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Review

The impact of seizures on pregnancy and delivery

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ABSTRACT

Purpose and methods: The treatment of women with epilepsy during pregnancy is known to increase the risk of teratogenic effects. Whether seizures during pregnancy have a deleterious effect on the developing child is difficult to determine, but recent animal studies, case studies, cohort studies and population studies have provided useful insights.

Results and conclusion: Seizures before pregnancy are a predictor for seizures during pregnancy, and catamenial epilepsy may also predict the course of seizures during pregnancy. A first epileptic seizure may also have implications for the pregnancy, depending on the seizure aetiology.

Seizures affecting maternal awareness and responsiveness may have cardiac effects on the foetus and may impact on the weight of the newborn. Status epilepticus in pregnancy is rare, but isolated cases of perinatal death and malformations after status epilepticus have been reported in women on antiepileptic drugs. Seizures during delivery occur in about 2% of pregnancies of women with epilepsy, and case studies indicate that the foetal heart may be affected. However, a diagnosis of epilepsy is not an indication *per se* for caesarean delivery. A well-planned pregnancy can reduce the likelihood of seizures occurring.

1. Introduction

The threat of seizures during pregnancy and the consequences that they might have on the developing foetus are fundamental reasons for the prescription of daily antiepileptic medication (AED) to a pregnant woman with epilepsy (WWE). As the pregnancy nears its end, questions and concerns related to the delivery will increase; are seizures likely during delivery and what are their possible impacts?

However, it is obvious that obtaining clear evidence on the effects of maternal seizures and AED treatment on a developing foetus is fraught and difficult. In this article we review and discuss the currently available evidence on the potential impact of seizures in pregnancy and delivery; this is the information upon which we, as clinicians, must use as the basis of our patient treatment and management decisions.

2. A first seizure during pregnancy

The focus of this article is WWE. However, in the clinical setting, the occurrence of a first seizure during pregnancy may have many other different impacts for the further treatment of the pregnant woman. In the first trimester, metabolic alterations, medications, and toxicology screens should be evaluated. In the second trimester, normal pregnancy-related physiological changes can result in lower blood pressure and dilatation of vascular spaces, and therefore syncopal events are a primary consideration. In the third trimester, diagnoses such as eclampsia, posterior reversible encephalopathy syndrome (PRES), and stroke are further possibilities. Mass lesions, infections, and sudden events from vascular malformations can occur at any time in pregnancy, and, given the clinical situation, appropriate imaging should be performed.

3. Impact of seizures in women with epilepsy

In the EURAP study, a prospective observational study from 42 countries [1], 3784 pregnant WWE were monitored throughout the entire course of their pregnancies and 66.6% of them were found to be seizure-free. The proportion of pregnancies without seizures was significantly lower in lamotrigine (LTG)-treated women (58.2%) than in pregnancies in women taking valproate (VPA) (75%), carbamazepine (CBZ) (67.35%), or phenobarbital (PHB) (73.4%). In addition, the LTG cohort also had significantly more generalized tonic clonic seizures (21.1%) than the VPA (11.5%), CBZ (12.6%), or PB (14.0%) cohort.

In a hospital-based retrospective study of 205 women, Borthen and coworkers [2] also found that the women with active epilepsy

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more often had preterm birth whereas pregnancy complications were not increased in the group with epilepsy and no AED treatment.

In a prospective study of 1297 pregnancies in WWE, Thomas and coworkers [3] found that, as in the EURAP study, the occurrence of seizures before pregnancy was the most important predictor of seizures during pregnancy. The women who experienced seizures in the pre-pregnancy month had a 15-times greater risk of seizures during pregnancy, and polytherapy also increased the risk of seizures during pregnancy; however, 47.5% of the WWE were seizure-free. The lower rate of seizure freedom in this study, compared with that reported in the EURAP study, may be due to the inclusion of WWE without AED and also the dose of drugs being relatively low. This study identified two peaks of seizure relapse (in the second to third month and in the sixth month), and also that those with generalized seizures had one peak during the first trimester.

A recently published retrospective cohort study evaluated the effect of pregnancy planning in WWE on seizure control during pregnancy and on maternal and neonatal outcomes [4]. Planned pregnancies had a significantly greater portion of patients receiving AED monotherapy and of not using VPA. This group also had a lower frequency of seizures during pregnancy as well as a significantly lower likelihood of altering their AED regime during pregnancy.

The impact of a specific pattern of seizures before pregnancy on the course during pregnancy has been recently investigated in a prospective follow-up of seizure course in women with catamenial epilepsy and women with noncatamenial epilepsy [5]. Seizure control was improved during pregnancy in the catamenial group, with 44.1% of the participants experiencing a reduction in seizures of $\geq$50%, whereas only 6.5% of those with noncatamenial epilepsy had a similar reduction in seizures.

3.1. Impact of focal seizures

The relative impacts of different seizure types are difficult to determine. A developing foetus in a mother's womb is not readily accessible for scientific studies, and therefore the immediate risk from a seizure is difficult to measure. Although these obstacles have hindered research, particularly on the effect of focal seizures where consciousness is not affected, it is generally accepted that these types of focal seizures have minimal effect on the foetus. However, in focal seizures where awareness and responsiveness are affected, trauma may occur. Case reports have also indicated that the developing child may be affected when the mother experiences a seizure of this type.

Although it is not easy to determine the status of a foetus during an attack that lasts only a couple of minutes, there are two reports in the literature on the effects on the foetus during focal seizures where maternal awareness was affected. Nei and coworkers [6] report on a woman with a history of febrile seizures who had experienced complex partial seizure (CPS) since the age of five years, beginning with automatisms and followed by 1–2 min of reduced consciousness. Her history also included some generalized tonic-clonic seizures (GTCS) and she experienced between 1 and 5 CPS per month during the pregnancy. At week 39 of the pregnancy, the estimated foetal weight was below the tenth percentile. At week 42 of the pregnancy, while having uterine contractions every 2–3 min, the woman suddenly sat upright, was unable to respond, had agitated eye deviation, showed repeating head nodding for 1 min, and was confused for 5 min. During this period she had a prolonged uterine contraction, with no return to baseline for 4 min, and the foetal heart rate fell from 140 to 78 beats per minute.

The other report, by Sahoo and Klein [7], refers to a patient who experienced partial seizures secondary to cavernous haemangiomas and had CPS, of which three had been secondary GTCS. During pregnancy, the patient's seizure frequency decreased to 0.25 per month during the first half of the pregnancy. She was admitted in her 7th month of pregnancy following two CPS and experienced a further CPS directly after admission, with right facial twitching and subsequent right arm and leg twitching. The patient was pale and sweating, and transiently hypoxic (75%). The seizure lasted 1 min. During the seizure, the foetal heart rate fell from 160 to 70 beats per minute, and returned to baseline 2 min after the seizure.

Importantly, for both cases, the patients delivered apparently healthy children.

3.2. Impact of generalized seizures

Generalized seizures are feared the most. In addition to the possibility of trauma, GTCS are also known to cause alterations in electrolytes, blood pressure, and oxygenation, all of which may harm the foetus [8]. Furthermore, the immature brain is very sensitive to abnormal experiences [9].

Most studies in pregnant WWE have been conducted while the women were using AED and this adds the complication of AED as a confounding variable. Animal studies may avoid this problem for investigating the effect of seizures *per se* on the foetus.

Antenatal hypoxia-ischaemia has been found to represent a risk factor for functional alterations of the brain structures and functions related to anxiety and fear [9]. Rat foetuses that were exposed to an intermittent hypoxia antenatally exhibited less motor activity and increased levels of anxiety [10]. The specific effects of seizures on the foetuses of rats have been studied in greater detail more recently. Vale and coworkers [11] used a pilocarpine-induced epilepsy model, and found a significant effect on specific hippocampal interneurons in the pups of mothers with epileptic seizures during pregnancy. The same animal model also demonstrated that the offspring of the epileptic mothers had deficits in motor coordination and increased immobility [12]. The placentas from the epileptic rat models had areas of ischaemic infarction. More recently, rats exposed to seizures *in utero* showed impaired social behaviour compared with rats with no intrauterine exposure to seizures [13].

In humans, some idea on the potential impact of GTCS on the developing foetus can be extrapolated from studies in eclampsia [14], where changes in foetal heart rate occur during convulsions. In WWE, only a few case studies have demonstrated a specific effect on the foetus after GTCS; two cases were described by Teramo and coworkers in 1979 [15]. The first foetus exhibited a 13-min continuous bradycardia tachycardia immediately after the seizure, and this was followed by a phase of tachycardia. The other foetus had a shorter period of bradycardia, followed by tachycardia and decreased heart rate. Intracranial haemorrhage *in utero*, resulting in foetal death after a maternal seizure, has also been reported [16]. A study of 106 pregnant WWE on AED therapy and experiencing more than one GTCS during pregnancy reported a significant association, with an overall five-times higher preterm risk, a shorter gestational age, and a reduced birth weight in boys [17].

Concerns have been raised regarding cognitive deficiencies in children born to mothers using AED [18]. Studies on 67 children born to mothers with epilepsy, of whom 13 did not use any AED, did not find any neuropsychological effects on the non-exposed children [19,20]. Nevertheless, there are indications that seizures in pregnancy may have an impact on the children's neurodevelopment. In a study by Cummings and coworkers on the neurodevelopment of children exposed to AED *in utero*, univariable analysis

identified that more than five GTCS in pregnancy had a significant and detrimental effect on neurodevelopment [21].

A study by Adab and coworkers was one of the first to associate a developmental risk with the occurrence of seizures during pregnancy [22]. By investigating 240 children above the age of six years, of whom 80 children had mothers with epilepsy who did not use any AEDs during pregnancy, they found three factors that were independently predictive of a low IQ. In addition to VPA therapy and lower maternal IQ, they found that five or more GTCS during pregnancy was an independent factor for low IQ.

As previously noted, an important problem in discerning the impact of seizures on the foetus is the potential confounding factor concerning the use of AED. A study by Chen and coworkers [23] is extraordinary in this respect; in this study, two nationwide population-based data sets compared 1016 untreated WWE with 8128 matched women without chronic disease. The epilepsy was documented by a diagnosis of epilepsy or convulsions and further confirmed by at least three consensus diagnoses during the two year-period prior to the delivery. Almost 50% of the WWE experienced seizures during pregnancy. The study found a clear association with the occurrence of seizures during pregnancy and the child being small for gestational age, and also that seizures during pregnancy were more likely to be associated with preterm delivery and lower birth weight.

Status epilepticus (SE) was reported in 21 (0.6%) of the 3784 pregnancies reported in the EURAP study [1], of these, ten were convulsive, and all cases were evenly distributed over the three trimesters. Perinatal death occurred in one of the women experiencing a convulsive SE and major congenital malformations were diagnosed in three children born to mothers who developed SE during the pregnancy. None of the mothers died.

4. Increased mortality in pregnant WWE?

From the maternal death registry in United Kingdom, Adab and coworkers [22] found that the odds for maternal death were 10-times higher for WWE than in the general population. They also noted that this seemed to represent an increased mortality risk during pregnancy, that is above the usual standard mortality rate of 2–3 for epilepsy throughout life as a whole, and also that the case histories in the reports suggested that seizure occurrence was often associated with stopping AED or with poor compliance. The question regarding increased mortality risk in WWE during pregnancy was recently explored [24], based on data in the successor to this registry, where all maternal deaths and their circumstances are reported in detail. Among 2,291,493 maternities, WWE accounted for fourteen deaths, among which SUDEP was diagnosed in 11 (79%). Of the remaining three deaths, one occurred while bathing, one was due to hypoxic brain damage, and the last was due to chest trauma with secondary sepsis following a seizure. Nine deaths occurred during pregnancy and five were postpartum. Nine deaths occurred in women treated with LTG, seven of whom used LTG in monotherapy. The epilepsy-related deaths in pregnant women were found to be relatively constant over the last 15 years, ranging from nine (between 1991 and 1993) to 19 (between 1994 and 1996) per year.

Maternal death from epilepsy in WWE was estimated to be 100 per 100,000, as compared with the overall mortality of 11 per 100,000. From these data it was estimated that the death rate from epilepsy among WWE during or shortly after pregnancy is 1:1000, which is ten times higher than in women without epilepsy. The study also pointed out that a general population-based study of SUDEP estimated an incidence of 0.35%, with much higher rates in intractable patient groups. It may be speculated that most WWE who become pregnant are less likely to have the most severe types epilepsy or serious comorbidities, and from this it may be extrapolated that the data suggest a particular risk associated with being pregnant for WWE. However, the SUDEP rate in the general population may not necessarily be applicable to women of fertile age; two recently published papers show that the SUDEP rate in younger epilepsy patients is closer to 10-times that of the general population, whereas the SUDEP rate in the general epilepsy population is estimated to be 2–3 times that of the general population [25,26].

5. Delivery

WWE have an increased risk of delivery complications, but the seizures *per se* do not explain this increased risk [2]. Cardiac effects on the child arising during a maternal seizure during labour and delivery have been reported in case studies as previously discussed [6,15]. In a rat study, in which the confounding effects of AEDs are avoided, perinatal asphyxia of 20 min resulted in a behavioural pattern resembling the hyperactive profile in ADHD children [27]. Seizures during delivery are, however, rare. In the EURAP study, seizures during delivery occurred in 2.6% of pregnancies in WWE on LTG and CBZ, in 1.9% in those using PHB, and in 1.4% of women exposed to VPA. The Kerala Registry of Epilepsy and Pregnancy [3] found that seizure relapse was highest during the three peripartum days, noting again that this study comprised women not on AED and many on relatively low doses of AED. This underlines a practical point during delivery for WWE; they should bring their own AEDs to the delivery and the medication should be taken at the usual times during labour.

Epilepsy is not considered as a reason for caesarean delivery, unless a seizure occurs during labour or the patient is unable to cooperate [28]. Reassurance and well-informed health care professionals in the delivery room is of importance for these patients.

6. Conclusion

Case studies have demonstrated that seizures may have an impact on the foetal heart during pregnancy and delivery, and a study of non-treated WWE demonstrated that seizures could also affect the size of the child. Recent studies have also indicated that seizures in pregnancy may be of importance for cognition. Status epilepticus is rare, but there are occasional reports of foetal deaths and malformations after SE in AED-treated women. Animal studies indicate that there can be specific effects of seizures on neurodevelopment. Whether pregnant WWE have increased mortality is not clear. Seizures at delivery are rare, and epilepsy is not, in itself, an indication for caesarean delivery. The frequency of seizures in pregnancy may be significantly reduced in women with catamenial epilepsy, and the risk of seizures during pregnancy may be decreased by careful planning.

Conflict of interest statement

None declared.

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