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REVIEW

# Management of women with epilepsy: from preconception to post-partum

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**Abstract**
*Purpose* The physiological changes during pregnancy can significantly alter antiepileptic drug (AED)'s absorption, distribution, metabolism and elimination, thus influencing their plasma concentration. Considering that the risks of using old and new AEDs during pregnancy are still debated, our aim is to review the available evidence on this topic.
*Methods* Narrative overview, synthesizing the findings of literature retrieved from searches of computerized databases.
*Results* The old AEDs generation (benzodiazepines, phenytoin, carbamazepine, phenobarbital and valproic acid) is teratogenic: minor congenital malformations, such as facial dysmorphism and other anomalies, occur in 6–20 % of infants exposed to AEDs in utero; this value is two times greater than the value reported in the general population. Major congenital malformations (MCM) such as cleft lip and cleft palate, heart defects (atrial septal defect, Fallot's tetralogy, ventricular septal defect, aortic coarctation, patent ductus arteriosus, and pulmonary stenosis) and urogenital anomalies were estimated to be 4–6 % of infants born from mothers treated with AEDs, compared to 2–3 % of the general population.
*Conclusion* It is essential to inform women treated with AED that planning pregnancy is necessary, when possible. The problems related to antiepileptic therapy and the possibilities of prenatal diagnosis should be accurately discussed with the patient, when possible before pregnancy: individual circumstances, desire to have children, severity of epilepsy, risks of seizures, family history of congenital malformations and all other potential risk factors must be considered, involving the patient in shared clinical decision-making.

**Keywords** Epilepsy · Pregnancy · Antiepileptic drugs · Pharmacokinetics · Prevention

## Introduction

Epilepsy is a condition characterized by a change of primary electrical activity in the brain, which causes recurrent crisis: it can be focal when originating within the networks limited to one hemisphere or generalized when it involves both of them. It can affect cortical and subcortical structures even without involving the entire cortex; the seizure is a transient event that can occur with typical absences, generalized tonic–clonic and myoclonic crisis, alone or in various combinations; the epileptic syndrome occurs in the absence of structural brain injury, suggesting a genetic aetiology [1]. 65 million people worldwide are affected by epilepsy and the prevalence is estimated to be approximately 700 out of 100.000 people

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[2, 3]. The prevalence is 15.4 % in sub-Saharan Africa, 5.4 % in Latin America, 12.4 in Europe and 5–10 % in North America [4]. According to the International league against epilepsy (ILAE), epilepsy could be considered as a brain disorder characterized by a persistent predisposition to develop seizures [5]. In clinical practice, this definition is usually applied when there are two unprovoked seizures, separated by a time interval >24 h, and a third seizure in the span of 10 years [5, 6]. After the first occurrence of unprovoked seizures, the recurrence risk is 40–52 % (60–90 % at 4 years) [7, 8]. Considering that the risks of using old and new antiepileptic drugs (AEDs) during pregnancy are still debated, our aim is to review the available evidence on this topic. In this regard, we performed a narrative overview, synthesizing the findings of literature retrieved from searches of computerized databases.

## Maternal physiological changes during pregnancy

Maternal changes occurring during pregnancy and involving all organs and systems, physiologically revert after childbirth. The heart increases its output from 40 to 50 % and this is accompanied by a consequent increase in the heart rate and a proportional increase in the stroke volume [9, 10]. Blood and plasma's volume increase causing a dilution of the haemoglobin concentration, thus the increased red blood cells require an additional contribution of iron [11, 12]. Changes occurring in the urinary system are: increase of the glomerular filtration rate, increase in renal function with consequent nitrogen's decrease and lower creatinine values [13]. The respiratory system is in part influenced by progesterone and partially offset by the volume of the uterus; concomitant increases in respiratory rate, pH and $O_2$ consumption, and minimal hyperemia and edema of the respiratory tract also occur in some cases [14, 15]. The compression exerted by the uterus on the gastrointestinal and hepatobiliary systems, on the rectum and on the last part of the colon may lead to constipation and gastroesophageal reflux, increasing abdominal pressure [16–18]. Alkaline phosphatase's level increases during the third quarter of pregnancy [19, 20]. Pregnancy also affects the function of many endocrine glands, in part because the placenta produces hormones and in part because a high percentage of this hormone circulates in blood bound to transporter proteins. In fact, this binding percentage is increased during pregnancy [21]: furthermore, thyroid's function is increased, as well as the adrenal glands' one. There are also increased levels of glucocorticoids, estrogens and progesterone, which alter glucose metabolism and insulin requirement [22, 23].

## Obstetric management of women with epilepsy

The incidence of epilepsy in the obstetric population undergoing AEDs therapy is 0.3–0.8 % [6, 24]. Studies about the frequency and the overall trend of seizures in pregnancy are conflicting: some state there is a reduction (22.7 %), others the opposite (24.1 %) and in many cases (53.2 %) no changes are observed [25]. Seizures can cause bradycardia and foetal death [26] in utero due to status epilepticus [27, 28]. Therefore, it is advisable to ensure a good control of seizures during pregnancy [29]. The risk of seizures during labour is low, but it is sufficient to justify the recommendation that the delivery should take place in a department of obstetrics with services for maternal and neonatal resuscitation and treatment of maternal seizures [1]. Seizures can be severe during labour, although they can rarely cause foetal asphyxia and affect active collaboration of the mother during childbirth. Planning a caesarean section is needed in some cases only: in patients who have a history of frequent seizures, because they show a higher risk of protracted crises before and during labour. On the other hand, in some cases, there are specific indications for vaginal delivery [30]. There are no documented contraindications for epidural analgesia and prostaglandins for local use and for induction of labour in case of therapeutic abortion. As widely reviewed by Borthen [31], recent studies strongly indicate an association between AEDs use, and complications during pregnancy and labour. In particular, women with epilepsy seem to have a higher risk of preeclampsia and gestational hypertension [31], bleeding in pregnancy [32], caesarean delivery [33, 34], excessive bleeding post-partum, preterm birth and small for gestational age child [35, 36]. It is unclear whether the increased risk of complications is due to epilepsy per se, AEDs use, or combination of both. Moreover, we should consider that several conditions, such as advanced maternal age, low parity, low Bishop score and low duration of labour are at a higher risk of caesarean section [37, 38], independently from the epileptic status. As far as neonatal outcomes are concerned, there have been identified small for gestational age children (SGA) [39, 40], low Apgar score at 1 min [34], deterioration of potential long-term cognition [41] and perinatal death [42].

## Modification of antiepileptic drugs' pharmacokinetics during pregnancy

The physiological changes occurring in pregnancy may also significantly alter the absorption, distribution, metabolism and excretion of AEDs and, consequently, their

plasma concentration [43]. Usually, AEDs concentration begins to decline significantly from the first to the third quarter of pregnancy. The influence of pregnancy on emotional and behavioural factors must be taken into account, as well as physical factors, such as emesis and pelvic distortion [44]. Thus, plasma concentration of AEDs, in particular those metabolized through glucuronidation, decreases during pregnancy [44]. This often happens to phenytoin, frequently to phenobarbital, carbamazepine and valproic acid [45]. Primidone's plasma concentration remains stable, whereas phenobarbital's (which derives from primidone) one is considerably reduced, mostly after childbirth [46]. The kinetics of new antiepileptic drugs is still poorly understood. Lamotrigine is the most studied: its concentration decreases during pregnancy, but sharply increases after childbirth [44, 45]. The mechanisms involved to explain these changes include reduction of the gastric motility [16, 18] and the concentration of albumin [47], increase of the plasma volume [11, 12], increase or decrease of the metabolic capacity and increase of the renal blood flow [13]. The behaviour of drugs with high protein binding, especially phenytoin and valproic acid, requires some additional considerations [45, 46]. Lower concentration of albumin that occurs during pregnancy leads to a reduction in the percentage of drug molecules bound to proteins. In response to a decrease of the total concentration, there is therefore a reduction of the pharmacologically active percentage of the drug (the unbound fraction) [44, 46, 47]. This phenomenon is particularly pronounced for valproic acid, the concentration of which is generally stable during pregnancy. In this and in other cases, monitoring the sole increase of the plasma concentration can be misleading [45, 48]. Furthermore, women with epilepsy have reproductive endocrine disorders [49] which include abnormalities of the menstrual cycle, anovulatory menstrual cycles [50, 51], which have been linked to AEDs treatment [50, 52]. They alter luteinizing hormone (LH) release, in response to gonadotropin-releasing hormone (GnRH) stimulation (Fig. 1) [53–56]. Some AEDs (phenobarbital, primidone, phenytoin, carbamazepine) are able to cause an increase of the activity of hepatic enzymes, whereas another AED (valproic acid) shows the very opposite action. The induction of CYP450 enzyme causes the reduction of serum concentrations of estradiol, testosterone, dehydroepiandrostenedione and increases the concentration of sex hormone-binding globulin (SHBG) [49, 55]. Therefore, clinical evaluation of plasma levels of antiepileptic drugs during and after pregnancy is important. Most cases do not require dose adjustment of AEDs, except those cases that show changes in the clinical situation.

## Risk of congenital malformations

The estimated incidence of congenital malformations in the general population is 2–3 %, whereas for women undergoing AEDs treatment it is −6 %. It is therefore clear that the incidence is doubled in the latter [57, 58]. Recent studies have investigated three possible causes for this: direct toxicity of AEDs, probable folate deficiency caused by AEDs themselves, and reduced enzyme activity of epoxide hydrolase caused by genetic alterations [59]. It has been reported that genetic differences in folate metabolism may explain the increased risk of congenital abnormalities, particularly neural tube defects in children of women with epilepsy treated with AEDs [60, 61]. A study [62] shows that commonly used anticonvulsants such as carbamazepine, phenytoin and sodium valproate, used during pregnancy, showed incidents of interference with folic acid metabolism, thus causing foetal anticonvulsant syndrome. The mutation in the methylenetetrahydrofolate gene (MTHFR which is involved in the processing of 5–10 methylenetetrahydrofolate to 5-methyltetrahydrofolate) in mothers treated with sodium valproate, phenytoin or carbamazepine in pregnancy is associated with foetal anticonvulsant syndrome [63, 64]. Moreover, the skewed distribution of genotypes in affected children probably reflects the association of foetal anticonvulsant syndrome with the maternal genotype [65]. The old generation of antiepileptic drugs such as benzodiazepines, phenytoin, carbamazepine, phenobarbital, and valproic acid is teratogenic. Minor congenital malformations, such as facial dysmorphism and anomalies occur in 6–20 % of infants exposed to AEDs in utero [66], about twice as the percentage that occurs in general population. MCM (major congenital malformations) such as cleft lip and cleft palate, heart (atrial septal defect, tetralogy of Fallot, ventricular septal defect, aortic coarctation, patent ductus arteriosus, and pulmonary stenosis) and urogenital defects are estimated to be about 6 % of infants born to mothers treated with antiepileptic drugs, compared with 2–4 % of the general population [67]. Treatment with valproic acid during the first month of pregnancy is associated with neural tube defects (spina bifida and anencephaly) which have been estimated to be about 1–2 % [68], while treatment with carbamazepine showed similar malformations with an incidence of 0.5–1 % [69]. Holmes et al. [70] confirmed these results, showing increased rates of MCM; the combined frequency of embryopathy was 20.6 % in women treated with AEDs, whereas it was 8.5 % in the control group, and this rate increased from 20.6 to 28.0 % with AEDs in polytherapy There is little information regarding the teratogenicity of new antiepileptic drugs. The association between exposure to antiepileptic drugs in

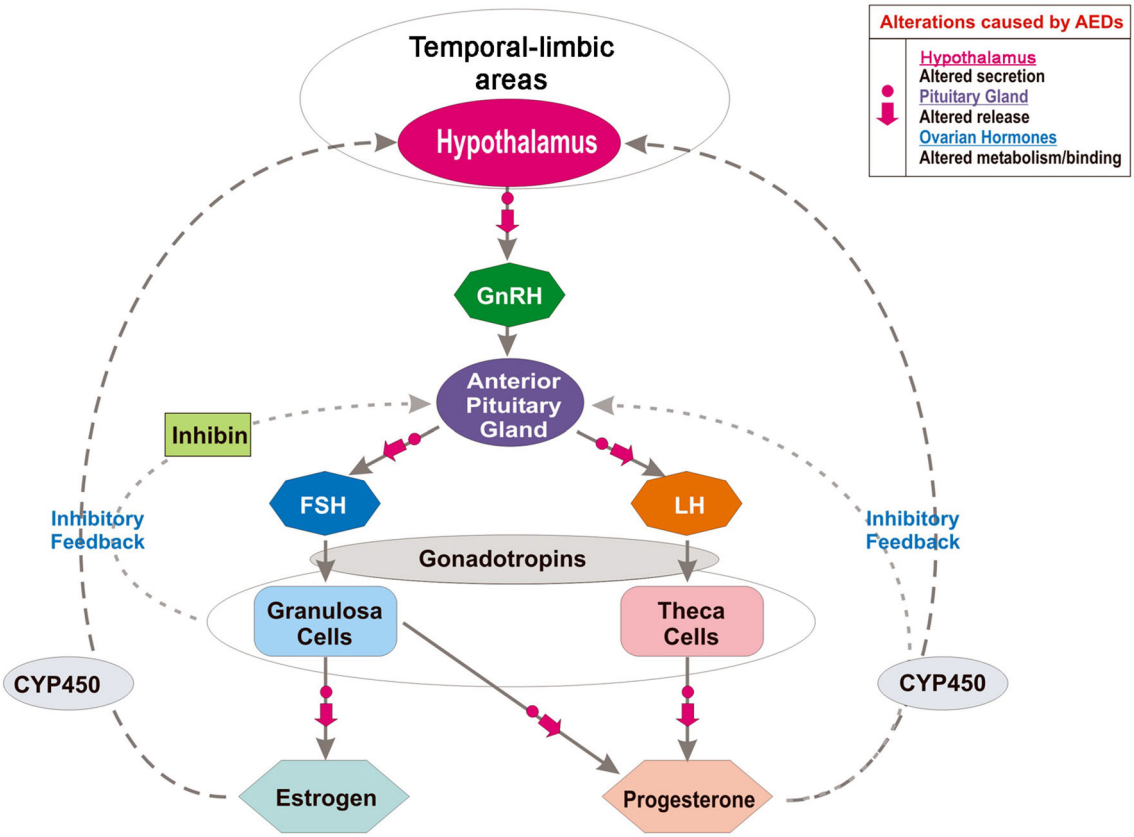


**Fig. 1** Influence of the antiepileptic drugs on hypothalamic–pituitary axis. The antiepileptic drugs (AEDs) could interfere on hypothalamic–pituitary pathways: LH (luteinizing hormone) releasing is altered in response to GnRH (gonadotropin-releasing hormone); some AEDs such as carbamazepine, phenytoin and phenobarbital induce the hepatic cytochrome P450 enzyme (CYP450) that causes a decrease in serum estradiol concentrations, testosterone and dihydroepiandrostenedione, while valproate inhibits CYP450 causing increased levels of adrenal and gonadal androgens. *CBZ* carbamazepine, *PHB* phenobarbital, *PHT* phenytoin, *VPA* valproate, *CYP* cytochrome P450 isozyme

pregnancy and congenital defects has been the subject of intense studies for more than thirty years [71–75]. Nevertheless, the results of the studies published so far do not allow us to define the actual risk of malformations in children of epileptic mothers, or to identify safer drugs [76]. Studies carried out in relatively large populations, but with low statistical power, show a trend to greater teratogenicity of valproic acid compared with other antiepileptic drugs. Several studies, on the other hand, suggest that the teratogenicity of valproic acid may in part be due to genetic factors and that, at least in some cases, finding the presence of neural tube defects in previous pregnancies significantly increases the risk of birth defects in subsequent pregnancies [68]. It is not currently possible to analyse the outcomes of pregnancies in women without a family history of malformations, and to determine the actual relationship between the exposure to valproic acid and the incidence of malformation [64–68, 70, 76]. As far as the use of polytherapy is concerned, many studies [64–68, 70, 76] suggest that the number of AEDs used by the mother is directly correlated with the risk of MCM. It is likely that the teratogenic risk depends on the type of the combination therapy, therefore any association should be evaluated separately. Studies of UK Epilepsy and Pregnancy Register and Lamictal International Registry showed that the treatment in polytherapy containing valproate may increase the rate of malformations [77]. These data are in agreement with several other studies [78, 79]. The result of these data indicates that polytherapy in pregnancy is not necessarily risky, as it is the type of drugs chosen. Therefore, it is important to pay attention to which drug to prescribe in polytherapy in a pregnant woman [78, 80]. For example, although Valproate alone generates an increased risk of malformations, it has a even more increased risk when used in combination with another AED [77]. These results demonstrate that pregnant women who require treatment with AEDs in monotherapy are exposed to a lower risk than women who practice a polytherapy with AEDs. As far as the role of the dose of the drugs administered to the mother is concerned, the scientific evidence is conflicting.

According to some Authors, high concentrations of phenobarbital and phenytoin increase the risk of malformations [81, 82], while other Authors do not consider it to be a relevant factor [83]. Only for valproic acid, data are more consistent, indicating the existence of a relationship between dose and teratogenicity [82]. The study by Mawer et al. [41] showed no statistically significant differences of MCM compared to controls, while the frequency of congenital malformations had a higher prevalence (6.6 %), with a peak (13.7 %) in women with epilepsy treated with valproate in polytherapy. The perspective is not encouraging: if the conventional studies have not yet defined the teratogenic risk of the older antiepileptic drugs (when they are the only alternative therapy), it is unlikely that we can get clear guidance on the new AEDs, generally less used in treatment of women of childbearing age [81]. Furthermore, the infants whose mothers had a history of epilepsy but took no anticonvulsant drugs during pregnancy did not have a higher frequency of those abnormalities than the control infants [70]. Finally, exposure to AEDs in utero could also impair cognitive function later in life. In this regard, valproate has been shown to have the most deleterious consequences on cognition, whereas human studies suggest a low risk for cognitive deficits with lamotrigine, levetiracetam, and carbamazepine [84].

The introduction of new antiepileptic drugs has further complicated the therapeutic strategy in women of childbearing age, as it is not possible to know the teratogenic risk related to the new molecules compared to conventional antiepileptic drugs; consequently, in the absence of reliable data, they should be considered potentially teratogenic. Many studies (Table 1), with rigorous methods and numerous cases, have sought to determine the incidence of MCM for every single drug.

## Recommendations and prevention

Epilepsy is not a contraindication for pregnancy. Over 95 % of women with epilepsy will have a term pregnancy and healthy children [85]. In the first trimester of pregnancy, it is recommended to avoid (if possible) valproate, phenytoin, phenobarbital and valproate in polytherapy with other AEDs [32, 41]. The use of contraceptives is important for women of childbearing age, to increase the percentage of planned pregnancies and therefore minimize the risk of complications. [86]. This should include the information about the risks associated with epilepsy and pregnancy, potential interactions with oral contraceptive therapy and recommend the integration of drugs with particular reference to folate [85–87].

## Monitoring of pregnancy, childbirth and postpartum

Pregnancy is a unique condition and AEDs can interact with pre-existing conditions, genetic variables and environmental factors. The focus on women with epilepsy of childbearing age should start before the occurrence of pregnancy [88]. Indeed, pregnancy can markedly affect the pharmacokinetics of several AEDs, and dose adjustment is often necessary during pregnancy to maintain the control of the crisis [89]. Preconception counselling should include patient education to ensure a clear understanding of the risks from uncontrolled seizures and possible teratogenicity of AEDs [88, 90]. Genetic counselling should be considered, especially in case of maternal/paternal idiopathic epilepsy and a positive family history of epilepsy [1]. A study by Kaneko et al. [80] found that the incidence of

**Table 1** Rate of major congenital malformations (MCMs) during antiepileptic drugs monotherapy

| Studies | CBZ Mean (cases) | LTG Mean (cases) | PHB Mean (cases) | PHT Mean (cases) | VPA Mean (cases) |
|---|---|---|---|---|---|
| Meador et al. [42] | 4.6 (4411) | 2.9 (1337) | 4.9 (945) | 7.4 (1198) | 10.7 (2097) |
| Wide et al. [58] | 4.0 (403) | | | | 9.7 (268) |
| Holmes et al. [70] | 5.2 (58) | | 4.7 (64) | 3.4 (87) | |
| Kaneko et al. [80] | 5.7 (158) | | | | 11.1 (81) |
| Matalon et al. [71] | 5.5 (795) | | | | |
| Artama et al. [72] | 4.0 (805) | | | 2.6 (38) | 10.7 (263) |
| Hernandez-Diaz et al. [73] | 2.5 (873) | | | | |
| Hunt et al. [74] | | 2.4 (1151) | | | |
| Weighted average | 4.1 | 2.8 | 4.9 | 6.8 | 10.6 |
| Number of cases | 7503 | 2288 | 1009 | 1323 | 2709 |

The weighted average was calculated taking into account the average incidence of MCMs in every single study

*CBZ* carbamazepine, *LTG* lamotrigine, *PHB* phenobarbital, *PHT* phenytoin, *VPA* valproate

birth defects is related to the number of drugs and to their dosing, establishing that the incidence of birth defects decreases with AEDs in monotherapy, given in doses that must not exceed 1000 mg/day (plasma concentrations not exceeding 70 microg/ml). To prevent seizures during labour, crisis control should be achieved during the third quarter of pregnancy by establishing the effective dose with the minimum dosage. Folic acid 0.4–0.8 mg/day [59, 60, 92] during the preconception period and 4–5 mg/day afterwards [1, 88, 91] should be given 3 months before conception and during the first trimester of pregnancy, to avoid malformations due to folate deficit. From 14 to 18 weeks of gestation, serum alpha-fetoprotein should be evaluated. Pregnant women, who take AEDs, must undergo ultrasound high-resolution screening for structural abnormalities at 18–20 weeks of gestation, by an appropriately trained sonographer [1, 88, 92]. Monitoring of serum concentrations of the drug must be performed monthly [91]. Vitamin K prophylaxis is recommended starting at 36 weeks of gestation, to limit the effects induced by AEDs on microsomal enzymes that degrade foetal vitamin K and inhibit the γ-carboxy-glutamic acid for the precursors of coagulation factors II, VII, IX and X [88, 93, 94]. In this regard, Pack [95] recommends administration of vitamin K, at a dose of 10 mg/day, during the last month; conversely other Authors [1] do not recommend vitamin K supplementation to the mother, but to the newborn. Breastfeeding is generally possible because AEDs' plasma concentrations are low and no adverse effects have been reported [88, 96, 97]. Special attention should be taken if the mothers are treated with ethosuximide, phenobarbital or primidone, which may induce sedation and lethargy in newborns [98].

**Table 2** Management of pregnancy in women with epilepsy

| Period | Management activities | Ref. |
|---|---|---|
| Diagnosis | The clinical diagnosis of epilepsy must be established on the basis of eyewitness testimony and diagnostic tests such as electroencephalogram (EEG), computed tomography (CT) or magnetic resonance imaging (MRI) | [1–8] |
| Counselling | Advise the patients who desire a pregnancy, and their family. Give a correct and complete information in case of detected foetal malformations, for the individual choice of continuation or termination of pregnancy | [91, 92] |
| Preconception | Adjust the therapy at the lowest effective dosage to control the severity and frequency of seizures. Avoid polypharmacy and use controlled release drugs. In women with epilepsy, the goal of the therapy is to maintain seizure control using the lowest effective AEDs dose. Monitoring of plasma concentrations of AEDs is suggested to optimize therapy during pregnancy. It is advisable (when possible) to use AEDs monotherapy not to exceed 1000 mg/day (plasma concentrations not exceeding 70 microg/ml). Suggest prenatal treatment with 0.4 mg/day of folic acid for low-risk patients, and 0.8 mg/day for high-risk ones | [1, 92, 102–105] |
| Pregnancy first trimester | Check levels of alpha-fetoprotein (AFP) and perform ultrasound to investigate foetal organogenesis. In the presence of clear indications, amniocentesis with control of the foetal karyotype should be proposed | [37, 40, 59, 60, 91–95] |
| | Continue the therapy with antiepileptic drugs at the lowest effective dose to control seizures | |
| | Perform accurate monitoring of plasma concentrations as an aid in optimizing therapy. Continue the treatment with 4–5 mg/day of folic acid | |
| Pregnancy second trimester | Check with ultrasound the proper foetal development. Continue the therapy with AEDs at the lowest effective dose to control seizures and perform monitoring of serum drug concentrations | [92–98] |
| Pregnancy third trimester | Check with ultrasound the proper foetal development. Continue the therapy with antiepileptic drugs at the lowest effective dose to control seizures and perform monitoring of serum drug concentrations | [91–98] |
| | Administrate Vitamin K1 (1 mg i.m.) to the infant at birth, to prevent bleeding disorders | |
| Childbirth | Plan the type of birth on the basis of obstetric indications, taking into account that 30 % of patients with epilepsy require a caesarean section | [31–37, 92–98, 100] |
| | During delivery venous access should be prepared for the timely administration of clonazepam or midazolam in the case of a seizure. In case of generalized tonic–clonic seizures, continuous cardiotocography (CTG) should be performed. The foetus should be monitored to prevent respiratory complications | |
| Breastfeeding | Breastfeeding is generally possible because AEDs' plasma concentrations are low and no adverse effects have been reported | [88, 96, 97] |
| Post-partum | The mother should be evaluated by a psychiatrist and a neurologist for the possibility of post-partum depression. The infant should be followed in the long term, from a psychiatrist and a neurologist to assess any cognitive deficits | [92, 93, 95] |

## Counselling

All epileptic women of childbearing age should have adequate information during preconception; clinical history must be assessed; both the type of AEDs and the dosage must be reassessed in relation to the clinical, obstetric and physiological situation [89]. The success of the counselling will be determined by a combination of care, collaboration of the patient and social context; a proper planning can reduce the adverse outcomes of pregnancy [99]. Planning must pay attention to the safety of the therapy during pregnancy, the potential neonatal, labour and delivery complications, and the management of neonatal and post-partum periods [100]. The counselling team, during preconception and pregnancy, should consist of a general practitioner, a neurologist, and an obstetrician, whereas during the time of childbirth and the post-partum there should also be an anesthesiologist, a neonatologist and a psychiatrist [101, 102]. The evidence suggests that adequate information and planning of pregnancy in women with epilepsy can help to minimize the risks associated with symptoms of the disease and the toxicity of AEDs (Table 2; Fig. 2). Finally, it is extremely important for the clinician to involve the patient in clinical decision-making, to make decisions together using the best evidence [103]. As far as shared decision-making is concerned, although little evidence is available on this matter in literature, we agree on using this protocol whenever more than one option is possible.

## Discussion

The teratogenicity of AEDs remains nowadays a problem to investigate. In literature, there are indeed many studies that have reported contradictory results. Among these studies, few Authors do not consider genetic predisposition as a cause of foetal malformations, regardless of the drug or its possible effect on the genetic background. The quantitative and qualitative analysis of published studies does not define the degree of the risk of malformations in children of mothers with epilepsy, neither identifies a scale of risk of the drugs. There were reports of birth defects in mothers treated with AEDs (especially regarding neural tube defects), but with significant rates of other musculoskeletal, cardiac, urogenital abnormalities, craniofacial dysmorphic features, hypospadias, cleft lip and palate, microcephaly. There is evidence of a "phenytoin syndrome" with growth retardation, microcephaly, craniofacial dysmorphism, hypoplastic nails and distal phalanges, cone epiphyses. The heterogeneity of data in literature and the absence of conclusive information is fundamentally dependent on methodological issues, most notably that of

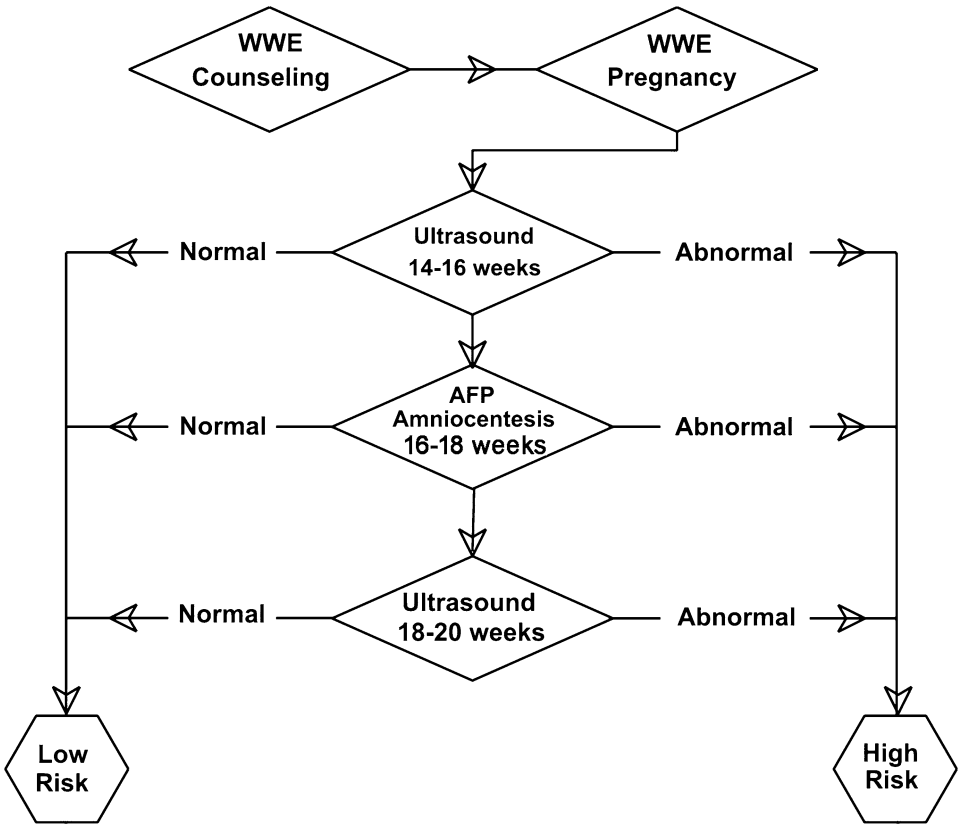


**Fig. 2** Flow diagram for major and minor congenital malformation screening. *WWE* woman with epilepsy, *AFP* alpha-fetoprotein

the sample size. Epilepsy is not a unique condition, possible drug associations are numerous, as well as potential risk factors. It is primarily for this reason that none of the published studies has in fact an adequate statistical power. These considerations have led researchers from different countries to work together to achieve prospective observational records, considered by many to be the only adequate means to collect an adequate sample within a reasonable time to evaluate the teratogenic risk of individual drugs and associations of them. Nevertheless, obstetric management of epileptic women could be influenced by several different conditions, such as the impact that some supplementations [104–107] or comorbidities [108, 109] may have on the status of the disease, necessity of pharmacological treatment [110, 111] or other obstetric interventions [112, 113] and drugs adsorption starting from the periconceptional period until post-partum. In this regard, each case should be managed considering all these variables, possibly performing a tailored treatment.

## Conclusions

Even considering that this report is a narrative (non-systematic) review of the literature data, it allows us to state that certainly epilepsy is not a contraindication for pregnancy. In fact, over 95 % of women treated with AEDs during pregnancy undergo safe pregnancy and delivery. The problems related to antiepileptic therapy and the possibilities of prenatal diagnosis should be discussed thoroughly with the patient, if possible before pregnancy, considering individual circumstances, desire to have children, severity of epilepsy, family history of congenital malformations and all other potential risk factors. Finally, considering that the quantitative and qualitative analysis of published studies does not define the degree of the risk of malformations in children from mothers with epilepsy, neither identifies a scale of risk of the drugs, we strongly encourage future studies, based on large cohorts and with rigorous methodology, to improve our current knowledge of the topic.

#### Compliance with ethical standards

**Conflict of interest** All Authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The Authors alone are responsible for the content and writing of the paper.

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