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Pregnancy outcomes in women with epilepsy and MTHFR mutations supplemented with methylated folate and methylcobalamin (methylated B12)

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ABSTRACT

Antiseizure medications (ASM) may contribute to adverse fetal outcomes in pregnant women with epilepsy (WWE). Folate processing (Methylenetetrahydrofolate reductase, MTHFR) gene abnormalities are common in women with epilepsy and depression. L-methylfolate supplements may bypass MTHFR deficiencies, yet their use in WWE during gestation or on fetal development is not well studied. We examine pregnancy histories of three WWE who supplemented with either folate or L-methylfolate and methylcobalamin (methylated B12) during pregnancies. Their pregnancy outcomes improved with L-methylfolate and methylcobalamin supplementation. L-methylfolate and methylcobalamin supplementation merits further study in WWE who have MTHFR mutations, fertility, recurrent miscarriage and or depression histories.

1. Introduction

Women with epilepsy (WWE) are more likely to have problems with conception, gestation and delivery of normal infants [1]. In addition, WWE remain at higher risk of mood dysfunction and depression [2]. Medications that lower burdens of depression, bipolar disorder and epilepsy may have teratogenic effects [1,2,4]. How antiseizure medication (ASM) might alter teratogenicity remains incompletely understood, however, in recent work ASM induction of de novo genetic variants is unlikely [5]. ASM or mood stabilizing medications such as carbamazepine (CBZ) and valproic acid (VPA) have been shown to increase risk of fetal neural tube defects (NTD) including spina bifida [1,3]. CBZ and VPA may include altered folate mechanisms, specifically decreases in levels of 5-formyl- and 10-formyltetrahydrofolate, which in turn may disrupt DNA methylation and histone acetylation pathways which may then alter cell division and migration [3,6].

Folate supplementation of up to 4 mg during gestation remains standard of care for WWE in the USA [1]. Use of folate supplements from pre-conception to delivery decreases the odds ratio of NTD development from 1.6 (95% CI 0.8–3.1) to 1.2 (95% CI 0.4–4.0) [1,7–10], however folate mitigation of teratogenic effects due to ASM *have not* been well documented [11,12]. Supplementary folate in women taking CBZ and VPA for instance, *does not* decrease rates of spina bifida [13]. Our epilepsy community remains focused on ASM that have the lowest risk of use in pregnancy. If we have to use a particularly teratogenic ASM in pregnancy such as VPA, the strategies to limit fetal risk often jeopardize maternal seizure control, particularly if first trimester doses are lowered or risky and quick substitution for less effective ASM occurs.

A potential risk factor for NTD can occur in folate pathways, specifically, a polymorphism that codes for 5,10-methylenetetrahydrofolate reductase (MTHFR) [6,14]. This gene makes folate bioavailable through methylation, permitting homocysteine to convert to methionine, a critical step for normal protein synthesis. If MTHFR cannot methylate folate, common findings in women who supplement with folic acid are elevations in serum folate. Polymorphisms in the MTHFR gene at C677T for both the homozygous (TT) and heterozygous (CT) genotypes are increased in women with genetic generalized epilepsies when compared to a woman *without* epilepsy, they are less well studied in women with focal epilepsy [6,15]. Many women with generalized epilepsy show superior control of their epilepsy when using VPA yet as a community we try to avoid this drug in women of reproductive

Abbreviations: WWE, women with epilepsy; MTHFR, Methylenetetrahydrofolate reductase; ASM, Antiseizure medication; ASD, Autism spectrum disorder.

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age due to side effect profiles including known teratogenicity. VPA teratogenicity may be further exacerbated in women who have defects in their MTHFR pathways [6].

Dietary folate, combined with dietary vitamin B12 are both required in converting homocysteine to methionine and ultimately lead to protein synthesis. [16] When these pathways do not function efficiently, homocysteine may elevate; hyperhomocysteinema in pregnancy and in neonates may correlate with worse fetal outcomes. [16,17] Additional risks of folate pathways not functioning well occur in the setting of limited bioavailable vitamin B12. [17]

5-methyltetrahydrofolate may be available as L-methylfolate and is used in the USA for the treatment of depression [18,19]. The supplement has few known adverse effects and bypasses MTHFR gene pathways, in essence becoming bioavailable when gene efficiency is otherwise compromised. In patients with MTHFR gene defects, data suggests prenatal supplementation with L-methylfolate is more successful at increasing bioavailable folate concentrations than unmethylated folic acid [20]. Furthermore, infertility-based supplementation of methylated folates in women *and* men with C677T MTHFR mutations may help with successful conceptions and gestations [20].

Somewhat remarkably, whether methylated versions of folate and vitamin B12 (methylcobalamin) taken by WWE helps avoid depression, seizure, fertility, or adverse fetal outcomes like spina bifida during pregnancy remains unknown. In this observational report we document pregnancy, seizure and mood histories with and without L-methylfolate or methylcobalamin for three women with epilepsy with known MTHFR mutations.

2. Case reports

After informed consent patients were interviewed regarding pregnancy, conception, miscarriage, mood and child developmental histories. Data are summarized on Table 1. No statistical testing was performed. Key findings include pregnancy outcomes on varied supplement or medication doses. Standardized practice models of adjusting antiseizure medication doses through serum drug levels checked every 6 weeks during gestation as were referrals to high risk Maternal Fetal Medicine specialists for surveillance ultrasounds during gestations and peri-delivery care. If available, homocysteine and folate levels are documented, these were not serially surveyed. Seizures did not occur during any of the successful pregnancies, nor were they thought to be causative of any of the miscarriages.

3. Discussion

3.1. Notes on cases

Patients one and two adopted methylated folate and methylcobalamin/injected B-12 supplementation after recurrent miscarriage or conception failures. We have no way of proving if these two supplements helped with subsequent successful pregnancies and deliveries, though successful pregnancies and deliveries suggested benefit. Importantly we did not see adverse outcomes. Particularly notable is the gestation failure for patient one's fourth pregnancy, which occurred on methylated folate though off of vitamin B12 injection therapies. All of the successful pregnancies occurred while on methylated folate and either injected or methylated B12 supplements in addition to standard prenatal multivitamin supplements.

Patient three's use of L-methylfolate therapies proved fundamental to her desire to even pursue pregnancy. Specifically, prior to her L-methylfolate supplementation, she was recurrently treated with electroconvulsive therapies for refractory depression and had not considered pregnancy. With L-methylfolate success in treating her depression, she no longer required ECT, and both her mood and epilepsy remained controlled during pregnancy and postpartum.

3.2. Limitations

This study has a small sample size, and as such miscarriage rates may be no different than chance. Folate and homocysteine levels were not serially surveyed in either the mothers or children, the children remain young at time of writing, and without neuropsychological assessment. Similarly, mood batteries in the mothers pre and post methylated folate or methylcobalamin supplementation were not done.

3.3. Risks of folic acid and B12 elevations in pregnancy

Limited data exists on risks of elevated folate during pregnancy. One study documents a U-shaped risk of third-trimester B12 and folate levels in mothers with a risk of autism spectrum disorders (ASD) in their offspring when levels are either low or very high [21]. Rhagavan et al. found *no risk* of maternal folate and MTHFR genotype status on ASD outcomes. Their study did not look at cohort use during gestation of methylated vs non-methylated versions of B12 and/or folate.

3.4. Implications

Many patients with genetic generalized epilepsies remain controlled on VPA, including during pregnancy [1]. Women on VPA therapies during pregnancy have the highest risk of adverse fetal outcomes [1]. Given MTHFR mutations are common in women with generalized epilepsy, should they wish to conceive and if they have to remain on VPA, pharmacogenetic targeting and preconception and pregnancy supplementation with L-methylfolate and methylcobalamin if MTHFR defects are present should be studied [19]. Similarly, women who were switched off of VPA preconception due to teratogenic concerns, that went on to have recurrent fetal loss or conception failures, should also be considered candidates for a similar workup and therapy approach.

Regardless of a generalized epilepsy diagnosis, our study suggests women with a variety of ofepilepsy classifications with/without mood disorders with recurrent conception failures, irrespective of medication profiles, could be screened for MTHFR mutations and if abnormal, consider supplementation with both methylcobalamin and L-methyfolate. We have not found homocysteine levels useful, nor folate levels practical in screening. Folate is often elevated in patients with MTHFR defects on supplemental folate and may be falsely reassuring. Those patients, however, merit formal study. Specifically with outcomes looking at safety, seizure controls, dosage of methylated vitamins, gestation success, incidence of neonatal stroke or hypoxic ischemic issues, use of supplements during breast feeding, incidence of spina bifida along with longer term neonatal and neurodevelopmental outcomes, including ASD. In addition, measurements of depression preconception, during gestation, and post-partum could also be checked.

4. Conclusion

After either recurrent fertility setbacks or depression in prior pregnancies, three WWE with known MTHFR mutations had successful pregnancies when supplementing with L-methylfolate and methylated folate or methylcobalamin. Fetal and maternal risks of exposure to methylated vitamins are not well known. Prospective studies of methylated folate and methylcobal-

Table 1

	Age of epilepsy onset	Epilepsy diagnosis	History of Miscarriage	Pregnancy history	Medications during successful pregnancy	MTHFR genotype, homocysteine, folate, and B12 levels (if known)	Psychiatric comorbidities	Status of children's developmental milestones
Patient 1	7	Generalized onset, motor, tonic clonic	First, second and fourth pregnancies age 33, 34,38; all first trimester miscarriages occurred on prenatal vitamins with additional folate and leveitracetam. No methylated folate or methylcobalamin for pregnancies 1 and 2; At age 38: miscarriage while on L-methylfolate but not also taking methylcobalamin. Missed the B12 shot in the month prior to miscarriage.	Third pregnancy at 36 via vaginal delivery resulted in a healthy boy. She was seizure-free throughout pregnancy. Fifth pregnancy at : age 39, 39 week c-section and. seizure-free throughout pregnancy.	Methylcobalamin B12 oral or parenteral B12 injections. Levetiracetam 1500 bid, L-methylfolate 7.5 mg daily, and prenatal vitamins daily	Homozygous for the C677T mutation. Homocysteine level 6 umol/L (prior to L-methylfolate), folate l> 20 ng/ml (i.e. elevated) tested when not on methylfolate, vitamin b12 699.3 pg/ml (normal)	History of major depressive disorder and postpartum depression after her first child while on L-methylfolate and methylcobalamin and levetiracetam. This occurred in the setting of sleeping poorly and breastfeeding. No depression after her second child while on l-methylfolate and methylcobalamin. She was switched from levetiracetam to valproic acid postpartum.	Normal development for both children now age 8 and age 5
Patient 2	4	Focal epilepsy with impaired awareness seizures	First pregnancy, age 32, first trimester miscarriage after 1 year of attempted conception. No L-methylfolate or methylcobalamin but she was on folate, levetiracetam and zonisamide	Seccond pregnancy at 34 via c-section at 38 weeks gestation. Seizure-free throughout pregnancy. Third pregnancy at 36 and 40 week gestation via c-section. Seizure-free throughout pregnancy	Cholecalciferol (vitamin D3) 2000 IU dailyL-methylfolate 5 mg daily, methylcobalamin B12 5 mg daily, levetiracetam 1500 mg bid, prenatal vitamins, and zonisamide 200 mg daily	Heterozygous C667T mutation and A1298C. Homocysteine normal at 6.4 umol/L (pre L-methylfolate), folate > 19.9 ng/mL (elevated) in second pregnancy.	Postpartum depression after her second child though reported getting better.	Normal for both children at age 4 months and age 29 months
Patient 3	28	Focal epilepsy with focal impaired awareness seizures	N/A	First pregnancy: uncomplicated vaginal delivery age 33 at 38 weeks gestation. Seizure-free through pregnancy.	Methylcobalamain B12 100 mcg, sertraline 25 mg daily, L-methylfolate 15 mg daily, vitamin D2 (ergocalciferol), prenatal vitamins, quetiapine 400 mg daily, lamotrigine 500 mg AM and 400 mg PM	Homozygous C677T mutation, homocysteine normal at 11.4 umol/L (pre-L-methylfolate)	Bipolar I disorder, history of depression, prior to L-methylfolate supplementation with recurrent electroconvulsive therapy. This , was not required again after L-methylfolate add. edN No postpartum worsening of depression and she continues to work with psychiatrist.	Normal at age 40 months, speech therapy though all other language measures normal or above average.

amin in WWE with/without mood disorders and known MTHFR mutations and infertility or recurrent fetal loss, or females administered folate altering ASM such as VPA during pregnancy are warranted.

Ethical statement

Informed consent was obtained for this case write up and the work has been carried out in accordance with The Code of Ethics of the World Medical Association.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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