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SUPPLEMENT – ITALIAN LEAGUE AGAINST EPILEPSY

Italian Consensus Conference on Epilepsy and Pregnancy, Labor and Puerperium

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Summary

To facilitate an integrated and rational approach to the care of women with epilepsy of childbearing potential, a group of experts appointed by Italian scientific societies in the fields of epileptology, neonatology, pediatrics, neuropediatrics, child neuropsychiatry, obstetrics, and gynecology held a joint meeting in Santa Trada di Cannitello, Reggio Calabria, Italy, on October 15–16, 2004, with the aim of reaching consensus on the optimal management of these women. An ad hoc system for the classification of available published evidence and the opinions of experts was developed and used to grade recommendations on different aspects related to counseling, diagnostic, and treatment issues. The present document summarizes available evidence on the reciprocal interactions between epilepsy, antiepileptic drugs, fertility, contraception, pregnancy, delivery, breastfeeding, and the offspring. Recommendations are made concerning the information and counseling that should be provided to women with epilepsy with respect to issues related to contraception, conception, pregnancy, labour, and puerperium. More detailed recommendations on the same issues are provided to physicians and other healthcare professionals involved in the care of these women, with special reference to choice of effective contraception, optimization of antiepileptic drug therapy, use of prenatal diagnostic tests and other monitoring procedures, and appropriate management practices in relation to childbirth, puerperium, and the care of the child.

KEY WORDS: Epilepsy, Antiepileptic drugs, Fertility, Contraception, Pregnancy, Puerperium, Clinical management, Consensus paper, Italian League against Epilepsy.

The management of women with epilepsy is complex and requires a multidisciplinary approach. However, there is currently no real coordination in Italy among the different professionals involved, and the advice given by the epileptologist will often differ from that given by the gynecologist, neonatologist, or pediatrician. As a result,

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decisions on specific diagnostic or therapeutic procedures risk being determined more by a woman's ''confidence'' in a given specialist than by an appraisal based on scientific evidence and, hence, good medical practice.

To address these concerns, experts appointed by a number of Italian scientific societies held a joint meeting in Santa Trada di Cannitello, Reggio Calabria, on October 15–16, 2004, with the aim of establishing guidelines on diagnostic and therapeutic procedures for women with epilepsy who are of childbearing age. Subsequent revisions resulted in a practical guide to be published in the official journals of the scientific societies and posted on their websites, and circulated in brochures to be distributed to general practitioners throughout Italy. Overall, these guidelines are aimed at standardizing and improving the management of women with epilepsy.

In addition to the Italian League against Epilepsy (LICE), which promoted the National Consensus Conference, the scientific societies involved in the meeting included the Italian Society of Child Neuropsychiatry (SINPIA), the Italian Society of Pediatric Neurology (SINP), the Italian Society of Gynecology and Obstetrics (SIGO), the Italian Association of Hospital Obstetricians and Gynecologists (AOGOI), the Italian Society of Neonatology (SIN), and the Italian Society of Pediatrics (SIP).

Aims and Methods

Given the discrepancies in literature reports, the first guidelines on the care of women with epilepsy published in the 1990s left many questions unanswered (Delgado-Escueta & Janz, 1992; Zahn, 1998). More recently, the management of women with epilepsy who are of childbearing age has been further complicated by the introduction of new-generation antiepileptic drugs (AEDs). Although there are still many knowledge gaps, existing guidelines need to be updated in light of recently acquired lines of evidence. The aim is to establish key parameters and provide the information required to understand and critically interpret evidence from recent studies by means of a qualitative assessment of reproductive risk in women with epilepsy.

The recommendations given in this document are based on scientific evidence resulting from a review of available literature and the opinions of experts who participated in the consensus conference. An ad hoc system was devised for the classification of evidence: Because literature reports are observational and deal with specific topics, none of the published classifications were applicable to studies on the interaction between epilepsy and pregnancy. Some recommendations lacking solid scientific evidence may still receive a high strength of recommendation based on clinical experience and the general principles of epilepsy management. Other recommendations, such as those concerning procedures for prenatal diagnosis, are given a high-strength level even in the absence of solid scientific evidence because they clearly have the potential for improving secondary prevention without posing any risk to the mother or the fetus.

The classification of evidence adopted is shown in Table 1, whereas the levels of evidence (LoEs) are summarized in Table 2 and the strengths of recommendation (SoRs) are listed in Table 3. The criteria for classification are outlined in the Appendix (Supporting Information). An additional list (Supporting Information) includes references alongside their assigned level of evidence in square brackets [A–F].

Fertility

Women with epilepsy seem to have slightly lower fertility rates than women in the general population. However, because women with epilepsy have lower marriage rates, fertility rates among married women with epilepsy are comparable to those reported in the general population (Olafsson et al., 1998; Tettenborn et al., 2002; Artama et al., 2004).

Controversial views on fertility reflect those on endocrine disturbances and polycystic ovary syndrome (PCOS), which some claim to be more frequent in women with epilepsy taking AEDs, particularly those treated with valproic acid (Tettenborn et al., 2002; Rasgon, 2004). Valproic acid is alleged to exert these effects directly or indirectly by inducing obesity and thereby facilitating the development of insulin resistance, increased testosterone

Table 1. Classification of evidence

Class	Classification
A	High-quality prospective studies[a]
	Systematic review (with statistical homogeneity) of class A studies
B	Good-quality prospective and/or historical population-based studies
	Systematic reviews (with statistical homogeneity) of class B studies
C	Moderate-quality prospective and/or historical population-based studies
	High-quality retrospective studies
	Systematic reviews of class C studies
D	Low-quality prospective and/or historical population-based studies
	Well-performed retrospective studies
	Systematic reviews of class D studies
E	Small cohort studies
	Case series or descriptive studies
	Low-quality retrospective studies
F	Consensus conferences, expert committees' advice, opinions of experts, opinions or clinical experiences; other evidence

[a]Enrollment blind to outcome measures; at least 9 months before initiation of pregnancy (studies on epilepsy outcome), mothers included in a previous prospective class A or B study.

Table 2. Levels of evidence

I	More than one class A study and/or class A systematic review
II-1	Class B and class C evidence with consistent results and/or one class A study
II-2	Class B and class C evidence with generally consistent results
III	Class C evidence and extrapolations from class B studies
IV	Class D or class E evidence or classes A, B, and C evidence with inconsistent results
V	Class F evidence

Table 3. Strength of recommendations

1	Strongly recommended treatment or procedure
2	Recommended treatment or procedure
3	No evidence either against or in favor of a treatment or procedure
4	Treatment or procedure advised against because probably useless and/or harmful
5	Treatment or procedure strongly advised against

levels, and other reproductive disorders (Tettenborn et al., 2002; Rasgon, 2004). The controversy emerged in the 1990s after publication of some Finnish studies (Isojarvi et al., 1993). However, these studies have substantial limitations because of their retrospective nature, lack of randomization, lack of rigorous diagnostic criteria and morphologic assessments, and enrollment of a population selected for menstrual and endocrine disturbances (Rasgon, 2004). Indeed, recent studies failed to find specific morphologic ovarian changes in women with epilepsy, and suggested the possible lack of a causal association between PCOS and use of valproic acid or other AEDs (Tettenborn et al., 2002; Rasgon, 2004).

Contraception

Benzodiazepines, gabapentin, levetiracetam, pregabalin, tiagabine, valproic acid, vigabatrin, and zonisamide do not alter the plasma levels of contraceptive steroids and hence do not impair the efficacy of hormonal contraception (Perucca, 2006).

By contrast, carbamazepine, felbamate, phenobarbital, phenytoin, oxcarbazepine, and primidone stimulate the metabolism of estrogens and progestins by enzyme induction, thereby reducing their plasma levels and hence their contraceptive activity (Perucca, 2006; Thorneycroft et al., 2006). Topiramate reduces the levels of ethinylestradiol but not those of norethindrone at doses above 200 mg/day (but not at doses below 200 mg/day, whereas at 200 mg/day the interaction appears to be minimal) (Perucca, 2006). Lamotrigine, at a daily dose of 300 mg, causes a moderate reduction in the levels of levonorgestrel but not those of ethinylestradiol (Perucca, 2006); whether lamotrigine doses below 300 mg/day affect the plasma levels of contraceptive steroids remains to be established.

The use of the combined contraceptive pill in women treated with enzyme-inducing AEDs, and vice versa, the use of enzyme-inducing AEDs in women taking combined contraceptive pill, is possible provided appropriate precautions are taken to ensure a minimal predefined exposure to both progestins and estrogens (see Recommendations) (Thorneycroft et al., 2006). However, the use of contraceptive formulations containing high doses of ethinylestradiol (>50 μg) is undesirable in the general population because of the associated vascular risk (Petitti, 2003), and because no data are available on the risks associated with the use of these formulations in women taking enzyme-inducing AEDs. Given the variability in the magnitude of interaction (also in relation to the dose and type of AED used), the use of high-dose combined contraceptive steroids preparations may result in relatively high hormone levels in some women treated with enzyme-inducing AEDs, whereas in others the same preparations may not provide sufficient contraceptive cover.

Women taking enzyme-inducing AEDs should avoid biphasic and triphasic oral contraceptives because the low progestagen content in the first phase of the pill-taking cycle may adversely affect their contraceptive efficacy (Thorneycroft et al., 2006). For the same reason, use of progestagen-only oral contraceptives is undesirable in these women (Thorneycroft et al., 2006).

Among nonoral hormonal contraceptives, subdermal hormonal implants and transdermal patches are not recommended in women taking enzyme-inducing AEDs because the efficacy of these preparations may be reduced. On the other hand, no interaction has been reported with the use of levonorgestrel-releasing intrauterine devices (Mirena, Schering S.p.A., Milan, Italy) and copper-releasing intrauterine devices, but the use of hormone-releasing intrauterine devices has not been extensively assessed in women taking enzyme-inducing AEDs (O'Brien & Guillebaud, 2006; Thorneycroft et al., 2006). Although some authors claim that the efficacy of injectable depot medroxyprogesterone acetate formulations is not reduced by coadministration of enzyme-inducing AEDs, long-term use of these formulations is undesirable because it may result in many adverse effects, in particular reduced bone density caused by a decrease in estrogen levels (Wooltorton, 2005). This effect is of special concern, since enzyme-inducing AEDs have also been associated with a reduction in bone mineral density (Battino, 2000). In addition, transdermal progestagens are not indicated because of their relatively low progestagen content, which may be susceptible to the effect of drug–drug interactions (Thorneycroft et al., 2006).

If necessary, women with epilepsy may use emergency hormonal contraceptives. Some authors suggest that higher doses of these contraceptives should be used in women taking enzyme-inducing AEDs (Scottish

Intercollegiate Guidelines Network, 2003; O'Brien and Gilmour-White, 2005).

Contraceptives may also affect plasma concentrations of AEDs. Intake of ethinylestradiol in women on lamotrigine monotherapy reduces the plasma concentrations of lamotrigine by 40–60% (Perucca, 2006), possibly worsening seizure control. Conversely, withdrawal of combined hormonal contraceptives in women treated with lamotrigine may have the opposite effect, with the risk of precipitating manifestations of lamotrigine toxicity. This interaction follows a cyclic pattern: Plasma lamotrigine concentrations decrease during the 21 days of pill intake and increase during the contraceptive-free week (Perucca, 2006). Lamotrigine levels do not seem to be reduced by estrogen-containing contraceptives when lamotrigine is used in combination with valproic acid (Tomson et al., 2006), whereas it remains to be determined whether this interaction is influenced by coadministration of enzyme-inducing AEDs. Combined hormonal contraceptives may also reduce the plasma levels of valproic acid, but the changes in plasma valproic acid concentration during the 21-day pill-taking period compared with the pill-free interval are less marked than those reported for lamotrigine (Galimberti et al., 2006; Perucca, 2006). The 10-monohydroxy derivative (MHD) of oxcarbazepine, the active metabolite primarily responsible for the pharmacologic activity of oxcarbazepine, shares with lamotrigine and valproic acid a metabolic pathway involving conjugation with glucuronic acid. In view of the evidence that the pharmacokinetics of MHD are altered during pregnancy (see subsequent text), it cannot be ruled out that plasma MHD levels may also be reduced by estrogen-containing preparations, even though no data on this potential interaction are currently available.

Pregnancy

Clinical course of epilepsy

Good seizure control is paramount during pregnancy, especially in the light of the observation that maternal mortality rates are higher in women with epilepsy compared to the general population (Adab et al., 2004). In addition, convulsive seizures in the mother may cause fetal bradycardia (Teramo et al., 1979), and status epilepticus has been associated with intrauterine fetal death (Teramo & Hiilesmaa, 1982; The EURAP Study Group, 2006).

Studies on the natural history of epilepsy during pregnancy have reported discordant and, often, poorly comparable findings. Methods are not uniform across studies, and many reports do not provide information on enrollment criteria or definitions of changes in seizure frequency, the duration of the observation period before pregnancy, the role of pharmacotherapy, or other confounders potentially influencing the clinical course of epilepsy during pregnancy.

A review of 27 studies published between 1884 and 1980 (Schmidt, 1982b) totaling 2,165 pregnancies, showed that on average seizure frequency increased during pregnancy in 24.1% (4–67%) of women with epilepsy, decreased in 22.7% (0–82%), and remained unchanged in 53.2% (4–96%). The mean rate of improvement in another 18 studies was slightly lower (13.5%), whereas the incidence of worsening was similar (24.5%) (Dravet et al., 1982; Remillard, 1982; Schmidt et al., 1983; Otani, 1985; Bardy, 1987; Gjerde et al., 1988; Specchio, 1989; Wilhelm et al., 1990; Lander & Eadie, 1991; Tanganelli & Regesta, 1992; Kilpatrick & Hopper, 1993; Tomson, 1994; Vidovic & Della Marina, 1994; Sabers et al., 1998; Kaneko et al., 1999; Thomas et al., 2001). Four studies reported that an increase in seizure frequency was more common during the first and third trimesters of pregnancy and was reversible after delivery (Remillard, 1982; Schmidt et al., 1983; Bardy, 1987; Sabers et al., 1998). On the other hand, Tomson et al. (1994) found that seizure frequency tended to diminish in the first trimester of pregnancy, with no further changes in the second and third trimesters. Some studies reported an intraindividual variability in seizure frequency, even among different pregnancies in the same patients (Sabers et al., 1998). Lastly, a recent prospective study analyzing approximately 2,000 pregnancies (The EURAP Study Group, 2006) showed that about 60% of women with epilepsy did not have seizures during pregnancy and that partial epilepsy, and polytherapy and monotherapy with oxcarbazepine were independently associated with an increased risk of seizure worsening during pregnancy (The EURAP Study Group, 2006). Thus far, only one retrospective study has investigated whether changes in seizure frequency during pregnancy could be due to random fluctuation (Kilpatrick & Hopper, 1993). This study reported a worsening in seizure frequency in 41% of pregnant women compared to 24% in controls (nonpregnant women). However, dose reductions and withdrawal of treatment were more common among pregnant women. Moreover, the risk of seizure worsening in this study was found to increase slightly but significantly with disease duration.

Eight studies have examined the relation between increased seizure frequency, type of seizures and/or epileptic syndrome, frequency of seizures before pregnancy, and disease duration (Remillard, 1982; Bardy, 1987; Specchio, 1989; Tanganelli & Regesta, 1992; Kilpatrick & Hopper, 1993; Tomson et al., 1994; Sabers et al., 1998; Kaneko et al., 1999). The correlation between worsening of seizure control and seizure type, when reported (Remillard, 1982; Tanganelli & Regesta, 1992; Tomson et al., 1994; Kaneko et al., 1999), was mainly confined to women with focal seizures. Some studies have also reported that a good seizure control before pregnancy, especially when long-lasting, exerted a protective effect toward subsequent worsening during pregnancy

(Remillard, 1982; Specchio, 1989). On the other hand, the occurrence of frequent seizures before pregnancy was associated with worsening of seizure control in up to 50% of all patients (Tanganelli & Regesta, 1992; Sabers et al., 1998). Other potential risk factors, including metabolic and hormonal profiles, psychological distress, sleep disorders and, above all, irregular intake of AEDs, need to be explored in a more systematic manner.

Five studies reported the occurrence of seizures during labor or in the immediate postpartum period (24 h) in 66 of 2,628 cases (2.5%) (Otani, 1985; Bardy, 1987; Wilhelm et al., 1990; Tanganelli & Regesta, 1992; Richmond et al., 2004). The risk seems to be higher when seizure control during pregnancy is incomplete (The EURAP Study Group, 2006).

Data from 12 studies estimated at 1.1% the frequency of status epilepticus during pregnancy (43 of 2,915 cases) (Canger, 1982; Remillard, 1982; Schmidt et al., 1983; Otani, 1985; Bardy, 1987; Gjerde et al., 1988; Wilhelm et al., 1990; Tanganelli & Regesta, 1992; Tomson et al., 1994; Sabers et al., 1998; The EURAP Study Group, 2006), which is in line with other literature reviews (Schmidt, 1982a, 1982b). The EURAP Study Group (2006) reported only one case of intrauterine death related to status epilepticus and no cases of maternal mortality among 36 cases of status epilepticus (12 convulsive cases) during pregnancy.

Modifications of AED pharmacokinetics

Pregnancy gives rise to major physiologic changes that may significantly influence the absorption, distribution, metabolism, and renal elimination of drugs, thereby affecting their plasma concentrations, sometimes to a clinically significant degree (Perucca, 1987). In most cases, plasma AED concentrations decrease during pregnancy and promptly return to prepregnancy levels following delivery. Free plasma concentrations of drugs highly bound to plasma proteins (phenytoin, valproic acid and, to a lesser extent, carbamazepine) generally decrease to a lesser extent than total concentrations (Yerby et al., 1990, 1992a).

In general, the plasma concentration of AEDs begins to decline from the first trimester. In the third trimester, the mean decline is 55–61% for total phenytoin, 18–31% for free phenytoin, 0–42% for total carbamazepine, 0–28% for free carbamazepine; 50–55% for phenobarbital, 55% for primidone, 70% for primidone-derived phenobarbital, 50% for total valproic acid, and 0–29% for free valproic acid (free valproic acid concentrations, may actually be increased by 25% at delivery compared with prepregnancy values) (Tomson & Battino, 2007). It should be noted, however, that interindividual variability may be high (Tomson & Battino, 2007).

Among the newer AEDs, lamotrigine has been the most extensively studied. Its pharmacokinetics change dramatically, and the mean plasma concentrations of lamotrigine decline by 68% during pregnancy, albeit with a significant interindividual variability. An increase in seizure frequency has also been reported (Tomson & Battino, 2007). The reduction in plasma lamotrigine levels during pregnancy is appreciably attenuated by coadministration of valproic acid (Tomson et al., 2006). There is more limited evidence that pregnancy is also associated with a major reduction in the plasma levels of the MHD of oxcarbazepine (Tomson & Battino, 2007) and, possibly, levetiracetam (Tomson & Battino, 2007). No information is available on potential alterations in the pharmacokinetics of other new-generation AEDs (gabapentin, vigabatrin, pregabalin, tiagabine, topiramate, and zonisamide) (Tomson & Battino, 2007).

In clinical practice, pharmacokinetic changes can be assessed only by measuring plasma drug concentrations before, during, and after pregnancy (Committee on Educational Bulletins of the American College of Obstetricians and Gynecologists, 1997; Quality Standards Subcommittee of the American Academy of Neurology, 1998; Krishnamurthy, 2002). In general, AED dosage should not be modified unless there are changes in clinical response (seizure relapse, increased seizure frequency, adverse effects). However, laboratory parameters may prompt dose adjustment in some cases. For example, the optimal plasma concentration of each AED can often be established for each patient before conception (''optimum individualized therapeutic value''). In this regard, a reduction of plasma AED concentrations during pregnancy to levels previously associated with the occurrence or worsening of seizures in the same patient may warrant an increase in dosage, especially after the first trimester of pregnancy. Any dose modification should be made on an individual basis and potential risks should be weighed against achievable benefits. In interpreting analytical data for AEDs highly bound to plasma proteins (namely, phenytoin and valproic acid) and comparing them with the ''optimum individualized therapeutic values,'' the association of pregnancy with an elevation in the free fraction should be taken into account (Yerby et al., 1992a, 1992b; Pennell et al., 2004). In other words, the reduction in the free (pharmacologically active) plasma concentration may be of a much smaller magnitude than the reduction in total concentration. In the absence of direct measurements of free drug concentrations, changes in the free fraction of phenytoin and valproic acid may be estimated from plasma albumin levels (Perucca & Crema, 1982).

The frequency of plasma AED monitoring during pregnancy will depend on the specific clinical conditions and the type of AED used. Monthly monitoring is recommended for AEDs with major and poorly predictable pharmacokinetic changes, such as lamotrigine, phenobarbital derived from primidone and, probably, levetiracetam and the MHD of oxcarbazepine. If dosage has been increased

during pregnancy, more frequent monitoring may be useful in the 3 weeks following delivery (even as frequently as every 4–5 days for drugs with a relatively short half-life such as lamotrigine, levetiracetam, and the MHD of oxcarbazepine).

Clinical course of pregnancy and delivery

In the past, women with epilepsy were considered at greater risk for obstetric complications. Recent studies, however, suggest that with appropriate medical management the incidence of complications in women with epilepsy is similar to that of the general population (Olafsson et al., 1998; Fairgrieve et al., 2000; Scottish Intercollegiate Guidelines Network, 2003; Richmond et al., 2004; Crawford, 2005).

Vaginal delivery is recommended in all women. Seizures and status epilepticus during labor are rare and are generally associated with the occurrence of seizures during pregnancy (see preceding text). These events may cause fetal hypoxia and could hamper maternal collaboration. Maternal collaboration may be also reduced to a lesser extent by prolonged and frequent complex partial seizures. Under these circumstances, urgent cesarean delivery may be indicated, but its appropriateness should be evaluated on an individual basis (Barrett & Richens, 2003).

There are no specific indications for elective cesarean delivery, the only exception being women with epilepsy who have frequent seizures and are, therefore, at high risk for seizures during labor (Scottish Intercollegiate Guidelines Network, 2003; National Institute for Clinical Excellence, 2004; Richmond et al., 2004).

Epidural anesthesia is not contraindicated in women with epilepsy, either during labor or cesarean delivery, and may even lower the risk of seizures by reducing stress and pain. Finally, there are no documented contraindications to the use of locally administered prostaglandins for the induction of labor or voluntary pregnancy termination.

Risk of congenital malformations

The incidence of congenital malformations in the offspring of women with epilepsy is 3–10%, which corresponds to a 2- to 3-fold increase over the rate observed in the general population (2–4%).

Maternal seizures do not seem to increase the risk of congenital malformations (Speidel & Meadow, 1972; Fedrick, 1973; Starreveld-Zimmerman et al., 1973; Shapiro et al., 1976; Nakane et al., 1980; Annegers & Hauser, 1982; Beck-Mannagetta et al., 1982; Dravet et al., 1982; Koch et al., 1992; Yerby et al., 1992a, 1992b; Steegers-Theunissen et al., 1994; Kaneko et al., 1999; Fonager et al., 2000; Holmes et al., 2001; Kaaja et al., 2003; Sabers et al., 2004), although some discrepancies in the literature exist on this issue (Nakane et al., 1980; Majewski et al., 1981; Kaneko et al., 1988; Lindhout et al., 1992; Olafsson et al., 1998). The hypothesis that epilepsy per se increases the risk of congenital malformations was originally advanced in a large American and Finnish study (Shapiro et al., 1976). Although some subsequent reports found an increased risk in the absence of antiepileptic therapy or in the children of fathers with epilepsy (Meyer, 1973; Majewski et al., 1981; Beck-Mannagetta et al., 1982; Koch et al., 1982; Friis & Hauge, 1985; Rating, 1987; Koch et al., 1992), a recent meta-analysis concluded that there is no increased risk (Fried et al., 2004). The findings of this meta-analysis, however, should be interpreted with caution given the criteria used to select the studies, the small number of these studies, and their small sample size. A recent large prospective study failed to find any significant difference in the occurrence of congenital malformations between children of untreated women and children exposed to monotherapy during pregnancy (Morrow et al., 2006).

The association between exposure to AEDs and an increased risk of congenital malformations is, in any case, well documented. A genetic susceptibility to the teratogenic effects of AEDs is suggested by several family-based studies, case–control studies in patients with oral clefts (Dronamraju, 1970; Erickson & Oakley, 1974; Greenberg et al., 1977; Friis, 1979; Kelly et al., 1984a; Abrishamchian et al., 1994) or neural tube defects (NTDs) (Robert & Guibaud, 1982; Lindhout & Meinardi, 1984) and by cohort studies (Meadow, 1970; Elshove & van Eck, 1971; Starreveld-Zimmerman et al., 1973; Annegers et al., 1974; Knight & Rhind, 1975; Weber et al., 1977; Nakane et al., 1980; Annegers & Hauser, 1982; Nakane, 1982; Dansky, 1989; Oguni et al., 1992; Ornoy & Cohen, 1996; Canger et al., 1999; Kaneko et al., 1999; Dean et al., 2002).

The most common malformations found in newborns exposed to AEDs in utero are the same as those most commonly reported in the general population (congenital heart disease, orofacial clefts, hypospadias, and limb-reduction defects). There is evidence that the risk of NTDs is increased in offspring exposed to valproic acid (1–2%) (Robert & Guibaud, 1982; Bertollini et al., 1985; Lindhout & Schmidt, 1986; Kallen et al., 1989; Omtzigt et al., 1992; Canger et al., 1999; Samrén et al., 1999; Arpino et al., 2000; Hernandez-Diaz et al., 2001) and, to a lesser extent, carbamazepine (0.5–1%) (Rosa, 1991; Arpino et al., 2000; Hernandez-Diaz et al., 2001). An increased risk of congenital heart disease has been reported in offspring exposed to barbiturates (Annegers et al., 1978; Dravet et al., 1982; Nakane, 1982; Canger et al., 1999; Arpino et al., 2000). The association between congenital heart disease and exposure to barbiturates was confirmed by data from the North American Registry (Holmes et al., 2004), although the authors failed to comment on it: in that registry, 4 of 77 newborns exposed to phenobarbital monotherapy had congenital heart disease (5.2%). Finally, some

studies have suggested that exposure to valproic acid may carry a higher risk of hypogenesis or agenesis of limbs (Arpino et al., 2000; Rodriguez-Pinilla et al., 2000) and hypospadias (Samrén et al., 1999; Arpino et al., 2000), and that the risk of orofacial clefts may be higher after exposure to barbiturates (Nakane et al., 1980; Kallen et al., 1989; Arpino et al., 2000) and lamotrigine (Holmes et al., 2006). The latter findings are based on less solid evidence, but deserve to be mentioned given their implications for prenatal diagnosis.

After excluding from the comparison offspring exposed to valproic acid, exposure to each of the following AEDs has been reported in different studies to be associated with a higher frequency of fetal malformations compared with other drugs: carbamazepine (Lindhout, 1982; Samren et al., 1997; Samrén et al., 1999; Diav-Citrin et al., 2001; Kaaja et al., 2003), primidone (Nakane et al., 1980; Kaneko et al., 1999), phenobarbital (Nakane et al., 1980; Waters et al., 1994; Olafsson et al., 1998; Holmes et al., 2004), and phenytoin (Fedrick, 1973; Dravet et al., 1982; Lindhout, 1982; Tanganelli & Regesta, 1992; Olafsson et al., 1998; Sabers et al., 1998). In addition to valproic acid (see subsequent text), phenobarbital is among the AEDs most frequently associated with congenital abnormalities; in particular, valproic acid and phenobarbital are the only AEDs which the North American Registry found associated with a significantly increased risk compared with the general population (6.5% risk, compared to an estimated 1.6% risk in the general population). It should be noted, however, that in that study, the number of exposures to phenobarbital was quite small (N = 77).

In recent years, debate has grown on the potentially greater teratogenic effect of valproic acid. Many studies have reported a higher incidence of congenital malformations in offspring exposed to valproic acid compared to offspring exposed to carbamazepine (Wide et al., 2004; Morrow et al., 2006), lamotrigine (Morrow et al., 2006), or other monotherapies (Wyszynski et al., 2005). These results should be viewed with caution, since there have also been studies that did not identify an increased risk of congenital malformations in offspring exposed to valproic acid given as monotherapy (Bertollini et al., 1987; Omtzigt et al., 1992; Dean et al., 2002) or combination therapy (Nakane et al., 1980; Lindhout et al., 1984; Kaneko et al., 1992; Olafsson et al., 1998; Sabers et al., 1998) compared to other commonly used AEDs. Such discrepancies may result from the presence of potential confounders. For example, a positive family history of congenital malformations is an important risk factor: in particular, the risk of recurrence of neural tube defects in women not exposed to AEDs ranges between 3% and 8% (Mitchell et al., 2004) and is, therefore, considerably higher than that found not only in the general population but also in cohorts exposed to valproic acid. Surprisingly, only four of the studies cited previously took into consideration a family history of congenital malformations (Kaneko et al., 1999; Kaaja et al., 2003; Vajda et al., 2003; Morrow et al., 2006) and only one of them (the U.K. Registry) identified a statistically significant increase in risk after exposure to valproic acid compared to other monotherapies, with a 6.2% incidence of congenital malformations with valproic acid (N = 715) compared to 2.2% with carbamazepine (N = 927) (Morrow et al., 2006). Although the same study found a trend toward a lower incidence of congenital malformations with lamotrigine (2.2%, N = 617) compared to valproic acid, the rate of congenital malformations in offspring exposed to lamotrigine at doses equal to or higher than 200 mg/day (5.4%) was similar to that observed in offspring exposed to 600–1,000 mg/day valproic acid (6.1%). Valproic acid is, however, the only AED for which a correlation between dose and risk of congenital malformations has been demonstrated in the majority of high-quality studies (Jager-Roman et al., 1986; Samren et al., 1997; Kaneko et al., 1999; Samrén et al., 1999; Mawer et al., 2002; Duncan, 2003; Vajda et al., 2003; Artama et al., 2005), although not in all such studies (Kaaja et al., 2003; Sabers et al., 2004; Wyszynski et al., 2005). Recently, a single study reported that a relationship between dose and teratogenic risk may also exist for lamotrigine: in fact, in the U.K. Registry the dose of lamotrigine in pregnancies associated with fetal malformations was significantly higher than that recorded in pregnancies without malformations (Morrow et al., 2006). In addition, a report from the North American Registry suggested that prenatal exposure to lamotrigine may be associated with an increased risk of orofacial clefts (Anonymous, 2006; Holmes et al., 2006).

Most studies have reported an increased risk of congenital malformations in the offspring of mothers treated with polytherapy compared to monotherapy, with a particularly high increase in risk in offspring exposed to more than two drugs (Kaneko et al., 1988, 1999; Lander & Eadie, 1990; Shakir & Abdulwahab, 1991; Olafsson et al., 1998; Holmes et al., 2001; Kaaja et al., 2003; Wide et al., 2004). Not all studies, however, have confirmed this finding (Kallen, 1986; Eskazan & Aslan, 1992; Jick & Terris, 1997; Canger et al., 1999; Diav-Citrin et al., 2001; Richmond et al., 2004).

In conclusion, available information indicates that the risk of congenital malformations is increased among offspring of women with epilepsy, and that this increase may be attributed largely to the effects of AEDs. However, the incidence of congenital malformations varies 20-fold across published studies (Barrett & Richens, 2003), mainly because of methodologic differences. In fact, there are major differences in the populations studied, the diagnostic criteria used to identify abnormalities, exclusion criteria, and the denominators used to calculate the risk of malformations. The variability in malformation rates is also related to substantial methodologic deficiencies

(Battino, 2001; Dolk & McElhatton, 2002; Barrett & Richens, 2003; Tomson et al., 2004), especially failure to control for potential risk factors. Although current evidence is inconclusive, several findings suggest that exposure to valproic acid, and possibly barbiturates, is associated with a higher risk of congenital malformations than exposure to carbamazepine and other commonly used AEDs. Valproic acid is also the drug for which a relationship between malformation risk and administered dose has been repeatedly demonstrated.

Adverse effects on fetal growth and postnatal development

Data on the risk of delayed fetal growth after prenatal exposure to AEDs are not univocal at least in part for methodologic reasons. In particular, measures are expressed at times as absolute values, at times as ratios between absolute values and gestational age, and in other instances as frequencies that refer to national or international standards (Battino et al., 1999). Some studies have found an increased risk for all parameters (Hvas et al., 2000), others an increased risk for head circumference only (Steegers-Theunissen et al., 1994; Wide et al., 2000a, 2000b), and others no differences compared to the general population (Kallen, 1986; Gaily & Granstrom, 1989; Olafsson et al., 1998; Sabers et al., 1998; Fonager et al., 2000; Thomas et al., 2001; Vajda et al., 2003). The risk of delayed fetal growth has been associated, in different studies, with the use of phenytoin (Hanson et al., 1976), phenobarbital, primidone (Hiilesmaa et al., 1981; Battino et al., 1999; Holmes et al., 2004), and carbamazepine (Hiilesmaa et al., 1981; Wide et al., 2000b). Reports on a correlation between drug dose and fetal growth are scant and limited primarily to phenobarbital (Battino et al., 1999). The risk for delayed fetal growth seems to be higher in patients on polytherapy (Wide et al., 2000a, 2000b).

Discordant data also exist on the psychomotor development of children exposed to AEDs in utero (Barrett & Richens, 2003; Adab, 2004). Earlier studies reported a lower intelligence in children of women with epilepsy, whereas most recent studies failed to find any cognitive deficits or any specific cognitive dysfunctions in children with normal intelligence. Few longitudinal studies have been undertaken to date, and among these most of the so-called prospective findings were confined to maternal parameters, since children were examined for the first time many years after birth. The risk of systematic confounding errors is very high because the etiology of developmental delay involves a large number of risk factors, the importance of which has been widely documented in the general population. No study has addressed most of these factors and the majority have ignored epilepsy-related factors, and in particular how seizures and the effects of AEDs may have affected a mother's ability to care for her children. Another critical issue is the confusion between normal and pathologic outcomes. Indeed, normal IQs are sometimes considered as signals of an increased risk of mental retardation solely because they are slightly, but statistically significantly, reduced compared with internal and external controls. These issues might explain why some studies have found an increased risk of delayed psychomotor development in children of women with epilepsy (Speidel & Meadow, 1972; Hanson et al., 1976; Majewski et al., 1981; Hill, 1982; Hattig, 1987; Van der Pol et al., 1991; Scolnik et al., 1994; Leonard et al., 2006), whereas others have reported normal intelligence (Kelly et al., 1984a, 1984b; Losche et al., 1994; Steinhausen et al., 1994; Gaily et al., 1998; Wide et al., 2000a, 2000b) or a transient delay compared to normal controls (Shapiro et al., 1976; Jager-Roman, 1982; Gramstrom, 1982; Koch, 1983; Nomura, 1984; Fujioka, 1984) or children of fathers with epilepsy (Beck-Mannagetta & Janz, 1982), and others again reported specific cognitive disturbances in children of normal intelligence (Nelson & Ellenberg, 1982; Gaily et al., 1990; D'Souza et al., 1991; Van der Pol et al., 1991; Leavitt et al., 1992; Vanoverloop et al., 1992; Dessens et al., 1994; Losche et al., 1994; Rovet et al., 1995; Ornoy & Cohen, 1996; Gaily et al., 1998; Adab et al., 2001; Wide et al., 2002; Adab et al., 2004; Gaily et al., 2004; Vinten et al., 2005).

Although some authors claim that cognitive dysfunctions correlate with the type of epilepsy (Gaily et al., 1990, 1998; Hirano et al., 2004) and maternal seizures (Nelson & Ellenberg, 1982; Gaily et al., 1990, 2004; Leonard et al., 1997; Adab et al., 2004; Hirano et al., 2004), the major prognostic factors are likely to be maternal IQ (Rovet et al., 1995; Adab et al., 2004; Gaily et al., 2004; Eriksson et al., 2005) and maternal educational level (Gaily et al., 1990, 1998; Wide et al., 2002; Hirano et al., 2004). In separate studies, prenatal exposure to valproic acid (Hattig, 1987; Koch et al., 1999; Ohtsuka et al., 1999; Adab et al., 2004; Gaily et al., 2004; Eriksson et al., 2005), phenytoin (Hanson et al., 1976; Leavitt et al., 1992; Vanoverloop et al., 1992; Scolnik et al., 1994), phenobarbital (Van der Pol et al., 1991), carbamazepine (Jones et al., 1989; Ornoy & Cohen, 1996), and primidone (Koch et al., 1999) has been associated with a possible higher frequency of cognitive deficits, but many discrepancies exist (Shapiro et al., 1976; Hill, 1982; Leavitt et al., 1992; Scolnik et al., 1994; Gaily et al., 1998, 2004). Similarly, a correlation between the number of AEDs taken during pregnancy and cognitive disturbances in the children has been suggested by some authors (Leavitt et al., 1992; Losche et al., 1994; Ornoy & Cohen, 1996; Leonard et al., 1997; Koch et al., 1999; Wide et al., 2002; Gaily et al., 2004; Hirano et al., 2004) but not by others (Shapiro et al., 1976; Van der Pol et al., 1991; Gaily et al., 1998; Wide et al., 2002). The role of confounding factors was clearly demonstrated in two recent studies showing that the correlation between negative outcomes and maternal use of AEDs was no longer statistically

significant after adjustment for maternal education level (Gaily et al., 1998; Eriksson et al., 2005). In addition, a large prospective, population-based study from the United States reported a significantly higher risk of mental retardation in children of black women with epilepsy compared with children of white women with epilepsy (Camp et al., 1998).

Very few studies have addressed socioeconomic status (Reinisch et al., 1995; Koch et al., 1999; Wide et al., 2002), paternal education level (Gaily et al., 1990), and perinatal risk factors (Hill, 1982; D'Souza et al., 1991; Van der Pol et al., 1991; Losche et al., 1994; Ornoy & Cohen, 1996; Wide et al., 2002). An Australian study published in 2006 showed a higher incidence of mental retardation in children of women with epilepsy, which remained significant after correcting for several sociodemographic factors. The study design, however, did not allow for differentiation of the effects of epilepsy from the effects of therapy or any concomitant diseases (Leonard et al., 2006).

Among the AEDs potentially implicated as a cause of cognitive deficits after prenatal exposure, valproic acid has been the focus of the most recent studies. Although several studies have reported specific cognitive deficits in children whose mothers used valproic acid during pregnancy (Hattig, 1987; Koch et al., 1999; Ohtsuka et al., 1999; Adab, 2004; Gaily et al., 2004; Eriksson et al., 2005), these findings are subject to an important extent to confounding factors (Adab, 2004). For example, in some of the studies it is possible that the association between prenatal exposure to valproic acid and cognitive deficits could be at least in part due to a lower educational level of valproic acid–treated mothers (Gaily et al., 2004; Eriksson et al., 2005).

Prenatal diagnosis

Several factors influence the accuracy of prenatal diagnosis including the type of fetal abnormality, gestational age at the time of testing, the quality of instrumentation, operator skills, and time spent on examination (Royal College of Obstetricians and Gynecologists, 2008). Standard morphologic evaluation is scheduled at the 19th to 21st week of gestation, and fetal anatomy must be evaluated according to the SIEOG guidelines (Società Italiana di Ecografia Ostetrico-Ginecologica, 2006).

Transvaginal ultrasound evaluation of neural tube defects (13th week of gestation) allows identification of all cases of anencephaly and myelomeningocele, but the diagnostic accuracy in detecting spina bifida is lower (Blumenfeld et al., 1993). For spina bifida, the association of microcephaly and scalloping of the frontal bones (lemon sign) and obliteration of the cisterna magna and curvature of the cerebellar hemispheres (banana sign) has a 98% diagnostic sensitivity within 24 weeks of gestation (Van den Hof et al., 1990).

Cardiac defects are identified by screening ultrasonography in 40–50% of cases and by fetal echocardiography in 80–90% (Comstock, 2000; Robinson et al., 2003). Fetal echocardiography should be performed after 20 weeks of gestation, and its diagnostic sensitivity depends on the type of anomaly (Società Italiana di Ecografia Ostetrico-Ginecologica, 2006). Interventricular defects are difficult to visualize, and interatrial defects even more so, whereas prenatal diagnosis of patent ductus arteriosus is not possible given the physiologic situation of the fetal circulation. Other congenital defects, such as semilunar valve stenosis and aortic coarctation, may not manifest until the third trimester. The risk of cardiac defects increases exponentially in relation to the thickness of nuchal translucency, which can be assessed by ultrasound at 10–13 weeks of gestation. The risk is particularly high when nuchal translucency is above the 99th percentile in fetuses without chromosomal abnormalities. A thorough cardiac examination is recommended even before the 20th week of gestation in cases at risk (Hyett et al., 1999).

In the majority of cases, orofacial clefts can be detected by bidimensional ultrasound imaging at around the 20th week of gestation. Expert operators are able to distinguish monolateral from bilateral defects, and isolated cleft lip from cleft lip associated with cleft palate. Although the degree of extension to the posterior palate is generally difficult to assess, accurate evaluation is crucial for prognosis in terms of surgical implications and risk of complications affecting swallowing, suction, speech, and hearing. With a targeted ultrasound examination, the diagnostic sensitivity increases from 27% (Stoll & Clementi, 2003) to 73%, with a further increase in sensitivity to 83% for evaluations performed after the 20th week of gestation (Robinson et al., 2001). Cleft lip and cleft palate are diagnosed in 91% and 46% of cases, respectively, by using the bidimensional technique, and in 100% and 90% of cases, respectively, when the examination is complemented with the tridimensional technique (Chmait et al., 2002).

Folic acid and vitamin K prophylaxis

In the general population, the use of folic acid for at least 3 months before conception has been shown to decrease the risk of occurrence and recurrence of NTDs by 50–70%, and the risk of other congenital malformations by 10–20% (Taruscio et al., 2005). There is no specific evidence that folic acid will reduce the occurrence of neural tube defects or other malformations in the offspring of women with epilepsy (Hernandez-Diaz et al., 2001).

Since 1958, more than 40 cases of early hemorrhagic disease have been reported in newborns of mothers taking enzyme-inducing AEDs (Kaaja et al., 2002). Recent studies have questioned the need for oral vitamin K administration in women at the end of pregnancy (Kaaja et al., 2002; Choulika et al., 2004), also in view of the fact that vitamin K is routinely administered to the newborn.

Puerperium

Although breastfeeding is often discouraged in women with epilepsy who are taking AEDs, this recommendation is usually unjustified because the amount of drug ingested with the maternal milk is extremely small and in any case lower than that transferred to the fetus through the placenta.

The milk-to-maternal plasma concentration ratio of phenytoin, valproic acid, and carbamazepine is less than 0.6, although pharmacologically relevant plasma concentrations of carbamazepine have occasionally been reported in breastfed infants (Tomson, 2005). Because ethosuximide, phenobarbital, and primidone are cleared very slowly in the newborn, they tend to accumulate, albeit at a modest rate (Tomson, 2005): if signs of sedation occur, it is desirable to measure the plasma concentrations of these AEDs in the infant and, if necessary, recommend mixed feeding (Crawford, 2005). The same considerations apply to lamotrigine, which may reach plasma concentrations potentially sufficient to induce pharmacologic effects in breastfed infants. The few data available on the accumulation of levetiracetam, topiramate, and gabapentin in breastfed infants suggest that the plasma levels of these drugs in the infant are generally very low.

Recommendations

Fertile age, contraception, and conception

Women should be informed that:

(1) Carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone and, at doses higher than 200 mg daily, topiramate reduce the plasma concentrations of estrogens and/or progestins, and may, therefore, reduce the efficacy of contraceptive preparations [LoE II; SoR 2]. Full efficacy of the contraceptive pill cannot be guaranteed, even at doses higher than those normally prescribed [LoE V; SoR 1].

(2) Use of preparations containing estrogens, or a combination of estrogens and progestins, in women treated with lamotrigine, particularly in monotherapy, may lower plasma lamotrigine levels by 50% or more and may, therefore, impair seizure control. Withdrawal of the contraceptive in these patients may result in increased lamotrigine levels and potential symptoms or signs of toxicity [LoE II-1; SoR 1]. The interaction of lamotrigine with estrogen-containing contraceptives does not seem to occur (or at least occurs to a lesser extent) when lamotrigine is used in combination with valproic acid [LoE II-1; SoR 1]. Use of combined contraceptive steroids may also lower the plasma levels of valproic acid, although the decrease in plasma valproic acid levels seems to be generally of a lesser magnitude than that reported for lamotrigine [LoE II-2; SoR 2].

(3) Menstrual irregularities and endocrine disturbances should be carefully monitored, especially in obese women [LoE III; SoR 2].

(4) The risk of congenital malformations among infants of women with epilepsy taking AEDs is higher than that in the general population. It should be noted, however, that in general more than 90% of mothers with epilepsy have normal newborns, and AED intake should not be considered a contraindication to initiating or carrying a pregnancy to term [LoE II-2; SoR 1].

(5) None of the AEDs may be considered safe. There is evidence that valproic acid, especially at high doses, may carry a higher risk of congenital malformations than carbamazepine and, perhaps, other commonly used AEDs. Valproic acid carries a 1–2% specific risk of NTDs, whereas this risk is 0.5–1% with carbamazepine [LoE II-2; SoR 1]. Prenatal exposure to barbiturates has also been associated with a higher risk of congenital malformations, particularly congenital heart disease, but the evidence is inconclusive [LoE II-2; SoR 1]. Lastly, the risk of congenital malformations is probably higher in the offspring of women treated with polytherapy [LoE II-2; SoR 1].

(6) AED therapy should be optimized at least 6 months before conception. The reduction or withdrawal of AED therapy during pregnancy is pointless because any congenital malformations occur in very early stages of development [LoE V; SoR 1]. The reduction or withdrawal of AED therapy during pregnancy is also hazardous [LoE V; SoR 1] because although maternal seizures do not seem to increase the risk of congenital malformations [LoE II-2], they may be harmful to both the mother and the fetus. Mothers should be strongly encouraged to maintain adequate compliance with drug therapy.

(7) Assessment of the global risk of congenital malformations should take into account all factors at individual (concomitant maternal diseases, exposure to other potential teratogens) and familial (occurrence of congenital malformations in relatives) levels [LoE V; SoR 1].

(8) The majority of severe congenital malformations may be identified by ultrasonography, although this technique cannot detect all possible anomalies [LoE III; SoR 1].

(9) All women of childbearing potential should receive folic acid prophylaxis because this reduces the risk of some fetal abnormalities, including neural tube defects, in the general population (LoE V; SoR 1). However, there is no evidence that folic acid prevents congenital malformations induced by AEDs [LoE III].

(10) There is inconclusive evidence that the use of AEDs, particularly valproic acid, during pregnancy may be associated with an increased risk of cognitive disturbances in the child (especially reduced verbal IQ, in the case of valproic acid) [LoE IV; SoR 3]. However, the occurrence of cognitive disturbances is influenced by genetic and/or environmental factors and, in severe

epilepsies, by suboptimal care of the child due to the effects of maternal seizures and maternal AED therapy [LoE V].

Recommendations to the physician:

(1) The regular occurrence of ovulation should be assessed prior to instituting any antiepileptic therapy and at every follow-up visit [LoE V; SoR 2].

(2) Women taking AEDs that reduce the plasma levels of both estrogens and progestins (carbamazepine, felbamate, oxcarbazepine, phenobarbital, phenytoin, and primidone) should be advised to prefer, for hormonal contraception, levonorgestrel-releasing intrauterine devices, used with the same modalities as in the general population [LoE III; SoR 2]. A less desirable alternative for hormonal contraception in these women is a contraceptive pill containing 1 mg norethindrone (or 0.15 mg levonorgestrel, or 0.30 mg norgestrel) in combination with 50 μg ethinylestradiol. Women taking this combination should be advised to use nonhormonal contraceptive methods simultaneously for the first 3 months and to increase the dose of the contraceptive if breakthrough bleeding occurs (LoE V; SoR 1). If the interacting AEDs are withdrawn, the physician should wait for 2 months before reducing the dose of the combined hormonal contraceptive [LoE V; SoR 2].

(3) Women taking AEDs that reduce the plasma levels of progestins only (topiramate, at doses >200 mg/day) or ethinylestradiol only (lamotrigine, 300 mg/day) should equally be advised to prefer, for hormonal contraception, levonorgestrel-releasing intrauterine devices, used with the same modalities as in the general population. The use of the contraceptive pill is less desirable in these women. If a contraceptive pill is prescribed, it is probably preferable to use a conventional pill containing 30 μg ethinylestradiol in order to reduce possible risks of overdosage, even though a modest reduction in contraceptive efficacy cannot be excluded at this dosage. The dose of the oral contraceptive should be increased if breakthrough bleeding occurs [LoE V; SoR 2].

(4) Women taking AEDs that reduce the plasma levels of estrogens and/or progestins (carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone and, at doses >200 mg/day, topiramate) should be advised to avoid oral contraceptive formulations of progestins alone, as well as subdermal and transdermal formulations. Biphasic and triphasic oral contraceptives should also be avoided in these women, because the low progestin content of these preparations during the first phase may lead to reduced contraceptive efficacy [LoE V; SoR 1]. Prolonged use of depot medroxyprogesterone acetate formulations, which according to some authors retain contraceptive efficacy even in the presence of enzyme-inducing AEDs, is not recommended because of possible adverse effects, particularly on bone mineral density [LoE V; SoR 2]. For emergency contraception, higher contraceptive dosages should be used, although specific indications are lacking [LoE V; SoR 3].

(5) Women taking AEDs that do not reduce the plasma levels of estrogens and progestins (gabapentin, levetiracetam, pregabalin, tiagabine, valproic acid, vigabatrin, and zonisamide) should follow the recommendations for contraception applicable to the general population [LoE II; SoR 2].

(6) The efficacy of nonhormonal contraceptive methods is not modified by AEDs.

(7) The plasma concentrations of lamotrigine, valproic acid, and the active monohydroxy-metabolite of oxcarbazepine should be monitored when oral contraceptives are started and withdrawn, and adjustments in the dosage of these AEDs should be made if clinically indicated [LoE II-1; SoR 1].

(8) If initiation of antiepileptic therapy is indicated, the AED considered to be most effective for seizure control should be used [LoE II-2; SoR 1]. Valproic acid should be avoided if other AEDs with comparable efficacy are available, especially in women who would object to a possible therapeutic abortion. Unless no alternatives are available, it is particularly important to avoid valproic acid in women with a positive family history of neural tube defects [LoE V; SoR 1].

(9) In women taking AEDs, pregnancy should be planned well ahead whenever possible, and drug therapy should be optimized at least 6 months before conception by reviewing the diagnosis [LoE V; SoR 1] and by using the most efficacious AED, possibly in monotherapy, at the minimum dosage required for seizure control [LoE V; SoR 1]. The ''optimum individualized therapeutic plasma concentration value'' of the prescribed AED should be identified, if possible. Before switching gradually from an effective therapy with valproic acid to therapy with another AED of potentially comparable efficacy, the balance of risks versus benefits should be assessed on an individual basis. Well before conception, physicians should evaluate the risk-to-benefit ratio of a gradual withdrawal of AED therapy in women who had been seizure-free for at least 2 years, and in women who have only rare nonconvulsive seizures [LoE V; SoR 1].

(10) All women of childbearing potential should receive folic acid supplements. The optimal dose of folic acid is unclear. Some authors recommend 0.4–0.5 mg/day, and 5 mg/day for women taking valproic acid or carbamazepine [LoE IV; SoR 2]. In Italy only 5 mg folic acid preparations are available.

Pregnancy

Women should be informed that:

(1) Seizure frequency does not change during pregnancy in approximately two-thirds of cases [LoE II; SoR 2]. A possible worsening of seizures is often caused by irregular AED intake [LoE II; SoR 2].

(2) Correct management of pregnancy requires awareness of the implications associated with the seizure disorder and its therapy (see previous and subsequent sections). Regular follow-up should be planned.

Recommendations to the physician:

(1) According to the National Health Plan, prenatal diagnosis of malformations should involve three so-called first-level ultrasound scans (10th-13th, 20th-22nd, and 30th-34th weeks) and the determination, at week 16, of maternal α-fetoprotein level.

(2) The following second-level ultrasound scans should be considered: (a) Within week 13, fetal nuchal translucency should be assessed as a marker of the risk of congenital heart disease [SoR 3], and the possible occurrence of neural tube defects should be investigated by vaginal ultrasonography [SoR 3]. (b) At week 18, fetal morphology should be assessed, with special reference to the facial morphology, the spine, and the heart [SoR 3]. (c) After week 20, a cardiac echocardiography color Doppler examination should be performed [SoR 3].

(3) If possible, the plasma concentrations of lamotrigine, the MHD of oxcarbazepine and primidone-derived phenobarbital should be evaluated on a monthly basis [LoE V; SoR2]. The plasma concentrations of other AEDs should be monitored at least at every trimester and during the last month of pregnancy, if possible [LoE V; SoR 2]. Free (unbound) plasma concentrations of phenytoin and valproic acid should be measured when possible [LoE V; SoR 1], because the total concentration of these drugs may underestimate the pharmacologically active concentration, especially during the last months of pregnancy [LoE V; SoR 2].

(4) Monitoring plasma concentrations of AEDs is also recommended if there are major changes in clinical status or when poor compliance is suspected [LoE V; SoR 1], or when dosage is adjusted [LoE V; SoR 2].

(5) The dosage of AEDs should be increased only if worsening of seizures occurs or when there are reasons to believe that a reduction in plasma AED concentrations in a compliant patient entails a significant risk of seizure recurrence [LoE V; SoR 2].

(6) In patients treated with enzyme-inducing AEDs (carbamazepine, phenobarbital, phenytoin, primidone, and oxcarbazepine), oral vitamin K (10 mg/day) may be prescribed during the last month of pregnancy [LoE V; SoR 3].

Delivery and puerperium

Women should be informed that:

(1) AED therapy must be taken regularly during labor and puerperium [LoE V; SoR 1]. It is important to comply with any checks and follow-up visits recommended by the attending physician.

(2) There are no contraindications to breastfeeding, which is, therefore, encouraged [LoE II-1; SoR 1].

(3) Excessive alterations of the sleep–wake cycle should be avoided as far as possible.

Recommendations to the physician:

(1) For delivery, the recommendations applicable to the general population should be followed. Cesarean delivery should be considered only in women who have (or are at high risk for) frequent convulsive seizures or frequent and prolonged complex partial seizures hampering maternal collaboration [LoE V; SoR 2].

(2) Epidural anesthesia can be administered [LoE V; SoR 3].

(3) There are no specific indications concerning the type of anesthesia to be used for cesarean delivery [LoE V; SoR 3].

(4) There are no contraindications to the use of prostaglandins for the induction of labor and therapeutic abortion [LoE V; SoR 3].

(5) Counseling should be provided after delivery to avoid maternal sleep deprivation (e.g., by storing maternal milk in the refrigerator and seeking the collaboration from the partner or another family member for the night feed) [LoE V; SoR 1].

(6) Counseling should be provided for the care and transport of the infant, especially when maternal seizures are frequent and/or result in loss of consciousness [LoE V; SoR 1].

(7) If possible, maternal plasma AED concentrations should be measured at 2–4 and 12 weeks postpartum [LoE V; SoR 2], especially when dosage had been modified during pregnancy. In women treated with lamotrigine, oxcarbazepine, and primidone who required at least a 30% increase in the dose of these drugs during pregnancy, the plasma concentration of lamotrigine, the MHD of oxcarbazepine, and phenobarbital should be monitored immediately after delivery and every 4–5 days for 2–3 weeks [LoE V; SoR 1].

(8) Infants breast-fed by mothers treated with barbiturates or lamotrigine should be assessed for possible signs of sedation and, if necessary, mixed feeding should be recommended [LoE II 1; SoR 1].

(9) If the mother has frequent seizures and/or cognitive deficits, the child should be monitored closely and kindergarten attendance should be encouraged, particularly when there are indications of a psychomotor delay possibly caused by environmental factors [LoE V; SoR 2].

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Appendix

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Classification of the evidence

Appendix S2. List of scored references

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