

## **UKTIS OFFICIAL POSITION STATEMENT**

**March 2023**

**High-dose folic acid (FA) use in pregnancy and risk of childhood cancer (Vegrim *et al.*, 2022)**

**Summary: A 2022 population-based comparative cohort study indicates an association between maternal high-dose FA supplementation in pregnancy and increased cancer risks (up to 20 years of age) among the offspring of women with epilepsy (WWE).**

The study findings indicated an approximate 3-fold increased risk of cancer among the offspring of WWE who used high-dose ( $\geq 1$  mg/day) FA in pregnancy. Although increased, the absolute risk of cancer among the high-dose FA-exposed was low (1.4% compared with 0.6% in the unexposed population).

Although this observational study is of high-quality, several methodological limitations limit the conclusions that can be drawn. Additionally, the finding is unconfirmed as no further studies have investigated the association. It is therefore not possible to conclude that high-dose FA supplementation in pregnancy among WWE is directly associated with an increased risk of cancer in the offspring. However, there are uncertainties over the clinical benefits of high-dose FA use in pregnancy, complicating the risk-benefit assessment.

Although the clinical benefits of high-dose FA are assumed rather than confirmed in some groups where use in pregnancy is advised, based on the findings of the Vegrim *et al.* study alone, UKTIS do not currently plan to alter their guidance about high-dose FA use among women using antiseizure medications (ASMs) in pregnancy,

---

Disclaimer: Every effort has been made to ensure that the details included in this position statement are accurate and up-to-date at the time of writing. However, the statements and clinical recommendations included cannot cover every eventuality, and the information providers cannot be held responsible for any adverse outcomes of the measures recommended. This information is intended for use by healthcare professionals only and may require expert clinical interpretation: such cases should be discussed with UKTIS. The final decision regarding treatment options for an individual patient remains the clinical responsibility of the prescriber. This material may be freely reproduced for education and not for profit purposes within the UK National Health Service. No linking to this website or reproduction by or for commercial organisations is permitted without the express written permission of UKTIS.

---

### **Background**

A population-based comparative cohort study published in JAMA Neurology in November 2022 indicates an association between high-dose folic acid (FA) supplementation in pregnancy and increased childhood cancer risks among the offspring of women with epilepsy (WWE).<sup>[1]</sup>

UKTIS have been asked to provide an official opinion about the study findings, and whether altered clinical recommendations should be considered about high-dose FA use among WWE using anti-seizure medications in pregnancy.

## ***Study summary***

A tabulated summary of the Vegrim *et al.* 2022 study is provided in the appendix, with key details described below:

### Methods

Study design – Population-based observational comparative cohort study.

Data source – Exposure, outcome and covariable data collected from linked national healthcare registers (to provide information on prescriptions, maternal diseases, obstetric data and childhood cancer) in Sweden, Denmark and Norway, 1997 to 2017.

Study sample – Children were followed up from birth until the date of first cancer diagnosis or censored at the date of death, emigration, 20th birthday, or the end of data period (Dec-17).

Statistical analysis techniques – Cox proportional hazards modelling with age of the child as time scale, and high-dose FA exposure as the dependent variable. Maternal age, education, number of hospitalisations, smoking, maternal BMI and previous birth of a child with a major congenital anomaly included as co-variates. Birth year, country of residence and sex of the child were included as strata within the models.

### Important definitions

Use of high-dose FA was defined as at least one filled prescription of either 1 mg or 5 mg FA supplement between 90 days before the first day of the last menstrual period and birth. A mean daily dose (based on the number of tablets dispensed over the duration of the pregnancy) was also calculated.

### Analyses

Primary analysis – Cumulative incidence of cancer at age 20 years by high-dose FA exposure status, stratified by maternal epilepsy status.

Secondary analysis – As in primary analysis but further stratified by antiseizure medication (ASM) exposure status.

Key sensitivity analyses – (i) Risk of childhood cancer among children of WWE (irrespective of FA exposure status); (ii) as in primary analysis but excluding women with exposure to carbamazepine or sodium valproate; (iii) as in primary analysis but excluding women with a history of cancer, tuberous sclerosis or diabetes, or children with congenital or chromosomal anomalies; (iv) impact of higher mean daily dose (over the cumulative course of the pregnancy).

### Main findings

#### *1. Study sample stratified by maternal epilepsy status:*

(i) Increased risk of cancer among offspring of WWE exposed to high-dose FA (n=18/5934, IR 42.5 per 100k person years) compared with WWE who were high-dose FA unexposed (n=29/21,850, IR 18.4 per 100k person years), aHR 2.7 (95% CI; 1.2 to 6.3).

(ii) No increased risk among women without epilepsy exposed to high-dose FA compared with women without epilepsy who were high-dose FA unexposed: aHR 1.1 (95% CI; 0.9 to 1.4).

#### *2. Study sample further stratified by maternal ASM exposure status:*

(i) Increased risk among WWE exposed to ASM and high-dose FA compared with WWE exposed to ASM but high-dose FA unexposed: aHR 3.0 (95% CI; 1.1 to 7.9)

(ii) Unable to assess the risk among WWE unexposed to ASM due to the small size of the cohort with these exposure parameters (n=403) and no recorded cases of cancer in the offspring.

(iii) Unable to assess the risk among women without epilepsy exposed to ASM due to the small size of the cohort with these exposure parameters (n=819) and no recorded cases of cancer in the offspring.

(iv) No increased risk among women without epilepsy unexposed to ASM but exposed to high-dose FA compared with women without epilepsy unexposed to ASM but high-dose FA unexposed: aHR 1.1 (95% CI; 0.8 to 1.4).

### 3. Sensitivity analyses:

(i) Cancer risk increased among children exposed to ASM *in utero* (any indication) when compared with children unexposed to any ASM (regardless of FA exposure): aHR 1.5 (95% CI, 1.1 to 2.1). However, the risk estimate for this cohort was lower than that observed among those also exposed to high-dose FA (see findings 1 (i) and 2 (i) above).

(ii) Removing mothers with any prescription fills for carbamazepine or valproate from the primary analysis slightly attenuated the risk estimate: aHR 2.4 (95% CI; 0.9 to 6.5).

(iii) Removal of mothers with cancer before pregnancy (n=454), tuberous sclerosis (n=23), or diabetes (n=1,292, including gestational diabetes) did not alter the findings.

(iv) A higher cumulative dose of FA (mean dose  $\geq 4$  mg/day) was associated with a higher risk estimate for cancer in the offspring of WWE (compared with unexposed children of WWE – aHR 3.4, 95% CI; 1.1 to 10.7) than with lower cumulative doses (mean dose  $< 4$  mg/day – aHR 2.9, 95% CI; 1.2 to 7.2). However, there was no statistically significant difference between the two.

### **Interpretation of study findings from Vegrim et al.**

The study authors concluded that maternal use of high-dose FA ( $\geq 1$  mg/day) may be associated with an increased risk of cancer among children of mothers with epilepsy. While this conclusion is generally supported by the study findings, there are important study limitations which may impact interpretation and the clinical response:

1. **Risk of bias.** Exposure misclassification and impacts from unmeasured confounding are both concerns. High-dose FA exposure was defined based on prescription records, which does not guarantee maternal use, and the study did not have access to data on maternal serum folate levels, over-the-counter supplement use, or dietary intake. As the majority of the cancer cases occurred  $>10$  years after *in utero* exposure (there could be a number of risk factors which presented in this long time period, common to WWE who use high dose FA, that have not been accounted for in the study). Additionally, the study being observational means that it is not possible to assign causality to the high-dose FA exposure.

2. **Imprecision.** Stratification of data through the different exposure characteristics (WWE yes/no, high-dose FA exposure yes/no, ASM-exposed yes/no) decreases the sample size, thereby producing wide confidence limits, and in some cases (see findings 2 (ii) and (iii) above), the inability to calculate the risk (due to the lack of events). It is therefore probable that a small change in the number of exposed and affected individuals could have altered the statistical significance of the findings.

3. **Inconsistency/publication bias.** No other studies have investigated this exposure and outcome, which means it is not possible to assess inconsistency/publication bias. However, the

lack of other studies is important because certainty in a body of evidence is highest when there are several studies that show consistent results.

**4. Confounding due to *in utero* ASM exposure.** Despite the large study sample, there were not enough high-dose FA-exposed children with cancer to generate risk estimates for the offspring of WWE who filled prescriptions for FA but not for ASMs. This is because ASM was used by almost the entire cohort of WWE filling prescriptions for high-dose FA (n=5,531/5,934, 93.2%). It was also shown that there was no detectable increased risk of childhood cancer among children born to women without epilepsy who used high-dose FA. This suggests that the use of ASMs may be an important contributory factor. However, due to the small number of WWE not using FA (and the lack of cancer cases in their offspring), the study lacked statistical power to demonstrate an interaction between ASM and high-dose FA use. Although it is difficult to disentangle the impact on cancer risks due to *in utero* ASM exposure from that of exposure to high-dose FA, it is noted that the cancer risk among ASM-exposed (irrespective of FA exposure status) was lower than the estimate for the offspring of WWE exposed to high-dose FA (see finding 3 (i) above). Additionally, when carbamazepine and sodium valproate-exposed women were excluded from the analysis, the risk estimate was only slightly attenuated (see finding 3 (ii) above).

**5. Biological Plausibility.** The authors do not provide a hypothesis as to the mechanism by which high-dose FA may increase cancer risk in the offspring of WWE but not in women without epilepsy. Childhood cancer as an outcome is a heterogeneous group of conditions, likely to have numerous risk factors/aetiological factors.

**6. Magnitude of effect.** Generally, where there is a greater than 2-fold increased risk demonstrated in an observational study, it is suggested that data confounding may not completely explain the increased risk. This study indicated a greater than double risk of childhood cancer in both the analyses of WWE using high-dose FA, and WWE using ASMs and high-dose FA. Therefore, it may be plausible that unmeasured confounding may not completely explain the association. However, the confidence intervals for the risk estimates were wide, and this imprecision may mean that small corrections to the risk estimates through statistical adjustments could have resulted in non-statistically significant increased risks being produced. Additionally, as cancer is a relatively rare outcome, small changes in the number of exposed and affected offspring may have larger effects on the risk estimates and their confidence limits.

**7. Higher risk with higher cumulative dose.** Although those exposed to a higher cumulative dose of FA ( $\geq 4$  mg/day) trended towards higher cancer risks than those with lower cumulative doses ( $< 4$  mg/day), the difference between the two groups did not reach statistical significance. Even if the difference had been significant, a dose relationship would be subject to the same confounding issues as the primary analysis.

#### ***High-dose FA use and risk-benefit considerations***<sup>[2]</sup>

Folate requirements are increased 5- to 10-fold during pregnancy (with peak maternal folate requirements at around five months' gestation). Pregnant women are at risk of folate deficiency. It is well-established that periconceptual folate *deficiency* is associated with increased risks of neural tube defects (NTDs) and that peri-conceptual FA supplementation reduces these risks.

Some studies suggest a reduced risk of miscarriage and congenital heart defects with peri-conceptual FA supplementation. However, there is no conclusive evidence of a protective effect.

Conflicting evidence also exists as to whether gestational folate supplementation (i.e. continued after the periconceptual period) reduces the risk of preterm delivery and low infant birth weight, and some studies have suggested that neurodevelopmental outcomes may be improved in children exposed to FA *in utero*, although data confounding is possible (women who continue folate use throughout pregnancy may have a better socioeconomic status/have increased health literacy/educational attainment themselves).

Currently, definitive evidence that folate supplementation beyond the point of fetal neural tube closure is beneficial is lacking. It is also unclear whether the use of high-dose FA provides any additional benefit above standard doses for those advised to use it. This is particularly true for those using the subgroup of ASMs which do not clearly impair maternal folate status. There are uncertainties over the clinical benefits of high-dose FA use in pregnancy which further complicates the risk-benefit assessment in light of the findings from Vegrim *et al.*

### **Conclusion**

The study findings from Vegrim *et al.* indicate an approximate 3-fold increased risk of cancer among the offspring of WWE who used high-dose ( $\geq 1$  mg/day) FA in pregnancy. Although increased, the absolute risk of cancer among the high-dose FA-exposed, as indicated by these data, was 1.4% (95% CI; 1.2 to 6.3%), in comparison with 0.6% (95% CI; 0.3 to 1.1%) in the unexposed; therefore, the absolute risk of cancer remains low.

Although this observational study is considered to be of high-quality, methodological limitations limit the conclusions that can be drawn. The lack of any other observational or basic scientific studies investigating the association mean that it is not possible to conclude, within a reasonable degree of certainty, that high-dose FA supplementation in pregnancy among WWE is directly associated with an increased risk of cancer in the offspring. However, there are uncertainties over the clinical benefits of high-dose FA use in pregnancy which complicate the risk-benefit assessment. Further research is therefore required.

Based on the findings of the Vegrim *et al.* study alone, UKTIS do not currently plan to alter the recommendation that women using ASM in pregnancy should be offered high-dose FA.

### **References**

1. Vegrim, H.M., Dreier, J.W., Alvestad, S., Gilhus, N.E., Gissler, M., Igland, J., Leinonen, M.K., Tomson, T., Sun, Y., Zoega, H., Christensen, J. and Bjørk, M.H. Cancer Risk in Children of Mothers With Epilepsy and High-Dose Folic Acid Use During Pregnancy. *JAMA Neurol.* 2022 Nov 1;79(11):1130-1138. PMID: [36156660](https://pubmed.ncbi.nlm.nih.gov/36156660/)
2. UKTIS Monograph. Use of folic acid in pregnancy. February 2018. Version 2.0. Available from <https://uktis.org/monographs/use-of-folic-acid-in-pregnancy/> [Accessed March 2023].

## Appendix

Table 1: Overview of the Vegrim et al. study (Cancer risk in children of mothers with epilepsy and high-dose folic acid use during pregnancy)

Author and year	Study design and setting	Study population	Statistical analysis techniques and co-variates	Main outcome measure and key findings	Interpretation and UKTIS comments
Vegrim et al., 2022	Population-based observational cohort study  Data collected from linked national healthcare registers (Sweden, Denmark and Norway), 1997 to 2017	3,379,171 children including:  27,784 born to WWE (with 5,934 exposed, and 21,850 unexposed to high dose folic acid)  3,351,387 born to women without epilepsy (with 46,650 exposed, and 3,304,741 unexposed to high dose folic acid)	CoxPH modelling with age of the child as time scale  Maternal age, education, ASM exposure, number of hospitalisations, smoking, body mass index, and previous birth of a child with a major congenital anomaly included as co-variates  Birth year, country of residence, sex of the child as strata within the models	<b><i>Risk of childhood cancer (&lt;20 years) by high dose (&gt;1 mg/d) folate exposure status:</i></b>  a) Increased risk among WWE exposed to high-dose folate (n=18/5934, IR 42.5 per 100k person years) vs. WWE high-dose folate unexposed (n=29/21,850, IR 18.4 per 100k person years), aHR 2.7 (95% CI; 1.2 to 6.3)  b) No increased risk among women without epilepsy exposed to high-dose folate vs. women without epilepsy high-dose folate unexposed: aHR 1.1 (95% CI; 0.9 to 1.4)  c) Increased risk among WWE exposed to ASM and high-dose folate vs. WWE exposed to ASM high-dose folate unexposed: aHR 3.0 (95% CI; 1.1 to 7.9)  d) Increased risk of leukaemia among WWE exposed to high-dose folate: aHR 7.3 (95% CI; 1.5 to 35.2), insufficient data to assess risks for all other specific types of cancer  e) Dose response relationship is possible as there were higher risks	ASMs were used by almost the entire cohort of WWE filling prescriptions for high-dose folic acid (n=5,531/5,934, 93.2%). Therefore, maternal use of ASM in pregnancy or other characteristics inherent in these women could explain the findings. However, removing CBZ and NaVAL from the cohort did not substantially alter the risk estimate, and ASM exposure was associated with a lesser increased risk of childhood cancer (aHR 1.5 – see finding f).  The long lag time between <i>in-utero</i> exposure, and the time to cancer event means that a considerable impact from unmeasured confounding cannot be discounted (from the footnotes in Table 2, it appears that most of the cancer events in the high-dose folic acid exposure group occur >10 years after delivery). Due to the rarity of childhood cancer, the study population was not sufficiently large enough to include a wider variety of co-variable risk factors in the statistical models, therefore the adjusted data may remain confounded.  Childhood cancer as an outcome is a heterogenous group of conditions, likely to have numerous risk factors/aetiological factors.  As this study was observational, the usual

			<p>among those born to WWE who used doses <math>\geq 4</math>mg daily vs. unexposed (aHR 3.4, 95% CI; 1.1 to 10.7) and those <math>&lt; 4</math>mg daily vs. unexposed (aHR 2.9, 95% CI; 1.2 to 7.2), but the difference between these two populations (<math>\geq 4</math>mg daily vs. <math>&lt; 4</math>mg daily) was not statistically significant</p> <p>f) Cancer risk increased among children exposed to ASM in utero for any indication (aHR 1.5, 95% CI, 1.1 to 2.1) compared with that of children unexposed to any ASM (regardless of folic acid exposure)</p> <p>g) Maternal epilepsy was not associated with childhood cancer (aHR 1.0, 95% CI; 0.7 to 1.4)</p> <p>h) Exclusion of mothers with a history of cancer, TB or diabetes, or children with congenital or chromosomal anomalies did not change the risk estimates</p>	<p>concerns with use of prescription data to define exposure exist (i.e. potential for exposure misclassification).</p> <p>Some of the findings are based on small numbers of exposed and affected infants, producing wide confidence limits. It is therefore probable that a small change in the number of exposed and affected individuals could have altered the statistical significance of the findings.</p> <p>The study did not have a sufficient sample size to allow estimates of cancer risk among WWE who did not use ASMs, nor women without epilepsy who used ASMs.</p>
--	--	--	---	--

**Key:** WWE – women with epilepsy, CoxPH – Cox Proportional Hazards, IR – incidence rate, aHR – adjusted hazards ratio, 95% CI – 95% confidence interval, ASM – antiseizure medication, TB – tuberculosis, CBZ – carbamazepine, NaVAL – sodium valproate.