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Antiepileptic drug therapy and congenital defects

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Summary. - The present paper is a literature review on congenital malformations observed in the offspring of epileptic mothers. The conditions which are here considered are both morphologic and functional defects. To prevent one or more of these defects it is essential to understand the precise etiologic role of the antiepileptic drugs, which seem to be of primary importance, and their mechanism of action, as drug therapy cannot be stopped during pregnancy being indispensable for the well-being of the mother and fetus. At this state of knowledge a proportion of defects can be prevented if optimal therapy is followed right from the preconceptional period: to this end, a set of guidelines is suggested and discussed.

Key words: epilepsy, antiepileptic drugs, teratogens, pregnancy, malformations, preconceptional counselling.

Riassunto *(Terapia antiepilettica e difetti congeniti)*. - Il presente lavoro è una revisione della letteratura sui difetti congeniti osservati nei figli di madre epilettica. Le patologie prese in considerazione sono le alterazioni morfologiche e funzionali. Allo scopo di prevenire una o più di queste patologie è importante capire il ruolo eziologico dei farmaci anticonvulsivanti, che sembra determinante, e il loro meccanismo d'azione. E' infatti impossibile prevenire i vari difetti sospendendo i farmaci nel periodo gravidico poiché sono indispensabili per la salute della madre e del feto. L'articolo si conclude considerando che sin dal momento attuale una quota di difetti può essere prevenuta e vengono fornite alcune linee-guida che tendono ad ottimizzare la terapia sin dal periodo preconcezionale.

Parole chiave: epilessia, farmaci antiepilettici, teratogeni, gravidanza, malformazioni, consulenza preconcezionale.

Introduction

The improved medical treatment of epilepsy has allowed many women with epilepsy to lead normal lives, including to marry and have children [1]. Recent reports indicate that approximately 3-5 per thousand infants are born to women with epilepsy [2-4]. If so, it can be estimated that every year in Italy between 1,800 and 3,000 infants are born to epileptic mothers and most will have been exposed to antiepileptic drugs (AED) during the prenatal period.

The majority of these children will be normal while others will present one or more of the functional or morphological defects reported in the literature (Table 1). If these effects are associated only to maternal epilepsy and are independent of treatment, then none of them can be prevented, unless the totality of epileptic women renounces to have children. On the other hand, should the AED have some causal role, be it a direct, indirect or contributing role, stopping the treatment cannot be considered as an option, since seizures are harmful both to the mother and fetus. Therefore, to prevent congenital defects in these children, we must understand the specific role of AED and their mechanism of action; if the mechanism can be modified or counteracted, the drug probably may be still used, otherwise changing the therapy to a less harmful regimen must be considered.

In this review we will discuss whether or not AED are harmful to the developing fetus, their mode of action, and the measures which, at this state of knowledge, can be taken to promote the children's health.

Morphologic and functional defects

Malformations

Malformations and AED in general. - Since the first formal investigations in Germany [5] and in England [6], a great number of cohort (historical and prospective) and case-control studies have been performed and a number of reviews have been published [7-11]. Though dealing with different populations, patients and drug regimens and using different methodologies, most of the studies have consistently shown some common results:

a) women with epilepsy have a twofold higher risk to have a child with major malformations compared to nonepileptic women;

b) malformations in the offspring of treated women are almost twice as frequent compared to those of untreated women, which in turn have a similar frequency to that of nonepileptic women.

Table 1. - Adverse reproductive outcomes reported in infants of women with epilepsy

Perinatal, neonatal and infant death (*)
Prematurity
Hypoxia
Prenatal growth deficiency (*)
Coagulation disorders during neonatal period (*)
Drug withdrawal symptoms (*)
Feeding difficulties (*)
Major congenital malformations (*)
Minor congenital anomalies (*)
Postnatal growth deficiency (*)
Developmental delay (*)
Childhood tumours
Seizures (*)

(*) Significantly increased incidence compared to children born to women without epilepsy.

It must be realized that the two groups of epileptic women, treated and untreated, may be significantly different from a biomedical point of view [12].

Furthermore, some studies have provided evidence that:

a) the frequency of malformations is increased among the offspring of mothers treated with polytherapy [4, 13-17] and those treated for a longer period of time before the pregnancy [17];

b) the frequency of malformations among offspring of epileptic fathers is similar to that of general population and is lower than for treated mothers; however, conflicting results have been reported [18] and there exists a possible bias due to the fact that fathers and mothers may not be comparable for fertility, as epileptic men tend to marry less often than epileptic women;

c) the frequency of malformations among infants of nonepileptic mothers treated regularly with phenobarbital is not increased [19], while the frequency of malformations among epileptic women on regular phenobarbital was twice higher.

It must be realized that dosages and period of treatment may not be comparable in the two groups of women.

The excess risk for malformations observed among the offspring of treated women, compared to nonepileptic and to untreated epileptic women, does not uniformly apply to all types of defects. For three defects in particular the relative risk is high:

a) cleft lip +/- palate (CLP), 9 to 13 times more frequent among the offspring of treated epileptics;

b) cleft palate (CP), 3 times more frequent;

c) congenital heart defects (CHD), twice as frequent.

There is apparently a uniform increase for all types of CHD except maybe for a preponderance of conotruncal defects associated with exposure to trimethadione (TMD) [20-22]. It may be worthwhile, however, to re-evaluate the risk for CHD since recently diagnostic accuracy has greatly improved.

Given a population frequency in Italy for CL of 0.5 per 1,000, for CP of 0.4 per 1,000 and for CHD of 8 per 1,000 [23], the frequency among treated epileptics can be estimated as 16 per 1,000 for CHD, 5 per 1,000 for CL and 1.2 per 1,000 for CP.

Other defects have been found to have a higher incidence among children of epileptic mothers, though with less uniform relative risk among studies, probably because the magnitude of risk is less elevated or because greater statistical power is required. In one case-control study, hypospadias, diaphragmatic hernia, hydrocephaly and spina bifida were found to be more frequent among the offspring of epileptic women [24, 25].

Malformations and specific AED. - Some studies tried to analyze the risk contribution for each specific AED. An association between valproic acid and spina bifida was suggested by Elisabeth Robert in Lyon. This hypothesis was confirmed both in the Lyon Malformations Registry [26] and in the Italian Birth Defect Registry [27]. A relative risk of 20 and an exposure attributable risk of 1% was estimated by a large collaborative international study [28]. A similar estimate of 1,5% (95 cl, 0.42-3.00) was suggested by Lindhout and Schmidt [29] summarizing data from 13 study groups on 393 infants exposed to VPA with or without other AED.

The risk observed for spina bifida was not seen for other neural tube defects (anencephaly and encephalocele).

Recently an excess of preaxial limb deficiency in infants exposed to valproic acid has been reported [30, 31]. This finding has yet to be confirmed by more formal epidemiological studies.

Recently, Rosa [32] has suggested that a specific risk of spina bifida is present also after carbamazepine (CBZ) treatment. The magnitude of the risk has been estimated around 0.6%.

A large collaborative study to determine specific drug-malformation associations was conducted on 318 malformed infants born to epileptic mothers in six different areas in the world [33]. Since the study was limited to malformed infants, the confounding effect of the disease and the ascertainment bias could be eliminated while the heterogeneity of the drug-malformation distribution could be analyzed. 150 malformed infants were exposed to monotherapy (52 phenobarbital (PB), 47 valproic acid (VPA), 26 phenytoin (PHT), 14 CBZ, 11 others) and 168 to polytherapy. A significant association was detected between maternal use of valproic acid and spina bifida (OR = 16.9), while a weaker, non significant one, was found between CBZ and spina bifida (OR = 3.4). Facial clefts were associated with both PHT (OR = 1.5) and PB use (OR = 7.6) and with polytherapy (OR = 2.4). This approach and sample size had the power to detect even subtle differences among various treatment regimen. It can be estimated that the 318 malformed

children studied would arise from a total of about 2 million births. The mere fact that the study detected differences in risk between different drugs and different malformations indicates that the AED contribute differently to the teratogenic hazard associated with maternal epilepsy.

Minor anomalies and fetal AED syndromes

Several studies [34-40] have shown that minor anomalies occur significantly more often in the offspring of AED treated mothers compared to nonepileptic controls. The frequency of subjects affected as well as the number of minor anomalies per subject are increased.

The higher frequency of minor anomalies did not have a drug specificity in the Rating' study [41], where a similar prevalence for monotherapy with PHT, VPA and primidone (PRM) was found. Several studies observed an higher frequency in polytherapy than in monotherapy [36, 39, 41].

Minor anomalies may occur alone or may be associated with pre or postnatal growth deficiency, major malformations and mental delay. These features constitute the main findings of the fetal PHT syndrome [42]. Similar findings have been however also reported with PB or PRM [41, 43-49], oxazolidinediones [20- 22, 50] VPA [51-59] and CBZ [60, 61].

It is still debated whether a specific syndrome exists for each drug, since there is a great deal of overlap between observed patterns.

Among the minor anomalies described in the offspring of epileptic mothers (e.g.: hyperthelorism, epicanthus, eyelid ptosis, low nasal bridge, nail hypoplasia, distal phalanges hypoplasia) nail and or distal digital hypoplasia seem to be the most specific effect of AED, mainly of PHT. Digital and nail hypoplasia have been observed following exposure to PRM, VPA, CBZ and PB [35, 60-64]. Kelly [65] observed that digital hypoplasia, detectable at X-ray examination, occurred in 44% of children exposed to PHT monotherapy compared to 23% exposed only to phenobarbital. Andermann *et al.* [37] found a high prevalence of dermal arches on the fingers of children of treated epileptic mothers (18.7%) compared to children of untreated epileptic mothers (2.1%), suggesting that dermal arch patterns may serve as a sensitive indicator for the teratogenic effects of AED on the fetus. In a Finnish study [66] PHT exposure was associated with a significantly elevated prevalence (11%) of radiologically defined distal phalangeal hypoplasia. The second and fifth digit were most frequently affected. Distal phalangeal hypoplasia was not accompanied by other serious abnormalities. The subgroup of children exposed to phenytoin levels above 40 mmol/l showed more prominent effects than did the subgroup exposed to lower or unknown concentrations. These findings were supported by D'Souza *et al.* [67] who found that nail hypoplasia was related to high maternal serum concentrations of PHT.

In conclusion, the existence of many separate syndrome linked to specific AED seems unlikely. There is some evidence that suggests there may be a Fetal Antiepileptic Drug Syndrome due to any AED which may disturb both morphogenesis and phenogenesis. It is difficult to say whether or not specific minor anomalies are associated to a given AED, e.g., PHT with digital and nail hypoplasia. There is no evidence that Fetal AED Syndrome is present in the offspring of epileptic fathers or untreated mothers [41, 43, 64, 68].

Further studies on minor anomalies are needed which should objectively evaluate the offspring in order to minimize the observer bias; for instance the examiner should be blind to drug exposure information. These studies can be performed using the recently available methods of anthropometric measurements [69-72], should include a similar evaluation of the parents, careful follow-up of the children, as many craniofacial dysmorphic features may change with advancing age [37, 38, 66, 73] and must take in consideration the length of therapy as well as the maternal plasma levels of AED during the first weeks of gestations.

Prenatal growth and head circumference at birth

Dansky and Finnell [9] reviewed 29 cohort studies where at least one of the prenatal growth parameters, birthweight (BW), length, head circumference (HC) were studied.

When HC has been considered a decrease in the mean or an increased frequency of microcephaly has been always reported (13 out of 13 studies). Only 9 studies out of 27 have found a reduction in BW. This overview may suggest that a reduction of HC is most probable and not affected by other confounding factors, reduction in BW is debatable and the conflicting result may be due to methodological problem (e.g.: choice of the control group, standardization by confounding factors). Low BW when present is however more marked after polytherapy than after monotherapy and there may be a dose-effect relationship [39, 74-78].

The explanation why a reduced HC is present in offspring of epileptic mothers is not easy. Dansky *et al.* [77] using multivariate techniques found that the variates significantly associated with a reduced HC were: cigarette smoking, low socioeconomic class, occurrence of a major seizure during pregnancy, polytherapy, and increased mean dose or plasma level of PHT in the first trimester or over all trimesters combined. In a Japanese study [76] the reduction in HC at birth was linked to the total cumulative drug dosage taken during pregnancy. The smallest HC have been observed in a Finnish study among the offspring exposed to CBZ monotherapy or to combination therapy which included PB or PRM [79]. In an Italian study [80] where 164 infants of epileptic mothers were studied the reduced HC was found

associated to polytherapy (59 subjects), PB monotherapy (55 subjects) and in the offspring of epileptic without treatment in pregnancy (26 subjects) but not in VPA or CBZ monotherapy (13 subjects). In this study the untreated women were more numerous than in other studies. The results could indicate that: a) the sample size is important to detect a small reduction in HC; b) epilepsy per se may influence the HC at birth. These conclusion were confirmed by a recent Finnish study where the head circumference was studied in 121 children at 5.5 years [81].

The pathogenesis of the reduced HC and prenatal growth is unknown, but it has been suggested that AEDs may interfere with thyroid function. Among women with seizure disorders receiving AED therapy, decreased levels of thyroxine and thyrotropin in maternal serum during pregnancy and in cord blood have been found [82-84]; these observations were found to correlate with reduced HC at birth. The observation that VPA does not inhibit intrauterine fetal growth [57] and does not alter T4 e TSH levels [85] may support this hypothesis. The slightly lowered GH levels in the cord and neonatal blood caused by AED treatment may also be implicated in the mechanism of delayed prenatal growth [8].

Postnatal somatic development

Most papers suggest a delay in somatic growth in children of treated women [86-90]. The delay is however evident only in the first two or three years of life and disappears thereafter. In the Finnish study by Gaily and Ganstrom [90], the growth delay was confined to the first months of life and among children exposed to monotherapy was more prominent for PB, less evident for PHT and almost nonexistent for CBZ. Jager-Roman *et al.* [89] reported that polytherapy seemed to correlate with higher incidence of reduced somatic growth, with PRM appearing to have the strongest negative effect.

Psychomotor development

The literature concerning functional development is controversial [43, 19, 74, 34-36, 90-96] but the majority have reported an increased risk for developmental delay linked to AED, especially when used in polytherapy.

Shapiro *et al.* [19] compared children exposed in utero to AEDs and normal controls; compared to controls, test scores at 4 years were lower for children born to treated mothers but not to treated fathers. Nelson and Ellenberg [92] found a frequency of IQ below 70 at seven years in 6.5% of exposed children and in 3.4% in nonexposed controls. There were no differences among different treatment regimens and no effect of phenobarbital in the children of treated nonepileptic women. Hill *et al.* [35] followed 59 children of AED exposed children and controls until the age of 9 years. Children exposed to polytherapy had a lower score during the first 3 years compared to those exposed to a single AED. At 9 years of age, 19% of the children of epileptic mothers had an IQ below 90 compared to 4% of the children of non epileptic controls. Among the offspring of treated mothers there were more often language learning disabilities. These were related with IUGR, failure to thrive in the first few months, a major malformation, 9 or more minor anomalies, exposure to multiple AEDs. These findings agree with the results of other studies where the polytherapy and the number of drugs [92-95] or PB [71, 96], valproic acid [97], was considered as a major risk factor. In the Finnish population based study, which may provide a better estimate of the overall risk of developmental deficiency, Gaily *et al.* [91] found a prevalence of mental deficiency of 1.4% and of borderline intelligence of 1.7%, close to the general population rates. However, they found an increased frequency of specific cognitive dysfunctions and the risk was associated with maternal partial seizures and maternal seizures during pregnancy, but not with exposure to AEDs. In this study the number of women treated with polytherapy was very low and drug levels during pregnancy were relatively low.

These partially conflicting results may be due to many factors: the age of study subjects, differences in methodology, sample size in each subgroup studied, type of therapy. More standardized studies are needed.

Childhood tumours

There have been some case reports of childhood tumours in children exposed to PHT and other AEDs [98-100]. Recently Koren *et al.* in a series of 188 neuroblastoma found an exposure to PHT in 1.5%. Although their data do not suggest an association between PHT in pregnancy and postnatal neuroblastoma, it is still possible that there is an increased risk for neuroblastoma in children exposed to PHT [101].

Other perinatal outcomes

Withdrawal symptoms. - Clinical manifestations of the withdrawal syndrome in exposed newborns include hyperirritability, tremor, seizures, vomiting, poor sucking, sleep disturbances [96, 102-106]. They appear shortly after birth, usually are self limited and disappear in few weeks, but may last for as long as six months after delivery [35]. PHT, PB and PRM are more often responsible compared to CBZ and VPA [107]. These symptoms do not affect psycomotor developmental [108].

Spontaneous haemorrhage. - In newborns exposed to PHT, phenobarbital or PRM, a bleeding tendency may develop during the first day of life and is related to decreased levels of vitamin K-dependent clotting factors

in the newborn despite normal levels in the mother [109]. This form of drug-induced bleeding disorder should be distinguished from the physiologic deficiency that occurs in normal infants between the second and fifth day of life. Drug-induced haemorrhages occur earlier and may be life-threatening. They can be prevented by prophylactic administration of vitamin K 20 mg per day orally to the mother for 2 weeks antepartum, or 10 mg IM 4 hours before birth [110, 111]. Clotting studies and appropriate therapy should be instituted few hours after delivery [112]. Haemorrhage secondary to thrombocytopenia may also be an occasional adverse effect [113].

Mechanism of functional and morphological teratogenesis

A number of epidemiologic studies in man show that AEDs play a primary role in determining major malformations, a fetal AED syndrome, and a host of adverse effects particularly on growth and development. Though important, AEDs are not the only determining factors, as demonstrated by the reports of discordant effects on pairs of brothers and twins exposed to the same drug regimen [42, 114- 118]. Among the factors which determine the teratogenic effects of the AED and may account for its variability the most important seem to be:

Drug regimen

In previous paragraphs the effect of the different drugs and the differences between monotherapy and politherapy have been widely exemplified and discussed.

Dosage

Experimental studies have demonstrated a dose-response relationship between PHT or VPA and adverse outcomes [119-120]. Few human studies evaluated maternal drug dosage and even fewer studied plasma drug concentrations during pregnancy. Occurrence of minor anomalies have been found to be positively associated with the dose of PB [49], dose of PRM [41], plasma concentrations of PHT [38]. Variability of the effect may be also due to individual differences in drug metabolism and interactions.

Variations of the pharmacokinetics of AED during pregnancy

In general, pharmacokinetics changes in pregnancy appear to be greatest for PHT and VPA, less for PB and least for CBZ [121-125]. Drug level fluctuations observed with valproic acid may be important in view of the fact that high peak levels of the drug induce anterior NTD in experimental animals [120, 126].

Folate concentration

Meadow [6] first speculated that AEDs may cause malformations by inducing folate deficiency. PHT interferes with the metabolism of folate and vitamin D [127, 128], PB serum levels are inversely correlated with serum folate levels [129] and PHT depresses folate levels in epileptic patients [130]. Folate deficiency was found in pregnant women chronically treated with AEDs [131-134].

Folate deficiency may constitute a greater hazard to the developing fetus than to the adult. Although an earlier study failed to detect any relationship between folate levels in the mother and adverse health effects in the fetus, including malformations [129], more recent studies did [132, 8].

The importance of optimal levels of folate and other nutrients has been shown in animal models, where folinic acid administrated together with valproic acid reduced the incidence of neural tube defects and embryo culture supplementation with vitamins and aminoacids reduced the incidence of malformations [8, 127].

The capacity of the fetus to detoxify arene oxide metabolites

The existing experimental literature indicates that the oxidative metabolites produced during the biotransformation of PHT, mephophenobarbital , CBZ and VPA may be responsible for the majority of adverse reproductive consequences of therapy. The arene oxide metabolites of some AEDs are controlled by the epoxide hydrolase enzyme (EH) and have become prime candidates for the fetotoxicity of AED in humans, as well as in the experimental models [15, 135]. It has been postulated that these metabolites may have a maternal, placental and/or fetal origin [136]. Strickler *et al.* [137] found that the occurrence of major malformations, such as CHD and microcephaly, but not prenatal growth and minor anomalies, correlated with the capacity to detoxify arene metabolites, as measured by the *in vitro* lymphocyte toxicity of PHT metabolites. Family studies suggested autosomal codominant inheritance of the detoxification defect. Buehler *et al.* [138] found that low epoxide hydrolase activity in amniocites, detected prenatally, correlated with clinical findings of fetal AED syndrome in the newborn. They suggested that the EH activity was regulated by a single gene with two alleles; individuals homozygous for the recessive allele would be at risk for the clinical features of fetal AED syndrome if exposed to AEDs.

Type of maternal epilepsy

The type of epilepsy may modify the teratogenic effect of AEDs because some forms of epilepsy may share common genes for susceptibility to some

malformations or because the severity of epilepsy may determine the choice of the drug regimen. Most reported studies do not indicate that congenital anomalies are related to the type and/or severity of maternal epilepsy [12, 19, 35, 38, 41, 68, 93, 116], though some studies noted an association between congenital anomalies and certain types of epilepsies [139, 140].

The genetic basis of the susceptibility to the pattern of congenital anomalies observed in AED-exposed infants was examined experimentally in three inbred mouse strains [141, 142]. Outcome variability appeared to be related to genotypic differences in the susceptibility to specific PHT induced malformations. Therefore the authors postulated that the expression of isolated malformations involves liability genes for each organ system, while the expression of the overall pattern of abnormalities is due to the interaction of multiple liability genes for several developmental systems [143].

Guidelines

Guidelines for caring epileptic women in reproductive age

All epileptic women in reproductive age should be considered potentially as being in the preconceptional period or even in pregnancy. Any modification of the therapy needs to be carefully evaluated and should not take place if an unplanned pregnancy has already started. According to our experience less than 60% of epileptic women planned the pregnancy.

The control of fertility can be achieved with the usual methods. Every woman should choose the method which suits her best, taking into account her ethics, life style and physiological characteristics. Those who choose to use hormonal pills should be told that the contraceptive effectiveness may be impaired by PHT, phenobarbital, CBZ and possibly ESM because of drug interaction; VPA and benzodiazepine (BDZ) do not appear to have a major influence on the efficacy of oral contraceptive.

Since reproductive counselling and management is the single most important component of primary prevention, it should be offered periodically to the women.

The accuracy of the diagnosis and the usefulness of a treatment with AED must be checked periodically.

Women in childbearing age should be treated according to the usual therapeutic rules: if possible with a single drug, at the lowest effective dose, as determined by serum levels. The endpoint which guides the choice of the treatment is, as usual, the state of wellbeing of the woman.

From a reproductive standpoint, monotherapy with phenobarbital seems to be associated with the lowest risk to the child. When possible, valproic acid should be avoided since among all AEDs it carries the highest risk for the most serious malformation (spina bifida). If valproic acid must be used, it should be given in monotherapy and not as a single daily dose regimen, as the adverse effects are believed to result from unpredictably high serum peak levels. Polytherapy should be used only as a last resort and for limited periods of time, in conjunction with a stricter control of fertility. Women free of seizures for more than two years should be evaluated for the possibility to withdraw the therapy.

The aim of reproductive counselling, periodically offered to the women, is mainly to inform her about the risks which can be prevented by regular obstetric follow-up from early pregnancy and by optimal AED regimen. The risks include worsening of symptoms during pregnancy, pregnancy complications (toxaemia, bleeding, abruptio placentae), congenital malformations, prenatal growth retardation, fetal AED syndrome, neonatal complications. The magnitude of the risk and the specific outcomes should be discussed in depth. A positive attitude is of great importance as often the risk is perceived as as an all or nothing setting. Since the most serious malformations associated with AEDs may be diagnosed during pregnancy, the advantages and limitations of prenatal diagnosis should be discussed. It must be stressed that in any case each woman, epileptic or not, has a background risk of having one or more reproductive adverse outcomes due to factors unrelated with epilepsy and AEDs and that epileptic women can achieve normal pregnancy and offspring in more than 90% of cases.

Women with epilepsy should also be informed of the recurrence risk of seizures in their children (approximately 4%), and that optimal neonatal and childhood care is required since their children are at risk of developmental problems.

Although clear evidence in humans is lacking, available data in experimental animals suggest that routine folate supplementation, may be recommended, preferably as folinic acid, beginning before conception.

Guidelines for the care of the newborn and child

Birth should take place in a clinical unit related to a neonatology department with experience in high-risk pregnancies. A neonatologist must be always present during delivery.

Symptoms of sedation and withdrawal syndrome must be searched for and treated. These symptoms have been described more often in newborns exposed to PRM, PB and BDZ.

The adminstration of vitamin K to the mother before delivery and to the newborn soon after birth is highly recommended to prevent the risk, small but present, of cerebral haemorrhage.

Special care should be taken to avoid feeding difficulties and poor weight gain. Breastfeeding should be considered on an individual basis, according to the

mother's desire to breastfeed, the newborn's conditions and the drug regimen. AEDs differ greatly in transmission rates into human milk and in half-lives. Assuming therapeutic plasma levels in the mother, it can be estimated that an infant taking a litre of milk per day would ingest at most few milligrams of AED per day and, hence, with most of the drugs no side effects may be expected in the newborn. Only if the mother is taking PB, PRM or BDZ it is advisable to reduce or discontinue breast feeding for the first 7 days postpartum.

During the first months after delivery, special care must be provided to the non seizure-free mothers to avoid seizure-related accidents.

During infancy, a program of regular follow-up should be undertaken by a developmental specialist. Parents should be aware that developmental delay related to the AED, if present, may be transitory and that the environment of the child's care is the most important single factor for the ultimate development. Special help should be offered to the mother at regular intervals.

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