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Consensus article

Belgian consensus on recommendations for standards of care for women with epilepsy before, during and after pregnancy

Paul BOON[1], Henri HAUMAN[2] Benjamin LEGROS[3], Bernard SADZOT[6], Kenou VAN RIJCKEVORSEL[4] and Michel VAN ZANDYCKE[5]

Departments of Neurology, [1]Universitair Ziekenhuis Gent ; [2]Algemeen Ziekenhuis Sint-Maarten -CEPOS, Duffel ;
[3]Hôpital Erasme, Université Libre de Bruxelles ; [4]Cliniques Universitaires Sant-Luc, Woluwé-Saint-Lambert ;
[5]Algemeen Ziekenhuis Sint-Jan, Brugge ; [6]Centre Hospitalier Universitaire Liège

Abstract

Women with epilepsy (WWE) have an increased risk of complications during pregnancy, which however can be minimized by optimal, interdisciplinary patient management. The aim of any therapy is to achieve an optimal balance between avoidance of seizures, which may be harmful to both mother and foetus, and minimization of foetal and neonatal exposure to deleterious influences of antiepileptic drugs. Suitable measures include early and regular counselling of the young WWE about contraception and planning of pregnancy, optimisation of drug treatment (choice of the right drug and dosage also in view of altered pharmacokinetics, avoidance of polytherapy, therapeutic drug monitoring etc.), in-time folate substitution, and close follow-up of the patient during and after pregnancy. Until now, many issues such as underlying factors of malformations have not been clearly elucidated. Nonetheless, chances for an unproblematic pregnancy of WWE are high.

Key words : Epilepsy ; pregnancy ; anti-epileptic drugs.

Introduction

Epilepsy is among the most common neurological diseases and affects approximately 4-10 individuals per 1000 (Morrow *et al.*, 2003). For Belgium, these numbers translate into about 70.000 people with epilepsy, of which about 20% are of childbearing age. In this country, women with epilepsy (WWE) give birth to over 700 babies per year.

It is well known that pregnancy in epilepsy is associated with increased maternal and fetal risks. This is due to the disease itself, e.g. genetic risks or the possible effect of maternal seizures on the foetus, as well as the treatment with antiepileptic drugs (AED). Optimisation of care in women of childbearing potential, especially around pregnancy, may lead to better results ; maintaining high standards is of paramount importance. In order to review the existing evidence in the literature as well as to discuss long-standing personal experience about how to treat women before, during and after pregnancy, a group of Belgian experts held a workshop in Brussels on October 31st, 2003 and February 16th, 2004. The consensus of these meetings is summarized in the present article.

Fertility and counselling

There is no general agreement on whether WWE have lower fertility as compared to the general population (Herzog *et al.*, 1986 ; Olafsson, Hauser *et al.*, 1998 ; Tettenborn *et al.*, 2002). Recent studies have shown a higher than average rate of early and unwanted pregnancies, with a higher fertility rate among the 18-20 years-old compared with the general population (Wallace *et al.*, 1998). Recent data from the UK suggest that preconceptional counselling is not a standard procedure, and that less than 50% of pregnancies are planned, which is similar in the general population (Fairgrieve *et al.*, 2000). Thus, it is strongly recommended to implement *early* counselling of the adolescent female, which should be *updated* on a regular basis. Assisting the patient in planning a pregnancy increases the likelihood of a good outcome (Tettenborn *et al.*, 2002). With the patient being well informed and involved in treatment issues, a pregnancy without problems becomes more likely.

I. CONTRACEPTION

Attempts to normalize lifestyle and to optimize quality of life in WWE should include the option of a reliable method of birth control, including oral contraceptives. Despite the well-known effects of estrogens on lowering the seizure threshold, it has not been shown that oestrogen-containing oral contraceptives worsen seizures in epileptic patients (Guberman 1999).

Oral contraception is the most effective contraception technique and should be recommended also in WWE. However, there is evidence that some oral contraceptives may fail when combined with AED, because of the inducing effects of the latter on oestradiol and progesterone (Guberman 1999).

Phenobarbital, primidone, phenytoin, carbamazepine, topiramate, felbamate and oxcarbazepine induce the hepatic P450 microsomal isoenzyme CYP3A4, which may lead to a higher rate of breakthrough bleeding and contraceptive failure (Yerby 2001 ; Crawford 2002 ; McAuley *et al.*, 2002).

In contrast, valproate, lamotrigine, vigabatrin, gabapentin, tiagabine, and levetiracetam, do not induce hepatic enzymes and therefore do not interact with the oral contraceptive pill. Conversely, oral contraception can alter the metabolism of AED : the levels of lamotrigine are reduced to a clinically important extent (Sabers *et al.*, 2003).

Consequently, women treated with an *enzyme-inducing* AED should receive a contraceptive pill containing a high dose of oestrogens (50 micrograms). For women on a *non-enzyme-inducing* AED, a contraceptive preparation with a lower dose of oestrogen can be used. In WWE treated with lamotrigine, the serum level should be checked. If clinically relevant, the dose of lamotrigine should be adapted after the initiation or the withdrawal of the contraceptive pill.

In case of treatment with enzyme inducing drugs, depot preparations of medroxyprogesterone can be used but with reduced intervals between injections (from 3 months to 6-8 weeks). Accordingly, subcutaneous implants (levonorgestrel) should be avoided because of reduced efficacy.

II. Pregnancy

Increased risk for the mother

Specific issues should be considered in an epileptic woman planning a pregnancy, with an important one being the interplay of the epileptic disease with pregnancy. First, the disease itself puts the patient at an increased risk, equalling a ten times increase in standard mortality ratio in WWE. According to recent registry data, epilepsy is the third most common cause of death during the pregnancy (after cardiac arrest and stroke) (Barrett *et al.*, 2003). While the absolute number is extremely low, most fatal outcomes are seizure-related. A typical scenario is that a woman discovers she is pregnant and decides to stop her AED (Barrett *et al.*, 2003). The occurrence of seizure-related maternal death underlines the absolute necessity to avoid poor compliance or withdrawal of the antiepileptic drug treatment.

Secondly, it is likely that the clinical manifestations of the seizures may be altered during pregnancy. Seizure frequency increases in 15-37% of pregnancies, it remains stable in 50-80%, and decreases in 13-25% (Knight *et al.*, 1975 ; Schmidt *et al.*, 1983 ; Delgado-Escueta *et al.*, 1992). Among the reasons for increased seizure risk are pharmacokinetic variations, poor compliance, sleep deprivation, and vomiting (Tettenborn *et al.*, 2002). WWE have an increased risk of pre-eclampsia, pregnancy-induced hypertension, and bleeding (Yerby 2003).

Increased risk for the offspring

Also the risk for the foetus during pregnancy is increased. In general, maternal (but not paternal) epilepsy is associated with a higher risk of epilepsy in the offspring. Congenital malformations remain the most commonly reported adverse outcomes of pregnancies in WWE : in children of untreated WWE, the rate is approximately 6-9%, compared to 3-5% in the general population (Finnell *et al.*, 1995). Fetal exposure to AED is associated with an increased risk of pre-term birth, congenital malformations, intrauterine growth retardation and neonatal hemorrhage (Yerby 2003).

Altered pharmacokinetic and pharmacodynamic characteristics of AED

Pharmacokinetic and pharmacodynamic characteristics of most AED may change. This may be due to reduced protein binding and increased drug metabolism. Although reduction of the AED concentration is not always accompanied by an increase in seizure frequency, and considerable controversy remains on this relationship, many studies report that an increase in seizures tends to be associated with subtherapeutic AED serum levels (Dansky *et al.*, 1982 ; Janz 1982 ; Schmidt *et al.*, 1983 ; Pennell 2003). This holds true for the majority of AED, pharmacokinetic changes being mostly unpredictable in the individual patient.

These changes are rapidly reverted during the postpartum.

Seizures during pregnancy

Seizures may increase the risk of maternal and fetal injury, miscarriage, and developmental delay, cognitive dysfunction and seizures in the offspring (Ottman *et al.*, 1988 ; Gaily *et al.*, 1990 ; Granstrom *et al.*, 1992 ; Yerby 2000). Convulsive *status epilepticus* during pregnancy carries very high maternal and fetal mortality rates (31% and 48%, respectively) (Teramo *et al.*, 1982). *Generalized tonic clonic seizures* can cause maternal and fetal hypoxia and acidosis (Stumpf *et al.*, 1978). A single brief *tonic clonic* seizure has been shown to cause depression of fetal heart rate for over 20 minutes (Teramo *et al.*, 1979). Such seizures can cause fetal intracranial haemorrhage, miscarriage and stillbirth (Minkoff *et al.*, 1985 ; Zahn *et al.*, 1998 ; Yerby 2000).

A complex *partial seizure* was reportedly associated with a strong, prolonged uterine contraction and foetal heart deceleration for 3.5 minutes (Nei *et al.*, 1998). Seizures during pregnancy can also cause trauma, with possible ruptured fetal membranes or abruption.

The independent role of the seizures on teratogenicity has not been fully elucidated (Barrett *et al.*, 2003).

It appears that the combined risks associated with uncontrolled seizures during pregnancy are higher than the risks of WWE being exposed to AED (Yerby 2001).

Obstetrical issues

WWE have an increased risk of pre-eclampsia, pregnancy-induced hypertension, bleeding, preterm birth, prolonged labour, labour induction and artificial labour (Yerby *et al.*, 1985 ; Crawford 2002).

There is also an increased frequency of stillbirth and neonatal death (Nelson *et al.*, 1982 ; Yerby *et al.*, 1994 ; Vajda *et al.*, 2003). For example, according to the current reporting of an Australian observational register of 292 completed pregnancies, 256 (88%) resulted in a healthy live birth, 19 (6.5%) in a live birth with a birth defect, four in an induced abortion because of a detected malformation on ultrasound, one in premature labour with a stillbirth and 12 (4%) in spontaneous abortions (Vajda *et al.*, 2003). In case of vitamin K deficiency – caused by foetal exposure to enzyme-inducing AED – there may be an increased risk of bleeding in the newborn child (< 1%) but the conclusions of different studies are not congruent (Cornelissen *et al.*, 1993 ; Kaaja *et al.*, 2002). Only in 2-4% of women, there is an increased risk of seizures during (prolonged, artificial) labour or in the following 24 hours (Hiilesmaa *et al.*, 1985 ; Delgado-Escueta *et al.*, 1992). The perception of the obstetrician is that deliveries of epileptic mothers are per se associated with high risk, and therefore caesarean sections are often performed (Olafsson, Hallgrimsson *et al.*, 1998 ; Swartjes *et al.*, 1998). This should not lead to overtreatment.

Malformations : risk factors

Epilepsy per se may be teratogenic, although this has been clearly shown only in the study of Lindhout (Lindhout *et al.*, 1992). In addition, a variety of additional risk factors have been identified which may predispose children of WWE to malformations. For example, the personal and familial *medical history* is of importance, as the malformation rate is increased in case of a previous pregnancy with malformation, or *maternal malformations* or *diabetes*. The general *status* of the mother (deficiencies of zinc, folate, selenium, vitamin C, cyanocobalamin etc.), age, presence of anaemia, and maternal weight before pregnancy seem to have some impact.

Low folate levels have been associated with foetal malformations in humans and animals. Some studies suggest that blood folate concentrations are significantly lower in WWE with abnormal pregnancy outcome (Dansky *et al.*, 1982 ; Biale *et al.*, 1984). Recently, a study suggested that low serum folate concentration is an independent risk factor for major malformations (Kaaja *et al.*, 2003). Some AED such as phenytoin, carbamzepine, valproate, lamotrigine behave as folic acid antagonists or impair its absorption (Hernandez-Diaz *et al.*, 2000).

There is some controversy about the association of a particular *seizure type* and the teratogenic risk. Maternal seizures of *all types* during the first trimester are associated with a high malformation rate of 12.3%, compared with a malformation rate of 4% for infants of WWE not exposed to seizures (Lindhout *et al.*, 1992).

The *antiepileptic treatment* as such is also a risk factor. A series of observations suggests that AED can cause malformations : offspring of treated mothers have consistently higher malformation rates as opposed to those with no treatment ; mean plasma AED levels of valproate are higher in mothers with children who have birth defects (Vajda *et al.*, 2003) ; mothers with polytherapy have higher malformation rates as compared to those on monotherapy (Finnell *et al.*, 1995 ; Kaneko *et al.*, 1999 ; Kaaja *et al.*, 2003).

It is unclear, yet not unlikely, that major malformations are more common in mothers with a low level of education (Kaaja *et al.*, 2003). This might well reflect the importance of patient's information, education and collaboration for the preconception preparation.

Some of these risk factors can be modified. It is of importance that counselling is implemented early since by the time most women realize they are pregnant, malformations already may have developed. The major organ systems have formed by late in the first trimester and the posterior neuropore closes by day 27 of gestation (Yerby 2003).

The potential for AED to cause complications in pregnancy should be discussed at the time of diagnosis and at subsequent visits, when appropriate. It should be considered in any adolescent with epilepsy and certainly by any physician caring for an adolescent even in patients with developmental delay.

Practice recommandations for taking care of pregnant WWE

a. *Before pregnancy*

Counselling of WWE about benefits and risks of AED

WWE need to know the risks associated with the pregnancy and the use of AED during pregnancy. They also need to know that seizures can be harmful to mother and foetus and that risks can be reduced with proper care (Yerby 2003).

WWE should be counselled that healthy parents have an up to 3-5% risk of having a child with major malformation, and that given the current

state of the art, the best measure is to practice risk reduction (Yerby 2003). Conversely, the overall chance giving birth to a healthy child is 92-96% (Tettenborn *et al.*, 2002).

Contact with the relevant physicians (gynaecologist, general practitioner) should be established at a preconception visit. In order to plan the periconceptional care, it is recommended to actively ask the patient for her personal planning.

Folate supplementation in high doses

Folate supplementation is an important measure. In a study, malformation rate in 66 non-supplemented pregnancies was 16% as compared to 0% in 33 infants of folate supplemented mothers (Biale *et al.*, 1984). Several trials in the general population demonstrate that periconceptional folate supplementation reduces the risk for recurrence of neural tube defects in women with a previously affected pregnancy. However, few case-reports of WWE showed no protection (Craig *et al.*, 1999 ; Duncan *et al.*, 2001).

Since in the general population the utility of folate supplementation in reducing the risk for neural tube defects is clearly established, WWE, like all women of childbearing age, should take folate supplementation. However, the dosage recommended by the Centers for Disease Control (0.4 mg/d) may not be enough for women who do not metabolize folate effectively (Center for Disease Control and Prevention 1992 ; Hernandez-Diaz *et al.*, 2000).

While the exact dose is not known, it is usually suggested that 2.5-5 mg should be taken per day by women on AED treatment (Zahn *et al.*, 1998). Especially if the pregnancy is planned, it must be taken before conception, and daily up the 12th week thereafter (Nulman *et al.*, 1999 ; Vigabatrin Paediatric Advisory Group 2000).

Antiepileptic drugs

Complete seizure control is the goal of medical therapy. A drug that is relatively safe but fails to control seizures is of little value (Yerby 2003). Nonetheless, the indication for drug treatment must be clear. When a pregnancy is discussed, the diagnosis and treatment of epilepsy should be re-evaluated. If the diagnosis is confirmed, in most cases AED will be indicated. However, stopping AED may be an option. About 60% of patients treated for epilepsy can be expected to become seizure-free. About half of these patients may be able to be withdrawn successfully from AED after a seizure-free period of at least two years. In this perspective, the risk of seizure exacerbation or recurrence needs to be assessed carefully (Annegers *et al.*, 1979 ; Anonymous 1991).

The AED chosen to treat WWE of childbearing age should be a first-line agent appropriate for the seizure type and epilepsy syndrome (Morrow *et al.*, 2003).

If AED discontinuation or changes are made, they should be made before conception or preferably, completed at least 6 months before conception. Medication change post-conception does not reduce the risk of major malformations and may compromise seizure control (Anonymous 1998).

High peak plasma concentrations of valproate have been suggested to be associated with an increased risk of malformations in rodents. Monotherapy with valproate at the lowest possible effective dose administered three or four times daily is therefore recommended. Whether this recommendation can be extrapolated for other AED remains unclear mainly because compliance is inversely related to the number of dose administrations. It seems reasonable to advocate the use of sustained-release preparations (Delgado-Escueta *et al.*, 1992 ; Royal College of Physicians 1997 ; Nulman *et al.*, 1999).

It is to be stressed that polytherapy carries a higher teratogenic risk. The risk increases with the number of AED (Finnell *et al.*, 1995 ; Kaneko *et al.*, 1999 ; Kaaja *et al.*, 2003).

No AED is known to be absolutely safe, as even the sparse data on new AED suggest that malformations can occur with exposure to these compounds. The use of the newer AED should be thoroughly investigated with regard to their teratogenic potential (Kaaja *et al.*, 2003 ; Yerby 2003).

So far, published data do not show consistent differences between AED. Regardless of the presence of specific risks associated with certain drugs, by now no significant differences in the rates of teratogenic malformations have been shown. Hence, there is currently not enough evidence to advocate switching from one AED to another (Morrow *et al.*, 2003). The optimal AED plasma level should be established for each patient before conception and should be the level at which seizure control is the best possible for that patient without debilitating side-effects. AED levels should be regularly followed (Annegers *et al.*, 1979 ; Anonymous 1991).

b. *Routine procedures during pregnancy*

The table summarizes the recommended procedures around and during a pregnancy of a WWE. Notably, counselling during the pregnancy should be performed by the neurologist and the obstetrician jointly.

Folic acid supplementation should be started as soon as contraception has been stopped.

After conception, the follow-up protocol must include an early *ultrasonography* to determine with accuracy the gestational age, anatomic ultrasonographies and determination of maternal alpha fetoprotein serum level.

Table 1

Checklist for management of WWE, with focus of issues around pregnancy

Any time	Start counselling of WWE early (adolescents), refresh information regularly Prefer oral contraception : – if on enzyme-inducing AED : 50 micrograms estrogens – if on non enzyme-inducing AED : lower estrogens doses are sufficient – if on LTG : control LTG drug levels
Pre-conception	Patient education : inform on risks, but also on high chances of good outcomes Start folic acid supplementation 4mg/d (immediately after contraception is stopped) Determine AED level at which patient's seizure are controlled Establish communication with relevant physicians, contact gynaecologist Adapt, but do not stop AED
First post-conception visit	(Repeat) patient education Measure AED level Ask for expected date of conception Plan pregnancy follow-up visits Ask for patient's approval to include her in pregnancy register (EURAP)
12th week GA	Ultrasonography AED level
15th week GA	Maternal serum screen (alpha fetoprotein)
16th week GA	Anatomic ultrasonography
26th week GA	AED level
36th week GA	AED level Start vitamin K 10 mg (+ calcium dose + vitamin D in case of phenobarbital and phenytoin) Plan for acute seizure treatment during labour and delivery
Delivery	Examine neonate for anomalies/ defects Administer vitamin K 1 mg intramuscularly to the neonate Encourage breast feeding Educate mother about safe handling of child (e.g. during bathing)
First 4 weeks post-partum	AED level, and possible adjustment of doses Watch for AED toxicity

WWE = women with epilepsy, GA = gestational age, AED = antiepileptic drug.

Routine determinations of *free plasma concentrations* for those AED that are highly protein-bound (phenytoin, valproate and to a lesser degree : phenobarbital, oxcarbazepine, carbamazepine and primidone) should theoretically be performed. However, this option is not available in the majority of clinical practices in Belgium. Monitoring AED concentrations, including lamotrigine, is recommended at the beginning of each trimester and during the last month of pregnancy. Additional visits are indicated for seizure occurrence, side-effects or suspected non-compliance.

If the patient presents after conception, the AED treatment should never be stopped. The dose of AED should be divided in 3-4/day and folate supplementation should be started if the pregnancy is still in the 1st trimester.

c. *Labour and delivery*

The individual risk for elective delivery should be discussed in time (well before date of delivery) between the obstetrician and the neurologist. WWE should not deliver at home. According to the increased obstetrical risk for the mother and the foetus, and the increased risk of epileptic seizures during labour and delivery, it is important that delivery takes place in a specialised unit, equipped with facilities for maternal and neonatal resuscitation (Anonymous 1998 ; Crawford *et al.*, 1999). Epidural anaesthesia is possible and should be handled as in other women (Tettenborn *et al.*, 2002).

In the case of women with daily non-convulsive seizures or more than one generalised tonic-clonic seizure per week, caesarean section should be considered.

d. *Post partum*

WWE should be seen by the neurologist shortly after delivery. Neurological advice should be sought within the first week and before discharge from the hospital. The neonate should be monitored for signs of drowsiness, which can occur with some AED (Morrow *et al.*, 2003). Likewise, the baby should be examined for anomalies and malformations, and should receive vitamin K 1mg intramuscularly (Anonymous 1998 ; Crawford *et al.*, 1999).

The maternal AED doses must be readjusted immediately after birth because metabolic changes normalize quickly after birth. The decision to change the AED dose should be made on an individual basis. Because of these changes, the patient must be examined for clinical signs of toxicity.

In the interaction between a WWE and her child, the risk of injury to the infant largely depends on seizure type and frequency. Any such risk can be minimized by training WWE about safe handling and bathing techniques, feeding and practice around the home.

As in the general population, breast feeding is recommended because there are no specific contraindications in WWE related to the epilepsy itself

(Delgado-Escueta *et al.*, 1992 ; Pennell 2003). Phenobarbital, primidone and benzodiazepines can result in drug accumulation and symptoms of sedation can occur in some newborns. In this case, breastfeeding must be stopped (Tettenborn *et al.*, 2002 ; Morrow *et al.*, 2003). In general, the benefits of breast feeding usually far outweigh any minor risks to the baby (Crawford 2002).

Conclusion

Patient counselling about contraception and all pregnancy-related issues as well as close supervision of pregnancies are important measures to lower the increased risks for WWE and their offspring. Primary care physician, neurologist and obstetric teams should manage these patients in close cooperation to optimise chances for uneventful pregnancies and deliveries of healthy infants. Many questions and issues concerning WWE and pregnancy remain unresolved. Increased awareness by neurologists of potential problems and active collaboration to the European pregnancy registry for WWE (EURAP) may lead to practical answers to some of these questions and may allow to design more evidence-based guidelines. EURAP in Belgium can be contacted through the following E-mail address : eurapbelgium@UGent.be

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P. BOON, M.D., Ph.D.,
Reference Center for Refractory Epilepsy,
Department of Neurology (1K12),
University Hospital Ghent,
De Pintelaan 185,
B-9000 Gent (Belgium).
E-mail : Paul.Boon@UGent.be.