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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