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EPILEPSY, PREGNANCY AND ANTIEPILEPTIC DRUGS

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Abstract Clinical and basic researches on epilepsy and pregnancy, in particular of antiepileptic drugs (AEDs) on the fetus and the epileptic mother, and those of pregnancy on the course of epilepsy were reviewed.

The complete control of seizures in the pregestational period and regular drug taking are very important for better management of pregnant epileptics with medication, since the seizure frequency remains mostly unchanged when the patient's compliance is good. If the serum level decreases, one must confirm the patient's compliance. Once compliance has been established, the dose should be increased only when seizures occur.

Most AEDs cross the placenta and some cause unwanted effects on the embryo, the fetus, or the newborn.

Thus pre-conceptional counselling should ensure that an epileptic embarks upon a pregnancy with her epilepsy well controlled by a minimal dose of AEDs, and adequate answers for the questions raised by the patient should be given to prevent poor compliance.

There is an increased risk of major congenital malformations among the offsprings of women with epilepsy, most of whom are on AEDs. Part of this increase is due to exposure to AEDs. Other factors also appear to play an important role. Prevention of malformation can take place before the onset of the pregnancy by decreasing the dose of the drug and/or changing from a combination of AEDs to a single drug, since there is a dose-response relation for teratogenesis and a greater occurrence of congenital malformation when the mother receives combined AED therapy.

An aspect of prenatal growth deficiency that has raised concern is that brain growth may be affected, producing microcephaly and mild to moderate mental retardation. However, the delay in the physical development of the offspring may be transient. The psychomotor retardation continued only through infancy, if they were nursed properly.

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Key words : malformation, compliance, folic acid, seizure frequency, hormone

てんかん，妊娠，抗てんかん薬

兼　子　　直

抄録　てんかん妊婦の管理治療基準設定のため，神経精神科医，産科婦人科医，小児科医よりなる共同研究チームを結成し，「てんかん，妊娠，抗てんかん薬」について包括的に予期的研究をした．本稿では，この研究過程でこれまで得られた知見をもとに，基礎的，臨床的諸報告をも参照し，てんかん者の妊娠，出産，出生児の各種問題点を考察した．取り上げた主要な論点は，

(1)　妊娠のてんかん発作に及ぼす影響

(2)　抗てんかん薬の妊娠，出産，胎児，新生児

に対する影響である．

これらの問題点を，抗てんかん薬体内挙動，各種ホルモン・葉酸・血液凝固系等の変動，奇形発現の機序，児の精神身体の発達，服薬妊婦の授乳の可否等を中心に解析し，現状で考えられる対策，今後の検討すべき点につき述べた．

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I. Introduction

Recent improvements in diagnosis and therapy for epileptic disorders have allowed many epileptic women to lead normal lives including marriage, child bearing, and employment.[1,2]

For most women with epilepsy, antiepileptic drug (AED) therapy is necessary even during pregnancy. Doctors in charge, therefore, will encounter many questions about side-effects of AEDs and insidious effect of epilepsy on pregnant women and their fetuses. In correctly handling epilepsy and pregnancy there still remains many gaps in our knowledge, in particular the possible fetal effects of AED and the pregnancy on epilepsy.

Some recent studies, however, have increased our knowledge considerably in the last few years, allowing for a better treatment of epileptic mothers and their offspring. This paper reviews some of the cilnical and basic researches on epilepsy and pregnancy, in particular the effects of AEDs on the fetus as well as the epileptic mother, and those of pregnancy on the course of the disease. For comprehensive information on this matter, readers are referred to such recent publications as "Epilepsy, Pregnancy and the Child" (eds. : JANZ, D. *et al.* 1982, Raven, New York) and "Antiepileptic Drugs and Pregnancy" (eds. : SATO, T. and SHINAGAWA, S. 1984, Excerpta Medica, Amsterdam), and to some recent reviews.[3~5]

II. The Effect of Pregnancy on Epilepsy

Studies into the effect of pregnancy and puerperium on the course of epilepsy varies substantially in their findings. The frequency of seizures will often change. In a few cases there is a decrease in seizure frequency, which is usually explained by better medical supervision during pregnancy. However, other patients may have fits more frequently during pregnancy. In KNIGHT and RHIND's[6] study of 153 pregnancies in 59 epileptics, seizure frequency was decreased in 5%, unchanged in 50%, and increased in 45%. CANGER, *et al.*[7] observed an increased seizure frequency in 41%, whereas 9% improved, and 50% were unchanged. Similar results were also obtained by REMILLARD, *et al.*[8] In contrast to these results, in a prospective study of 32 epileptic women, SCHMIDT, *et al.*[9] found an increased seizure frequency in only 8% and stated that pregnancy did not significantly increase seizure propensity. In a prospective study of larger cases, BARDY[10] and OTANI[11] reported most of the cases showed unchanged seizure frequency during pregnancy and puerperium.

Several mechanisms including patient's poor compliance, a decrease in serum levels of AEDs, hormonal changes, and psychological factors have been suggested[9~13] for the exacerbation of epilepsy in pregnancy.

(1) Patient's compliance

In OTANI's[11] study, patient's compliance was poor in 27% of the subjects (110 pre-

gnancies), and in the cases with regular drug taking, 80% showed no change in seizure frequency whereas only 16% exhibited an increase and 4% a decrease. Main reasons for poor compliance were the patient's anxiety about teratogenecity of AED, the harmful effects of the drug on their newborns by breast feeding, and carelessness in drug taking. Poor compliance is considered to be one of the main factors for the increased seizure frequency.

(2) Hormonal and vitamin changes

In pregnancy, progesterone and estradiol levels in the blood and urine excretion of estriol, estrone, and estradiol gradually increase to maximum values during the last trimester of pregnancy, while chorionic gonadotropine reaches its peak in the first trimester and decreases towards the end of pregnancy.[14] The cerebral cortex is more sensitive to stimuli in pregnancy. This is probably due to hormone-mediated intracellular electrolyte change. The effect of hormones, therefore, should have some important role on the seizure susceptibility. CANGER, *et al.*[7] found the hormonal concentrations to be of the same magnitude as those in nonepileptic pregnant women, though patients with increased seizure frequency tended to have slightly higher estrogen levels than the other patients. Consistent with these findings, estrogen has increased the extent and severity of seizures in animal experiments.[15~18] Focal cerebral lesions are activated in animals by estrogen as indicated by an increase of epileptic discharges.[19,20] Activation of focal spikes and precipitation of epileptic seizures were reported in epileptic patients following the intravenous injection of estrogen.[19] Catamenial exacerbation of seizures is probably due to increased activity of estrogen during the immediate premenstrual period.

On the other hand, progesterone and testosterone have produced mild reductions of seizure susceptibility in rats, cats, and dogs.[18,21] According to LAIDLAW,[22] progesterone has been implicated as a factor governing seizure frequency during the midluteal phase in patients with catamenial epilepsy. In non-pregnant women with partial epilepsy, BACKSTRÖM reported[23,24] a positive correlation between the number of secondarily generalized seizures and the mean estrogen/progesterone ratios, and a negative correlation to plasma progesterone levels. Three periods without ovulation showed an increase in the number of both generalized and partial seizures during days of high estrogen. The correlation of hormonal changes to the frequency of partial seizures was less significant and different from patient to patient.[25] The recent study of OTANI, *et al.* revealed that the high ratio of estradiol/progesterone in the puerperium could be a possible factor for the increase in seizure frequency.

Several observations have found a relationship between abnormalities of paroxysmal discharges in the brain and changes in gonadotropine levels in monkeys, rats, and rabbits,[26,18] but in humans. OTANI[25] failed to confirm this relationship. It has been suggested that glucocorticoid has epileptogenic effect not only in experimental animals but also in the humans.[27~29] In the second and third trimesters, the cortisol level was higher in the patients who had seizures during pregnancy than those who had not.[25] It is, however,

not clear whether or not the high cortisol level is responsible for the increase of seizures, because the cortisol level has a trend towards positive correlation with AED doses in these periods, and this might be a reflection of the severity of the epilepsy.

As to the implication of hGH, TSH, T3, and T4 levels, there was not a significant correlation between these hormone concentrations and the change in seizure frequency.[13]

Therefore, the estrogen/progesterone ratio seemed to be a more important factor on seizure susceptibility rather than the level of estrogen alone. The impact of hormonal factors on the seizure susceptibility, however, needs to be established in a study with a larger number of cases.

OTANI, *et al.*[25] verified that pregnant epileptic women under AED therapy showed significantly lower serum folic acid levels than the normal pregnant women. In the second trimester, epileptic patients who developed seizures showed slightly higher folic acid levels than those who did not. Accordingly, the possibility that folic acid level is connected with the occurrence of seizures during pregnancy can not be entirely excluded.

(3) Metabolic factor

During pregnancy, an increase in body weight and hemodilution occur. The average increase in weight gain exceeds 10 Kg, and more than 15% of this gain, which is partly caused by retention of sodium and water, is due to an increase of blood plasma volume.[30] The weight gain has been associated with an increased seizure frequency.[31~33] Some studies, however, failed to confirm the correlation between seizure frequency and change in body weight or total body water in catamenial epilepsy.[34,23] Mild compensated alkalosis due to hyperventilation may also be responsible for inducing seizures.

Other metabolic factors including lower concentration of sodium, potassium, calcium, and magnesium during pregnancy, may precipitate seizures.[35] So far, however, no conclusive data has linked changes in any metabolic factors with an improvement or an exacerbation of seizure frequency during pregnancy.

(4) Psychological factor

Pregnancy-related psychological problems, i. e. ambivalence toward the child or husband, fear of the risks having a child with epilepsy and anxieties about harmful effects of AED on the newborn can lead to loss of sleep or hyperventilation which can precipitate seizures.

Further, psychological problems, discussed elsewhere in this paper, not only result in poor compliance which can contribute to increase seizures,[11] but also precipitate epileptic seizures by a psychological mechanism.

(5) Pharmacological factor

Recent observations have shown that the blood levels of some AEDs are lower in pregnant than in nonpregnant patients.[9,11,35,37] A decrease in the plasma or serum concentration of the drugs has frequently been observed. However, the extent and the time course of AED fluctuation vary considerably not only from patient to patient but even from pregnancy to pregnancy in the same patient.

Attempts to correlate drug levels in the blood and seizure frequency showed a

close temporal relationship in some patients.[9,11,33,37,38] A decrease in the blood level is not always associated with an increase in seizure frequency. Despite a decreased serum level, the seizure frequency even decreased in 8% of the subjects, remain unchanged in 79% and increased in 13%.[11] Correspondingly, increased seizure frequency is not always associated with a lowered drug level.[9,11,37,39,40] In 3 out of 5 patients who showed increased seizure frequency in this author's study group (Table 1), the drug level decreased.[11] Accordingly, the change in AED disposition is one of the main factors for the change in seizure frequency during pregnancy, but may not be a critical one.[41]

Table 1 Relationship between changes in seizure frequency and those in serum level of antiepileptic drug

Serum Level	Seizure Frequency			Total
	Increase	Decrease	No change	
Increase	2	1	0	3
Decrease	3	2	19	24
No change	0	0	3	3
	5	3	22	30 cases

Possible causes for the decrease in the serum level during pregnancy include a lower rate of intestinal absorption due to a decrease in the motility of gastrointestinal tract; modification of the composition of the gastric juice, which may alter the bioavailability of orally administered drugs[42]; an increase in the free fraction of the plasma level of phenytoin (PHT)[43] and phenobarbitone (PB)[9] in the last trimester of pregnancy, which presumably results from the gradual decrease in the concentration of plasma protein that occurs during pregnancy[43]; an increase in the metabolism and hepatic clearance of certain AEDs during pregnancy; an increased renal clearance of primidone (PRM) and its metabolites[44]; and an impaired drug compliance resulting mainly from psychological mechanisms.[11,37]

Mean values of the plasma level indicate that the decrease in the level is greatest with PHT, less with PB, and not significant with PRM and carbamazepine (CBZ).[36] BATTINO, *et al.*,[45] NAU, *et al.*,[44] and the author's group[46] observed a decrease in PRM serum level during pregnancy.

The increase in the apparent serum clearance of PHT, PRM, PB derived from PRM and valproic acid (VPA) was significant, but not for PB, CBZ nor for ethosuximide (ESM).[11] Likewise, BATTINO, *et al.*[45] found that the apparent plasma clearance of PB, PRM-derived PB, CBZ, and PRM has significantly increased during pregnancy.

The mechanisms underlying decreased serum or plasma level of AEDs and the increase in the apparent serum or plasma clearance were further studied by this author's group.[46] The metabolism of PRM to PB and phenyl-ethyl-malonamide (PEMA) was not accelerated during pregnancy, and the increased maternal distribution volume was the responsible factor for the decrease in the serum level of PRM during pregnancy.[46] Therefore, the increased maternal distribution volume, poor compliance, reduced intestinal absorption, and increased renal clearance are considered to be important factors in the decrease of AED levels during pregnancy.

When the serum level decreases gradually as the pregnancy progresses one can consider that the decrease in the level might be caused by increases in maternal weight

gain resulting in an increase in the distribution volume, and when the decrease in the level is steep one must confirm the patient's compliance.

(6) Other possible factors

HUHMAR and JARVINEN[47], and KNIGHT and RHIND[6] found a correlation between the general severity of epilepsy and aggravation during pregnancy. Although BARDY[10], SCHMIDT, *et al.*[9] and CANGER, *et al.*[7] failed to comfirm this tendency, OTANI[11] conducted a well controlled study that found patients whose seizure had been pregestationally controlled showed an increase in seizures of only 26%, and among these cases, the compliance was poor in more than half of them.

The increased number of seizures were not found to be related to seizure type,[6,11,47] nor to the different trimesters of pregnancy, labour, and puerperium[47,11] although some investigators[6,7,48] found an increased frequency in the first trimester.

Suggestions that the worsening of epilepsy could be related to the sex of the fetus[6,49] have not been confirmed.[7,11] Several other factors might be related to the exacerbation of epilepsy during pregnancy, e. g., maternal age at delivery, number of previous deliveries, duration of epilepsy, and duration of therapy.

Among these factors, only the mean duration of therapy was significantly shorter for the group who showed a decrease in seizure frequency compared to the groups who showed an increase or no change in seizure frequency.[11] The clinical significance of this, however, is unknown.

To sum up the change in seizure frequency during pregnancy, most of the patients remain under unchanged seizure frequency provided that the patients take their drugs regularly and the complete control of seizures are obtained in a pregestational period.

III. The Effect of AED on Pregnancy and Labour.

(1) Fertility and incidence of abortion

Fertility seems to be normal in epileptic women on antiepileptic drugs, while impairment of potency and infertility in male epileptic patients has been reported.[50] The incidence of spontaneous abortion is higher in epileptic mothers using antiepileptic drugs than that in normal pregnant women, while there was not a significant difference in the incidence of artificial abortion.[51,52] Earlier studies of SPEIDEL and MEADOW[53] and KNIGHT and RHIND[6], however, concluded that spontaneous abortion was not more common in epileptics. These reports are unfortunately less concerned with obstetrical histories than with individual pregnancies. The increase in the incidence of spontaneous abortion is at least partly explained by a decrease in thyroid hormone concentrations as a result of antiepileptic medication during pregnancy[54], since thyroid hormones play a significant role in maintaining pregnancy.

(2) Complications during pregnancy

The incidence of threatened abortion or threatened preterm delivery does not seem significantly higher in epileptic women than in the general population.[55,52]

Table 2 Obstetrical findings in 116 epileptic women (E-group) compared with 160 non-epileptic women (C-group)

	E-group		C-group	
	No.	(%)	No.	(%)
Frequency of obstetric histories				
1-para	40	(34.5)	61	(38.1)
2-para	9	(7.8)	29	(18.1)
3-para or more	0		4	(2.5)
spontaneous abortion				
once	16	(13.8)	7	(4.4)
twice	1	(0.9)	2	(1.3)
3 times or more	2	(1.7)	1	(0.6)
preterm delivery	0		0	
artificial abortion				
once	21	(18.1)	34	(21.3)
twice	13	(11.2)	12	(7.5)
3 times or more	1	(0.9)	5	(3.1)
Frepuency of complications during pregnancy				
threatened abortion	5	(4.3)	6	(3.8)
threatened preterm delivery	2	(1.7)	5	(3.1)
pregnant toxemia (severe)	12	(10.3)	3	(1.9)
(mild)	13	(11.2)	6	(3.8)
PROM*	6	(5.2)	19	(11.9)
iron deficiency anemia	7	(6.0)	10	(6.3)
hydramnios	0		1	(0.6)
ablatio placentae	0		2	(1.3)
acute inflammation	2	(1.7)	0	
Method of delivery				
spontaneous delivery	84	(72.4)	153	(95.6)
vacuum extraction	9	(7.8)	3	(1.9)
forceps delivery	11	(9.5)	0	
breech extraction	3	(2.6)	4	(2.5)
cesarean section	9	(7.8)	0	

No. : number of cases

* : premature rupture of the membranes.

The incidence of pregnant toxemia has been repeatedly reported, but the incidence and the difference of pregnant toxemia between epileptic women and the general population have not been ascertained. In our subjects (Table 2)[52], pregnant toxemia occurred more frequently in epileptic mothers than in the controls. The discrepancies of pregnant toxemia seen in the papers may have resulted from different doses of AEDs which reflects the severity of the disease, or the psychological and the socioeconomic conditions of the subjects included in each study. An increase in placental abruption among epileptic women reported by MONSON, *et al.*[56], and HILL *et al.*[57] was not confirmed by OGAWA *et al.*[58] Women receiving AEDs are often deficient in folic acid and they have an increased chance of developing overt anemia. The frequency of iron deficiency anemia, however, was about the same among epileptic women and control pregnants. The mean gestational age at delivery did not differ significantly between epileptic women and controls.[59,52] However, when only preterm and postterm deliveries were used as basis, epileptic mothers showed slightly higher figures than control mothers.[52]

(3) Complications during delivery

With regard to obstetric operations, patients who receive operative delivery as a result of disordered uterine action seem to be no more frequent among epiletic women than in the general population. The duration of labour of epileptic mother is slightly shorter than that of general population, with the mean duration of labour being about 12 hours.[52,59]

The amount of blood loss at delivery of epileptic mother tends to be higher than that of control mothers.[52,60,61] As drug dosage increased, the blood loss tended to increase. Causes for the increased bleeding may include hypotonic uterine activity, placental complications, and antiepileptic medication, but in our subjects, no placental complications were observed, whereas AED significantly affected the coagulation system of pregnant mothers.[60,61]

IV. The Effects of AED on the Fetus and the Infant

Maternal drug use affects the fetuses and newborns in many ways. The incidence of toxic effects on fetuses and newborns of mothers treated with AEDs during pregnancy vary widely in different reports. Such a wide variability is mostly due to the methodology used for collecting the data and the lack of well prepared prospective studies. To overcome these problems collaborative study groups were organized in some countries (Berlin, Helsinki, Hirosaki, Milan, and Montreal groups) and they have been producing considerably reliable data taking into account such factors as the stage of pregnancy at which the drug was administered, and the length of exposure on the dose of the drug, etc.

(1) Placental transfer of AED

On the basis of available data it appears that the ratio between the concentration in the umbilical cord blood and that in the maternal venous blood is identical for most AEDs,[62] while valproic acid (VPA) and diazepam are significantly higher in the umbilical cord blood than that in the maternal blood.[63~65] In general, the fetal tissue is in equilibrium with the maternal circulation and, in the case of chronic drug administration, has to be considered as another tissue compartment where drugs may or may not accumulate depending on their physiochemical properties and the relative blood flow. In this respect the fetus will not behave differently from the maternal tissue. However, concerning the higher concentrations of VPA and diazepam in cord blood as compared to maternal blood, the decreased protein binding of VPA and diazepam in mothers at birth was considered to be responsible for the increased placental transfer and fetal accumulation of these drugs, because fetal protein binding was more extensive than maternal protein binding. In fact, nearly all the drugs prescribed during pregnancy cross the placenta and reach pharmacologically active concentrations in the embryo or fetus.

(2) The effects of AED and epilepsy on the fetus and the neonate

So far, special attention has been paid to the problems of fetal growth (retardation in utero), congenital malformations, and hemorrhagic tendencies in the fetus/neonate

in the majority of the studies.

i) Fetal distress, and perinatal/neonatal mortality

With regard to the incidence of fetal distress, a comparison between the pregnant epileptic patients and the general population revealed that the rate of fetal distress in the former was significantly higher than that in the latter, and NOMURA *et al.*[66] stated that infants born to epileptic mothers were more likely to be hypoxic in the subpartum period than those in the general population.

It is widely recognized that perinatal, as well as neonatal mortality rates are higher (1.2 to 2.5-fold)[67] in infants born to epileptic mothers, while a high stillbirth rate has not been confirmed.

ii) Fetal growth (retardation in utero)

Fetal growth has been studied from two viewpoints : birth weight, and the growth and development of the fetus/neonate. Most papers published to date report no significant difference in birth weight between the infants of epileptic and non-epileptic mothers, with the exception of a report from Norway[68] which showed slightly smaller than expected birth weights for the infants of epileptic mothers, though the effects of certain factors (e. g. social class) could not be excluded.[30] Next, the growth and development of the feto-neonatal head should be discussed. Very scant data has been available up to the present on the functional development of the feto-neonatal vertex. Most papers state that the vertex circumference in neonates born to epileptic mothers may be significantly smaller than in the neonates of non-epileptic mothers.[62,69] The cause of this reduced vertex circumference remains unsolved ; however, KANEKO, *et al.*[70] are of the opinion that a lowering of thyroxine and thyrotropine levels could be causally related to the reduced circumference in neonates born to mothers treated with AEDs based on their determination of human growth hormone, thyroxine, and thyrotropine in umbilical cord blood.

iii) Coagulopathy

One of the most life-threatening problems in the newborn of an epileptic mother is the coagulopathy caused by a decrease in vitamin K-dependent clotting factors thought to be a result of AED treatment.[71]

There is a report of severe neonatal bleeding, in particular intracranial bleeding, possibly related to the use of AEDs, and prophylactic administration of vitamin K1 or K2 is advocated for all infants born to epileptic mothers treated with AEDs, as well as to the mothers during the last week of pregnancy. In the author's subjects, a slight but significant prolongation both of prothrombin and thrombin time was observed, and a significant decrease in the Hepaplastin test. From an analysis of seven clotting factors (I, II, V, VII, VIII, IX, X) only factor X showed lower levels than in the controls, the remaining vitamin K-dependent factors (II, VII, and IX) remained at almost the same level as in the control group.[61] Since the bleeding seems to occur early in the neonatal period in infants of treated epileptic women, KAWAMURA, *et al.*[61] recommend that the Normotest be used in screening for hemorrhagic diathesis in these infants at

Table 3 Analysis of risk factor by wilcoxon rank sum test

item	category	normal	malformed	total	test statistics
Drug score	DS=0	18	2	20	Z=−2.469*
	0<DS< 5	40	3	43	P= 0.014
	5≦DS<10	46	4	50	
	10≦DS<15	30	7	37	
	15≦DS<20	19	6	25	
	20≦DS<25	7	1	8	
	25≦DS	6	3	9	
VPA	DS=0	146	19	165	Z=−2.161*
	0<DS<2	0	0	0	P= 0.031
	2≦DS<4	4	0	4	
	4≦DS<6	3	0	2	
	6≦DS<8	6	3	9	
	8≦DS<10	4	3	7	
	10≦DS<12	0	0	0	
	12≦DS<14	2	1	3	
	14≦DS<16	0	0	0	
	16<DS	1	0	1	
CBZ	DS=0	112	13	125	Z=−1.999*
	0<DS<2	1	0	1	P= 0.046*
	2≦DS<4	16	2	18	
	4≦DS<6	15	4	19	
	6≦DS<8	13	3	16	
	8≦DS<10	5	4	9	
	10≦DS<12	2	0	2	
	12≦DS<14	2	0	2	
	14≦DS<16	0	0	0	
	16≦DS	0	0	0	

Drug score : see reference No. 86.
VPA : Valproic acid, CBZ : Carbamazepine.

birth and shortly afterwards.

iv) Congenital malformation

More than 40 years after the introduction of PHT for the therapy of epilepsy, it is now generally accepted that maternal intake of AED during pregnancy is associated with an increased frequency of congenital malformations in the offspring.[73,74] The incidence of a major malformation occurring is 5-10%[73,75~77] and for minor malformations the rate is more than double.[77] Nearly all possible malformations are found, and the most common is congenital heart disease. The cleft lip and/or palate are also common, while malformation of the central nervous system, renal, genital and skeletal system are less common.

The results of 13 retrospective studies reviewed by JANZ[74] showed that in the offspring of treated epileptics the risk of cardiac malformations was three to eight times higher than in the control group, while children of untreated epileptics had no increased risk.

Children from treated pregnancies have malformations about 1.2 times more often than those from untreated pregnancies,[74,77] and the risk for children of epileptic mothers appears to be 1.8 to twice the risk for control children.[5] Malformations are more often in children of epileptic mothers than in children of epileptic fathers.[2,75,78~80] Although the differences in the studies are not always statistically significant, all showed the same

Table 4 Incidence of congenital anomalies in live-born infants exposed to CBZ, VPA and combination of these drugs

Drug combinations	No. of exposed infants	No. of malformed infants	Rate (%)
CBZ	8	1	12.5
VPA	3	0	—
CBZ+α (except for VPA)	43	7	16.3
VPA+α (except for CBZ)	12	5	41.7
VPA+CBZ$\pm\alpha$	16	6	37.5

pattern, justifying the conclusion that AEDs have a teratogenic effect.

Minor anomalies such as hyperterolism, epicanthus, low inserting ears with dysplastic auricules, and hypoplasia of the finger nails or distal phalanx of the fingers have been related to the treatment of epileptic mothers with PHT or some other drugs.[57,81,82] However, these abnormalities are not drug specific. The same is true for the major malformations, since each malformation or minor anomaly is not always confined to a specific AED.

It is unknown whether or not the various AEDs are associated with different risk figures. KANEKO, *et al.*[77] and NAKANE, *et al.*[83] found no significant association between malformed infants and PHT exposure, while DANSKY, *et al.*[84] found a positive correlation between plasma concentration of PHT and malformations. In the study of KANEKO, *et al.*,[85] maternal total dose of AEDs/day, VPA and CBZ during the first trimester of pregnancy were significantly related to the malformation (Table 3). KANEKO, *et al.*[77,86] and SHAPIRO, *et al.*[75] excluded the possibility that PB could induce malformations. However, NAKANE, *et al.*[83] found a significant association between malformations and PB and PRM intake in their retrospective study.

There is some evidence of an association between exposure to diones and increased malformation rates. Among 53 reported pregnancies in which the fetuses were exposed to trimethadione or paramethadione, among the 40 live births, 33 newborns (83 %) had at least one major malformation.[82] NAKANE, *et al.*[83] also found a highly significant association between trimethadione and malformations in the offspring. DANSKY, *et al.*[84] found that trimethadione was associated with a high risk of congenital heart disease in the offspring. There is a growing evidence from several countries that there is a greater occurrence of congenital malformations when the mother receives combined AED therapy. Regarding the possible teratogenic actions of VPA and CBZ, KANEKO, *et al.*[77,86] (Table 4) and LINDHOUT, *et al.*[87] reported that the combination of VPA and CBZ, and CBZ+VPA+PB were significantly associated with a very high incidence of congenital malformation (about 50%) compared with the rate in infants born to the mothers with other combinations of AEDs. LINDHOUT, *et al.*[87] suggested that an accumulation of CBZ-10, 11-epoxide or other epoxide intermediates were responsible for the malformations, while GLATT, *et al.*[88] found no harmful effects of epoxide intermediates of CBZ.

Apart from these report, NAU, *et al.*[65] found that the teratogenecity of 4-en-VPA, one of the metabolites of VPA was similar to that of VPA, while other metabolites 2-en-VPA, 4, 4-dien-VPA and PGA were not embryotoxic. KANEKO, *et al.*[90] recently observed that the percentage of serum level of 4-en-VPA/maternal drug in the mother during pregnancy who had a malformed infant was significantly higher than those of mothers who had not. In the same report, the level of the 4-en-VPA was very low when compared to that of 2-en-VPA or other VPA metabolites. Therefore, this report may partly support Nau's results, but like PHT,[91] an involvement of other epoxide intermediates including that of 2-en-VPA also should be studied. Folate metabolism may be implicated, since folic acid deficiency can occur in mothers using AEDs during pregnancy.[58] OGAWA, *et al.*[92] demonstrated that the folate level of mothers who had malformed infants showed a slightly lower level than those who had not, but the difference failed to reach a statistically significant level. Therefore, an implication of folate has not been verified.

As to possible risk factors besides AEDs, STARREVELD-ZIMMERMANN[93] noted that mothers of malformed children had a significantly higher incidence of seizures during pregnancy, while ANNEGERS, *et al.*,[94] BECK-MANNAGETTA, *et al.*,[80] and NAKANE[95] did not found this relationship. BOSSI[5] recently reviewed a study of 71 cases taken from several studies and found that 23 patients had absence seizures with or without "grand mal", 28 had "grand mal" only, 14 had partial seizures with or without secondary generalization, and 5 had unclassified seizures. ANNEGERS, *et al.*[94] found a higher malformation rate in newborns of mothers with generalized epilepsy (11%) than in newborns of mothers with partial seizures (4%), while KANEKO, *et al.*[77] obtained the results that simple partial sizures might be related to the increased malformation. These findings therefore do not conclusively support the hypothesis that the seizure type may be relevant for the increased malformations in the offspring. Maternal age was not found to be a factor for the increased rate of malformation.[77,86] A possible role for genetic factors was suggested by NAKANE,[51,83] DANSKY, *et al.*[84] and GREENBERG, *et al.*[96] found an increased malformation rate in the families of malformed children. These findings, however, were not confirmed by FRASER, *et al.*,[97] and ANNEGERS and HAUSER.[98] The author's group recently found in the prospective study that the occurrence of sezures during the first trimester of pregnancy, the drug score (total daily dose of AEDs), simple partial seizure, and the drug combination of VPA+CBZ had significant relevance to the increased malformations.[77,86] However, these factors were interrelated, and the author suspect that the simple partial seizure might be a reflection of the treatment of patients with partial seizure with the combination of VPA and CBZ. Further, the occurrence of seizure during the first trimester could be a reflection of the severity of the disease, with severe epileptic patients having to be treated with larger dose of AEDs.[85] Therefore, it is the author's opinion at this stage that the total daily dose of AEDs and the combined usage of VPA+CBZ are the most critical factors for the increased malformation rate.

Table 5 Antiepileptic drug concentrations in maternal serum and milk

Drug	Milk concentration (μg/ml)	Serum concentration (μg/ml)	M/S ratio (%)	N
Phenytoin	0.64±0.03	2.96±0.37	18.84± 1.16	115
Phenobarbitone	4.38±0.31	11.78±0.74	34.55± 1.51	131
Primidone	3.47±0.26	5.01±0.38	72.35± 3.19	104
Carbamazepine	2.02±0.14	4.70±0.25	43.42± 1.69	72
Valproic acid	2.99±1.10	25.03±3.20	9.66± 3.18	22
Ethosuximide	23.00±2.05	32.00±4.54	78.32±10.38	6

Each value is the mean±S.E.
M/S ratio indicates milk concentration/serum concentration ratio
N=number of samples.

v) Withdrawal syndrome

A withdrawal syndrome caused by AEDs was intensively studied by HIRANO, *et al.*[96] Infants born to mothers who have taken AEDs throughout pregnancy or in the last trimester may have symptomes such as hyperirritability, tremor, convulsion, vomiting, poor suckling, and excessive crying appearing mainly 1 to 3 days postpartum and lasting for as long as some months after delivery.[57,99] Of the AED withdrawal symptoms, hyperirritability, tremor, convulsion, vomiting, poor suckling and excessive crying were observed as the most frequent symptoms, while hyperactivity and sleep disturbance were rarely seen. Maternal age at delivery, seizure type, etiology of epilepsy and the occurrence of seizures were not correlated with the incidence of the withdrawal syndrome, while PHT, PB and PRM appeared to be the primary causes for the syndrome in neonates rather than CBZ or VPA.[96]

vi) Breast feeding

The supply of mother's milk is important to the infant as it provides it with immunological protection. However, AEDs indirectly administered to the neonate via the breast milk by serial administration can produce undesirable effects.[100,101] The relative disparity in the transfer rate to milk of various AEDs are shown in Table 5.[100~102]

Serum levels of AEDs in infants receiving mixed or breast feeding showed a transient increase during the first week postpartum. This increase was ascribed to the drugs administered indirectly via the breast milk. Some infants became drowsy when suckled by their mothers and could not complete their feeds. Elimination of the drugs, especially PB and diazepam, from neonatal serum is delayed for the first 5 to 7 days. Breast milk contained rather low concentrations of the drugs in treated mothers when their blood levels remained within the therapeutic range. However, the slow PB and diazepam metabolism may present some hazard to the infant. Therefore, it is advisable for mothers taking PB, PRM, and diazepam to reduce or discontinue breast feeding for the first 7 days postpartum.[103]

vii) Physical and psychomotor retardation at follow-up

An increased incidence of physical and mental subnormality was reported during a follow-up study of these infants, and recently these findings were reviewed by HELGE.[104]

The small head circumference at birth of infants born to epileptic mother[3,62,69,104~106] normalized after the first 6 months of life.[107]

Concerning neurological findings, some of the infants of epileptic mothers showed neurological abnormalities including muscular hypotonia. Most of these neurological abnormalities normalized within the first 3 to 12 months of life, and NOMURA *et al.*[107] found that the higher the AED dosage the higher the incidence of the neurological abnormalities.

The psychomotor development of children exposed to AEDs during pregnancy was retarded,[108,109] and the retardation was more often encountered in children born to epileptic mothers with partial epilepsy rather than generalized epilepsy.[109] There was a negative correlation between total dose of AEDs/day and the developmental quotient (DQ) score in the field of language understanding in younger children (about 1.5 years in age) but not in older children (about 3 years). Head circumference of the infants at birth was significantly correlated with the development of speech in the younger children of epileptic mothers. There was no observable negative effects of breast feeding on the psychomotor development of the children. The educational background of the mother significantly affected the psychomotor development of her child more in the older children rather than in the younger children. These results suggest that the adverse effects of AEDs matter more at a younger age, but later on, the environment of the child's care is more important for the psychomotor development of the children. This, in turn, suggests that the psychomotor development of an epileptic mother's offspring can develop normally, if the child is properly treated.[109]

V. Conclusions and Some Recommendations

Today, epileptic women can safely conceive and give birth in the same way as non-epileptic women. However, since risks and difficulties during pregnancy, delivery, and child-care remain greater for epileptics than for non-epileptics, some special considerations are necessary.

Multiple physicians are frequently involved in the medical care of the gravid patient. It is important for the attending physician providing medical care for the gravid patient be aware of all drugs prescribed for his patient by each physician. Most of the AEDs cross the placenta and some cause unwanted effects on the embryo, the fetus, or the newborn. The type and the severity of these effects will depend upon factors such as the stage of pregnancy, the dose administered and the time of exposure. Therefore, the drugs should be administered in a better way, based on a more rational and informed approach. Accordingly, conception should no longer just happen, but be planned so that the fetus will be conceived under the best physical conditions, to ensure in the most beneficial intrauterine environment possible without exposure to massive dose of AEDs.

The complete control of seizures in a pregestational period and regular drug taking

are very important for better management of pregnant epileptics with medication, since there is a report indicating that if the patient's compliance is good, the seizure frequency is considered to remain mostly unchanged.

Periodical monitoring of the serum level of AED is also important even if the epileptic seizure is controlled. If the serum level decreases, one must confirm the patient's compliance. Once compliance has been established the dose should be increased only when seizures occur.

Thus pre-conceptional counselling should ensure that an epileptic embarks upon a pregnancy with her epilepsy well controlled on minimal dose of AEDs, and with an adequate explanation about the questions raised by patient should be given to prevent poor compliance.

There is an increased risk of major congenital malformations among the offspring of women with epilepsy, most of whom are on AEDs. The risk for all abnormalities in these infants appears to be about 10%, which is approximately more than double the rate of malformations in the general population. Part of this increase is due to exposure to AEDs. Other factors also appears to play an important role. Dysmorphic craniofacial features and digital defects have also been associated with gestational exposure to AED medication. This constellation was at one time termed phenytoin syndrome, but it has subsequently been revealed not to be drug-specific. The risk of this syndrome is probably more than 10%. Prevention of malformation, on the basis of the data available to date, can therefore take place before the onset of the pregnancy by decreasing the dose of the drug and/or changing from a combination of AEDs to a single drug, since there may be a dose-response relation for teratogenesis and a greater occurrence of congenital malformations when the mother receives combined AED therapy.

An aspect of prenatal growth deficiency that has raised concern is that brain growth may be affected, producing microcephaly and mild to moderate mental retardation. The child may not nurse well, cry excessively and have cyanotic attacks caused by apnea due to withdrawal syndrome. It is important, however, to rule out other causes of cyanotic attacks such as electrolyte imbalance, hypoglycemia, congenital cardiac defects, or cerebral malformations. It is also necessary to determine the serum levels of the AEDs in the infant for the diagnosis to be established.

The physical and psychomotor development of infants born to epileptic mothers was delayed. However, physical development and neurological abnormalities normalized within one year of age suggesting that the delay in the physical development of the offspring may be transient. The psychomotor retardation, which was at least partly caused by AED therapy, continued only through infancy. Later on, however, psychomotor development may be much more dependent on the child care environment making it likely that the child will show an improvement in development if they are treated properly.

Every epileptic pregnant women should be admitted to a well-equipped hospital or

maternity center with adequate facilities and manpower, if possible, in the first trimester of pregnancy and prior to the onset of labour. The antepartum and intrapartum fetal heart rate monitoring at each visit is necessary to detect fetal distress as early as possible. For all epileptic mothers, postpartum and intrapartum care and advice are especially important since "puerperal blues" and/or "depression" are likely to provoke epileptic seizures.

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