DOI: https://doi.org/10.4038/jccp.v55i2.8080

Epilepsy in pregnancy

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Journal of the Ceylon College of Physicians, 2024, **55**, 154-159

Abstract

This review explores the complex relationship between epilepsy and pregnancy, focusing on the effects of epilepsy on pregnancy outcomes, the influence of pregnancy on epilepsy, the teratogenic effects of anti-seizure medications, the role of vitamin K supplementation, and the management of epilepsy during pregnancy. By synthesizing recent research and clinical guidelines, the review provides a comprehensive overview of the challenges faced by women with epilepsy during pregnancy and the strategies employed to manage these challenges effectively.

Key words: epilepsy in women, pregnancy outcomes, antiseizure medications, teratogenicity

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, affecting approximately 1% of the global population.[1] Women of childbearing age represent a significant portion of this demographic, making the management of epilepsy during pregnancy an important issue.[2] The interplay between epilepsy and pregnancy is complex, involving potential risks to both maternal and foetal health.[3] Effective management requires a balance between controlling seizures and minimizing risks to the foetus from anti-seizure medications (ASMs).[4] This review aims to provide a detailed exploration of these challenges, offering insights into the current best practices.

Effect of epilepsy on pregnancy

Pregnancy complications in women with epilepsy

Women with epilepsy (WWE) are at an elevated risk of various pregnancy complications, influenced by both the condition itself and the medications used to manage it.[5] Understanding these risks and their links to specific ASMs is essential for optimizing care.

Convulsions, either generalized tonic-clonic or focal to bilateral tonic-clonic, are dangerous to WWE not only because of the risk of seizure-related falls and blunt trauma but also because of potential harm to the foetus from the possibility of hypoxemia and asphyxia.[6] Focal seizures that do not evolve to tonic-clonic convulsions are thought unlikely to have a major impact on the foetus. However, anecdotal evidence suggests that focal seizures can cause transient foetal distress, with foetal heart rate deceleration for up to 2.5 minutes.[7]

WWE are at a significantly higher risk of pregnancy-induced hypertension (PIH) and preeclampsia. Studies suggest that WWE are at a 1.5- to 2-fold increased risk of developing preeclampsia compared to the general population.[8] This increased risk may be related to the hemodynamic changes caused by seizures, particularly generalized tonic-clonic seizures, which can exacerbate endothelial dysfunction, a key feature of preeclampsia.[9]

The risk of stroke is higher in WWE due to factors such as the prothrombotic state of pregnancy, the potential for increased blood pressure due to PIH or preeclampsia, and hemodynamic changes associated with seizures.[10,11] The use of enzyme-inducing ASMs,

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Received 03 September 2024, accepted 04 October 2024.

such as carbamazepine and phenytoin, may increase the risk of hemorrhagic stroke due to their anticoagulant properties.[2] Conversely, ASMs like valproic acid (VPA), which affect platelet function, may raise the risk of thromboembolic events, further complicating the management of epilepsy during pregnancy.[13] WWE are also at increased risk of gestational diabetes mellitus (GDM). GDM is associated with risks such as macrosomia, cesarean delivery, and neonatal hypoglycemia.[14] The use of certain enzyme-inducing ASMs, such as phenytoin has been linked to an increased risk of hyperglycaemia.[15] Additionally, VPA, a non-enzyme-inducing ASM, is associated with weight gain and insulin resistance, further increasing the risk of GDM.[16]

Placental abruption, the premature separation of the placenta from the uterine wall, is more common in WWE, particularly in those with poorly controlled seizures.[17] Generalized tonic-clonic seizures can lead to acute increases in intra-abdominal pressure, causing placental detachment and increasing the risk of antepartum hemorrhage, foetal distress, and preterm birth.[18]

Preterm labour and delivery are more common in WWE, with studies indicating a twofold increase in the risk of preterm birth compared to the general population.[19] Preterm birth is associated with increased neonatal morbidity and mortality, including respiratory distress syndrome, intraventricular hemorrhage, and long-term neurodevelopmental sequelae.[19] The increased risk of preterm birth in WWE is likely due to the effects of seizures on uterine contractions, the side effects of ASMs, and the presence of other complications like PIH and placental abruption.[19]

WWE are more likely to undergo cesarean delivery compared to the general population.[20] Higher cesarean rates in WWE may be influenced by concerns about the potential for seizures during labour, the presence of other obstetric complications, and the effects of ASMs on the progression of labour. The need for a controlled delivery environment in women with poorly controlled epilepsy may lead to a more conservative approach favouring surgical delivery.

WWE have a higher risk of maternal mortality compared to women without epilepsy, with sudden unexpected death in epilepsy (SUDEP) being a leading cause.[21] The risk of SUDEP may increase during pregnancy due to physiological changes that lower seizure thresholds, potential non-adherence to ASMs due to concerns about teratogenicity, and the increased physical and emotional stress associated with pregnancy. Polytherapy is associated with a higher risk of SUDEP compared to monotherapy which suggests uncontrolled epilepsy requiring polytherapy to be a risk.[21]

Effect of pregnancy on epilepsy

Seizure frequency and pregnancy

The effect of pregnancy on seizure frequency varies widely among WWE. The predictor of seizure control during pregnancy is seizure control during the 9 months prior to conception.[22] Approximately two-thirds of women may experience no change in seizure frequency in comparison to their non-pregnant state.[22] An increase in seizure frequency during pregnancy may be seen in a minority, especially in WWE with a greater frequency of drug modifications compared to their non-pregnant states.[22]

Hormonal changes during pregnancy, particularly fluctuations in oestrogen and progesterone levels, can alter seizure thresholds and influence seizure activity.[23] Women with catamenial epilepsy (a condition where seizure frequency correlates with the menstrual cycle) are particularly susceptible to increased seizures during pregnancy due to these hormonal fluctuations.[23]

Pharmacokinetics of antiseizure medications during pregnancy

Pregnancy significantly alters the pharmacokinetics of ASMs, necessitating careful monitoring and dosage adjustments.[13] Increased plasma volume, altered protein binding, and enhanced renal clearance during pregnancy can lead to lower serum levels of ASMs, potentially resulting in breakthrough seizures if doses are not adjusted accordingly.[13] For instance, serum levels of lamotrigine can decrease by up to 50% in the third trimester due to the effects of oestrogen on its metabolism, highlighting the need for frequent monitoring and dose adjustments.[13] Similar pharmacokinetic changes have been observed with other ASMs, such as levetiracetam (increase in renal clearance and volume distribution), necessitating careful titration to maintain therapeutic efficacy. Serum levels of phenytoin and VPA which are ASMs with high protein binding can reduce in pregnancy due to the lower concentration of albumin that occurs during pregnancy which in turn leads to a reduction in the percentage of drug molecules bound to proteins.[24] Thus, the reduction in the total concentration of the drug leads to reduction in the pharmacologically active percentage of the drug (the unbound fraction).

Teratogenic effects of antiseizure medications (ASMs)

Teratogenicity of specific ASMs

The teratogenic potential of ASMs is a significant concern in managing epilepsy during pregnancy. VPA is particularly associated with a high risk of major congenital malformations (MCMs), including neural tube defects, facial dysmorphism, and cognitive impairments.[5] The teratogenic effects of VPA have prompted changes in clinical guidelines, with recommendations against its use in women of childbearing age unless no suitable alternatives are available.[6] The prevalence of MCMs based on registry data is depicted in Table 1.

Newer ASMs, such as lamotrigine and levetiracetam, have demonstrated a more favorable teratogenic profile, with lower risks of MCMs compared to older drugs like VPA and phenytoin.[12] The EURAP registry, a large international cohort study, has provided valuable data showing that lamotrigine and levetiracetam are associated with lower risks of congenital malformations when used as monotherapy during pregnancy. Thus, it is recommended that WWE who are planning to conceive be on ASMs such lamotrigine and levetiracetam prior to conception when considering their safety profile during pregnancy.

Beyond structural malformations, there is growing concern about the long-term neurodevelopmental effects of in-utero exposure to ASMs.[14] Studies have shown that prenatal exposure to VPA is associated with an increased risk of lower IQ, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD).[16] Topiramate might also be problematic, based on a cumulative incidence analysis from a population registry. These findings have led to changes in clinical practice guidelines, emphasizing the importance of minimizing foetal exposure to high-risk ASMs like VPA.

Place of vitamin K in pregnancy

Vitamin K supplementation is crucial in preventing hemorrhagic disease of the newborn (HDN), especially in infants born to mothers taking enzyme-inducing ASMs.[7] These ASMs, including phenytoin, phenobarbital, and carbamazepine, induce hepatic enzymes that accelerate the degradation of vitamin K, leading to reduced levels of clotting factors in the newborn.[7] While guidelines such as the Green-top Guideline No. 68 by the Royal College of Obstetricians and Gynaecologists[25] suggest supplementation of vitamin K to both the mother (oral supplement for the last few weeks of pregnancy) and the neonate (parenteral formulation, 1mg at birth), evidence is insufficient to recommend antenatal maternal vitamin K supplementation for all pregnant WWE taking enzyme-inducing ASMs.

Table 1. Foetal malformation risk (data from pregnancy registries*)

Drug	*Malformation risk*	*Most frequent major congenital malformation*
Valproic acid	4.7%-10%	Neural tube defects, hypospadias, cardiac malformations
Topiramate	4.2%-7.7%	Orofacial clefts
Phenobarbital	5.5%-7.4%	Cardiac malformations
Phenytoin	2.9%-6.7%	Cardiac malformations
Carbamazepine	2.6%-5.6%	Cardiac malformations
Lamotrigine	2.0%-3.4%	Cardiac malformations, Oro-facial clefts
Oxcarbazepine	1.8%-3.3%	**Oro-facial clefts
Levetiracetam	0%-2.4%	**Cardiac malformations, **Neural tube defects

*Registries: International Register of Antiepileptic Drugs and Pregnancy, North American Antiepileptic Drug Pregnancy Register, UK Epilepsy and Pregnancy Register, Medical Birth Register of Norway, Swedish Medical Birth Register

**Rarely reported

Management of epilepsy in pregnancy

Preconception counseling and planning

Effective management of epilepsy during pregnancy begins with preconception counseling and planning.[8] WWE should be counseled on the potential risks associated with ASMs, the importance of maintaining seizure control, and the need for folic acid supplementation to reduce the risk of neural tube defects.[8] Registry data for pregnant WWE has not yet shown a reduction of MCMs with folic acid supplementation. However, strong evidence indicates neurocognitive benefits in children born to WWE who received periconceptional folic acid supplements of at least 0.4 mg/day.[26] Preconception counseling has been shown to significantly improve pregnancy outcomes, including lower rates of MCMs and better seizure control during pregnancy.

Medication management

The choice of ASMs during pregnancy should prioritize both maternal seizure control and foetal safety.[9] Evidence from studies and specific birth registry analyses consistently shows that exposure to VPA carries an elevated risk of MCM and is not recommended and it is recommended to taper VPA prior to conception wherever possible. Lamotrigine and levetiracetam monotherapy have the lowest risk, and drugs such as topiramate and phenobarbital carry an intermediate risk of MCMs.[26] Thus, it would be advisable if WWE are on either lamotrigine or levetiracetam wherever possible prior to conception.

Monotherapy is generally preferred over polytherapy, as it is associated with a lower risk of teratogenicity.[26] Studies have shown that women on monotherapy have better pregnancy outcomes compared to those on polytherapy, highlighting the importance of careful medication selection. It is further emphasized that polytherapy with VPA combinations, topiramate combinations, and phenobarbital combinations carry elevated risk of MCMs.

Frequent monitoring of ASM levels is essential during pregnancy to ensure therapeutic efficacy and prevent seizures.[18] However, facilities for such monitoring are limited in developing countries such as Sri Lanka. When therapeutic drug monitoring is not available, clinicians often rely on clinical judgment, adjusting doses based on the patient's seizure frequency, side effects, and gestational age. This approach typically involves cautious, gradual increases in ASM doses, particularly during the second and third trimesters, when drug clearance rates are most pronounced. While this strategy can help maintain seizure control, it carries risks of both over-treatment, leading to potential toxicity, and undertreatment, which may result in seizure exacerbation. Close clinical observation and patient-reported symptoms are essential in guiding dose adjustments to balance the risks to both the mother and foetus. Thus, empirical dosage increments are recommended for lamotrigine, an initial increase of 20-25% of the pre-pregnancy dose may be necessary, with further adjustments made based on clinical response.[27] Similarly, for levetiracetam, a 20-30% increase may be considered, although close clinical monitoring remains crucial. These adjustments help to account for the increased clearance of these drugs during pregnancy.

In addition to pharmacokinetic monitoring, regular obstetric assessments are crucial to monitor foetal growth and well-being, particularly in women with poorly controlled epilepsy.[11]

Delivery and postpartum considerations

The management of epilepsy extends into the delivery and postpartum periods. The mode of delivery should be based on obstetric indications, with vaginal delivery preferred in the absence of contraindications. However, seizure control remains a priority during labour and delivery, and the availability of intravenous ASMs is recommended in case of acute seizure activity.[25] Postpartum, the risk of seizures may increase due to sleep deprivation, stress, and rapid changes in ASM metabolism, necessitating close monitoring and support during this period. Watch out for ASM toxicity especially in the case of increase in ASM doses during the pregnant state due to altered pharmacokinetics which is elaborated above. Doses of such ASMs need to be titrated down to pre-pregnant doses quickly.

Advice during lactation

WWE should be encouraged to breastfeed.[26] The evidence suggests that breastfeeding is safe when the mother is on carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate, VPA, or phenytoin. Close monitoring for the infant could be advisable when the breastfeeding mother is taking phenobarbital, clobazam, or clonazepam due to effect of sedation on the infant. The magnitude of ASM transfer to the baby through breast milk that is required to affect neonatal and childhood outcomes is not known. Furthermore, robust evidence of such outcomes is lacking.

Conclusion

Epilepsy in pregnancy presents significant challenges that require a multidisciplinary approach to optimize outcomes for both the mother and foetus. The teratogenic effects of ASMs, the importance of vitamin K supplementation, and the need for individualized treatment plans highlight the complexity of managing epilepsy during pregnancy. While advances in ASMs have improved the safety profile of epilepsy treatment during pregnancy, careful planning, monitoring, and management remain essential. Future research should focus on optimizing treatment protocols, understanding the long-term outcomes for children exposed to ASMs in utero, and improving the overall care of pregnant WWE.

Author declaration

No conflict of interests.

Key messages

1. WWE face higher risks of pregnancy complications, including pregnancy-induced hypertension, preeclampsia, stroke, gestational diabetes, placental abruption, preterm labor, and an increased likelihood of cesarean delivery.
2. Seizures, particularly generalized tonic-clonic seizures, pose significant risks to both the mother and foetus, including potential harm from falls, trauma, hypoxemia, and foetal distress.
3. Pregnancy alters the pharmacokinetics of ASMs, necessitating careful monitoring and dosage adjustments to maintain therapeutic levels and prevent seizures. Serum levels of ASMs like lamotrigine and levetiracetam decrease due to increased clearance during pregnancy.
4. The teratogenic potential of ASMs is a major concern, with drugs like valproic acid being associated with a high risk of congenital malformations. Newer ASMs such as lamotrigine and levetiracetam have a more favourable teratogenic profile.

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