2016: a study in the five Nordic countries, United States, and Australia. Pharmacoepidemiol Drug Saf. 2020;29(8):913–22.
35. Patel N, Viguera AC, Baldessarini RJ. Mood-stabilizing anticonvulsants, Spina bifida, and folate supplementation: commentary. J Clin Psychopharmacol. 2018;38(1):7–10.
36. Cohen MJ, Meador KJ, Loring DW, Matthews AG, Brown C, Robalino CP, et al. Behavioral outcomes and neurodevelopmental disorders among children of women with epilepsy. JAMA Neurol. 2024;81(1):19–29.
37. Herzog AG, Mandle HB, Cahill KE, Fowler KM, Hauser WA. Predictors of unintended pregnancy in women with epilepsy. Neurology. 2017;88(8):728–33.
38. Olesen C, Sondergaard C, Thrane N, Nielsen GL, de Jong-van den Berg L, Olsen J, et al. Do pregnant women report use of dispensed medications? Epidemiology. 2001;12(5):497–501.
39. Danish Health Authorities. Volume sold for medications associated with ATC-code B03BB01 in Denmark from 2005–2017. https://medstat.dk/en/viewDataTables/medicineAndMedicalGroups/%7B%22year%22:[%222017%22,%222016%22,%222015%22,%222014%22,%222013%22,%222012%22,%222011%22,%222010%22,%222009%22,%222008%22,%222007%22,%222006%22,%222005%22],%22region%22:[%220%22],%22gender%22:[%22A%22],%22ageGroup%22:[%22A%22],%22searchVariable%22:[%22sold_volume%22],%22errorMessages%22:[],%22atcCode%22:[%22B03BB01%22],%22sector%22:[%222%22]%7D

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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