3rd Congress of the European Academy of Neurology
Amsterdam, The Netherlands, June 24 - 27, 2017

Teaching Course 7

Treatment of women with epilepsy - Level 1-2

Management and treatment of women with epilepsy during pregnancy

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Introduction
The goal for the treatment of epilepsy during pregnancy is to obtain the best possible control of seizures with minimum adverse effects for the mother and child. Therefore, the challenge for the physician and the therapeutic dilemma is to balance the risk of harmful effects associated with exposure of the developing foetus to antiepileptic drugs (AEDs) against the benefits to the mother in maintaining an effective antiepileptic treatment regimen.
Fortunately, more than 90% of women with epilepsy (WWE) experience unproblematic pregnancies and deliver normal infants, but many factors have to be taken into consideration and need to be planned already before the pregnancy.

Pre-conception counselling
Pre-conception counselling should in principle be offered regularly to all WWE with a childbearing potential but the evidence suggest that information given at the hospital is far from always remembered by the patient (1) and therefore needs to be systematically and regularly repeated if it shall be successful and adequate.
It is of high importance that the women know that planning the pregnancy is essential and that potential risk factors need to be reduced prior to pregnancy. Some AEDs have a higher teratogenic potential than others and many of the drugs have complex pharmacokinetic properties that can be altered by the pregnancy. Also, the mother’s ability to care for an infant, risk of seizures, mode of

Conflict of interest: The author has no conflict of interest in relation to this manuscript
delivery, breastfeeding, and genetics must be discussed carefully to ensure that the patient can take informed decisions about the pregnancy in proper time.

At time of seeking pregnancy, it is recommended to have a multidisciplinary approach involving the general practitioner, an obstetrician, an epileptologist / neurologist, and if possible also a specialised epilepsy nurse. As for all other women, folic acid supplementation is recommended to start prior to conception to reduce the risk of congenital malformation but it still remains to be shown if there are any additional effects of higher folic acid supplementation for WWE taking AEDs because the teratogenic mechanisms may be different (2).

**Effects of epilepsy on the pregnancy and offsprings**

*Obstetrical complications:*

WWE are a vulnerable group that needs special obstetric management and have to be monitored carefully. Various obstetric complications, which includes premature delivery, preeclampsia, gestational hypertension, induced labour, caesarean delivery, and postpartum haemorrhage are generally more frequently reported for women with epilepsy than for other women (3-5). Maternal mortality risk is increased more than 10-fold compared to women without epilepsy (3). Epileptic seizures and in particular occurrence of generalized tonic-clonic seizures during pregnancy is associated with prematurity and shorter gestational age (6-8) also in WWE without AED treatment (9).

It remains unclear whether the increased risk of complications is due to the AED therapy, the epilepsy per se, psychological factors, or combinations of these (10) but taken the higher complication risks together, it is generally recommended that deliveries of WWE should occur at high-risk obstetric unit affiliated with a paediatric department and with neurological service.

*Neonatal outcomes:*

Use of AEDs during pregnancy is associated with increased rates of major congenital malformations, intrauterine growth retardation, and long-term cognitive and behavioral dysfunction of the offspring (11-14).

These risks are related to specific AEDs, the number of AEDs and to drug dosages. Therefore, whenever possible, AED treatment should aim at seizure control with monotherapy at the lowest effective dose. For the teratogenic and neurodevelopmental risks related to the individual AED’s, please see other sections of this teaching course.
Children of WWE have an increased risk of being born with low Apgar scores (15), low birth weight (<2500 g), and small for gestational age (4, 5, 7, 9, 16-18). Intrauterine growth retardation is associated with exposure to many AEDs, in particular with valproate (9, 16), topiramate (9, 17) and to polytherapy (6, 16).

**Effects of pregnancy on the epilepsy**

*Seizure control in pregnancy:* Most women with epilepsy can expect their seizure control to be unaffected by the pregnancy (19-21). More than 70% of patients pass through the pregnancies without changes in seizure frequency and two-thirds remain complete seizure-free (19, 22). A minor proportion of WWE experience reduced seizure frequency whereas approximately one-quarter to one-third of pregnant have increased seizure frequency or seizure recurrence during the course of their pregnancy (22, 23). Status epilepticus occurs in 1 – 2% of pregnancies in women with epilepsy but does not seem to be more frequent than in other periods of life (19, 22).

*Seizure deterioration in pregnancy:* Increased seizure frequency or seizure recurrence during the pregnancy is of major concern for several reasons. Poorly controlled epilepsy can cause miscarriage and affect maternal and foetal health (8) and seizure deterioration may pose serious consequences for the everyday social life. The majority of women who seek pregnancy have well-controlled epilepsy and are otherwise healthy and usually not restricted in their daily activities by their epilepsy. Even a single breakthrough seizure for these women may have major psychosocial consequences with e.g. negative influence on family dynamics and driving privileges (24, 25).

Breakthrough seizures in women who have been seizure-free up until the pregnancy tend to occur most frequently during the first trimester and is most likely is due to non-compliance (21) whereas seizure deterioration can occur throughout pregnancy and does not seem to be related to specific trimesters (19, 22).

Labour and delivery is the period with the highest risk of seizures. The risk of having a generalized tonic-clonic seizure during labour is approximately 1 – 2% and when taking all types of seizures together, on average 5% of WWE will experience a seizure during labour or within the first 24 hours after delivery. This is a nine-fold increase in seizures compared to the risk during pregnancy in general (26-28).
Risk factors for deteriorated seizure control

Pregnancy is associated with numerous physiological, endocrine, and psychological changes that might influence seizure activity (21, 29, 30). Each pregnancy tends to have its own seizure pattern, which means that even if a serious worsening of seizures occurs during one pregnancy, the woman does not need to be discouraged if she wants to become pregnant again.

Patients who are seizure-free before pregnancy are less likely to experience seizure deterioration during their pregnancy (31), whereas patients with focal epilepsy, with use of polytherapy, and with specific AEDs (lamotrigine and oxcarbazepine) have the highest risk of seizure worsening (22).

Pregnancy can alter the pharmacokinetics of most AEDs and lead to increased clearance of the drugs. Fall in the plasma concentration is the most common explanation for seizure deterioration during pregnancy and may be avoided by dose adjustment to maintain pre-pregnancy levels (32).

In particular, lamotrigine (23, 33), oxcarbazepine (34), and levetiracetam (35, 36) have increased clearance during pregnancy and require close monitoring throughout pregnancy.

Decreased plasma concentrations of AEDs may also be a consequence of excessive nausea, vomiting, and non-compliance especially during the first trimester. Many women have concerns about the potentially harmful effects of medications taken during pregnancy, and they often have an intuitive resistance to take AEDs and to accept increases in the dosages. Intended non-compliance may therefore be a consequence. These negative results of patient insecurity and misunderstanding can be prevented in many case by systematic pre-pregnancy patient education and continued close contact between the patient and the caregivers throughout the pregnancy (21).

Hormonal changes, sleep deprivation, anxiety, and psychosocial stress provoked by the pregnancy may also influence negatively on seizure susceptibility (30).

Therapeutic drug monitoring during pregnancy

It is reasonable to assume that declining active AED concentrations in pregnancy are associated with a risk of increased risk of seizures. Therefore, a reasonable regimen for treatment of pregnant WWE is to check AED levels (when possible) before conception and monthly, with dose adjustments to maintain an effective and stable plasma level throughout pregnancy. This approach has been supported by the AAN practice guidelines, at least for women who are treated with lamotrigine, carbamazepine, oxcarbazepine, levetiracetam, and phenytoin (37). However, some controversy has existed as to whether AED dose adjustment is required based on decreased plasma concentrations alone, particularly in the vulnerable pregnancy period when teratogenic potential
exists in relation to higher doses of the drugs. It could be claimed that patients should be treated on the basis of clinical findings, i.e. changes in seizure control, and not on changes in plasma concentrations. However, giving the fact up to 80% of women who conceive (21) have been seizure-free for long periods of time leading up to pregnancy and, as loss of seizure control may pose serious consequences for their everyday social life, it is not acceptable to wait for breakthrough seizures to increase the dose.

An algorithm for dose adjustment before, during, and after pregnancy has been suggested for treatment with lamotrigine (38), but probably works applicable to all AEDs for which plasma concentrations are expected to be altered during pregnancy. Ideally, the AED dose should be adjusted individually before pregnancy to the lowest effective dose, and the optimal plasma level should be determined and used as a reference concentration (RC) for the pregnancy. If the plasma concentration falls below RC, the AED dose should be increased by 20–25% and the plasma concentration checked after 4 – 5 weeks. The procedure should be repeated every 4 – 5 weeks throughout pregnancy. If the plasma concentration is higher or has not fallen to below the RC, the dose should not be changed, but the plasma level should be re-determined after 4 - 5 weeks. This close monitoring of plasma concentration and adjusting the dosage to maintain stable plasma levels throughout pregnancy can reduce the risk of seizure deterioration to approximately 9%, at least for lamotrigine monotherapy (39).

In settings, where therapeutic drug monitoring is not available, might routine increase of the dose of some AEDs be advisable, i.e. increase the dose of lamotrigine and oxcarbazepine by approximately 20 – 25% in second and third trimester. However, notably, the magnitude of plasma level alterations is very difficult to predict and all of these issues with pros and cons have to be carefully discussed with the patients for their individual decisions. For patients who are treated with phenytoin and valproate, which are both more than 90% protein–bound, the free levels of these drugs should be followed during pregnancy rather than the total levels.

**Breastfeeding**

Women with epilepsy should in general be encouraged to breastfeed their infants regardless of which AED they use (40, 41). The benefits of breastfeeding clearly outweigh the theoretical adverse risk of continued AED to the nursed infant. Some studies even suggest that breastfed children may have a higher long-term performance compared with children who were not breastfed (42).
References

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