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Review

Obstetrical complications in women with epilepsy

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ABSTRACT

Purpose: Better knowledge of risk factors for women with epilepsy giving birth.
Method: Investigating all studies reporting complications in pregnancy and deliveries in women with epilepsy during the last 15 years.
Results: Studies have observed that women with epilepsy have a higher risk of preeclampsia, gestational hypertension, bleeding in pregnancy, caesarean delivery (CD), excessive bleeding postpartum, preterm birth, and small for gestational age. It has been unclear whether the increased risk of complications is due to the epilepsy per se, the use of antiepileptic drugs (AED), or the combination of both factors. Recent studies strongly indicate an association between AED use, and complications in pregnancy and labour.
Conclusion: Newer drugs commonly used in treatment of epilepsy are associated with an increased risk of pregnancy complications, as well as complication during labour and delivery.

1. Introduction

Epilepsy is a common neurological disease with a lifetime prevalence of 0.6% in developed countries and 1.5% in developing countries [24]. The prevalence of epilepsy in epidemiological studies is estimated to 0.3–0.7% in pregnant women [8,15]. Improved diagnosis and therapy of epilepsy have allowed more women with epilepsy to conceive [18]. The vast majority of these women will have uneventful pregnancies. However, epidemiological studies enrol the entire spectrum of the disease, and women being pregnant may represent the healthy proportion of the population with well-controlled epilepsy [8,29,35].

Epilepsy is one of the most common causes of seizures during pregnancy. It may require continuous drug treatment, also during pregnancy, to avoid seizures. This treatment is potentially teratogenic and women with epilepsy will have to balance the risk of serious seizures against the risk of teratogenic exposure to the foetus [13,33]. It has also been demonstrated an increased risks of pregnancy complications in women using AEDs [8]. It has been unclear whether the risk of complications is due to epilepsy per se, the use of AEDs or the combination of these factors.

This review comments on the papers, focusing on how epilepsy and medications during pregnancy affects maternal outcomes.

2. Obstetrical outcomes

Most women with epilepsy have uncomplicated pregnancies and normal deliveries [8,33]. However, pregnancies of women with epilepsy represent a greater risk of complications, and seizure frequency may alter [20,30]. Until recently, very little was known about the association between AED and spontaneous abortion in women with epilepsy. A epidemiological study from Denmark including 4700 pregnancies with AED did not observe any increased risk of abortion in women with epilepsy [4]. In this study 34% were using lamotrigine.

In a study from 1973, Bjerkedal and Bahna used data from the Medical Birth Registry of Norway to study women with epilepsy delivering during 1967–1968. They demonstrated an increased risk of bleeding in pregnancy, an increased risk of preeclampsia, induction of labour, low birth weight <2500 g and a higher mortality rate in the neonatal period. There was no information about medication in this study [5]. In 1985, Yerby and his collaborators studied birth certificates from Washington State during 1980–1981. They identified 204 women with epilepsy and used a random of 612 women without epilepsy as controls. They observed an increased risk of previous foetal loss [Odds ratio (OR): 2.66 (95% confidence interval (CI): 1.01–6.98)], preeclampsia [OR: 2.45 (1.17–5.51)], low Apgar score <7 after 5 min [OR: 3.74 (1.57–8.88)], and low birth weight <2500 g [OR: 2.79 (1.35–5.74)] in women with epilepsy [37]. They also demonstrated an increased risk of induction for labour [OR: 4.29 (1.77–10.39)] and an increased risk of CD [OR: 1.93 (1.31–2.83)]. However, in a Finnish study, they were not able to demonstrate

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any increased risk of complications in 152 women with epilepsy compared with 152 women without epilepsy [17]. A lot of studies followed, none were able to demonstrate any pregnancy complications in women with epilepsy [12,19,21,36]. In 2004, a Canadian group was looking at the obstetrical and neonatal outcome in all women with epilepsy giving birth at a tertiary referral hospital. They identified 414 births with epilepsy and 81,759 births without epilepsy. They observed an increased risk of hypertension, induction of labour and CD in women without epilepsy. They could not observe any significant difference in the rate of outcome when women with AED use were compared with women without AED use. In 2009, a study from Norway using data from the Medical Birth Registry of Norway, reported an increased risk of pregnancy complications [8]. Our national register-based cohort study comprised a total national population collected 1999–2006, and included 942 women with epilepsy using AED during pregnancy. This unselected cohort was compared with the full national cohort of women without a history of epilepsy. We observed a low, but definitely increased risk of gestational hypertension, OR: 1.5 (1.0–2.2). Primiparous women had the highest risk OR: 2.4 (1.0–5.4). Women with epilepsy using AED also had an increased risk of mild preeclampsia, OR: 1.7 (1.2–2.3). This finding was supported by our hospital-based study where women with epilepsy and AED use was examined in more detail [7]. In this study a sample of 205 consecutive deliveries at Haukeland University Hospital with a confirmed diagnosis of maternal epilepsy in the Medical Birth registry of Norway (MBRN) in the period 1st January 1999 to 31st December 2006, were identified. A control group of 205 women with the same age and parity, delivering at the same date were used. We observed that women with epilepsy and AED use had an increased risk of severe preeclampsia and early vaginal bleeding, OR: 5.0 (1.3–19.9) and OR: 6.4 (2.7–15.2), respectively. These data were adjusted for maternal education, smoking, body mass index, medical conditions and diabetes. The increased risk of preeclampsia was related to use of lamotrigine monotherapy in pregnancy, OR: 7.5 (1.4–39.0). This effect of lamotrigine in pregnancy is similar to what has previously been reported for carbamazepine [35]. We also observed that both active epilepsy and no active epilepsy had an increased risk of severe preeclampsia, OR: 4.1 (1.0–16.8) and OR: 4.2 (1.0–17.4), respectively. This increased risk was only observed in AED users.

Bleeding in pregnancy was also related to both lamotrigine monotherapy, OR: 6.2 (2.0–19.3), and also to polytherapy including lamotrigine, OR: 8.6 (2.8–26.3).

The higher risk of hypertensive disorders in women with epilepsy is also observed in a study from India. They compared 718 women with epilepsy with 18,272 women without epilepsy during 1998–2005. Women with epilepsy had an increased risk of hypertension, OR: 1.42 (1.05–1.91) and preeclampsia OR: 2.05 (1.37–3.06) and there were no differences between AED users and no AED users. In this study, 40% were using carbamazepine and 2.5% were using lamotrigine [32].

Preterm delivery has been observed in women with epilepsy not using AEDs [21], but not in all studies [19,23]. In our population based study, we observed an increased risk of preterm birth before 34 weeks of gestation in women with epilepsy using AEDs, OR: 1.6 (1.2–2.1) [8]. In our hospital-based study, both epilepsy with and without AED use had an increased risk of preterm birth before 32 weeks of gestation [7]. The risk persisted after we adjusted for maternal age, and education, smoking, previous CD, preeclampsia, vaginal bleeding, medical conditions, and diabetes.

Children of women with epilepsy may be at increased risk of intrauterine growth restriction [9]. Causative factors could be the epilepsy, exposure to AEDs, seizures, genetic aspects as well as any underlying condition and environmental factors. A study from Sweden estimated the effect on head growth of exposure *in utero* to the new AEDs lamotrigine and gabapentin, and the old AEDs phenytoin, clonazepam, carbamazepine and valproate [2]. Carbamazepine had the strongest effect, whereas phenytoin, clonazepam, lamotrigine and gabapentin had no such effects. This finding is also demonstrated in a recent study from the Medical Birth Registry of Norway (MBRN) [34], and in a study from Finland [3].

The incidence of CD has been increasing worldwide. The incidence is also increasing for women with epilepsy. CD frequency varies between cohorts of women with epilepsy, both increased and no increased CD risk being reported [19,28,29,32,36]. Our national cohort study demonstrated an increased incidence of CD for women with epilepsy, OR: 1.4 (1.3–1.6) [6]. This was confirmed in our hospital study where women with epilepsy and AED use had a doubled risk for CD, OR: 2.3 (1.2–4.3) after adjusting for maternal education, smoking, body mass index, medical conditions and diabetes. However, when adding preterm birth in the regression analysis, the women with epilepsy had no longer any significantly increased rate of overall CD, OR: 1.7 (1.0–3.0) ($p = 0.065$) [7]. The higher incidence of CD among women with epilepsy most probably has a multi-factorial background. It can be mediated by the increase in foetal growth restriction, hypertensive disorders of pregnancy, and seizures in pregnancy. Most chronic medical disorders increase the likelihood of CD [22]. Epilepsy represents a significant disorder, but is not an indication for CD unless a seizure occurs during the second stage of labour and the patient cannot cooperate during a vaginal delivery because of sedation [11]. Another reason for the difference observed may be the high rates of CD in the healthy, obstetrical population in most other countries, in contrast to the low CD rate in Norway of 14.3% in the years studied [23,29,32]. Better knowledge of risk assessment in women with epilepsy giving birth, will probably decrease the rates of CD in these women. The guidelines of the National Institute for Health and Clinical Excellence in United Kingdom, the American Academy of Neurology Practice Parameter update and the Italian Consensus Conference recommend vaginal delivery in women with epilepsy, with the exception of women with frequent seizures [1,14,25]. Only a few studies have explored complications for women with epilepsy during labour and delivery. Induced labour is more frequent in women with epilepsy, even though epilepsy is not an indication for induction [19,29]. This is also in accordance with our two studies [6,7]. In our national cohort study, we observed an increased risk of induction for women with epilepsy and AED use, OR: 1.6 (1.4–1.9) [6], similar to our hospital based study, OR: 2.3 (1.2–3.4) [7]. In the last study, we adjusted for maternal age, education, smoking, BMI $\geq$30, diabetes and medical conditions. According to guidelines in England and Norway, induction of labour in women with epilepsy should be evaluated on an individual basis [25,31]. Deliveries with forceps and vacuum do not occur with increased frequency in women with epilepsy [6,13,29]. This may be due to the high rates of CD, but most probably also reflects few complications during labour.

Postpartum haemorrhage has been defined as bleeding more than 500 ml during labour and after delivery [10]. We observed that women with epilepsy and AED use had an increased risk of postpartum bleeding, OR: 1.5 (1.3–1.8), operative vaginal deliveries having the highest risk [6]. This increased risk of bleeding was associated with use of valproate and lamotrigine during pregnancy. Most previous studies have not found any association between epilepsy and postpartum haemorrhage [16,19,26]. The differences may be due to patient selection and small sample sizes in the hospital based studies while our study comprises a whole national cohort. Our study is supported by a study from Sweden where an increased risk of postpartum bleeding after vaginal deliveries in women using AEDs was found [28]. Also in our hospital based study, we observed an increased risk of postpartum haemorrhage in women using valproate. We also observed that women with epilepsy and AED use had an increased risk of uterine atony, which

was probably a contributing factor for the excessive bleeding. Induction and CD also represent risk factors for postpartum haemorrhage, but these factors were not observed to influence bleeding in this study.

Careful management is essential to minimize the risks. Women with epilepsy should have a preconceptional dialogue with focus on the importance of a planned pregnancy with optimizing AED use, folate supplementation, the teratogenicity of AEDs versus the risks of seizures, and the risk of obstetric complications [27].

3. Conclusion

Although most women with epilepsy have uneventful pregnancies and healthy babies, they face certain challenges. Women with active epilepsy will usually require AED therapy during pregnancy in order to avoid adverse effects of uncontrolled seizures on themselves and their foetus. However, AEDs carry a potential risk of developmental toxicity as well as long-term effects to the foetus.

Women with epilepsy and AED use has an increased risk of preeclampsia, bleeding in pregnancy and preterm birth. These risks seem to be associated with the use of lamotrigine and also of carbamazepine. There is a higher frequency of low birth weight (<2500 g) and small head circumference at birth for children of mothers with epilepsy. These risks are associated with use of carbamazepine.

There is a tendency for a change in medication of young women with epilepsy from valproate to carbamazepine and lamotrigine. However, the use of these medications is linked to an increased risk of maternal complications. Women using all types of AEDs should therefore be monitored closely during pregnancy.

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Conflict of interest statement

There were no conflicts of interest.

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