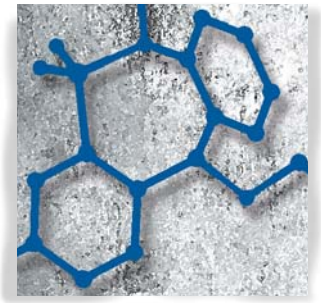
# *Pregnancy, epilepsy, and anticonvulsants*

*Bernhard J. Steinhoff, MD, PhD*



*The majority of epileptic disorders are not self-limiting over time, and therefore require a long-lasting and often even lifelong antiepileptic drug (AED) treatment. In women with epilepsy, the influence of their disease on the possibility and course of pregnancies, as well as the potential impact of the AED treatment on mother and child, are crucial questions.*

*This review addresses the clinically relevant knowledge concerning the impact of the disease itself and the AED treatment on fertility, pregnancy, delivery, the postpartum period, and teratogenicity. Some of the new AEDs appear to have a favorable profile due to a lack of clinically relevant interactions and promising teratogenic profiles. However, the finding of decreases in lamotrigine serum concentrations during hormonal contraception and pregnancy is an instructive example, showing that ongoing studies are urgently needed to further investigate still-unanswered questions. Several prospective multinational surveys are currently being performed, and should add essential information in this context.*

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## Fertile women with epilepsy

### Epilepsy and fertility in general

Patients with epilepsy have been reported to suffer from reduced fertility. The fertility rate ranges between 33% and 100% of the expected model,[1-3] and is reduced by 15% to 30% compared with healthy controls.[3-5] In twins, the fertility rate of the affected twin drops at the onset of the disease, compared with the healthy twin.[6] In a controlled study, patients with epilepsy reported less sexual intercourse, more frequent vaginismus, and reduced sexual interest compared with healthy controls.[6] Hyposexuality was reported in 34% of patients,[7] whereas other reports did not confirm a clear difference between patients with epilepsy and healthy persons.[8,9] Both reduced and normal fertility rates were reported for married women with epilepsy.[4,10] Overall, 50% of women with epilepsy suffer from dysfunctions such as amenorrhea, oligomenorrhea, abnormally shortened or lengthened menstrual cycles, polycystic ovaries (PCO) or the polycystic ovary syndrome (PCOS).[11-16]

**Keywords:** *epilepsy; antiepileptic drug; fertility; interaction; pregnancy; delivery; puerperium; teratogenicity*

**Author affiliations:** Director, Kork Epilepsy Center, Kehl-Kork, Germany

**Address for correspondence:** Prof Dr Bernhard J. Steinhoff, Medical Director, Epilepsiezentrum Kork, Landstrasse 1, 77694 Kehl-Kork, Germany
(e-mail: bsteinhoff@epilepsiezentrum.de)

# Pharmacological aspects

## Selected abbreviations and acronyms

| | |
|---|---|
| ***AED*** | *antiepileptic drug* |
| ***CBZ*** | *carbamazepine* |
| ***LTG*** | *lamotrigine* |
| ***OXC*** | *oxcarbazepine* |
| ***PB*** | *phenobarbitol* |
| ***PCOS*** | *polycystic ovary syndrome* |
| ***PHT*** | *phenytoin* |
| ***PRM*** | *primidone* |
| ***VPA*** | *valproic acid* |

### Epileptic syndromes and fertility

The fertility rate in epileptic women may be influenced by the underlying epilepsy syndrome. In women with temporal lobe epilepsies (TLE) abnormal findings with a possible impact on fertility are especially common: Abnormal menstrual cycles occur in 50% of women with TLE.[15] The rate of anovulatory cycles was 25% to 30% compared with a rate of 8% to 10% in healthy controls,[17] and 14% to 20%, compared with 0% of women with generalized epilepsy syndromes and 8% of healthy controls.[18] Data on patients with generalized epilepsy syndromes are somewhat conflicting: According to Webber and coworkers,[3] women with generalized epilepsies have the same fertility rates as women without epileptic seizures, independent of concomitant antiepileptic drug (AED) treatment, whereas a more recent article reported that anovulatory cycles occurred more frequently in this patient group (with valproic acid [VPA] treatment as an additional risk factor) than in patients with partial epilepsy syndromes.[1]

The functional circuits between temporal lobe structures and the hypothalamus may be responsible for the reduced fertility of women with temporal lobe epilepsies.[19] Ongoing epileptic activity from the temporal lobe has an influence on the hypothalamic-hypophyseal axis through the tight connections between the limbic system and hypothalamic nuclei that are responsible for the regulation, production, and secretion of gonadotropin-releasing hormone (GnRH). Ictal activity in the mesial temporal lobe leads to either a PCO by the increase in GnRH, with a consecutive rise in luteinizing hormone (LH) and fall in follicle-stimulating hormone (FSH), or conversely induces a fall in GnRH with a fall in LH and rise in FSH, thus leading to hypogonadotropic hypogonadism. Both developments cause a decrease in progesterone.[20] PCO has been associated with left-sided, hypogonadotropic hypogonadism with right-sided TLE.[16,21] Successful resective TLE surgery led to a restoration of reproductive functions,[22] which strongly suggests the involvement of TLE.

### Possible impact of antiepileptic drugs on fertility

It is methodically difficult to assess the potential impact of AEDs on fertility. Although chronic AED treatment has been claimed to cause a variety of long-term side effects, unequivocal data on the impact on fertility in female patients are rare.

In particular, AEDs that cause enzyme induction (see below) are potential candidates for a clinically relevant influence on sexual hormone levels that might contribute to fertility problems. Nevertheless, a closer look at the literature does not reveal consistent findings[2]: 33% of patients treated with carbamazepine (CBZ) suffered from reduced sexual interest.[23] VPA increased the risk of anovulatory cycles in another study.[1] In women receiving AED polytherapy anovulatory cycles were increased, but not significantly more often than in patients on monotherapy.[18] Bauer claims that abnormal menstrual cycles are more probably caused by the AED treatment than by the disease itself.[24]

In 1975, Schmitz and coworkers[25] reported increased FSH and LH levels with phenytoin (PHT) treatment, whereas others did not confirm this finding, either with PHT or CBZ.[26]

In healthy volunteers, CBZ or PHT dosing for 1 week caused rises in prolactin serum levels.[27] Elevated prolactin levels were also found in women on long-term AED therapy.[28] Others described that CBZ had no impact on prolactin and FSH, but lowered LH levels.[29] Finally, another report did not confirm any differences concerning basal gonadotropin and prolactin between patients receiving CBZ, VPA, phenobarbitol (PB), and healthy controls.[30]

A study in girls and young adults with epilepsy who were treated with VPA reported significantly elevated testosterone levels and hyperandrogenism at a rate of 57%.[31] With lamotrigine (LTG) no negative influence on the sexual hormone metabolism was found,[32] which may also be hypothesized for other new AEDs without a clinically relevant interaction profile.[33] In particular, the potential role of VPA for the risk of obesity, impaired insulin balance, and or PCO and PCOS has been actively discussed. This crucial question of the treatment with AEDs and fertility will be addressed in the following section.

## Obesity, PCO, PCOS, and antiepileptic drugs

Obesity is one of the most common adverse effects seen with long-term AED treatment, and has been reported for almost every AED.[33] Among the first-line AEDs, VPA is the main risk substance for obesity.[34,35,36] According to the literature, the incidence of obesity on VPA varies widely, and ranges between 8% and 59%.[37] Female patients who suffered from weight gain while on VPA had increased insulin levels and insulin resistance,[38] which was confirmed by the comparison with patients receiving CBZ or LTG.[39] Others reported normal insulin levels with VPA, CBZ, and oxcarbazepine (OXC) but still confirmed the almost specific weight gain on VPA.[40] This weight gain was completely reversible 12 months after replacing VPA by LTG, as were hyperinsulinism, increased serum testosterone, and abnormally high body mass index.[41]

Obesity due to metabolic effects of VPA has become a major subject of recent research, since it was hypothesized that this metabolic development may induce PCOS,[41] which is defined by the coincidence of oligo- or amenorrhea, hyperandrogenism, and the ultrasound detection of polycystic ovaries.[16] The most relevant findings in PCOS are shown in *Table I*.

Whether or not this is correct and specific for VPA is still a matter of controversy.[33] Other groups did not find relevant differences between PCOS and VPA, CBZ, PB, the total population, or untreated epilepsy patients.[30,42]

It has to be considered that the epilepsy itself may facilitate the development of PCOS by the metabolic changes mentioned above. A pilot study addressing this aspect reported that 25% of the investigated female patients with epilepsy suffered from PCOS, 80% of whom had not received AED therapy.[43] In another study, one third of the patients with PCOS were not on medication.[44]

## Oral hormonal contraception

### *Impact of AEDs on oral hormonal contraception*

The oral application of sexual hormones is the major method of contraception. Liver enzyme-inducing AEDs reduce the efficacy of oral contraceptives.[24,45] It was estimated that the rate of unintentional pregnancies in spite of hormonal contraception was five to 25 times higher if enzyme-inducing AEDs were used.[46,47] Among the AEDs that were reported to reduce the efficacy of hormonal contraceptives are CBZ, ethosuximide (ESM), felbamate (FBM), LTG, OXC, PB, PHT, primidone (PRM), and topiramate (TPM), with the latter AED showing reduced effect only on estrogen levels and at daily dosages above 200 mg.[20,24,48,49] The negative impact of ESM has been questioned elsewhere,[50] and the influence of AEDs that are not potent enzyme inducers, such as TPM or LTG, may result from different mechanisms, since TPM induces the estrogenic and LTG the gestagenic components.[51] It is unclear to what extent these findings are clinically relevant, since unintentional pregnancies were hitherto not reported in women who were treated with LTG and continued oral hormonal contraception.[24]

AEDs that induce the cytochrome P450 enzymes reduce the efficacy of oral contraceptives markedly. Under the influence of CBZ the levels of norethindrone and ethinyl estradiol drop by 58% and 42%, respectively,[48] OXC decreases the levels of ethinyl estradiol and levonorgestrel if a daily dosage of 1200 mg is given.[52,53] Other enzyme inducers such as PB, PHT, or PRM also unequivocally influence the metabolism of oral contraceptives so markedly that one cannot expect an acceptable contraceptive effect.[20,24,49,51] In a survey among neurologists and obstetricians, 27% of the former and 21% of the latter

| Clinical findings | Endocrinological, metabolic, and ultrasound findings |
|---|---|
| **Irregular menstrual cycles** | **Polycystic ovaries** |
| **Amenorrhea** | Increased LH levels |
| Impaired fertility | Increased LH:FSH ratio |
| Body hair and/or alopecia | **Increased androgen levels**—testosterone, |
| Acne | androstendion |
| Obesity | (dehydroepiandrosteronsulphate) |
| | Abnormal lipid profiles |
| | Insulin resistance |

**Table I.** Most relevant findings in polycystic ovary syndrome; main features are displayed in bold letters.[24] LH, luteinizing hormone; FSH, follicle-stimulating hormone

group reported failures of oral contraception in women taking AEDs. Surprisingly, in the very same survey, only 4% of the neurologists and 0% of the obstetricians knew the potential impact of the six most common AEDs on hormonal contraception.[54] AEDs that supposedly do not affect hormonal contraception are VPA, gabapentin (GBP), levetiracetam (LEV), pregabaline (PGB), tiagabine (TGB), vigabatrin (VGB), and zonisamide (ZNS).[20,24,49,51] One has to consider that the extent of this impact and the quality of the individual trial on the AEDs mentioned above vary widely.[20]

If oral hormonal contraception is the method of choice for a patient who is treated with enzyme-inducing AEDs, it is strongly recommended that preparations containing more than 50 µg of estrogen be considered.[55] If intermittent breakthrough bleeds occur, dosage should be increased to 75 to 100 µg.[56] Since the number of breakthrough bleeds and contraceptive failure differs significantly between ethinyl estradiol dosages of 50 and 100 µg, it has even been proposed that the higher dose be chosen from the start of the oral contraceptive treatment.[50] Breakthrough bleeding does not always indicate an unsatisfactory effect of the hormonal contraception. Conversely, one has to take into consideration that the suppression of breakthrough bleeds does not necessarily reflect a sufficient contraceptive effect.[24]

Another, though less important, mechanism that leads to reduced efficacy of oral contraceptives is the reduction in the free progesterone serum level that was described for PB.[57]

*Impact of hormonal contraception on epilepsy and AEDs*

There is no evidence for an impact of hormonal contraception on the course of the epilepsy itself.[58,59]

Over the last decade LTG was established as the major medication in women with epilepsy who plan pregnancies, due to its favorable safety profile, which will be discussed in a later section. If one considers this development, it is surprising that it took several years until a Danish group discovered the pronounced and clinically relevant influence of oral hormonal contraceptives on LTG.[60] This was soon confirmed by other studies.[61-64] It has been claimed that ethinyl estradiol, but not progesterones, are responsible for this reduction of the LTG serum concentration.[65] In women on hormonal contraception and LTG it is therefore reasonable to intensify therapeutic drug monitoring and either to increase the overall dosage to overcome seizure relapses during the fall of the LTG serum concentration or to consider a continuous hormonal contraception without a placebo interval.

**Other methods of hormonal contraception**

It has been suggested that the intramuscular application of sex steroids that bypasses the hepatic first-pass metabolism may be a way to achieve a higher contraceptive safety in patients on enzyme-inducing AEDs. However, the data on this issue are controversial, and not sufficient. It was shown that the efficacy of levonorgestrel is reduced.[66,67] Data on medroxyprogesterone are not yet available.[68] For safety reasons it was suggested that the injection interval should be shortened from 12 to 10 weeks.[54] Whether or not this is really effective is not absolutely sure.[25]

## Pregnancy—the mother's side

**The course of epilepsy during pregnancy**

There are no reliable predictors of the course of epilepsy during pregnancy.[55] It has been reported that the risk of seizure relapses corresponds to the seizure type, since an increase in seizure frequency was significantly more often found in patients with complex partial seizures than in cases with generalized tonic-clonic and absence seizures.[69] However, this series of 79 pregnancies is certainly too small to draw reliable conclusions. Similarly, the observation that a high seizure frequency prior to the pregnancy or the duration of the disease correlate with a higher risk of increased seizure frequencies during pregnancy,[70] result from statistically unconvincing sample sizes, and have been questioned somewhat.[71] Several prospective pregnancy registries are being maintained in order to generate more reliable data on the course of pregnancy in patients with epilepsy and on the impact of AEDs in epileptic and in nonepileptic women. In most instances the course of epilepsy does not change during pregnancy. According to several previously published surveys, the seizure frequency remains stable in 50% to 85% of pregnancies of epileptic women.[16,24,49,71,72] The assessment of 1956 pregnancies in 1882 patients revealed that 58.3% remained seizure-free throughout the whole period of pregnancy.[73] In another study, 63% of patients remained completely seizure-free.[74]

Electroencephalography (EEG) in women with epilepsy prior to and during pregnancy did not reveal any increase in epileptiform discharges.[75] Increases in the seizure frequency appear in approximately 20% to 35%, and decreases in 3% to 22%.[71] Data from the EURAP study registry, which are prospectively collected, suggest increases in seizures in 17.3% and decreases in 15.9%.[73] These rates are almost identical with data from Norway that report 17% and 15%, respectively.[74] Status epilepticus is a rare complication; it is thought to occur in less than 1% of pregnancies.[24] More recent data collected in almost 2000 pregnancies suggest an even lower rate (36 cases =0.02%).[73] The latter study reported one stillbirth as the only complication, and therefore indicated a lower risk for mother and child than previously reported (mortality rates of 31% for the mother and of 48% of the child,[24] tenfold increased mortality in women with epilepsy during pregnancy[76]) which has since been confirmed by others.[74] Seizures were observed in 2.7% and 3.5%, respectively, during delivery.[73,74] In the Norwegian study status epilepticus occurred in 1% with delivery.[74] The seizure risk is elevated ninefold on the delivery day; seizure rates reached almost 20% in one study.[77] Others report that seizures occur in 1% to 2% of patients during the 24 perinatal hours.[78,79] According to Bauer,[24] precipitating factors are:

1. Patients forget to continue their oral AED medication.
2. Sleep deprivation around the delivery, especially in patients with idiopathic generalized epilepsies.
3. Intermittent hyperventilation, again especially in patients with idiopathic generalized epilepsies.
4. The psychological stress during delivery.

An increase in seizures during the whole pregnancy period is explained by various factors such as lack of compliance because of fear of teratogenic AED effects, increased levels of the theoretically proconvulsive estrogens, modified gastric motility, and an increase in nausea and vomiting.[80] One other factor could be the influence of the metabolic changes during pregnancy on the pharmacokinetics of AEDs. Modified pharmacokinetics of AEDs may result from altered protein binding or increased hepatic metabolism.[80] Among the new AEDs, LTG has been advocated as a first-line drug due to its promising teratogenic profile[81,82,83]; this will be discussed in detail later in this article. Since therefore numerous patients are treated with LTG during pregnancy, it is clinically relevant to know that LTG serum levels drop during pregnancy due to a large increase in clearance, above 65%, and which may exceed 300%.[62,84,85] This was explained by the increased metabolism of LTG.[85] Accordingly, seizure relapses under LTG monotherapy during pregnancy and the necessity to increase the dosage were observed.[62,73,84,85] Similarly, OXC had to be increased during pregnancy due to seizure relapses.[73] Probably the underlying cause is similar, since reduced serum concentrations of the active metabolite 10-hydroxycarbazepine (MHD) were observed during the course of pregnancy.[86,87] Among the new AEDs it has been further observed that a significant fall in LEV serum concentration may occur,[85] the clinical relevance of which is still unclear. At least with LTG and OXC treatment therapeutic drug monitoring may be helpful.[85] More systematic studies of the effects of pregnancy on the pharmacokinetics of new AEDs are urgently required.[85]

Complications such as hyperemesis, vaginal bleeding, pre-eclampsia, or peripartal problems such as early contractions, weak contractions, or an increased caesarean section rate occur twice as often as in healthy women.[88,89,90] Finally, one should not ignore the fact that during pregnancy other possibilities exist that may trigger epileptic seizures, even in nonepileptic women. If unexpected seizure relapses occur in patients with epilepsy, one should therefore always consider and exclude potential additional causative factors such as cerebrovascular insults, cerebral processes, cerebral infections, toxic or metabolic causes, or eclampsia.[91]

## Risk factors for the child: possible complications during pregnancy, delivery, and the postnatal period

### Possible complications during pregnancy

Most probably generalized tonic-clonic seizures during pregnancy may threaten the child directly (trauma) and indirectly (reduced placental perfusion.)[55] However, there are no convincing data on these possible risks. We know that spontaneous abortions that correspond with seizures very rare.[71,92] However, the rate of stillbirths is higher (5.1% vs 2.4%) in women who have suffered from seizures during pregnancy than in seizure-free patients.[93] Complex partial seizures also temporarily influence the heart rate of the child due to contractions of the uterus and a resulting reduced fetal blood flow.[94]

Preeclampsia, placental bleeding, and immature delivery occur 1.5 to threefold more often in epileptic patients

than in the general population. Perinatal mortality is elevated by a factor of 1.2 to 2.[95] Abnormally low birth weights are found 2.8-fold more frequently. Children of women with epilepsy also have an elevated risk of low APGAR scores and perinatal asphyxia.[90] Over one decade perinatal mortality dropped continuously from 4.7% between 1977 and 1981 to 2.1% between 1987 and 1991.[55] The perinatal mortality rate in the German EURAP register is 1.4%.[96]

One important aspect of the perinatal period is the risk of intracerebral bleeding in the infant. Therefore, it has been suggested for some decades that during the last 4 weeks of pregnancy the mother should be supplemented by vitamin K in order to overcome coagulopathies of the child due to the vitamin K deficiency that has been mostly attributed to the impact of enzyme-inducing AEDs.[20,24,55] In addition, every child is supplied with vitamin K to minimize the bleeding risk. Recent data from a large cohort study in Finland,[97] however, do not support the necessity of vitamin K application: The authors followed 662 pregnancies of women taking enzyme-inducing AEDs. They were not given vitamin K, and no statistically significant difference was found concerning the risk of intracerebral bleeding compared with healthy controls.

**Genetic epilepsy risk**

If one excludes epilepsy syndromes with a very high genetic preponderance, such as benign familial newborn seizures, juvenile myoclonic epilepsy, tuberous sclerosis, and others,[98] the general risk of suffering from epileptic seizures during the first 20 years of life is 8.7% in case of a maternal and 2.4% in case of a paternal epilepsy.[99] Idiopathic epilepsies are associated with an epilepsy risk in the children of between 5% and 20%; this reaches 25% if both parents are affected.[24] Patients with epilepsy should make use of the possibilities of human genetic counseling in order to estimate the individual risk of epilepsy in their children.

**Postnatal period**

After delivery one has to consider reducing AED dosage again, if it has had to be reduced during pregnancy, to avoid postnatal intoxication of the mother. There is no general contraindication for breastfeeding. Since the children were exposed to the AED of the mother during pregnancy, breastfeeding may even help to avoid withdrawal symptoms in the child, since almost all AEDs are transported by breast milk.[24] The concentrations range widely and depend of the AED plasma protein binding.[24,71,100] The most frequent problem with breastfeeding may be sedation of the child, with consequent sucking weakness. Among the new AEDs the milk/serum level is 0.6.[101] Nevertheless, in children therapeutic ranges of LTG have been measured, due to the reduced metabolism of the drug in newborns.[102] Since LTG is among the most frequently used AEDs in pregnancy,[81,82,96,103] the behavior of the child should be watched carefully. This is certainly a general rule beyond pure LTG treatment. Although the recommendations vary widely,[100] for the classical AEDs there are no concerns about CBZ, PHT, and VPA.[104] Breastfeeding is also possible during the use of PB, PRM, and benzodiazepines, although the rate of sedation and sucking disturbances may be higher.[100,104,105] Close clinical monitoring is recommended in the case of PB and ethosuximide, which is highly concentrated in breast milk and occasionally reaches the same levels as in the maternal blood.[100] FBM is also considered to be required in order to satisfactorily judge the suitability of new AEDs for breastfeeding.[100,105]

## Teratogenicity

The risk of malformation is increased in children of mothers with epilepsy. Most references report malformation rates that are two to three times higher than in the normal population.[71,100,106-110] The maximum range varies between a 1.25-fold and a fivefold elevated risk.[111,112] One differentiates between minor and major congenital abnormalities. There is almost no major malformation that has not been mentioned in the context of epilepsies and AED treatment. Heart malformations, cleft lip and palate, skeletal deformities, diaphragmatic hernias, malformations of the central nervous system, gastrointestinal atresias, and urogenital malformations have most commonly been reported.[100] Heart failure and craniofacial clefts are the malformations with the highest incidence in children of women with epilepsy.[100] In order to estimate the increased risk of malformations accordingly, one has to keep in mind the spontaneous malformation rates in the general population. Figures in the literature vary from 0.4% to 6.4%.[113] Holmes et al[108] reported an incidence of 1.8%, according to other reports it ranges between 2% and 3%.[71,114] Malformations in children of women with epilepsy who did not take AEDs

during pregnancy are similar and range between 0% and 3.5% (in smaller cohorts than in the studies on the general population).[108,109,115,116] This suggests no epilepsy-specific additional risk. However, this is not necessarily true, since the underlying epilepsy syndromes in the above patients were apparently less active, since chronic medication was not required. Therefore data on active epilepsies without AED intake that would answer the question of epilepsy-specific teratogenicity do not exist, at least not in countries where sufficient epidemiological studies on the topic have been performed.

Whether or not children of fathers with epilepsy who are on AEDs have an increased teratogenic risk is a matter of controversy.[106,117] The available data do not allow to claim such an elevated risk unequivocally. An independent impact of AEDs is probable, since the risk of malformations is also higher in children of mothers who were on AEDS for reasons other than epilepsy.[108]

**Risk in women with epilepsy taking AEDs**

In women with epilepsy on AED therapy the teratogenic risk for major congenital malformations was reported to range between 4% and approximately 14%.[69,108,109,118,119] The ongoing pregnancy registries report incidence rates of 3.7% in Taiwan,[120] 4.2% in the UK registry,[103] and 6.4% in Germany.[96] Since association between the risk of malformations and the amount of individual serum peak concentrations has been suggested, multiple dosing, especially in the case of VPA, should be considered.[121]

Minor congenital malformations such as minor craniofacial abnormalities, epicanthus, or hypertelorism are relatively common in children of women with epilepsy and treatment with AEDs. However, it is almost impossible to assess precisely the impact of AEDs. It is apparent that these abnormalities are not drug-specific as was previously assumed, and that they are observed under the influence of each of the classical AEDs.[71,122,123,124] Reliable data on new AEDs are not yet available. A realistic estimate suggests that minor abnormalities are twice as frequent as in the general population (28% versus 14%).[125]

*Combinations of AEDs*

Polytherapy is a risk factor for congenital malformations, including new AEDs.[81,96,103,108,113,115] In the UK pregnancy registry, major congenital malformations occurred in 6.0% of children of mothers on polytherapy as opposed to a 3.7% incidence in patients on monotherapy ($P$=0.01) and 3.5% in women with epilepsy who were not taking AEDs.[103] Others described a higher incidence in monotherapy as compared with children of healthy controls or children of mothers with epilepsy but without AED intake.[108] Combinations with VPA carried a higher risk for malformations than other combinations.[103] The combination of VPA and LTG which is commonly used[96] was associated with a higher risk of major congenital malformations than the monotherapy with VPA[126] or any other combination with LTG.[81] If the AED treatment prior to pregnancy is changed from VPA to LTG for safety reasons, one should advise the patient about the dangers of falling pregnant while the combination is still taken.

*Classical AEDs*

The most important finding concerning teratogenicity that helped to raise awareness in the epilepsy community was the description of neural tube defects under the influence of VPA.[127] Neural tube defects develop between the 17th and the 30th day of a pregnancy.[128] The risk of neural tube defects with VPA is reported to range between 1% and 2%, with maximum figures of 5.4% during monotherapy.[71,122,129] In the present interim analysis of the German EURAP study, no neural tube defect with VPA monotherapy whas been observed.[96]

Major congenital malformations with VPA monotherapy occur in 6.2% to 11.1%.[52,76,103,109,130] Beyond neural tube defects, skeletal abnormalities, cardiovascular, urogenital, and cerebral malformations have been typically reported.[106] Dosages beyond 1000 mg per day appear to be associated with a markedly elevated risk of malformations[83,109,131,132] and should therefore be avoided if at all possible.

The rate of major congenital malformations with CBZ ranges from 2.2% and 5.7%.[76,103,109] Neural tube defects, cardiac malformations, hip dislocations, inguinal hernias, and hypospadia were reported as typical findings.[106] Recent data[103,115,116] indicate that the teratogenic potential of CBZ is probably not as high as was previously estimated.[110] The UK pregnancy registry reports an incidence of 2.2% of major malformations and thus the lowest rate of all AEDs.[103] Neural tube defects were reported in 0.5% to 1.0% in various series.[71,122,133]

The incidence rates of congenital major malformations with PRM, PHT, and PB were 14.3%, 3.4% to 9.1% and

5.1% to 12%, respectively.[109] Typical malformations under the influence of PHT are cardiac malformations, craniofacial clefts, and skeletal finger abnormalities.[118] In addition one should be aware of the fetal hydantoin syndrome that comprises pre- and postnatal growth retardation, microcephalus, and developmental delay combined with the abovementioned malformations.[106] Typical malformations with PB therapy are cardiac malformations and craniofacial clefts.[106] The German EURAP interim report does not mention major malformations with PRM and PB and one cardiac abnormality with PHT.[96] Clefts were also described with ESM therapy,[106] which was often given as an add-on AED. Animal studies emphasize the prenatal toxic effects of the drug.[134]

*New AEDs*

The teratogenic effects of new AEDs are difficult to assess. In almost all instances the data do not allow unequivocal conclusions. Animal studies that are usually performed using extensive dosages and that indicated teratogenic effects from LEV, TPM, OXC, and VGB but not from FBM, GPB, LTG and TGB[100] do not necessarily help to estimate the normal risk in humans. The only new AED that has been extensively studied in humans is LTG. According to the Lamotrigine Pregnancy Registry, the malformation rate was 2.9% and was therefore comparable to the spontaneous rate in the healthy population.[82] Major malformations with LTG monotherapy were not described in the ongoing EURAP registries of

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| **Before pregnancy** |
| • Information about genetic risks |
| • Check the necessity of continuing AED treatment |
| • Change to monotherapy without VPA if ever possible, data for CBZ and LTG are relatively favorable |
| • Initiation of folic acid, 0.8 mg per day, if enzyme-inducing AEDs are taken: 5 mg per day |
| • Discuss additional teratogenic factors such as smoking, drugs, alcohol |
| **First trimester** |
| • Continuation of AED treatment, even in the case of unplanned or unexpected pregnancy. |
| • Continuation of folic acid. If folic acid was not taken, it should be initiated prior to the 28$^{th}$ day of pregnancy and continued until the end of the first trimester |
| • Assessment of serum concentrations of AEDs |
| **Second trimester** |
| • Prenatal diagnostics (ultrasound, amniocentesis, etc) |
| • Assessment of serum concentrations of AEDs once per trimester, during treatment with LTG and OXC once per month |
| **Third trimester** |
| • Assessment of serum concentrations of AEDs once per trimester, during treatment with LTG and OXC once per month |
| **Delivery** |
| • Consideration of caesarean section in case of increasing or drug-resistant seizure frequency |
| • Consideration of temporary additional treatment with low-dose benzodiazepines, especially in case of prolonged delivery |
| • Caution with hyperventilation |
| **Postnatally** |
| • Application of vitamin K to the newborn |
| • Extensive search for malformations of the newborn |
| • Assessment of sedation or sucking weakness of the newborn. Consideration of assessment of AED serum concentration in the child. Decision on continuation of breastfeeding |
| • Dose reduction in case of intoxication signs in the mother (if the AED dosage was increased during the pregnancy). Assessment of AED serum concentration and dose adaptation if necessary |
| • No initiation of other AEDs during breastfeeding period (danger of side effects in the child) |
| • Caution with sleep deprivation, especially in case of idiopathic generalized epilepsy syndromes. The responsibility of the partner should be emphasized. |

**Table II.** Recommendations during pregnancy.[24] AED, antiepileptic drug; VPA, valproic acid; LTG, lamotrigine; OXC, oxcarbazepine

Australia or Germany.[96,132] The UK Pregnancy Registry reported a possible dose-dependency with a rate of malformations with LTG dosages above 200 mg that were approximately in the range of 600 to 1000 mg VPA.[103] This was not confirmed by the reanalysis of the data of the Lamotrigine Pregnancy Registry.[135] Finally, orofacial clefts were reported in a few cases,[83] but were not identified as a convincing drug-specific event in the ongoing registries.[81,82,96,103,132] Thus, the teratogenic risk of monotherapies with LTG appears to be moderate. More reliable data on other new AEDs are urgently needed.

**Folic acid prophylaxis**

Several studies have shown that folic acid or combinations of vitamins including folic acid were useful to reduce the risk of neural tube defects in pregnancies of women with a genetically elevated risk of having a child with a neural tube defect, and in women during their first pregnancy,[136,137,138] so that folic acid prophylaxis is generally recommended if pregnancies are planned. It is tempting to speculate that women with epilepsy who have an elevated risk of malformations with AED intake might benefit even more from folic acid prophylaxis. However, this hypothesis, though convincing, has not yet been proven by confirmatory studies.[118] In two patients on VPA, folic acid did not prevent neural tube defects.[138] Recommendations usually suggest high dosages such as 5 mg per day to overcome the theoretical drawback of enzyme-inducing AEDs.[24,49,100]
A summary of the recommended strategies to reduce the teratogenic risk in women with epilepsy is shown in *Table II*.

**Impact of AEDs on further development**

Data on the impact of AEDs on the further development of children of women with epilepsy are controversial,[100] if variables such as APGAR score, the risk of mental retardation, behavioral disorders, and the development of verbal skills are considered.[106,107,122,123] Reports of a higher risk of cognitive deficits in children whose mothers were on combinations of AEDs compared with monotherapies[140] may be influenced by a methodological bias, since the epilepsy syndromes in the former group may have been more active and more difficult to treat. However, data on the possibility that children of mothers who took VPA during pregnancy may have a higher risk of developing cognitive deficits, would rely on a methodologically convincing study, and this certainly requires further investigation.[141] Similar suggestions concerning children of mothers who were on CBZ treatment[71,123] have not been confirmed.[142] Other AEDS have not yet been sufficiently investigated concerning this important question.

## Conclusion

More recently, increasing interest in the influence of epilepsies themselves and antiepileptic drugs on several aspects of fertility, pregnancy, teratogenicity, and the development of the newborn have led to a considerably improved knowledge about these clinically most relevant issues. Still, a lot of questions remain to be answered. One may expect that at least some of these problems will be partially solved by currently ongoing international pregnancy surveys. ❑

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### *Embarazo, epilepsia y anticonvulsivantes*

*La mayoría de los trastornos epilépticos no son autolimitados a lo largo del tiempo, y por lo tanto requieren de un tratamiento de larga duración y a menudo de por vida con fármacos antiepilépticos (FAE). En las mujeres con epilepsia constituyen temas cruciales la influencia de la enfermedad en la posibilidad que ocurra el embarazo y en el curso de éste, como también el potencial impacto del tratamiento con FAE en la madre y en el niño.*
*Esta revisión aborda el conocimiento de relevancia clínica relacionado con el impacto de la enfermedad y del tratamiento con FAE en la fertilidad, el embarazo, el parto, el período del postparto y la teratogeneidad. Algunos de los nuevos FAE parecen tener un perfil favorable debido a la falta de interacciones clínicamente relevantes y a prometedores perfiles teratogénicos. Sin embargo, el hallazgo de una disminución en la concentración sérica de lamotrigina durante la anticoncepción hormonal y el embarazo es un ejemplo ilustrador, que demuestra que se requieren con urgencia resultados de los estudios que se están realizando para investigar diversas preguntas aun no respondidas. Algunas investigaciones multinacionales prospectivas que están desarrollándose en la actualidad deberían aportar información esencial en esta área.*

### *Grossesse, épilepsie et anticonvulsivants*

*La majorité des troubles épileptiques ne régressent pas seuls au cours du temps, et nécessitent donc un traitement antiépileptique de longue durée et parfois même à vie. Chez les femmes épileptiques, l'influence de leur maladie sur la possibilité ou le cours d'une grossesse, ainsi que l'impact éventuel du traitement antiépileptique sur la mère et l'enfant, sont des questions importantes.*
*Cet article s'attache aux connaissances cliniquement pertinentes concernant l'influence de la maladie elle-même et du traitement antiépileptique sur la fertilité, la grossesse, la délivrance, le post-partum et la tératogénicité. Certains nouveaux traitements semblent posséder des caractéristiques favorables grâce à l'absence d'interactions cliniquement significatives et à un profil tératogène prometteur. Cependant, la découverte d'une diminution des concentrations sériques de lamotrigine pendant la contraception hormonale et la grossesse est instructive et montre qu'il faut absolument de nouvelles études pour répondre aux questions non encore élucidées. Plusieurs études multinationales prospectives sont actuellement en cours et devraient permettre de compléter nos connaissances dans ce contexte.*



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