TRENDS IN PREGNANCY OUTCOME IN EPILEPTIC WOMEN OVER TWO DECADES: RELATIONSHIP TO MATERNAL ANTICONVULSANT THERAPY

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ABSTRACT

The prevalence of abnormal pregnancy outcomes in the offspring of 103 epileptic women followed prospectively during pregnancy between 1982 and 1989 was compared with that in the previous study of 119 pregnancies by Dansky et al. from the same institution.

Our results have shown a significant decrease in the prevalence of major malformations, as compared with the previous study: 8.8% vs. 21.1% ($P<0.01$). Monotherapy was more frequent and the mean number of drugs used during pregnancy was significantly smaller in the present study. Phenytoin, phenobarbital and primidone were prescribed less frequently in the present study, whereas carbamazepine and valproic acid were used more frequently. Plasma levels of valproic acid during pregnancy were higher in mothers of malformed babies. In the present study, plasma folate levels were significantly higher, and more patients were taking folate supplements during pregnancy.

In conclusion, the type and number of drugs used during pregnancy, as well as the plasma concentrations and serum folate levels, may determine the frequency of abnormal out comes.

RÉSUMÉ

La prévalence d'anomalies au cours de la grossesse issues de la descendance de 103 femmes épileptiques suivies en perspective entre 1982 et 1989 dans le même institut a été comparé avec l'étude antérieure de 119 grossesses par Dansky et al.

Les résultats ont montré une franche diminution dans la prévalence de malformations majeures en comparaison avec l'étude antérieure: 8.8% contre 24.1% ($P<0.01$). Dans notre étude, la monothérapie a été utilisée plus fréquemment et la quantité moyenne de médicaments administrée pendant la gestation a été nettement plus faible. La phenytoine, le phenobarbital et la primidone ont été prescrits moins fréquemment; par contre, la carbamazepine et l'acide valproique ont été utilisés plus souvent. Les dosages plasmatiques d'acide valproique pratiqués au cours de la grossesse ont montré des taux plus élevés chez les mères d'enfants malformés. Dans l'étude actuelle, le niveau des folates plasmatiques a été plus élevé, et plus de patientes ont ingéré des supplements foliques durant leur grossesse.

En conclusion, le choix et le nombre de médicaments utilisés durant la grossesse, les concentrations sériques et les taux de folates sanguins peuvent déterminer la fréquence des malformations.

PREFACE

This study was carried out in the Neurogenetics Unit of the Montreal Neurological Hospital and Institute, and in the Department of Neurology and Neurosurgery and the Centre for Human Genetics of McGill University. An ongoing prospective study of epilepsy and pregnancy has been conducted in the Neurogenetics Unit under the supervision of Dr. Eva Andermann since 1971.

The present investigation was prompted by the clinical observations of my supervisor, Dr. Eva Andermann, who felt that there had been a decrease in the rate of major congenital malformations observed in offspring of epileptic women in the past few years, as compared to the previous decade. However, neither the decrease in malformation rates nor the variation in the various risk factors which might contribute to the malformations had been statistically documented.

The purpose of this study was to compare the prevalence of abnormal pregnancy outcomes between 1982-1989 with the previous study by Dansky et al. (1989) from the same institution, as well as to compare the relative frequencies of the various risk factors in the two studies.

The following findings represent the contributions to original knowledge of the present study:

1. The results have shown a significant decrease in the prevalence of major malformations, as compared with the

previous study.

2. The use of monotherapy was more frequent, and the mean number of drugs used during pregnancy was significantly smaller in the present study.

3. Phenytoin, phenobarbital and primidone were prescribed less frequently in the present study, whereas carbamazepine and valproic acid were used more frequently.

4. Four of the eight major malformations in this study were observed among children exposed to VPA in the first trimester.

5. Plasma levels of valproic acid during pregnancy were significantly higher in mothers of malformed babies.

6. Plasma folate levels in all trimesters combined were significantly higher in the present study than in the previous study.

7. Valproic acid monotherapy was associated with the highest frequency of developmental defects, whereas carbamazepine alone or in combination was associated with the lowest frequency of major congenital malformations and of developmental defects.

In conclusion, our study points to a significant decrease in the rate of malformations in the past decade, and identifies the factors possibly contributing to this improved outcome, as follows: less frequent use of phenytoin, phenobarbital and primidone, and more frequent use of carbamazepine; a reduction in the use of anticonvulsant

drugs in combination with a greater reliance on monotherapy; and higher maternal serum folate levels during pregnancy.

I hope that this study will contribute to improved genetic counseling for epileptic women of childbearing age, and to better management of their pregnancies. I also hope that it will assure women with epilepsy that they have a good chance of having normal children if their anticonvulsant regimen is properly adjusted, preferably prior to pregnancy, and if their pregnancies are carefully monitored.

I could not have accomplished this work without the help of the following individuals:

My supervisor, Dr. Eva Andermann, examined the pregnant women with epilepsy and their children in both studies, and suggested the variables which should be analyzed.

Dr. Kenneth Silver, a pediatric neurologist at the Montreal Children's Hospital, examined many children of epileptic women in the present study, in order to detect any neurological or developmental abnormalities.

Dr. Christina Wolfson advised me on the statistical analysis of the data.

Dr. Frederick Andermann supported the various aspects of this study.

Dr. Allan Sherwin advised me about the newly introduced anticonvulsant drugs, and monitored the plasma anticonvul-

sant concentrations. Marie-Hélène Seni, Mary Huszthy, Lisa Andermann and Amrita Paul not only arranged patient appointments, but also helped in various aspects of this study.

Dr. Hirokazu Oguni, my husband, imparted much information about epilepsy to me, and helped me in the use of the computer.

I greatly appreciate all of their help.

ABBREVIATIONS

AF-AFP: amniotic fluid alpha-fetoprotein

AC: anticonvulsant

CBZ: carbamazepine

CBZ-E: carbamazepine-10,11-epoxide

CHD: congenital heart disease

CLP: cleft lip with or without cleft palate

DD: developmental defect

DPA: dipropylacetate

ESM: ethosuximide

FS-AFP: fetal serum alpha-fetoprotein

MS-AFP: maternal serum alpha-fetoprotein

PB: phenobarbital

PDH: postural deformity and hernia

PHT: phenytoin

PRM: primidone

VPA: valproic acid

VPM: valpromide

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INTRODUCTION

During the past two decades, an increased risk of congenital malformations in the offspring of women with epilepsy has been reported. A number of prospective and retrospective studies have been carried out in order to confirm or elucidate the relationship between an increased incidence of major malformations and various risk factors including anticonvulsant(AC) drugs (Reviewed in: Janz 1982a).

In a number of prospective studies (Table 1), the frequency of major malformations occurring in the offspring of epileptic women taking AC drugs ranged from 0.0-19.2%, with an overall frequency of 6.5%. This is significantly higher than the frequency of malformations not only in the normal control group but also in offspring of epileptic women not taking AC drugs during pregnancy. These investigations have not yet conclusively identified the teratogenic agents, but several factors have nonetheless been implicated in the etiology of the major malformations in these studies. They are: genetic predisposition, AC drugs and their metabolites, drug interference with folate metabolism, depression of cardiorespiratory function and fetal hypoxia due to maternal seizures. Of these factors, early fetal exposure to AC drugs appears to be etiologically the most potent.

There is, however, still considerable debate as to whether the malformations should be attributed solely to a

teratogenic effect of AC drugs or to a combination with other factors related to epilepsy.

Many attempts have been made to clarify which AC drugs are the most responsible for the increased incidence of major malformations. In the 1970's and early 1980's, phenytoin(PHT) and phenobarbital(PB) were considered to be more teratogenic than other AC drugs, although there were several reports that questioned these findings. PHT has also been suspected of producing certain minor congenital anomalies constituting the so-called "fetal hydantoin syndrome" (Hanson and Smith, 1975). In the past 10 years, several changes in the medical management of epileptic patients have taken place; 1) a change of strategy in AC drug therapy for epilepsy which advocates monotherapy rather than polytherapy, whenever possible; 2) routine monitoring of plasma AC concentrations which helps to determine the "optimal doses". These advances in medical treatment have brought not only improvement of seizure control but also fewer side effects for epileptic patients. Since the advent of plasma AC drug monitoring, several studies regarding the correlation between AC plasma concentrations and the incidence of major malformations have been conducted, one of which showed a highly significant positive correlation between major malformations and plasma PHT levels in the first trimester of pregnancy (Dansky et al, 1982b).

Dansky et al.(1982a) have studied the major malformations in offspring of epileptic women since 1971, and have

reported a number of risk factors related to the appearance of these malformations. In this study, the risk factors among pregnancies followed prospectively between the years 1982 and 1989 at the Montreal Neurological Hospital were compared with those analyzed by Dansky (1989) for pregnancies followed prospectively in the same institution between the years 1971 to 1984. There was no overlap in the pregnancies studied in the two series.

REVIEW OF THE LITERATURE

Over the past two decades, there has been considerable concern regarding the increased rates of congenital malformations among offspring of women with epilepsy. In 1963, Müller -Küppers, in a case report of a 3 1/2 year old male with microcephaly and submucous cleft palate exposed to mephenytoin in utero, first suggested that the defects represented an anticonvulsant drug-induced embryopathy. Soon after, an increased risk of congenital malformations in children of women with epilepsy was reported by other authors (Janz and Fuchs, 1964; Meadow, 1968). Anticonvulsant drugs taken during pregnancy were implicated as a possible etiological factor.

A. MINOR MALFORMATIONS

In 1972, Speidel and Meadow first noted that some children of epileptic mothers had a recognizable pattern of major and minor anomalies, though no single anomaly was consistently found in all the children. Following this, several studies appeared concerning the relationship between AC drugs and minor anomalies (Barr, 1974; Hanson et al., 1976). In particular, a relationship was reported between PHT and distal digital hypoplasia (Loughnan et al., 1973). Since then, PHT has been reported to be responsible for certain minor congenital anomalies, constituting the so-called "fetal hydantoin syndrome", which was first coined by Hanson

and Smith in 1975.

Andermann et al(1981b,1982) assessed the risk of minor congenital malformations in relation to the presence of major congenital malformations and to maternal use of anticonvulsant medications during pregnancy. Minor anomalies including digital hypoplasia with or without nail hypoplasia and dermal arch patterns were found significantly more frequently in the offspring of treated, as compared to untreated epileptic mothers. They concluded that the dermal arch pattern may serve as a subtle indicator of the teratogenic effects of anticonvulsant medication. Minor malformations, including altered dermatoglyphic patterns, could serve as indicators of altered morphogenesis and suggest the presence of a more serious underlying defect.

Rating et al (1982) also studied the incidence of minor anomalies in children of epileptic mothers, and concluded that children exposed to antiepileptic drugs in utero have significantly more minor anomalies than children of untreated epileptic mothers. Minor anomalies were more frequently observed after exposure to at least two antiepileptic drugs, as compared to monotherapy (Rating et al., 1982).

Dansky et al(1987) investigated the relationship between minor birth defects and anticonvulsant medication. They could not find a significant correlation between the response to in vitro PHT metabolite challenge and minor birth defects, including typical features of the "fetal

hydantoin syndrome". Their conclusion based on this evidence was that the various physical abnormalities observed in children exposed to phenytoin in utero may have a heterogeneous etiology. That is, the fetal outcome is probably multifactorial, involving a number of genetic and environmental factors.

B. MAJOR MALFORMATIONS

Dansky et al(1982a)at the MNI first studied the risk factors for abnormal pregnancy outcomes, including abortions, stillbirths, and major congenital malformations in a retrospective manner, comparing the incidence of the above mentioned outcomes in the offspring of epileptic women and epileptic men. They found that epileptic women had a significantly higher frequency of major congenital malformations in their offspring than did epileptic men. The frequency of malformations in offspring of epileptic women taking anticonvulsant medications in the first trimester of pregnancy was 15.9% as compared with 6.5% in offspring of epileptic women who took no medication in the first trimester. They concluded that antenatal exposure to anticonvulsants and family history of major congenital malformations are implicated as possible risk factors.

Based on these results, a prospective study in epileptic women was initiated by the same group in order to assess the relationship between maternal dose and plasma levels of anticonvulsants during pregnancy, and the frequency of ab-

normal outcomes. Dansky et al.(1981, 1982b) were able to confirm that antenatal use of PHT, PB, and primidone(PRM) alone or in combination was associated with an increased risk of congenital malformations in the offspring. The mean dose and plasma levels of phenytoin and of phenobarbital in the first trimester of pregnancy were significantly higher in mothers of malformed children than in mothers of normal children (Dansky et al, 1981; 1982b). Furthermore, there was a significant positive correlation between the frequency of congenital malformations in the offspring and maternal plasma levels of phenytoin during pregnancy (Dansky et al., 1981; 1982b). With regard to the relationship between maternal seizures during pregnancy and abnormal pregnancy outcomes, one-half of the malformed offspring were born to mothers who did not have any major seizures during the first trimester of pregnancy.

Other studies have shown a similar association between anticonvulsant exposure and congenital malformations. Lindhout et al(1982) also investigated the outcome of pregnancy in epileptic women prospectively. They revealed that infants exposed prenatally to PB or PHT show significantly more congenital anomalies than infants exposed to other antiepileptic drugs. Although dipropylacetate(VPA), carbamazepine(CBZ), and ethosuximide(ESM) seemed to be relatively safe, when administered alone or in combination with other drugs, combined exposure to PB and CBZ or DPA resulted in a significantly higher rate of congenital

anomalies in the infants, as compared to the frequency of anomalies on either drug taken without PB, with or without other medications.

Annegers and Hauser(1982) found that offspring of women with epilepsy who took anticonvulsant medications during the first trimester had a high rate of major congenital malformations (19 of 177 or 10%). They were unable to show any difference in the rate of congenital malformations between those exposed to phenytoin or to barbiturates, confirming the findings of Dansky et al(1982a) and of Lindhout et al(1982). They also could not find that the siblings, nieces, and nephews of probands with epilepsy were at elevated risk for major congenital malformations.

As Dansky et al have shown(1981; 1982a, b), antenatal exposure to anticonvulsant drugs appears to be one of the possible causes for the increased incidence of congenital malformations and other abnormalities among children of epileptic women. An experimental study in mice had previously revealed that the teratogenic effects of phenytoin correlate with increasing dosage and plasma levels during pregnancy (Finnell, 1980).

Serum anticonvulsant levels have been shown to decrease during pregnancy and return to prepregnancy levels postpartum (Dansky et al., 1982c). This fact may be one of the reasons why the seizure frequency increases during pregnancy (Remillard et al., 1982; Bardy, 1982). The mean ratio of plasma level to dose of phenytoin was found to be sig-

nificantly decreased during pregnancy (Dansky et al., 1982c). Factors which may explain this decline are: 1. decreased intestinal absorption; 2. decreased protein binding; 3. increased volume of distribution; 4. increased hepatic clearance; 5. increased renal clearance; 6. increased body weight, among others (Yerby, 1987). However, during pregnancy and postpartum, there was considerable variation in the plasma level/dose ratio among individuals; between different pregnancies of the same individual; and within pregnancies (Dansky et al., 1982c). Dansky et al. (1982c) suggested that there is some protective factor with respect to seizures operating in pregnant epileptic women, the most likely being progesterone. More recent studies have shown that, although there is a significant decrease in total anticonvulsant drug levels during pregnancy, the free levels of these anticonvulsants do not change significantly, because protein binding decreases during pregnancy (Perucca, 1987).

With respect to mechanisms of teratogenesis, both animal studies and human epidemiological studies suggest the existence of genetic differences in susceptibility to phenytoin-induced birth defects (Martz et al., 1977; Strickler et al., 1985; Dansky et al., 1987b). Strickler et al(1985) were able to demonstrate a strong correlation between a genetically-determined defect in phenytoin arene oxide detoxification and the frequency of major birth defects in the offspring. This correlation would suggest

that this inherited abnormality can strongly influence the likelihood of major adverse effects of the drug on the developing fetus. Thus pharmacogenetic differences in the detoxification of phenytoin arene oxide metabolites may contribute to the development of birth defects in children exposed to this drug in utero.

While focusing on the teratogenicity of AC drugs, some studies concluded that not only AC drugs, but also genetic predisposition, contributed to the congenital malformations. Bjerkedal et al. (1982a) found that congenital malformations did not occur more frequently in children of treated epileptic mothers than in children of control mothers. Janz (1982b) found no significant difference in the incidence of major congenital malformations between children of treated epileptic mothers and controls consisting of children of untreated epileptic mothers and of epileptic fathers. Friis (1979; 1982) found an increased frequency of parents with epilepsy among 391 patients with orofacial clefts in Denmark, without any difference between the incidence of epilepsy in mothers and in fathers.

C. SERUM FOLATE

As another risk factor, the serum folate level has been discussed. In 1972, Speidel and Meadow suggested that low serum folate levels in the mother may be associated with malformations in the fetus, since anticonvulsants of the barbiturate and hydantoin groups are known to reduce serum

folic acid levels. In experimental studies, folate deficiency has been shown to produce congenital malformations of many organ systems as well as embryonic death(Nelson et al., 1955; Kinney and Morse, 1964; Jordan et al., 1977; Crandall and Brazier, 1978). Furthermore, it is suspected of causing similar damage to the human fetus. Several studies showed that vitamin deficiency was a factor in the genesis of neural tube defects (Smithells et al. 1976, Sheppard et al., 1989), and Trots et al.(1987) demonstrated the reduction of neural tube defects by folate in mouse model. A number of studies have exhibited significantly lower folate levels in treated nonpregnant epileptics as compared with control subjects (Baylis et al., 1971; Dellaportas et al., 1982; del Ser et al., 1983). In normal pregnancy, maternal folate concentrations decline progressively due to the increased folate requirements of the mother and fetus (Scott et al., 1970; Baylis et al., 1971; Crandall and Brazier, 1978). Thus, epileptic women taking AED may have an increased risk of folate deficiency during pregnancy, and an adverse pregnancy outcome might occur if folate levels are inadequate in early pregnancy. Dansky et al(1987a)examined the relationship between folate deficiency during pregnancy and congenital malformations in the offspring. They found that a combination of PHT taken together with PB or PRM with or without other anticonvulsants was associated with the highest risk of folate deficiency, but blood folate levels were not correlated with

plasma VPA or CBZ levels in the small number of women studied. They concluded that anticonvulsants might increase the risk of folate deficiency and result in a significant increase of malformations during pregnancy.

However, several other studies (Hiilesmaa et al., 1983; Ogawa et al., 1985) did not find any association between low serum folate levels during pregnancy in epileptic women taking anticonvulsant drugs, and congenital malformations in their offspring.

D. DRUG INTERACTIONS

In recent years, the number of drugs taken by epileptic women during pregnancy has become the focus of various studies. In 1980 Nakane et al. found that the incidence of malformations was particularly high when three or more drugs were combined, increasing two fold in three-drug regimens and about fourfold in four-drug regimens, as compared with two-drug regimens. Some studies have reported that better outcomes occurred in women receiving monotherapy than polytherapy (Janz, 1982a; Yerby, 1987). Furthermore, Lindhout et al.(1982; 1984), and Kaneko et al.(1984) analyzed the relationship between particular combinations of AC drugs and congenital malformations, and found high rates of congenital malformations in subjects exposed to combinations of CBZ, PB, and VPA with or without PHT; as well as in combinations of VPA and CBZ with or without other agents.

1. CBZ AND VPA

CBZ and VPA have been introduced as AC drugs in North America in the past 10-15 years. Although CBZ was known as a relatively safe drug among AC drugs in terms of its teratogenicity, several recent studies have suggested that it may also have adverse effects on the fetus. In 1985, Niesen and Froscher reported one case exposed to CBZ in utero in which they observed distinct fingernail and toenail hypoplasia, and suggested that it might indicate a CBZ-induced growth inhibition. Hiilesmaa et al.(1981) noted that the head circumference of infants exposed in utero to CBZ was found to be significantly smaller as compared to control infants. Recently Jones et al.(1989) showed both prospectively and retrospectively a pattern of craniofacial and limb malformations and of developmental delay in children exposed to CBZ. Lindhout et al.(1984) raised the possibility that the low teratogenic potential of CBZ may be enhanced when the drug is taken together with other AC drugs, because other AC drugs may inhibit the synthesis of the detoxifying enzyme epoxide hydrolase and result in an accumulation of the CBZ-10,11-epoxide(CBZ-E). Meijer et al.(1984) found that a combination of valpromide(VPM) and CBZ results in a rise in the plasma concentration of the active CBZ-E metabolite, probably because of selective inhibition of the enzyme epoxide hydrolase.

E. VPA AND NEURAL TUBE DEFECTS

VPA taken during pregnancy has been associated with an increased risk of neural tube defects in the offspring since 1982. In that year, Robert and Guibaud in France reported that an unusually high proportion of infants with spina bifida (9/72) had mothers with epilepsy who were taking VPA during pregnancy. Lindhout and Schmidt (1986), in a collaborative prospective study, estimated the risk of spina bifida as 1.1 to 2.5% in children of women using VPA during pregnancy. Several animal studies have shown dose-related teratogenicity with VPA (Bruckner et al., 1983; Nau and Scott, 1987).

F. MATERNAL SERUM AFP

Since 1973, elevated maternal serum alpha-fetoprotein (MS-AFP) has been used to identify pregnancies at risk for open neural tube defects (Leek et al., 1973; Brock et al., 1973). Ventral abdominal wall defects, intestinal atresias, and sacrococcygeal teratomas have also been found to be associated with elevated MS-AFP (Clark et al., 1977; Schmidt and Muhlethala, 1975). Decreased MS-AFP has been associated with trisomy 21 (Cuckle et al., 1984; Merkatz et al., 1984). Amniotic fluid AFP (AF-AFP) is predominantly an ultrafiltrate of the fetal kidneys. The kidneys filter fetal serum AFP (FS-AFP) and excrete AFP into the fetal urine, a major source of amniotic fluid. Another source of AF-AFP may be transudation of FS-AFP though the nonkeratinized fe-

tal skin. MS-AFP is entirely synthesized by the fetus. Thus the level of MS-AFP during pregnancy changes with the stage of gestation, and may be of value in helping to predict a prenatal growth deficiency or major malformations. For normal fetuses, a linear relationship between fetal weight and maternal serum alpha-fetoprotein (both corrected for gestational age) is found ($r=0.41$, $p<0.01$) (Palomaki et al., 1988).

OBJECTIVES

The purpose of our study is to compare the incidence of major malformations in pregnancies studied prospectively between 1982 and 1989 with the incidence of such malformations found in the studies conducted by L.Dansky and her co-workers from 1971 to 1984.

Specifically our objectives are:

(1)To compare our results with the data of Dansky et al(1989) with respect to incidence of malformations; neonatal growth parameters; type, number and combination of anticonvulsant drugs used during pregnancy; and serum drug levels in each trimester;

(2)To determine positive and negative risk factors for malformations in the offspring;

(3)To study the teratogenicity of the newly introduced anticonvulsant drugs; and

(4)To examine the relationship between MS-AFP and the following parameters: serum AC drug levels, serum and red cell folate levels, and pregnancy outcome.

PATIENT MATERIAL

A. PRESENT MATERIAL

The patient material comprised 103 epileptic women who had 115 pregnancies followed prospectively at the Montreal Neurological Hospital(MNH) between 1982 and 1989, none of which were included in the study of Dansky et al(1989), which focused on women with epilepsy at the same institution who had pregnancies followed prospectively between 1971 and 1984. Among the 115 pregnancies in the present study, there were 90 with sufficient follow-up of the pregnancy outcomes (Table 2). Twelve patients are included with more than one pregnancy each. We excluded therapeutic abortions and artificial abortions, except when the reason for abortion was fetal abnormality.

B. PREVIOUS MATERIAL

This material was studied and reported by L.Dansky and her co-workers(1988, 1989). It comprised 94 epileptic women who had 119 pregnancies followed prospectively between 1971 and 1984 (Table 2). Nineteen patients had more than one pregnancy. Although there was no overlap between the pregnancies reported in the two studies, a few mothers had pregnancies in both studies.

METHODS

A. METHODS FOR OBJECTIVES 1 AND 2

Detailed medical, family, and reproductive histories were obtained according to a standardized protocol from the women and their husbands. This frequently necessitated several interviews and the medical information on patients and relatives was documented by reports from physicians and hospitals, whenever possible. The women were followed at monthly intervals until term and postpartum, whenever possible. At each visit, the pregnancy history, including maternal seizures and anticonvulsant intake, was reviewed, and blood anticonvulsant levels, as well as the serum and red cell folate levels, were monitored. The antenatal, delivery and neonatal records were reviewed for each pregnancy. Infants were examined by two physicians, including one child neurologist, at least once after delivery.

1. PREGNANCY OUTCOMES

The possible abnormal pregnancy outcomes were major malformations, minor malformations, spontaneous abortions and abnormal growth parameters.

Major malformations were defined as major structural defects present, or presumed to have been present, at birth. Major malformations were divided into two categories: developmental defects(DD) and congenital postural deformities and hernias(PDH).

The developmental defect group is defined as a morphologic defect of an organ, part of an organ, or a larger area of the body, resulting from an intrinsically abnormal developmental process. Types of abnormal morphogenesis are: (1) Incomplete morphogenesis: lack of development, hypoplasia, incomplete closure, incomplete separation, incomplete septation, incomplete migration, incomplete rotation, incomplete resolution of early form and persistence of early location, (2) Redundant morphogenesis, such as polydactyly (3) Aberrant morphogenesis, such as mediastinal thyroid gland.

The postural deformity group is defined as an abnormal form or position of a part of the body caused by nondisruptive mechanical forces. Important deformities include clubfoot, congenital hip dislocation, and congenital postural scoliosis.

The hernia group was added to the second category because inguinal and umbilical hernias are relatively common in the general population and clinically insignificant. Furthermore, some hernias are caused by mechanical forces (Gray et al., 1972).

The minor anomalies included in this study are listed in Table 3. All minor anomalies were noted for each infant, and the total number was used for comparison. When the minor anomaly was only slight, a score of 0.5 was given.

The growth somatic parameters (weight, length, and head circumference at birth) were obtained from the birth

records. The measured values of the somatic parameters were converted into standard deviation scores (SDS), which indicate the extent of deviation from the mean of the normal controls. The normal control values and standard deviation scores were obtained from the data of Usher and McLean(1969), based on the same hospital newborn population.

2. GENERAL RISK FACTORS

Alcohol intake and smoking during pregnancy, family history of congenital malformations, family history of epilepsy, maternal age, parity, and mean gestational age were analyzed. Alcohol intake and smoking during pregnancy were regarded as risk factors when, on a daily basis, more than one glass of wine was drunk or more than ten cigarettes smoked. These data were necessarily based on the information supplied by the patients. Gestational age was estimated on the basis of the date of the first day of the last menstrual period and the date of delivery. Weeks of gestation refer to completed weeks of gestation. Where there was disagreement between the estimated gestational age as determined by ultrasound ard by the last menstrual period, the ultrasound determination was used.

3. RISK FACTORS RELATED TO EPILEPSY IN MOTHER

Age at onset of seizures, duration of epilepsy, and seizures during pregnancy were carefully noted. Serum AC drug levels, and serum and red cell folate levels were

monitored pre-pregnancy, at monthly intervals during pregnancy, and postpartum.

4. MATERNAL SERUM AFP

Maternal serum AFP was monitored at each visit, at the same time as the anticonvulsant and folate levels.

More than 20 variables were compared between the previous and present studies, employing the statistical methods described below.

B. METHODS FOR OBJECTIVES 3 AND 4

We combined the data from the present and previous studies and calculated the rate of major malformations for each AC drug alone and in combination. In addition, we compared CBZ-E levels in patients on CBZ monotherapy and on combination therapy with CBZ and VPA. The ratios of CBZ-E/CBZ were compared before and during pregnancy in order to assess the changes in these ratios due to drug interaction and to pregnancy itself.

In the present study, we investigated the correlation between the serum AFP levels and the serum AC levels and serum folate levels at different stages of gestation, in an effort to determine whether the serum AFP levels are correlated with serum AC levels and/or serum folate levels. Since the serum levels of AFP change during pregnancy, two samples were chosen for analysis in each patient, one be-

tween the 16th and 20th week, and the other between the 20th and 24th week of pregnancy.

C. STATISTICAL METHODS

Student's t-tests and chi-square tests were the main statistical tests used in this study. When the sample numbers were particularly small, Fisher's exact probability test or Yates' correction were used. In addition, linear regression was employed, and the Spearman rank correlation coefficient was used when the distribution of the sample was asymmetrical about zero. We defined $P<0.05$ as a statistically significant difference.

RESULTS

A. OVERALL OUTCOME OF PREGNANCY

1. MAJOR MALFORMATIONS AND SPONTANEOUS ABORTIONS

Of the 116 pregnancies with known outcome in the previous study, 24.1% had major malformations (developmental defects in 11.2% and postural deformities and hernias in 12.9%)(Fig. 1, Table 4). In the present study, 8.8% of 90 pregnancies with known outcome had major malformations (developmental defects in 4.4% and postural deformities and hernias in 4.4%). Thus the frequency of major congenital anomalies decreased significantly in the present study ($p<0.01$)(Fig. 1, Table 4). The decrease in postural deformities and hernias was also statistically significant ($P<0.05$), whereas the decrease in developmental defects did not reach statistical significance. Six pregnancies (5.2%) in the previous study and nine (10%) in the present study ended in spontaneous abortion, and this does not represent a significant difference($P>0.05$)(Fig. 1, Table 4). The specific types of major congenital malformations and the corresponding AC drugs taken by the mothers during the first trimester of pregnancy in both studies are listed in Tables 5a and 5b.

With regard to individual anomalies, congenital heart defects (CHD) and foot deformities decreased dramatically, and cleft lip with or without cleft palate (CLP), hypospadias and subluxated hips also decreased in frequency

in the present study (Tables 6, 7). In the previous study, ventricular septal defects (VSD)(2.6%) occurred 10 times more frequently than in the general population (0.25%)(Bergsma, 1979)(Table 7). Foot deformities (3.2%) were 6 to 30 times more frequent than normal (0.1-0.5%)(Lovell, et al., 1986). The incidence of CLP (1.7%) was 17 times greater, that of hypospadias three times greater, and that of subluxated hips twice that observed to occur in the general population (0.1%, 0.5%, and 0.92% respectively)(Carter, 1969; Bergsma, 1979; Lindsay, 1979a, b; MacEwen et al., 1986)(Table 7).

In the present study, both atrial septal defects(ASD)(1.1%) and tetralogy of Fallot (1.1%) were 10 times higher than is normally the case (0.1%)(Table 7), although only one child with each was observed. There was no foot deformity. The incidence of CLP (1.1%) was 10 times higher than in the general population. No hypospadias or subluxated hips were observed.

As for inguinal hernia, both studies had almost the same incidence: 4.3% in the previous and 4.4% in the present study. This lies well within the risk of occurrence in the general population (1-5%)(Gray and Skandalakis, 1972; Bergsma, 1979; Klauber and Sant, 1985; First and Snyder, 1989)(Table 7).

2. MINOR ANOMALIES

Minor anomalies were carefully noted in 73 children in

the previous study, and in 64 children in the present study. In both studies, the number of minor anomalies in each child varied from 1 to 17. The distribution of the number of minor anomalies in each child in the two studies is plotted in Fig. 2. There was no significant difference between the two study groups with respect to the overall distribution of minor anomalies among the offspring (Fig. 2). However, when the number of children with ≤ 5 anomalies was compared with those with >5 anomalies for the two study groups, the difference was statistically significant ($P<0.05$)(Table 8).

3. GROWTH PARAMETERS AT BIRTH

No statistically significant difference was noted in head circumference(HC), body weight(BW) or body length(BL) between the two studies (Fig. 3, Table 9). In the present study, there was no significant difference in HC, BW and BL between the monotherapy and polytherapy groups. In the previous study and in both studies combined, HC was significantly lower in the polytherapy group than in the monotherapy group ($P<0.01$)(Fig. 4). A comparison of the BW and BL data recorded for the monotherapy and polytherapy groups of both studies combined revealed no significant differences.

B. COMPARISON OF RISK FACTORS BETWEEN BOTH GROUPS

1. GENERAL RISK FACTORS

The incidence of alcohol ingestion, smoking during pregnancy, maternal age at delivery, and gestational age did not vary significantly from one group to the other ($P>0.05$). The frequency of first-born children, and the distribution of first, second and third pregnancies also did not differ significantly between the two studies.

Only a positive family history of major congenital malformations in first, second, or third degree relatives reached a statistically significant difference, being higher in the previous study ($P<0.01$)(Table 10). In both studies, malformed offspring with CHD or CLP had no family history of these particular anomalies. However, half of the offspring with foot deformities, subluxated hips, and inguinal hernias, as well as the two afflicted with hypospadias, had a history of similar defects in other family members (Table 11).

2. RISK FACTORS RELATED TO EPILEPSY IN MOTHER

Tables 10 and 12 compare the two groups with respect to the frequency of major and minor epileptic seizures during the first and subsequent trimesters, age at onset of epilepsy, duration of epilepsy and distribution of epilepsy types. The previous study indicates that, over all trimesters of pregnancy, major seizures occurred in 45 preg-

nancies (40%) and minor seizures in 43 pregnancies (45%). The present study, on the other hand, lists 31 pregnancies with major seizures (37%) and 31 pregnancies with minor seizures (37%). The differences between the previous and present studies did not reach statistical significance ($P>0.05$) (Figs. 5, 6).

3. RISK FACTORS RELATED TO ANTICONVULSANT DRUGS

a) COMPARISON OF DISTRIBUTION OF MONOTHERAPY AND POLYTHERAPY IN BOTH STUDIES (Table 13)

In the previous study, 40% of all patients were treated with monotherapy and 57% with polytherapy (two or more AC drugs). The remaining 3% had no AC drugs. In the present study, there were 68% on monotherapy, 27% on polytherapy, and 5% without medication. Monotherapy was used with a significantly greater frequency in the present than in the previous study ($P<0.01$). Furthermore, the average number of AC drugs taken during pregnancy was significantly lower in the present study (1.3 vs. 1.7; $P<0.01$)(Table 13, Fig. 7).

There was also a significant difference in the types of AC drugs prescribed during the first trimester of pregnancy in the two studies (Table 14). In the present study, PHT, PB and PRM were prescribed less often (38% vs. 74% and 14% vs.44%, $P<0.01$; 6% vs. 17%, $P<0.05$), whereas carbamazepine and valproic acid were used more frequently (38% vs. 19% and

22% vs. 8%, P<0.01)(Table 14).

b) FREQUENCY OF MAJOR CONGENITAL MALFORMATIONS IN THE OFFSPRING IN RELATION TO MATERNAL ANTICONVULSANTS ISOLATED AND IN COMBINATION DURING THE FIRST TRIMESTER OF PREGNANCY (Figs. 8 and 9)

The previous study demonstrated that 50% of the pregnancies in which the mothers took PRM alone or in combination resulted in offspring with major malformations. It also showed that 26%, 25%, 25%, 22%, and 9% of the pregnancies in which the mothers were on PB, PHT, ESM, VPA, and CBZ respectively also resulted in offspring with major malformations (Fig. 8). The present study, on the other hand, shows that 20% of the pregnancies in which the mothers took VPA, 15.4% on PB, 8.6% on CBZ, and 2.9% on PHT with or without other anticonvulsants, resulted in offspring displaying major malformations. Only PHT resulted in a significantly lower frequency of major malformations in the present study (P<0.05)(Figs.8, 9).

c) FREQUENCY OF MAJOR CONGENITAL MALFORMATIONS IN THE OFFSPRING IN RELATION TO MATERNAL ANTICONVULSANT MONOTHERAPY OR POLYTHERAPY DURING THE FIRST TRIMESTER OF PREGNANCY (Figs. 10 and 11)

For monotherapy, the previous study associated 1 of 3 (33%) pregnancies on VPA, 2 of 7 (29%) on PB, 2 of 8 (25%) on CBZ, and 6 of 24 (25%) on PHT with major congenital mal-

formations. Furthermore, 5 of 9 (56%) of pregnancies in which the mothers took a combination of PHT, PB and PRM resulted in offspring with major malformations, as did 2 of 5 (40%) on PHT and PRM, 1 of 4 (25%) on PHT and VPA, 1 of 4 (25%) on PHT and ESM, and 4 of 27 (15%) on PHT and PB (Fig. 10).

In the present study, three of 12 pregnancies on VPA monotherapy (25%) resulted in offspring with major malformations, as did three of 24 (12,5%) on CBZ monotherapy, and one of seven (14%) on combined PHT and PB (Fig. 11). No major malformations resulted from 20 pregnancies on PHT monotherapy in the present study, and this represented a significant decrease of major malformations in the present as compared to the previous study ($P<0.05$)(Figs. 10, 11). The frequency of congenital malformations on CBZ monotherapy was also significantly decreased in the present study ($P<0.01$), and no developmental defects were recorded. One of two children exposed to VPA and PB in combination had an inguinal hernia.

d) PLASMA ANTICONVULSANT DRUG LEVELS AND THE OUTCOME OF PREGNANCY

(Figs. 12, 13, 14)

We compared the plasma AC levels of PHT (isolated and combined), CBZ (isolated and combined) and VPA (combined only) measured during the first, second, third and all trimesters combined for both groups.

In the case of PHT in combination, as well as in that of CBZ in combination, there was no statistical difference for any of the trimesters ($P<0.05$).

For PHT monotherapy, the present study recorded significantly higher plasma PHT levels for the first trimester than did the previous study. In the case of the other trimesters, there were no significant differences (Fig. 12).

For CBZ monotherapy, no significant difference in plasma CBZ levels between both groups was detected in any of the trimesters or in all trimesters combined (Fig. 13).

VPA was studied in combined form only because there was an insufficient number of patients on VPA monotherapy in the previous study to allow us to compare the findings with those in the present study. A statistically significant difference was seen for the second trimester and for all trimesters combined, with higher plasma levels in the present than in the previous study (Fig. 14).

e) COMPARISON OF SERUM FOLATE LEVELS BETWEEN THE PRESENT AND THE PREVIOUS STUDY

The patients in the present study had significantly higher serum folate levels than those in the previous study in the second and third trimesters and for all trimesters combined (Fig.15).

More patients in the present study were taking folate supplements during pregnancy than did those in the previous study (98% vs. 81%, $P<0.05$)(Table 15). Furthermore, the

previous study registered low serum folate levels (<4ng/ml) in the first and second trimesters of pregnancy in 14 out of 40 pregnancies (35%), as compared to 22 of 81 pregnancies (27%) in the present study. The difference is not statistically significant (P>0.05)(Table 15).

C. A COMPREHENSIVE SURVEY OF THE COMBINED DATA COMPILED IN BOTH THE PRESENT AND PREVIOUS STUDY

1. MAJOR CONGENITAL MALFORMATIONS IN THE OFFSPRING IN RELATION TO MATERNAL ANTICONVULSANTS DURING THE FIRST TRIMESTER OF PREGNANCY

In the case of AC drugs (isolated and in combination), major malformations occurred most frequently in the offspring of epileptic women taking PRM(40%), followed by PB(23%), ESM(22%), VPA(21%), PHT(18%) and CBZ(9%) (Fig. 16). Developmental defects were most frequent with PRM(24%), followed by VPA(13.8%), ESM(11.1%), PB(10.9%), and PHT(10.0%). CBZ was associated with the lowest frequency of developmental defects (1.8%), and this was significantly lower than the frequency of developmental defects for all other anticonvulsants combined (P<0.01).

The frequencies of developmental anomalies and of postural deformities and hernias were about equal for PHT, PB, and ESM, but developmental defects were most frequent with PRM and VPA.

In the case of isolated AC drugs, 27% of pregnancies

exposed to VPA monotherapy resulted in offspring with major malformations, as did 20% on PB monotherapy, 15% on CBZ monotherapy, and 13% on PHT monotherapy (Fig. 17). DD were seen most frequently with VPA monotherapy (27%), followed by PHT monotherapy (7%), and CBZ monotherapy (3%). No DD were seen in 10 children of mothers on PB monotherapy. The frequency of DD with VPA monotherapy was significantly higher than the frequency of DD for all other AC monotherapies combined ($P<0.01$). No DD were seen on VPA polytherapy, but the difference between VPA monotherapy and polytherapy was not statistically significant. The frequency of DD with CBZ alone or in combination was significantly lower than for all other anticonvulsants combined ($P<0.01$).

Postural deformities and hernias were most often associated with PB and CBZ monotherapy (20% and 12.5%, respectively). The frequencies of DD and PDH were about equal for PHT monotherapy (6.8% each). For specific drug combinations, 5 of 10 (50%) pregnancies on PHT, PB and PRM combined resulted in offspring with major malformations, as did 2 of 5 (40%) pregnancies on PHT and PRM, 1 of 4 (25%) on PHT and ESM, 1 of 6 (17%) on PHT and VPA, and 5 of 34 (15%) on PHT and PB (Fig. 17). Larger numbers of specific drug combinations would be required to draw definite conclusions about their relative teratogenicity.

Comparing the incidence of major malformations between the monotherapy and polytherapy groups for the two studies

combined, we find that, in the monotherapy group, these occurred in 19 of the 108 pregnancies (17.6%), whereas in the polytherapy group, they occurred in 17 of the 98 pregnancies (17.3%). The difference is not statistically significant ($P>0.05$)(Table 16). DD occurred in 8 of 108 pregnancies on monotherapy (7.4%), and in 9 of 98 pregnancies on polytherapy (9.2%), but the difference is also not statistically significant ($P>0.05$)(Table 16).

2. GROWTH PARAMETERS AT BIRTH IN RELATION TO ANTICONVULSANTS

a) MONOTHERAPY AND POLYTHERAPY

We compared HC in the monotherapy and polytherapy groups for both study groups combined. HC was significantly lower in the polytherapy than in the monotherapy group (Fig.4) ($P<0.01$). In addition, comparison of HC measurements when one, two, or three AC drugs were used also showed significant differences (one drug vs. two drugs, $P<0.01$, one drug vs. three drugs, $P<0.05$).

In the case of BL and BW, on the other hand, we failed to detect any statistical differences between the monotherapy and polytherapy groups.

b) INDIVIDUAL AC DRUGS

We compared HC when PHT monotherapy and PHT polytherapy were used, and proceeded to do the same for CBZ monotherapy and CBZ polytherapy, PB monotherapy and PB polytherapy and

VPA monotherapy and VPA polytherapy in order to identify the AC drug most responsible for lowering HC.

HC was significantly lower when CBZ or VPA was used in polytherapy than when the same drug was used in monotherapy. No significant difference was recorded, however, between PHT monotherapy and polytherapy, and this also holds true for PB.

D. COMPARISON, BASED ON THE PRESENT DATA, OF THE RISK FACTORS IN PREGNANCIES WITH NORMAL AND ABNORMAL OUTCOMES

1. NORMAL AND ABNORMAL OUTCOMES

No significant differences were found with respect to maternal age, gestational age, age at onset of seizures, family history of epilepsy, family history of congenital malformations, frequency of seizures during pregnancy, serum folate levels, alcohol ingestion or smoking during pregnancy, between pregnancies with normal and abnormal outcomes, and between the normal outcome and spontaneous abortion groups. Duration of epilepsy in the abnormal outcome group was longer than in the normal outcome group, although the difference was not statistically significant (Tables 17 and 18).

2. VPA PLASMA LEVELS

Three of the eight major malformations in the present

study were observed among children exposed to VPA monotherapy in the first trimester. We compared the plasma VPA levels in pregnancies on VPA monotherapy resulting in normal and abnormal outcomes. The plasma VPA levels for all trimesters combined were significantly higher in mothers of malformed babies than in those of normal babies (87± 21 μg/ml vs. 43± 34 μg/ml, P<0.01)(Fig. 18).

E. SERUM AFP, FOLATE, ANTICONVULSANT DRUG LEVELS AND OUTCOMES

We could not find any consistent relationship between serum anticonvulsant drug levels and AFP serum levels, or between serum folate levels and AFP levels (Fig. 19).

A few patients had AFP levels slightly above normal range once or twice during the pregnancy, but their children were normal. The evolution of AFP levels during pregnancy showed a normal pattern in all pregnancies, except in six patients. As these six normal-seeming pregnancies developed, AFP levels fluctuated unexpectedly. Two of these pregnancies were observed in one patient: the first pregnancy ended in a spontaneous abortion, and the second resulted in a malformed baby with CLP (Fig. 20).

F. DRUG INTERACTION AND METABOLISM OF CBZ

We compared the CBZ epoxide(CBZ-E) levels when CBZ was used in monotherapy and in combination with VPA (Fig. 21). The ratio of CBZ-E/CBZ in the VPA and CBZ combination was

higher than that in CBZ monotherapy for all three trimesters, and the difference is statistically significant for all trimesters combined ($P<0.01$).

When the CBZ-E level was measured in pregnant and non-pregnant epileptic women, it was found to be higher in the former in the first and third trimesters, and for all trimesters combined (Fig. 22).

DISCUSSION

In a continuing prospective follow up study of pregnant women with epilepsy monitored in the Neurogenetics Unit of the Montreal Neurological Hospital who delivered between 1982 and 1989, the outcomes of pregnancy were documented and compared with those reported in a previous study from the same institution by Dansky (1989). Although, prior to this study, the clinical impression appeared to suggest a decrease in the frequency of major congenital malformations in the past few years, this had not been statistically documented, and the various risk factors in this time period had not been analyzed in comparison to the pregnancies followed prospectively between 1971 and 1984. The results of the present study, when compared to those of Dansky (1989), showed a dramatic and statistically significant decrease in the incidence of major malformations in women with epilepsy taking AC drugs during pregnancy. The frequency of major malformations in the present study (8.8%) is also lower than that in other prospective studies [Kaneko et al., 1988 (14%)], and not significantly higher than in the general population (Table 19).

Although the teratogenic effects of AC drugs have been studied by many investigators, it is very difficult to compare the results of these studies. The criteria for patient ascertainment, the definition of major malformations, the distribution of epilepsy types, the proportion of intrac-

table patients, the treatment protocols, and a number of other factors which may influence pregnancy outcome differ among various centers. Lindhout (1982) included dysmorphism, mental retardation, ptosis and Down's syndrome as congenital anomalies, but these are not included in other studies (Kaneko et al., 1982, 1988; Dansky, 1989). Nakane et al. (1980) ascertained data from several institutions. Friis (1979) ascertained children with CLP, and determined the frequency of epilepsy among the parents of these children. In his review of the literature in 1989, he only focused on CHD and CLP. By contrast, the comparison between the present data and the data of Dansky et al.(1989) is valid, since the patients in these two groups have been followed in the same hospital according to the same prospective study protocol.

A. MAJOR MALFORMATIONS

Our results showed that both developmental defects, and postural deformities and hernias, decreased in frequency in the present study. This decrease was statistically significant for postural deformities and hernias ($P<0.05$), but did not reach statistical significance for developmental anomalies ($P<0.10$), probably because of the small numbers involved.

When we carefully analyzed individual malformations, those which showed the largest decrease in frequency between the two studies were CHD (6 vs. 1), and foot deformities (6

vs. 0)(Table 5). These and other major congenital malformations (CLP, subluxated hips) are known to be attributed to a multifactorial mode of inheritance in which both genetic and environmental factors interact to produce the final phenotype (Nora et al., 1967; Fraser, 1970; Carter, 1969; Lindsay, 1979a,b; MacEwen et al., 1986). We found that 2.8% of live births (2.6% of all outcomes) in the previous study showed ventricular septal defects(VSD), a rate 10 times higher than in the general population(0.25%) (Bergsma, 1979), whereas there were no offspring with VSD in the present study. The children with VSD in the previous study had no known family history of VSD or other CHD, which is believed to increase the incidence of VSD to a rate 20 times that for offspring without such a family history. Children with CHD other than VSD in both studies also had no family history of CHD. Among the six cases of CHD in the previous study, all six mothers were taking PHT (one PHT monotherapy, two PHT and PB, and three PHT, PB and PRM) during the pregnancy. In the present study, the only child with isolated CHD was born to a mother on VPA monotherapy. Thus it would seem that the contribution of genetic predisposition to CHD is less significant than the type and combination of anticonvulsant therapy during pregnancy. In the recent review by Friis (1989), he concluded that neither genetic factors or anticonvulsant medication seemed to increase the rate of CHD in children of epileptic patients. However, in our study, changing the strategy of medical treatment appears to

help decrease the occurrence of CHD, although we cannot totally rule out the influence of genetic and/or other environmental factors.

Pregnancy outcomes involving club foot were found in 3.7% of live births (3.4% of all pregnancies) in the previous study, which is 6 to 30 times higher than in the general population (0.1-0.5%)(Lovell et al,1986). Half of the offspring with club foot, however, had a positive family history of foot deformities, a factor that tends to suggest the recurrence of this defect in relatives [4.95% in the patient's sibs(Lovell et al, 1986)]. In the present study, there were no offspring with foot deformities, nor a family history of foot deformity. Among the six cases of club foot in the previous study, five mothers were taking PHT (three PHT monotherapy and two PHT,PB and PRM), and one mother was taking PB alone. The higher frequency of positive family history of the same malformation in the previous study suggests that genetic predisposition may contribute to the higher incidence of club feet noted in the previous study.

In addition, there were several other major malformations which were decreased in frequency in the present study: CLP, hypospadias, umbilical hernia and subluxated hips, though their number is too small to allow us to reach a definite conclusion. CLP has a high risk of recurrence in families (Carter, 1969; Lindsay, 1979a, b). The risk of recurrence in siblings is 30 to 40 times higher in probands with a positive family history of this defect. In both the

previous and the present studies, there was no positive family history of CLP in the relatives of offspring affected with this malformation. It is interesting that all mothers of children with CLP in both studies were taking PHT and PB during their pregnancies. Both mothers of children with this malformation in the previous study were taking PHT, PB and PRM during their pregnancies, and the mother in the present study took PHT and PB. However, the number of patients with this malformation is too small to conclude the drug specificity.

Recently several studies (Friis, 1979; Janz, 1982b) suggested that the etiology of this type of malformation was not only due to specific AC drugs, but multifactorial, because the malformation was observed in offspring of patients taking other AC drugs during their pregnancies as well as in offspring of epileptic fathers, and its risk of recurrence in families is high, as mentioned above. Friis (1979) also suggested a genetic association between facial clefts and epilepsy. However, this was not substantiated in his most recent study (Friis, 1989), where genetic factors were shown to be of minor importance in CLP as compared to the teratogenic effects of AC drugs. This study is in agreement with our findings.

Outcomes with hypospadias comprised 1.8% of live births (1.7% of all outcomes) in the previous study, a rate three times greater than in the general population (0.5%)(Bergsma, 1979). None of the offspring in the present study had a

similar malformation. The risk of recurrence in families, however, is reported as 12% (Bergsma, 1979). Both offspring with hypospadias in the previous study had a positive family history of urogenital anomalies (one hypospadias and one cryptorchidism). One of the mothers was on VPA monotherapy, and the other on CBZ monotherapy.

Subluxated hips were noted in 1.8% of live born offspring (1.7% of all outcomes) in the previous study, which is twice the general risk of occurrence (0.92%)(MacEwen et al., 1986). One of the two children with subluxated hips had a positive family history of the same deformity. One of the mothers was taking PB monotherapy, and the other was taking CBZ monotherapy. No such abnormality was detected in the present study.

With regard to inguinal hernias, there was no difference in the incidence between the two studies. The 5.5% noted in the previous study and the 4.9% in the present study lie within the range in the general population (1-5%)(Table 7)(Bergsma, 1979; Gray and Skandalakis, 1972; First and Snyder, 1989; Klauber and Sant, 1985). The previous study noted that half of the children with inguinal hernias had a positive family history of this defect; in the present study, on the other hand, there was no positive family history, but two of the four affected offspring had a history of premature delivery. The general risk of occurrence of inguinal hernia in premature babies is as high as 30% (Bergsma, 1979; Gray and Skandalakis, 1972; First and

Snyder, 1989; Klauber and Sant, 1985). Among the six children with inguinal hernia in the previous study, four mothers were taking PB + PRM (two PB and PRM, and two PHT, PB and PRM), two mothers were taking PHT + PB, and one was taking PHT + VPA. Among the four children with the same malformation in the present study, three mothers were taking CBZ monotherapy, and one mother was taking a combination of VPA and PB.

These results suggest that, along with the anticonvulsant drugs, genetic and other environmental factors play an important role in increasing the incidence of specific major malformations. The previous study noted that 17 of 28 malformed offspring had at least one malformed relative among the first, second or third degree relatives. In the present study, by contrast, none of the malformed offspring had a positive family history of abnormal outcomes. However since, for these malformations, the risk of recurrence in relatives is only a maximum of 5%, inheritance alone cannot explain why the rate of congenital malformations in the previous study was almost three times higher than the rate recorded in the present study. Furthermore, the prevalence of a positive family history of major congenital malformations in malformed offspring did not differ significantly from that in normal offspring in the previous study.

B. ETIOLOGY OF CONGENITAL MALFORMATIONS IN OFFSPRING

Dansky et al. (1982a) suggested that genetic

predisposition to congenital malformations would contribute to the production of these malformations when the fetus was exposed to AC drugs in utero.

Shapiro et. al(1976) reported that the incidence of CLP was greatest in children of epileptic mothers, less marked in children of epileptic fathers, and least marked in children of parents without epilepsy. This suggests a genetic association between CLP and epilepsy, in addition to the causative action of AC drugs.

1. COMPARISON OF RISK FACTORS IN PRESENT AND PREVIOUS STUDIES

When the various risk factors that both studies had focused upon were compared, statistically significant differences in the incidence of positive family history of congenital malformations, serum folate levels, type of AC drugs employed, average number of AC drugs, and frequency of monotherapy and polytherapy, were found between the two studies.

a) Family history of congenital malformations

Overall, there was a significantly higher incidence of positive family history of congenital malformations in the previous study (Table 10). This may be due to differences in obtaining family history data or differences in the patient population between the two studies. However, the explanation for these differences is not entirely clear.

b) Folate levels

The plasma folate levels were significantly lower in the previous than in the present study (Fig. 15). This is probably explained by the significantly lower rate of folate supplementation in the previous study. In normal pregnancies, maternal folate concentrations progressively decline due to the increased folate requirement of the mother and fetus(Del Ser et al., 1983; Chanarin et al. 1968; Willoughby and Jewell, 1968). In experimental studies, folate deficiency has been shown to produce congenital malformations of many organ systems as well as embryonic death (Nelson et al, 1955; Kinney and Morse, 1964; Jordan et al, 1977; Crandall and Brazier, 1978). Thus, the lower folate levels in the previous study may in part explain the higher rate of major congenital malformations in that study.

A study on the relationship between folate deficiency and fetal malformations conducted in the general population showed that these malformations are not frequently associated with and causally related to naturally occurring maternal folate deficiency (Scott et al., 1970). However, a number of investigations have shown significantly lower folate levels in treated nonpregnant epileptic patients (Baylis et al., 1971; Dellaportas et al., 1982), as well as in pregnant epileptic women (Hiilesmaa et al., 1983; Dansky et al., 1987a),as compared with control subjects. Dansky et al. (1987a)demonstrated that serum folate levels were significantly lower in pregnancies resulting in abnormal out-

comes than in those with normal outcomes. A significant negative correlation between serum folate and AC drug levels was also shown. PHT appeared to be the most potent AC for lowering the folate levels. A combination of PHT taken together with PB or PRM with or without other AC drugs was associated with a higher risk of folate deficiency. These results suggested a dose-response relationship between anticonvulsants, folate, and adverse pregnancy outcome.

However, Hiilesmaa et al. (1983) in Finland, as well as Ogawa et al. (1985) in Japan, did not find any association between low serum folate levels during pregnancy in epileptic women taking anticonvulsant drugs, and congenital malformations in their offspring. Since, from a statistical standpoint, the number of epileptic women showing low serum folate levels (<4ng/ml) did not vary significantly from the previous to the present study, it is possible that low serum folate levels are not the only factor related to the genesis of the major malformations. As Dansky suggested in her PhD thesis, the effects of AC drugs on the fetus might be due to their influence on folate metabolism (Dansky, 1989).

c) Anticonvulsant drugs

AC drugs have been held responsible for major malformations in animal studies, although proof of this has not been conclusively established in man. The most difficult problem in studies of teratogenicity of AC drugs in humans derives from the fact that it is difficult to evaluate the effects

of the individual AC drugs in a sufficient number of patients, because until recently polytherapy was a major component of antiepileptic drug treatment.

However, recent pharmacological advances in AC drug research have brought not only better seizure control and fewer side effects, but also more frequent reliance on monotherapy, which is suitable for the study of AC drug teratogenesis. Several preliminary reports have shown that outcomes on monotherapy are better than those on polytherapy(Janz, 1982a; Yerby, 1987).

Our results show that the average number of AC drugs used in the present study was significantly lower than in the previous study (1.3 vs. 1.7; $P<0.01$). Furthermore, monotherapy was employed more frequently in the present than in the previous study (68% vs. 40%; $P<0.01$), which suggests that polytherapy increases the risk of major malformations. The reason why polytherapy increases this risk cannot yet be definitely ascertained. The most plausible hypothesis is that complex AC drug interactions increase the level of some toxic teratogenic substances in the blood. At present, active epoxide metabolites are the substances most suspect of being the teratogenic agents responsible for increasing the risk of major malformations (Lindhout et al., 1984; Kaneko et al., 1988).

With respect to individual AC drugs, CBZ and VPA were used significantly more often in the present study, whereas PHT, PB, and PRM were employed less frequently. The

frequency of major malformations in the previous study (24.1%) appeared to be high in comparison to other prospective studies in the literature (Table 1). According to the previous study, administration of PRM alone or in combination during pregnancy was associated with an unusually high frequency of major malformations (50%), and this was especially high when PRM was used in polytherapy with PHT and PB (56%). As noted above, Dansky et al. (1987) found that this drug combination was also associated with the lowest folate levels during pregnancy.

The incidence of major malformations in relation to specific AC drugs in the present study agreed more closely with those recorded in other studies than did the previous study (Table 1). The rate of major malformations due to PHT alone or in combination was significantly lower in the present than in the previous study($P<0.01$). This rate (2.9%) was also lower than in most other reported prospective studies (Table 19). This decrease in the teratogenic effect of PHT in the present study may be due to increased use of monotherapy and increased folate levels in the present study. The plasma PHT levels were found to be significantly higher in the first trimester in the present study, probably because the metabolism of PHT was not induced by other AC drugs when monotherapy was employed.

The comparison of the outcomes for each of the AC drugs used alone or in combination proved to be difficult, because we could not pinpoint the effect of each AC drug in

polytherapy.

When the malformation rates in both groups were compared for each AC drug in monotherapy, it was found that, in the present study, there was a lower incidence of major malformations for each of the following drugs; CBZ, PHT, VPA and PB. There was a statistically significant decrease in the frequency of malformations seen with PHT ($P<0.05$), but the differences for the other anticonvulsants did not reach statistical significance, probably because of the small numbers involved. In the present study, developmental defects were not seen on CBZ or PHT monotherapy, although in the previous study they were seen in one of eight (12.5%) children exposed to CBZ monotherapy, and three of 21 (12.5%) children exposed to PHT monotherapy. In both studies, developmental defects were seen in the offspring of mothers with VPA monotherapy. While postural deformities and hernias were observed in the CBZ monotherapy as well as the PHT and PB monotherapy groups, they were not seen in the VPA monotherapy group in either study. Apparent differences in malformation rates between the two studies for monotherapy with the same AC drugs suggest that other factors, such as genetic predisposition or folate levels, could contribute to the development of the major malformations.

Maternal seizure frequency during pregnancy for both major and minor seizures was about the same in both studies. Seizures during pregnancy, whether generalized convulsive seizures or partial complex seizures, do not appear to in-

crease the risk of major malformations (Gjerde et al., 1988; Dansky, 1989).

C. MINOR MALFORMATIONS

With respect to minor malformations, there was no overall difference in the distribution of the number of minor malformations between the two studies. However, there were fewer children with five or more minor anomalies in the present study ($P<0.05$, Table 8). Thus, minor malformations also seem to show a trend toward decreased number in the present study.

In conclusion, the findings of the present study point to a significant decrease in the rate of major congenital malformations, and identify the factors possibly contributing to this improved outcome, as follows: a reduction in the use of AC drugs in combination, with a greater reliance on monotherapy; less frequent use of PHT, PB, and PRM, and more frequent use of CBZ; a lower genetic predisposition to major malformations; and higher serum folate levels. Our findings would also suggest that, of the above-mentioned factors, the reduction in the number of AC drugs employed and the increased use of monotherapy are clearly the most important. However, the higher incidence of major malformations noted in the previous study may in part be attributed to the increased genetic predisposition mentioned earlier (hypospadias, foot deformity, hernia), which interacted with

the effect of AC drugs. Thus, our findings may be said to support the multifactorial etiology of major malformations in the offspring of epileptic women.

D. COMBINED DATA FROM THE PREVIOUS AND PRESENT STUDIES

Since CBZ and VPA have been introduced for commercial use more recently, it has been difficult to evaluate their teratogenic properties because of an insufficient number of patients exposed to these drugs during pregnancy. Thus we have combined the results of the previous and present studies in order to analyze a large number of pregnancies exposed to each AC drug alone or in combination, and to compare their relative teratogenicity. In the case of the combined data for AC drugs used singly and in combination (Table 19), rates of malformation for almost all AC drugs were slightly higher than those noted in other prospective studies, except in the case of CBZ, whose malformation rate was about equal(Lindhout et al., 1982; Nakane et al., 1980; Kaneko et al., 1988)(Table 19). When AC drugs were used in monotherapy, the same tendencies were observed.

PRM used with or without other AC drugs had the highest malformation rate among all AC drugs, followed by PB, ESM and VPA (Fig. 16). Developmental defects were also seen most frequently with PRM, followed by VPA. PHT, PB and ESM were associated with about the same frequencies of developmental defects (10-11%), CBZ was associated with the lowest frequency of total malformations and of developmental

defects as compared to the other anticonvulsants, and these differences were statistically significant ($P<0.01$). VPA monotherapy was associated with the highest frequency of developmental defects (26.7%; $P<0.01$), whereas no developmental defects occurred in 14 offspring of patients on VPA polytherapy.

E. VPA

In recent reports, the malformation rates for VPA ranged from 2.5 to 25.9% for monotherapy(Rating et al., 1987; Huot et al., 1987; Lindhout and Schmidt, 1986) and 13.9 to 17% in combined and isolated therapy.

VPA has been associated with an increased risk of neural tube defects since 1982 (Robert and Guibaud, 1982; Bjerkedal et al., 1982b). The incidence of such defects in offspring exposed to VPA during pregnancy is 1.5 to 2.5% (Lindhout and Schmidt, 1986), which is about 20 times higher than is found in the general population. In our study, a fetus with spina bifida whose mother was on VPA monotherapy was identified on ultrasound examination, and the pregnancy was terminated. This resulted in an incidence of neural tube defect of 3.4%(1/29) in our combined VPA series.

Two other children whose mothers were on VPA monotherapy during their pregnancies, had CHD in the present study. One had isolated atrial septal defect(ASD), and the other had multiple congenital anomalies including tetralogy

of Fallot, microcephaly, microphthalmia, and arthrogryposis. In the study by Lindhout et al. (1982), one of the children whose mother was taking VPA alone also had tetralogy of Fallot, and two children whose mothers were on multiple therapy including VPA had CHD. Kaneko et al. (1988) found that one of the patients on combined VPA and diazepam therapy had a child with patent ductus arteriosus(PDA). Although the number of case reports is small, the relationship between VPA and CHD should be investigated further.

VPA is the latest AC drug to be put into use in treating epilepsy. It has an organic structure different from that of other AC drugs. Animal studies have shown dose-related teratogenicity with valproic acid(Whittle, 1976; Brown et al., 1980; Bruckner et al., 1983; Nau and Scott, 1987). A comparison of maternal plasma VPA levels during pregnancy in malformed and normal outcomes in the combined studies revealed a positive correlation between plasma VPA levels and abnormal pregnancy outcome, which is in line with the above mentioned experimental findings. The teratogenic effect of VPA is thought to originate in the reactive metabolites of VPA(2-propyl-4-pentanoic acid(4-en-VPA)) (Nau et al., 1984; Kondo et al., 1987). These findings, together with the fact that plasma VPA levels in the fetus are higher than in maternal blood(Kaneko et al., 1988), suggest that higher maternal VPA levels tend to increase the risk of malformation in the offspring.

F. CBZ

Experimental studies with mice revealed that CBZ was much less toxic to the fetus than PHT or PB (Bruckner et al., 1983; Nau and Scott, 1987). Early studies in humans showed that CBZ had no significant teratogenic effects (Granström and Hiilesmaa, 1982; Lindhout et al., 1982), and thus promoted its use during pregnancy rather than that of PHT or PB. However, insufficient research on the possible teratogenic effects of CBZ in man has been performed to date to yield any clearcut conclusions.

At this point in time, several prospective studies have appeared showing that the rate of malformations in offspring exposed to CBZ during pregnancy ranges from 8.5 to 10.8% in the isolated and combined studies (Lindhout et al., 1982; Nakane et al., 1980; Kaneko et al., 1988), and from 0 to 19.4% on CBZ monotherapy (Table 19). These figures include major and minor anomalies.

In our combined series, the rate of major congenital malformations on CBZ monotherapy was 15%, whereas it was 9% for all pregnancies on CBZ combined. This finding appears to contradict the reports according to which monotherapy is generally less teratogenic than polytherapy. However, if we consider the types of malformations associated with CBZ monotherapy, we find hypospadias in one infant, congenital subluxation of the hip in one infant, and inguinal hernia in three infants. In contrast to the malformations associated with other AC drugs, PDH were much more frequent with CBZ

monotherapy than DD (4 : 1). The genesis of the malformations, as well as the period of maximal susceptibility to teratogenic agents, varies according to the type of anomaly, as has been pointed out previously. Furthermore, it is thought that genetic predisposition may play a much larger role in the genesis of these malformations than has hitherto been believed.

G. PHT

Our combined study showed the rate of major malformations to be 18% for PHT used separately and in combination, whereas the rate was 13% for PHT monotherapy. These findings are in agreement with those of other studies.

After the first report of the possible teratogenic effect of anticonvulsants by Müller-Küppers (1963), the term "fetal hydantoin syndrome" was coined by Hanson and Smith in 1975 to designate a complex of minor anomalies in association with major anomalies and mental retardation in offspring exposed to PHT in utero. Subsequent research(Hanson et al., 1976; Hanson 1986;Martz et al., 1977) pointed to the strong fetal teratogenicity of PHT. However, this research was conducted on epileptic women who had been put on PHT medication in combination with other drugs, whereas only a few studies were performed on patients subjected to PHT monotherapy. Previous research had pointed to an increased incidence of minor malformations due to PHT use in polytherapy, but more recent research has shown that the

minor malformations resulting from PHT use in monotherapy are similar to those caused by other AC drugs in monotherapy(Yerby,1989), suggesting that the term "fetal hydantoin syndrome" should be changed to "fetal anticonvulsant syndrome".

In addition, several minor anomalies previously regarded as typically associated with "fetal hydantoin syndrome" were shown to be genetically linked to epilepsy (Janz, 1982b). Only hypertelorism and digital and nail hypoplasia seem to be specifically related to phenytoin exposure. The current concept of the syndrome therefore seems to be incorrect; most of the "typical" characteristics are not caused only by phenytoin (Dansky et al., 1982a; Lindhout et al., 1984; Yerby et al., 1989) but may also be associated with exposure to other anticonvulsants and/or have a genetic origin.

Previous studies from our institution (Dansky et al., 1982b) indicated that plasma PHT levels during pregnancy were higher in women with malformed offspring than in those with normal infants. Because there was only one malformed child exposed to phenytoin in the present study, we could not confirm this finding. However, the mother of this child had the highest plasma levels of PHT and PB during the first trimester of any of the mothers exposed to these drugs.

H. MONOTHERAPY VS. POLYTHERAPY

The incidence of major malformations was compared for

the monotherapy and polytherapy groups in both studies combined, and was found to be 17.6% and 18.9%, respectively. The frequency of malformations for VPA and CBZ was higher on monotherapy than on polytherapy. These findings contrast with previous studies, which found a two to three fold increase in malformations on polytherapy as compared to monotherapy (Lindhout et al., 1984; Nakane et al., 1980; Kaneko et al., 1988). However, Lindhout and Schmidt (1986) found a higher frequency of neural tube defects on VPA monotherapy. Thus other factors may contribute to the development of major malformations (e.g. type(s) and combination of AC drugs, folate levels, and genetic predisposition).

I. SERUM AFP LEVELS

Several studies(Burton et al, 1983; Wald et al., 1977) have demonstrated an increased risk of spontaneous abortion and stillbirth among patients with elevated maternal serum α -fetoprotein(MS-AFP) values. Elevated MS-AFP levels may be an indication of underestimated gestational age, multiple gestation, or fetal death; whereas abnormally low MS-AFP values may indicate overestimated gestational age, missed abortion, smaller pregnancy, or, perhaps, even an increased risk of fetal chromosomal anomalies, eg. Down's syndrome.

There is mounting evidence that an elevated MS-AFP level in the absence of a benign cause, such as twins or underestimated gestation, is a clear indication of high-risk

pregnancy. MS-AFP screening provides effective means for selecting patients who are at increased risk for neural tube defects (Burton, 1988; Aubrey et al., 1989). When seen in midgestation, it is associated with an increased frequency of intrauterine growth retardation and indicates, in addition, that there is a greater likelihood of congenital anomalies (Burton and Dillard, 1986; Slafia et al., 1988).

Early in gestation AFP is synthesized by the yolk sac and later by the fetal liver. Fetal serum AFP (FS-AFP) levels steadily increase until the end of the first trimester, and then gradually decline. However, due to the rapidly increasing fetal body weight throughout the second and third trimesters, the total synthesis of AFP continues to increase throughout the second trimester and plateaus during the early third trimester(Glick et al., 1988).

In this study, MS-AFP determinations were obtained during each trimester in 68 pregnant epileptic women taking AC drugs. Five pregnancies resulting in offspring with major malformations were included(one with CLP, one with ASD, one with multiple anomalies and two with inguinal hernia). There was unusual fluctuation of AFP values in the first and second trimesters in the pregnancy which resulted in a child born with CLP, although the values for each trimester lay within the normal range. The other four malformed offspring showed the usual progressive increase in AFP values. Abnormally high plasma MS-AFP levels were seen in the first trimester in only one case of spontaneous abor-

tion. Therefore it is too early to conclude that MS-AFP is useful in detecting abnormal outcomes other than neural tube defects during pregnancy in epileptic women taking AC drugs. Further research is required to elucidate this matter.

J. SPONTANEOUS ABORTIONS

The incidence of spontaneous abortion in epileptic women has been reported as ranging from 17 to 22%(Annegers et al., 1988), and this and other studies showed no statistically significant increase in the incidence of such abortions over that in the general population. Our previous, present, and combined studies have confirmed these results.

In the present study, the frequency of spontaneous abortions seemed to increase as compared to the previous study. However, the reason for this apparent increase is that patients were ascertained earlier in the pregnancy in the present study, and thus a larger number of spontaneous abortions could be detected.

K. PERINATAL GROWTH PARAMETERS

Perinatal growth retardation has been reported in offspring of epileptic women as compared to normal controls (Hiilesmaa et al., 1981; Andermann, 1982; Mastroiacovo et al., 1988). In most of the studies, head circumference(HC) and body weight(BW) tend to be smaller, although this is not the case for body length(BL). Several prospective investigations have studied the relationship between AC drugs and

growth retardation (Andermann, 1982).

Hiilesmaa et al.(1981) found a significantly decreased mean HC at birth in offspring of mothers who had been on CBZ monotherapy during pregnancy, as well as in offspring of mothers taking primidone or phenobarbital in combination as compared with controls. However, most of the individual HC values were still in the normal range. This decreased mean HC persisted up to the age of 18 months. Their findings suggested that phenytoin alone was not associated with small HC, but combined phenytoin and phenobarbitone administration could result in small HC.

Another study (Mastroiacovo et al., 1988) showed that HC and BW in offspring of epileptic mothers were significantly lower than in controls, regardless of whether the epileptic women were treated or untreated, and whether monotherapy or polytherapy was used. Since a reduction in head circumference was also observed in the babies of untreated epileptic women, the authors of this study concluded that the observed effect on fetal head growth can be interpreted as the result of an interaction between the effect of the maternal disease and that of the AC drugs.

Our results support the previous investigations. When the mean HC was compared for the monotherapy and polytherapy groups, the previous and the combined studies disclosed that HC was lower in the polytherapy group than in the monotherapy group, although there was no statistically significant difference in the present study. Concerning BW and

BL, there were no appreciable differences between the two studies (Fig. 3, Table 9), or between the monotherapy and polytherapy groups. With respect to individual AC drugs, CBZ and VPA in combination were associated with lower HC than was CBZ or VPA monotherapy, suggesting that the interaction between these two drugs is responsible for this difference.

L. CBZ-EPOXIDE

Higher rates of congenital anomalies have been found after prenatal exposure to particular combinations of antiepileptic drugs than to each of the drugs alone. Several studies have claimed that combined CBZ, PB and VPA polytherapy is associated with teratogenicity (Lindhout et al., 1982, 1981: Kaneko et al., 1988), although early studies showed that CBZ monotherapy had no significant teratogenic effect (Granström and Hiilesmaa, 1982; Lindhout et al., 1982). The mechanisms of teratogenesis of these drug combinations have not yet been clarified. One of the hypotheses is that the teratogenic activity of these drug combinations is due to metabolic interactions(Lindhout et al., 1981; Finnell et al., 1986). Many drugs are hydroxylated by the arene oxide pathway, in which epoxides are produced as intermediate metabolites. In general, epoxides can have teratogenic, mutagenic, carcinogenic, and hepatotoxic effects through covalent binding to macromolecules such as proteins and DNA(Jerina and Daly, 1974).

CBZ is known to induce metabolism via the arene oxide pathway. It has been shown that valproic acid may inhibit the induction of the enzyme epoxide hydrolase, which converts the 10,11-epoxide into less toxic products(Levy and Koch, 1982; Kerr et al., 1989). Therefore co-administration of CBZ, PB and VPA may alter the metabolism of CBZ resulting in elevated levels of its 10,11-epoxide metabolite.

In order to test this hypothesis, we determined the ratio of carbamazepine-10,11-epoxide to carbamazepine concentrations in the serum in patients with epilepsy who were treated with CBZ monotherapy and with CBZ and VPA in combination. The CBZ epoxide/CBZ ratio in those treated with combined VPA and CBZ was higher than that in CBZ monotherapy. When the CBZ epoxide/CBZ ratios were compared in pregnant epileptic women and in non-pregnant epileptic women, they were found to be higher in the former than in the latter. These results suggest that pregnancy itself as well as drug combinations result in a relative increase of CBZ epoxide levels, which could contribute to the development of major malformations. It should be noted that the epoxide binds less firmly to plasma proteins than the parent compound (Levy and Pitlick, 1982), thus effectively increasing the concentration of free epoxide even further.

M. PREDICTIVE TESTING

Previous studies have shown genetic variation in the elimination of toxic intermediates of PHT metabolites

(Strickler et al., 1985; Dansky et al, 1987), manifested by increased cytotoxicity in vitro.

Buehler et al., (1990) have demonstrated the possibility of predictive testing by measuring epoxide hydrolase levels in amniocytes. They have shown that the epoxide hydrolase levels appear to be regulated by a single gene with two allelic forms. Those individuals who are homozygous for the recessive allele would have low epoxide hydrolase activity and would therefore be at risk if gestationally exposed to AC drugs. This enzymatic assay may prove useful in determining which infants are at increased risk for AC drug-induced congenital malformations.

N. MANAGEMENT OF THE EPILEPTIC WOMAN OF CHILDBEARING AGE

Based on the above findings, the following suggestions can be made regarding the management of the epileptic woman of childbearing age.

1. Ideally the patient should be managed on CBZ or PHT monotherapy, employing the lowest doses and drug levels necessary for adequate seizure control. Any changes in AC medication should be instituted prior to pregnancy.
2. Folate supplements should be begun prior to pregnancy and continued throughout pregnancy.
3. All pregnancies of women with epilepsy who are taking AC medication should be carefully monitored with respect to seizure frequency, complications of pregnancy, AC drug levels, serum folate levels and MS-AFP levels. Careful

ultrasound examinations using high quality ultrasonography should be performed, looking specifically for major congenital malformations. If the MS-AFP or ultrasound findings are suspicious, amniocentesis should be carried out.

4. VPA should not be instituted as the first treatment for women of childbearing age. However, VPA may be used if it is the only medication which can achieve adequate seizure control, provided that the pregnancy is carefully monitored as described above in order to detect any major congenital malformations, particularly neural tube defects. As for other AC, the plasma levels should be kept as low as possible during the pregnancy, preferably at the lower limit or below the therapeutic range. This is particularly so since the free drug levels may increase during pregnancy.

5. Finally it is hoped that those fetuses which are at high risk of developing malformations can be detected by means of cytotoxic or enzymatic techniques as described in the section on predictive testing.

More detailed aspects of the management of the epileptic woman of childbearing age are discussed by Andermann et al.(1981a).

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Table 1

PREVALENCE OF MAJOR CONGENITAL ANOMALIES IN OFFSPRING OF EPILEPTIC WOMEN (PROSPECTIVE STUDIES)

AUTHOR(S)	YEAR	NO. OF BIRTHS	NO. OF MALFORMATIONS	INCIDENCE OF MALFORMATIONS (%)
Melchior et al.	1967	32	2	6.3
Cvetko	1969	35	3	8.6
South	1972	31	2	6.5
Goujard et al.	1974	72	2	2.4
Knight and Rhind	1975	140	5	3.6
Shapiro et al.	1976	305	20	6.6
Dansky et al.	1981	52	10	19.2
Hill et al.	1982	59	11	18.6
Biale and Lewenthal	1984	33	0	0.0
Kaneko et al	1984	112	5	4.5
Kelly et al.	1984	171	6	3.5
Rating et al.	1987	150	13	8.7
Buchanan	1988	26	0	0.0
TOTAL		1218	79	6.5
Previous study		116	28	24.1
Present study		90	8	8.8

Table 2

MATERIAL

	Number of women	Total number of pregnancies
1.PRESENT STUDY (1982-1989)	78 (103)	90 (115)
2.PREVIOUS STUDY (1971-1984) (Dansky et al)	94	119

Table 3

MINOR ANORMALIES LOOKED FOR IN BOTH STUDIES

1. epicanthal folds
2. wide spaced eyes
3. synophrys
4. low set ears
5. ear deformity
6. ear rotation
7. upturned nares
8. flat nose bridge
9. long philtrum
10. high arched palate
11. narrow palate
12. pilonidal crease
13. pilonidal dimple
14. finger deformity
15. finger nail deformity or hypotrophy
16. simian crease
17. toe deformity
18. toe nail deformity or hypotrophy
19. mouth deformity
20. others
    - capillary haemangioma
    - hyperflexibility of joints
    - hypotonia
    - prominent forehead
    - tarsus adduction
    - ichthyosis
    - curving back

Table 4 OUTCOMES OF TWO STUDIES

	PREVIOUS STUDY	PRESENT STUDY	STATISTICS
MAJOR MALFORMATIONS	28 (24.1%)	8 (8.8%)	X2=7.148 **
DEVELOPMENTAL DEFECTS	13 (11.2%)	4 (4.4%)	X2=2.233
POSTURAL DEFORMITIES AND HERNIAS	15 (12.9%)	4 (4.4%)	X2=3.405 *
SPONTANEOUS ABORTIONS	6 (5.2%)	9 (10.0%)	X2=1.107
NORMAL	82 (70.7%)	73 (81.2%)	
TOTAL	116	90	

* P<0.05
** P<0.01

Table 5a

OUTCOMES WITH ANOMALIES IN THE PREVIOUS STUDY AND THE PRESENT STUDY (DEVELOPMENTAL DEFECTS)

PREVIOUS STUDY			PRESENT STUDY		
DRUGS	DOSE mg/d	MALFORMATIONS	DRUGS	DOSE mg/d	MALFORMATIONS
PHT PB PRM ETH	300 500 1000	VSD HYPOSPADIAS UMBILICAL HERNIA	VPA	1500	ASD
PHT PB	300 120	VSD	VPA	750	LUMBAR SPINA BIFIDA *
PHT PB PRM	300 90 625-750	VSD	VPA	1000	MULTIPLE CONGENITAL ANOMALIES **
PHT	350	AORTIC STENOSIS ENDOCARDIAL FIBROELASTOSIS PATENT DUCTUS ARTERIOSUS	PHT PB	300 100	CLEFT LIP AND CLEFT PALATE
PHT PB PRM	300 750	COARCTATION OF AORTA			
PHT PB	200 15	HYPERTROPHIC CARDIOMYOPATHY WITH ENDOCARDIAL FIBROELASTOSIS AND CONDUCTION DEFECT			
PHT PB PRM	300 30 500	SCAPHOCEPHALY WITH CRANIAL LACUNAE AND SMALL POSTERIOR FOSSA TALIPES CALCANEOVALGUS			
PHT PB PRM	300 90-120 625	CLEFT LIP			
PHT PB PRM	300-400 50-200 250-375	CLEFT LIP + CLEFT PALATE			
VPA	1000	HYPOSPADIAS POLYDACTYLY SYNDACTYLY			
CBZ	600	HYPOSPADIAS			
PHT	300	HYDROCEPHALUS (DANDY-WALKER CYST)			
PHT	400	POLYCYSTIC KIDNEY URETERAL ATRESIA			

* diagnosed prenatally

** tetralogy of Fallot
microcephaly
microphthalmia
arthrogryposis

(Pena-Shokeir syndrome =type 1 is associated with multiple ankyloses, camptodactyly, facial anomalies and pulmonary hypoplasia. type 2 is associated with cerebral, ocular, facial and skeletal abnormalities. It affects newborn or very young infants.)

Table 5b

OUTCOMES WITH ANOMALIES IN THE PREVIOUS STUDY AND THE PRESENT STUDY [POSTURAL DEFORMITIES AND HERNIAS]

PREVIOUS STUDY			PRESENT STUDY		
DRUGS	DOSE mg/d	MALFORMATIONS	DRUGS	DOSE mg/d	MALFORMATIONS
PB	60	METATARSUS ADDUCTUS	CBZ	600	INGUINAL HERNIA
PHT	100	METATARSUS ADDUCTUS	CBZ	600	INGUINAL HERNIA
PHT	300	BILATERAL METATARSUS VARUS	CBZ	1300	INGUINAL HERNIA
PHT	200	BILATERAL TALIPES CALCANEOVALGUS	VPA PB	1000 90	INGUINAL HERNIA
PHT PB PRM	300 120 1000	BILATERAL TALIPES EQUINOVARUS INGUINAL HERNIA UMBILICAL HERNIA			
PHT PB PRM	300 125-250	BILATERAL INTERNAL TIBIAL TORSION			
PB PRM	 250-500	INGUINAL HERNIA UMBILICAL HERNIA			
PB PRM	30-60 125	INGUINAL HERNIA			
PHT PB	300 45-90	INGUINAL HERNIA			
PHT PB	400 100	INGUINAL HERNIA			
PHT VPA	300 750	INGUINAL HERNIA			
PHT PB PFMB	100 100 40	INGUINAL HERNIA			
PHT ETH	400 1250	UMBILICAL HERNIA			
PB	100	CONGENITAL SUBLUXATION OF HIP			
CBZ	800	CONGENITAL SUBLUXATION OF HIP			

Table 6

OUTCOMES WITH MAJOR MALFORMATIONS IN THE PREVIOUS SYTUDY AND THE PRESENT STUDY

TYPE OF ANOMALIES	PREVIOUS STUDY	PRESENT STUDY
1.DEVELOPMENTAL DEFECTS		
Congenital heart disease with or without other anomalies	6	2
Urogenital anomaly with or without other anomalies	3	0
Cleft lip with or without cleft palate	2	1
Others	2	1
2.POSTURAL DEFORMITIES OR HERNIAS		
Foot deformities	6	0
Subluxation of hips	2	0
Hernias (Inguinal and umbilical hernia)	8	4

Table 7

RISK OF OCCURRENCE AND RECURRENCE OF INDIVIDUAL MAJOR MALFORMATIONS FROM THE LITERATURE

TYPE OF MALFORMATIONS	REFERENCE		RISK OF OCCURRENCE	RISK OF RECURRENCE		PREVIOUS STUDY	PRESENT STUDY
				PATIENT'S SIB	PATIENT'S CHILD		
VENTRICULAR SEPTAL DEFECT	Bergsma,D.	1979	1/400 (full-term live births)	Predicted risk 5.0% Empiric risk 4.4%	Predicted risk 5.0% Empiric risk 4.0%	1.8%	0
ATRIAL SEPTAL DEFECT	Bergsma,D.	1979	1/1000	Predicted risk 3.2% Empiric risk 3.2%	Predicted risk 3.2% Empiric risk 2.5%	0	1.2%
AORTA COARCTATION	Bergsma,D.	1979	1/1600	Predicted risk 2.4% Empiric risk 1.8%	Predicted risk 2.4% Empiric risk 2.7%	0.9%	0
TETRALOGY OF FALLOT	Bergsma,D.	1979	10% of Congenital heart disease	Predicted risk 3.2% Empiric risk 2.7%	Predicted risk 3.2% Empiric risk 4.2%	0	1.2%
	Warkany,J.	1971	1/1000(in the babies hospital in New York)				
CLEFT LIP WITH OR WITHOUT CLEFT PALATE	Lindsay,W.K	1979a 1979b	CANADA. 1/930 U.S.A. 1/640 CAUCASIAN. 1/750		4% (17% both affected parent and sib)	1.8%	1.2%
	Carter,C.O.	1969		3.2-4.9%	3-4.3%		
HYPOSPADIAS	Bergsma,D.	1979	1/186	12.0%	?	1.8%	0
HYDROCEPHALY	Bergsma,D.	1979	1/2000	Autosomal ressesive or X-linked		0.9%	0
INGUINAL HERNIA	Bergsma,D. Gray,S.W. & Skandalakis,J.E.	1979 1972	1-5% (Full term) 30% (Premature)	?	?	5.5%	4.9%
	First,L.R. & Snyder,J	1989					
	Klauber,G.T. & Sant,G.R.	1985					
UMBILICAL HERNIA	Klauber,G.T. & Sant,G.R	1985	18.5%: White 42.3%: Black	?	?	1.8%	0
CLUB FOOT	Lovell,W.W. et al	1986	0.1-0.5%	4.95%	?	3.7%	0
SYNDACTYLY	Bergsma,D.	1979	1/3000	50.0%	50.0%	0	0
SUBLUXATED HIPS	MacEwen,G.D. et al.	1986	9.2/1000			1.8%	0

Table 8

MINOR ANOMALIES

	NO. OF MINOR ANOMALIES			STATISTICS
	≤5	>5	TOTAL	
PREVIOUS STUDY	20	53	73	X2 = 4.016 *
PRESENT STUDY	29	35	64	

* P<0.05

Table 9

GROWTH PARAMETERS (MEAN OF STANDARD DEVIATION)

	PREVIOUS STUDY	PRESENT STUDY	STATISTICS
HEAD CERCUMFERENCE	-0.420	-0.341	t=0.36
WEIGHT	-0.220	-0.038	t=1.09
LENGTH	-0.081	-0.204	t=0.55

Table 10

COMPARISON OF THE POSSIBLE RISK FACTORS BETWEEN PREVIOUS STUDY AND PRESENT STUDY

	PREVIOUS STUDY		PRESENT STUDY		STATISTICS
	+	−	+	−	
GENERAL RISK FACTORS					
ALCOHOL	34	79	14	53	χ 2=1.378
SMOKING	42	73	22	50	χ 2=0.460
FAMILY HISTORY OF CONGENITAL MALFORMATIONS	**49**	**50**	**10**	**65**	**χ 2=23.312 ****
FAMILY HISTORY OF EPILEPSY	43	57	35	43	χ 2=0.010
MATERNAL AGE (years)	26.1± 4.6		27.1± 4.35		t=1 596
MEAN GESTATIONAL AGE (weeks)	39.3± 1.7		38.6± 2.8		t=,.92
RISK FACTORS RELATED TO EPILEPSY IN MOTHER					
MAJOR SEIZURE 1ST TRIMESTER	26	87	21	61	χ 2=0.062
MAJOR SEIZURE ALL TRIMESTERS	45	69	31	53	χ 2=0.048
MINOR SEIZURE 1ST TRIMESTER	38	58	22	62	χ 2=3.039
MINOR SEIZURE ALL TRIMESTERS	43	52	31	53	χ 2=0.963
AGE AT ONSET OF SEIZURES (years)	12.3± 7.0		13.3± 7.2		t=1.001
DURATION OF EPILEPSY (years)	13.7± 6.8		13.8± 7.5		t=0.099
PREPREGNANCY	30	89	26	77	χ 2=0.022

* P<0.05
** P<0.01

Table 11

INCIDENCE OF MALFORMED OUTCOMES WITH SAME TYPE OF MALFORMATIONS IN THE FAMILY HISTORY

	PREVIOUS STUDY		PRESENT STUDY		
TYPE OF MALFORMATIONS	N	NUMBER OF OFFSPRING WITH SAME TYPE OF FAMILY HISTORY	N	NUMBER OF OFFSPRING WITH SAME TYPE OF FAMILY HISTORY	
CONGENITAL HEART DISEASE	6	0	1(ASD)		0
CLEFT LIP WITH OR WITHOUT CLEFT PALATE	2	0	1		0
HYPOSPADIAS	2	HYPOSPADIAS 1 CRYPTORCHIDISM 1	0		0
FOOT DEFORMITY	6	FOOT DEFORMITY 3	0		0
SUBLUXATED HIPS	2	SUBLUXATED HIPS 1	0		0
INGUINAL HERNIA UMBILICAL HERNIA	8	INGUINAL HERNIA 4	4		0
MULTIPLE ANOMALY WITH TETRALOGY OF FALLOT	0	0	1	MULTIPLE ANOMALY	1
SPINA BIFIDA	0	0	1		0

Table 12

COMPARISON OF THE TYPE OF EPILEPSY BETWEEN PREVIOUS AND PRESENT STUDIES

TYPE OF EPILEPSIES	NUMBER OF WOMEN		STATISTICS
	PREVIOUS STUDY	PRESENT STUDY	
Primary Generalized	35 (37%)	32 (31%)	χ 2=0.581
Secondary Generalized with or without focalization	9 (10%)	9 (9%)	χ 2=0.002
Partial Complex	25 (27%)	27 (26%)	χ 2=0.010
Partial Simple	14 (15%)	11 (11%)	χ 2=0.453
Partial (focus undetermined)	3 (3%)	9 (9%)	χ 2=1.762
Epilepsy Unclassified	7 (7%)	14 (13%)	χ 2=1.357
Epilepsy Unlikely	1 (1%)	1 (1%)	χ 2=0.418
Total	94	103	χ 2=5.505

* P<0.05
** P<0.01

Table 13

DISTRIBUTION OF MONOTHERAPY AND POLYTHERAPY:
COMPARISON OF PREVIOUS AND PRESENT STUDIES

THERAPY	PREVIOUS STUDY (N=116)	PRESENT STUDY (N=90)	STATISTICS
MONOTHERAPY	47 (40%)	61 (68%)	] χ 2=16.615 **
POLYTHERAPY	66 (57%)	24 (27%)	
NO MEDICATION	3 (3%)	5 (5%)	χ 2=0.534
AVERAGE NUMBER OF AC DRUGS	1.7± 0.74	1.3± 0.63	t=3.81 **

* P<0.05
** P<0.01

Table 14

TYPES OF DRUGS TAKEN DURING THE FIRST TRIMESTER:
COMPARISON OF PREVIOUS AND PRESENT STUDIES

NAME OF DRUGS	PREVIOUS STUDY (N=116)	PRESENT STUDY (N=90)	STATISTICS
PHT	86 (74%)	34 (38%)	P=26.076 **
PB	51 (44%)	13 (14%)	P=19.268 **
PRM	20 (17%)	5 (6%)	P=5.441 *
ESM	8 (7%)	1 (1%)	P=2.793
CBZ	22 (19%)	34 (38%)	P=8.135 **
VPA	9 (8%)	20 (22%)	P=2.793 **
CZP	0 (0%)	2 (2%)	P=0.805

* P<0.05
** P<0.01

Table 15

SERUM FOLATE LEVELS

	PREVIOUS STUDY		PRESENT STUDY		STATISTICS
	+	−	+	−	
FOLATE SUPPLEMENTATION	92	17	46	1	X2=4.591 *
<4ng/ml 1st & 2nd TRIMESTERS	14	26	22	59	X2=0.457

* P<0.05

Table 16

COMPARISON OF THE INCIDENCE OF MAJOR MALFORMATIONS BETWEEN MONOTHERAPY AND POLYTHERAPY GROUPS

	MONOTHERAPY	POLYTHERAPY	STATISTICS
DEVELOPMENTAL DEFECTS	8	9	X2=0.044
POSTURAL DEFORMITIES AND HERNIAS	11	8	X2=0.067
TOTAL MAJOR MALFORMATIONS	19	17	X2=0.019
TOTAL OFFSPRING	108	98	

Table 17

COMPARISON OF THE POSSIBLE RISK FACTORS BETWEEN PREGNANCIES WITH NORMAL OUTCOMES AND SPONTANEOUS ABORTIONS

	NORMAL OUTCOMES		SPONTANEOUS ABORTION		STATISTICS
	+	−	+	−	
GENERAL RISK FACTORS					
ALCOHOL	11	58	2	6	χ 2=0.022
SMOKING	18	52	3	5	χ 2=0.085
FAMILY HISTORY OF CONGENITAL MALFORMATIONS	9	48	0	7	χ 2=0.311
FAMILY HISTORY OF EPILEPSY	26	32	4	5	χ 2=0.115
MATERNAL AGE (years)	27.0± 4.4		28.2± 3.7		t=0.898
GESTATIONAL AGE (weeks)	39.0± 1.9		12.4± 3.2		
RISK FACTORS RELATED TO EPILEPSY IN MOTHER					
MAJOR SEIZURE 1ST TRIMESTER	16	49	3	6	χ 2=0.024
MAJOR SEIZURE ALL TRIMESTERS	26	59	3	6	χ 2=0.044
MINOR SEIZURE 1ST TRIMESTER	16	51	3	6	χ 2=0.042
MINOR SEIZURE ALL TRIMESTERS	23	40	3	6	χ 2=0.034
AGE AT ONSET OF SEIZURES (years)	13.4± 7.3		15.4± 6.4		t=0.870
DURATION OF EPILEPSY (years)	13.7± 7.8		12.8± 6.6		t=0.378
SERUM FOLATE LEVELS <4ng/ml 1st & 2nd TRIMESTERS	16	45	4	3	χ 2=1.593

* P<0.05
** P<0.01

Table 18

COMPARISON OF THE POSSIBLE RISK FACTORS BETWEEN PREGNANCIES WITH NORMAL AND ABNORMAL OUTCOMES IN THE PRESENT STUDY

	NORMAL OUTCOMES		ABNORMAL OUTCOMES		STATISTICS
	+	−	+	−	
GENERAL RISK FACTOR					
ALCOHOL	11	58	1	4	χ 2=0.153
SMOKING	18	52	1	4	χ 2=0.062
FAMILY HISTORY OF CONGENITAL MALFORMATIONS	9	48	1	7	χ 2=0.079
FAMILY HISTORY OF EPILEPSY	26	32	2	6	χ 2=0.465
MATERNAL AGE (years)	27.0± 4.4		27.2± 5.6		t=0.098
GESTATIONAL AGE ※ (weeks)	36.0± 8.7		31.7± 8.4		t=1.370
RISK FACTORS RELATED TO EPILEPSY IN MOTHER					
MAJOR SEIZURE 1ST TRIMESTER	16	49	2	6	χ 2=0.169
MAJOR SEIZURE ALL TRIMESTERS	26	59	2	6	χ 2=0.005
MINOR SEIZURE 1ST TRIMESTER	16	51	3	3	χ 2=0.830
MINOR SEIZURE ALL TRIMESTERS	23	40	5	5	χ 2=0.216
AGE AT ONSET OF SEIZURES (years)	13.4± 7.3		10.7± 8.3		t=0.883
DURATION OF EPILEPSY (years)	13.7± 7.8		16.6± 6.4		t=1.189
SERUM FOLATE LEVELS <4ng/ml 1st & 2nd TRIMESTERS	16	45	1	6	χ 2=0.053

※ including abortions

* P<0.05
** P<0.01

Table 19

RATE OF MALFORMATIONS IN THE LITERATURE

AUTHOR	YEAR	MALFORMATION RATE (%) PHT		PB		PRM		CBZ		VPA		TOTAL	METHOD
		M	C	M	C	M	C	M	C	M	C		
Millar & Nevin	1973	-	40.0 (5)	-	8.0 (2)	-	0 (2)	-	-	-	-	6.4 (110)	prospective
Starreveld-Zimmerman et al.	1973	0 (3)	11.3** (124)	-	-	-	-	0 (1)	0** (50)	-	-	7.4 (297)	retrospective
Nakane et al.	1980	0 (26)	7.9 (496)	15.8 (19)	9.4 (413)	-	-	-	8.5 (129)	-	-	-	prospective & retrospective data are used
Lindhout et al.	1982	-	17.7 (51)	-	18.5 (65)	-	13.0 (23)	-	10.8 (74)	-	13.9 (65)	8.2 (184)	prospective
Lindhout and Schmidt	1986	-	-	-	-	-	-	-	-	2.5 (120)	1.5 (393)		prospective
Bertollini et al.	1987	4.6 (153)	-	2.8 (250)	-	-	-	1.4 (70)	-	8.2 (62)	-	3.5	retrospective
Rating et al.	1987	-	-	-	-	-	-	-	-	25.0 (16)	16.7 (30)		prospective
Haas et al.	1987	-	-	-	-	-	-	-	-	2.5 (120)	0.2 (1838)		prospective
Kaneko * et al.	1988	14.6 (137)	0 (10)	9.9 (71)	0 (2)	17.4 (92)	0 (4)	19.4 (67)	10.0 (10)	25.9 (27)	0 (3)	14.0 (172)	prospective
Wladimiroff et al.	1988	3.7 (27)	-	5.9 (17)	-	-	-	4.4 (45)	0** (38)	3.0 (33)	-	3.1 (162)	prospective
Jones et al.	1989	-	-	-	-	-	-	9.3 (54)	2.9 (35)	-	-	9.3 (54)	prospective
		-	-	-	-	-	-	25.0 (8)	25.0 (4)	-	-	25.0 (8)	retrospective
MNI,	1971-1984	25.0 (24)	24.0 (86)	28.6 (7)	25.5 (51)	100.0 (1)	50.0 (20)	25.0 (8)	9.0 (22)	33.3 (3)	22.2 (9)	24.1 (116)	prospective
MNI,	1982-1989	0 (20)	2.9 (34)	0 (3)	7.7 (13)	0 (1)	0 (5)	12.5 (24)	8.8 (34)	25.0 (12)	20.0 (20)	8.8 (90)	prospective
MNI,	1971-1989	13.6 (44)	18.3 (120)	20.0 (10)	23.4 (64)	50.0 (2)	40.0 (25)	18.5 (32)	10.7 (56)	26.7 (15)	20.7 (29)	17.5 (206)	prospective

* major and minor anomalies are included
** only polytherapy (without monotherapy)
()= Number of cases

M = monotherapy
C = monotherapy and polytherapy are included

Fig. 1

Comparison of major anomalies and spontaneous abortion in the offspring between previous and present studies

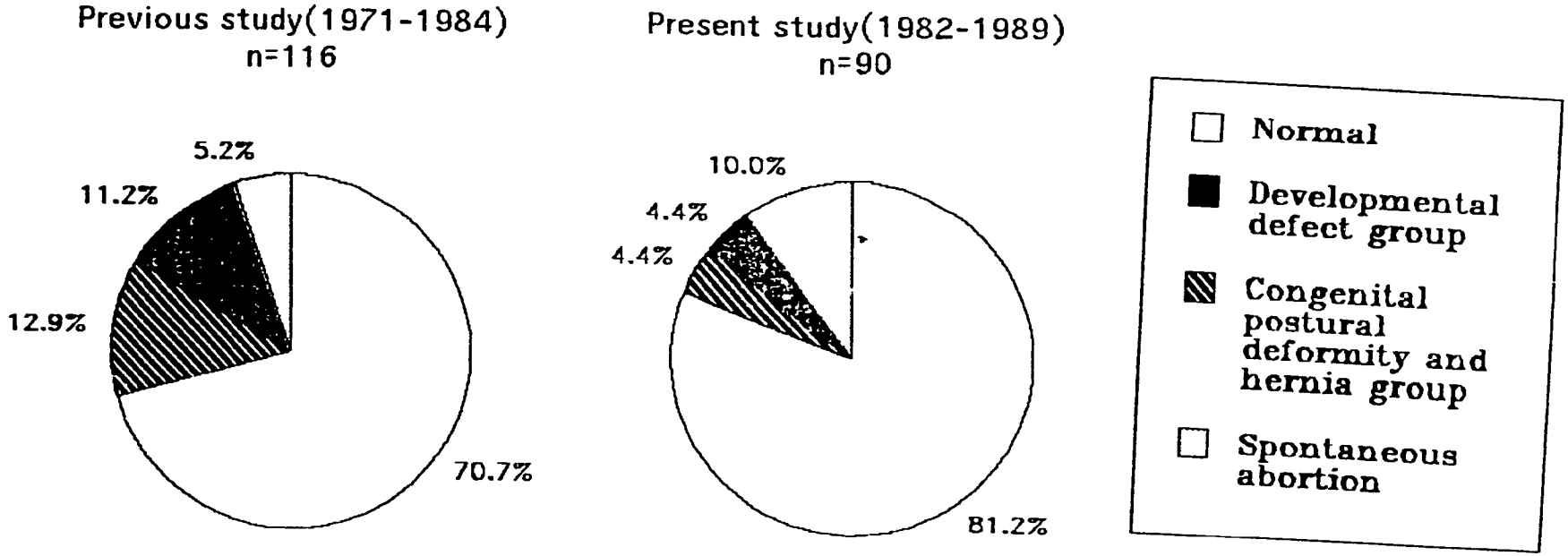


Fig. 2 Comparison of minor anomalies in the offspring between previous and present studies

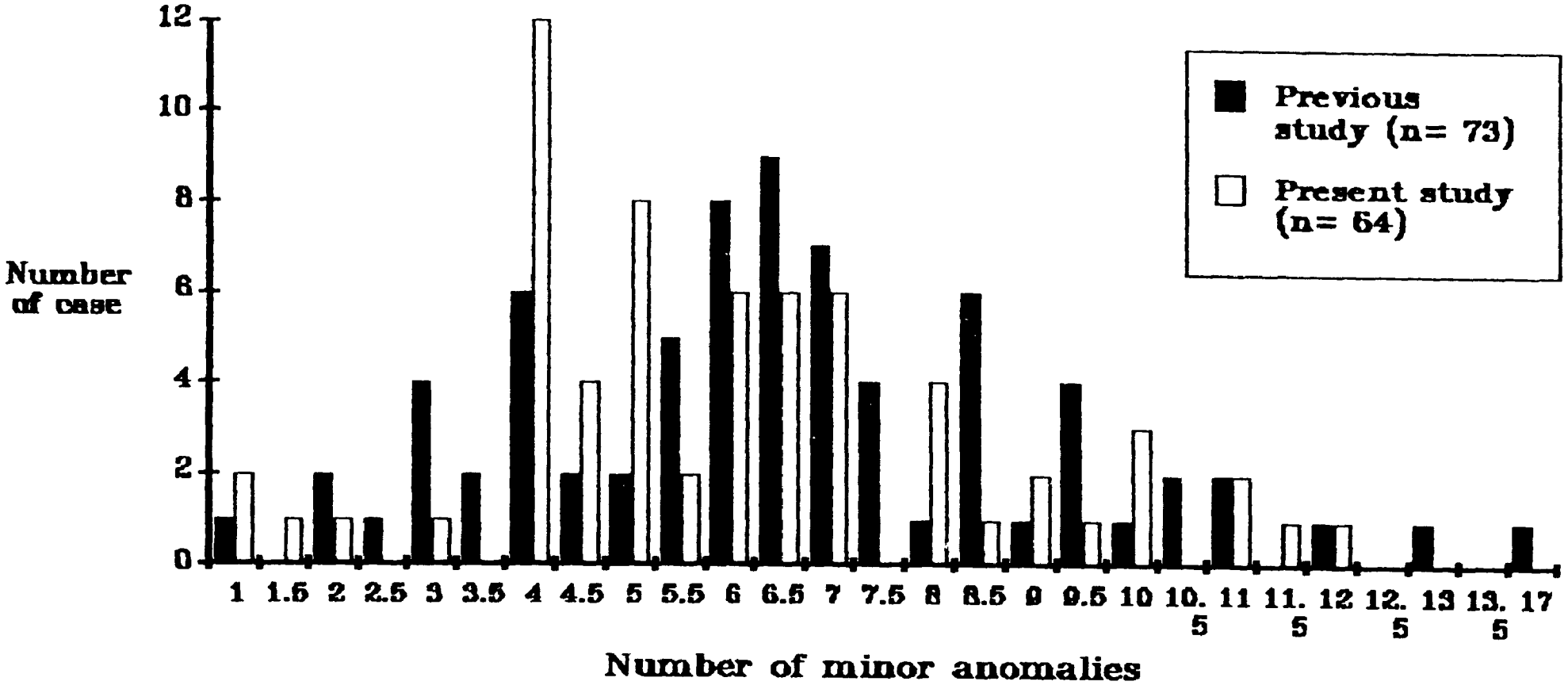


Fig. 3

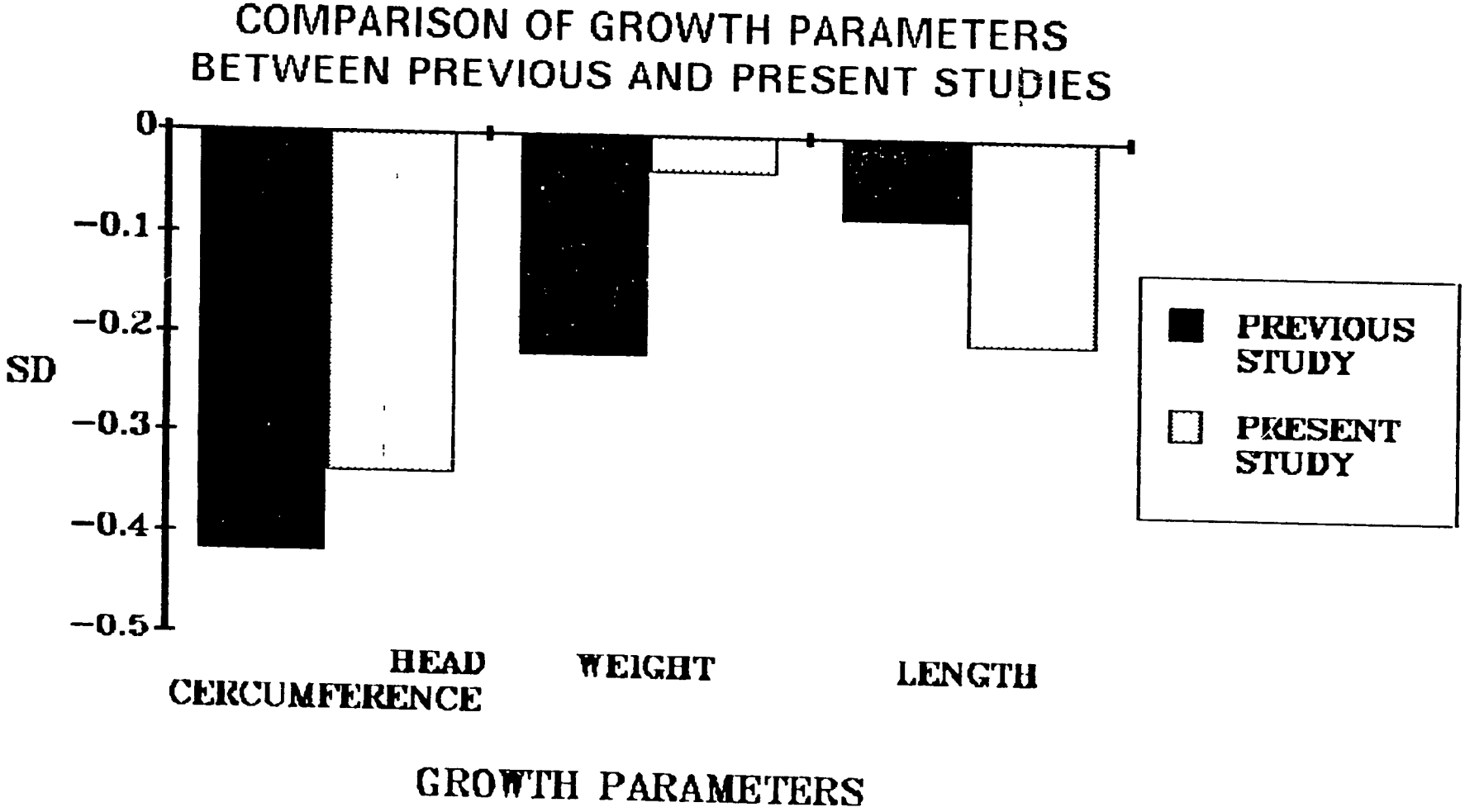
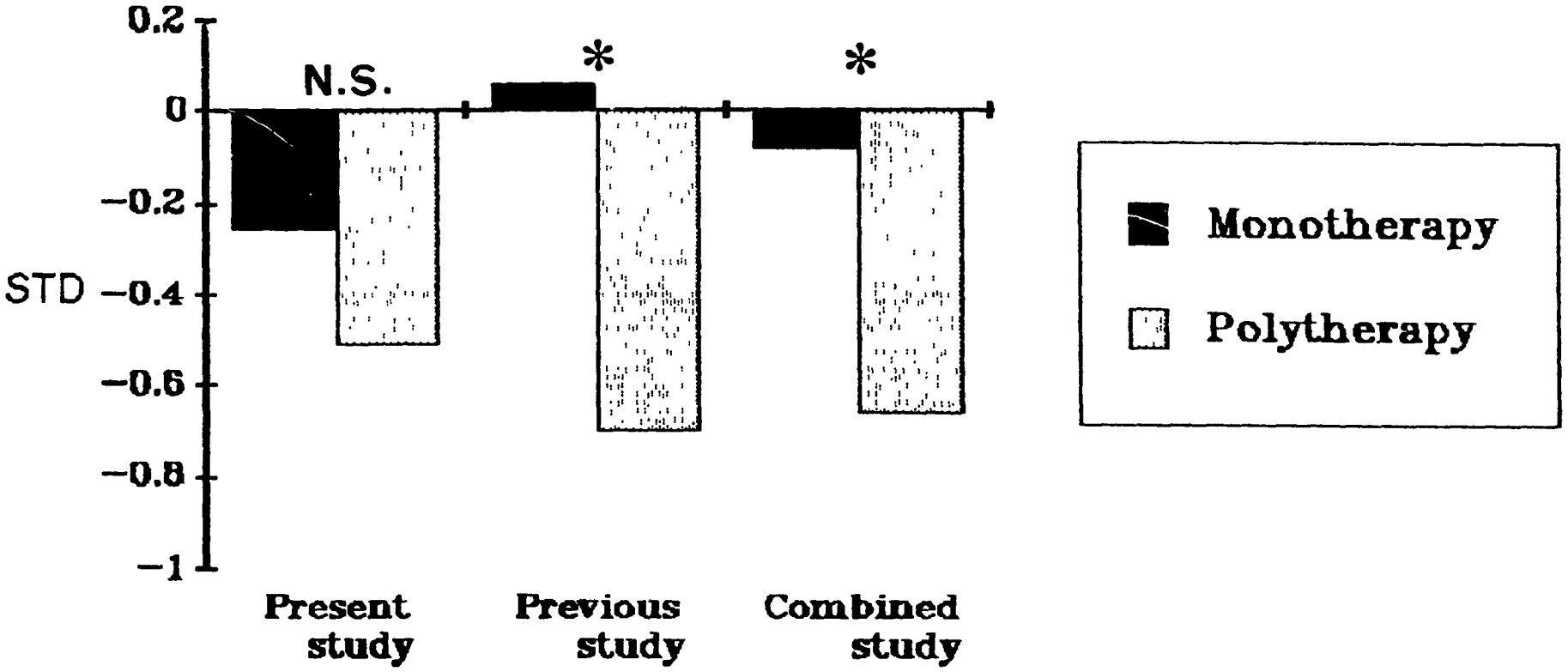

COMPARISON OF GROWTH PARAMETERS
BETWEEN PREVIOUS AND PRESENT STUDIES
0
−0.1
−0.2
−0.3
−0.4
−0.5
SD
HEAD CERCUMFERENCE
WEIGHT
LENGTH
GROWTH PARAMETERS
PREVIOUS STUDY
PRESENT STUDY

Fig. 4

Comparison of the head circumferences at birth between infants exposed to monotherapy and polytherapy in the present and the previous study



* P<0.01

Fig. 5

Occurrence of major seizures during pregnancy

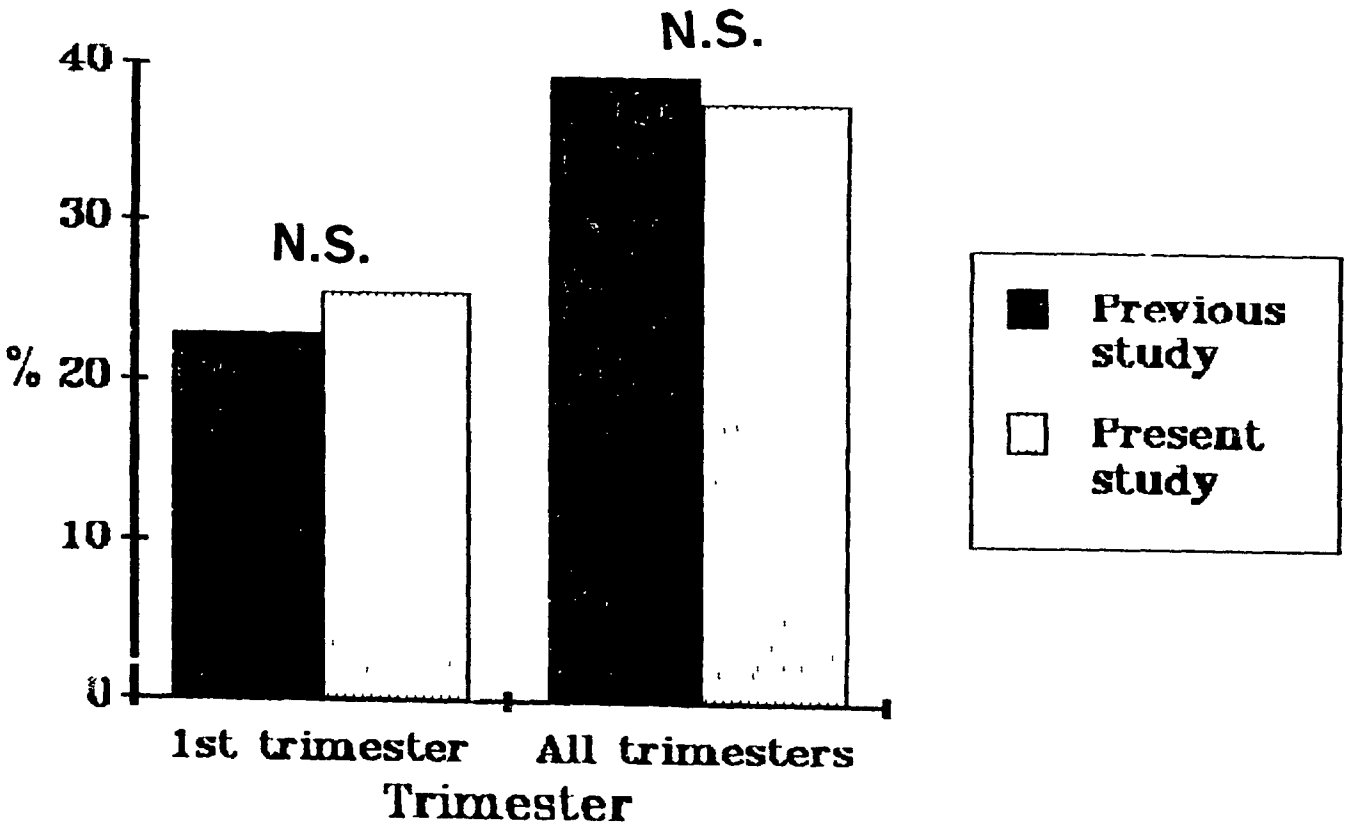


Fig. 6 Occurrence of minor seizures during pregnancy

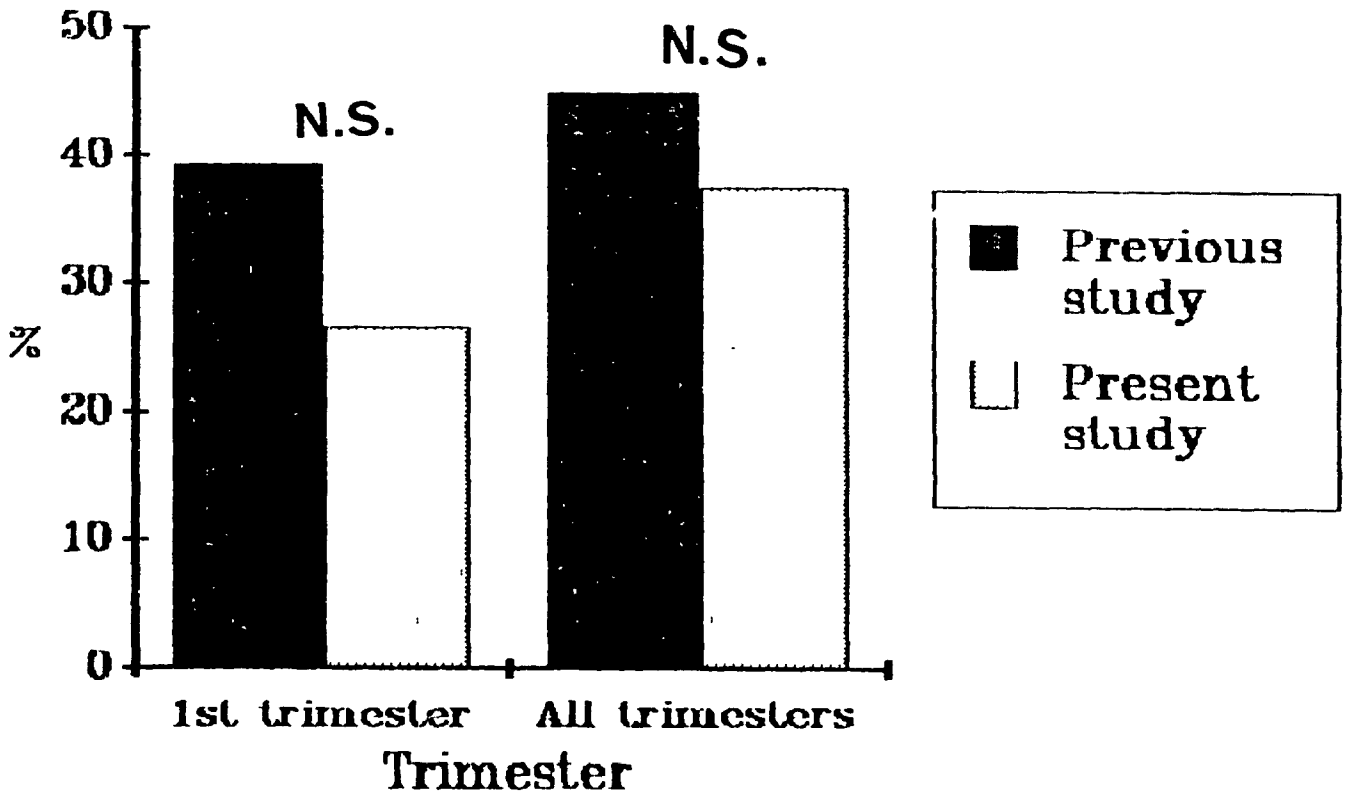


Fig. 7

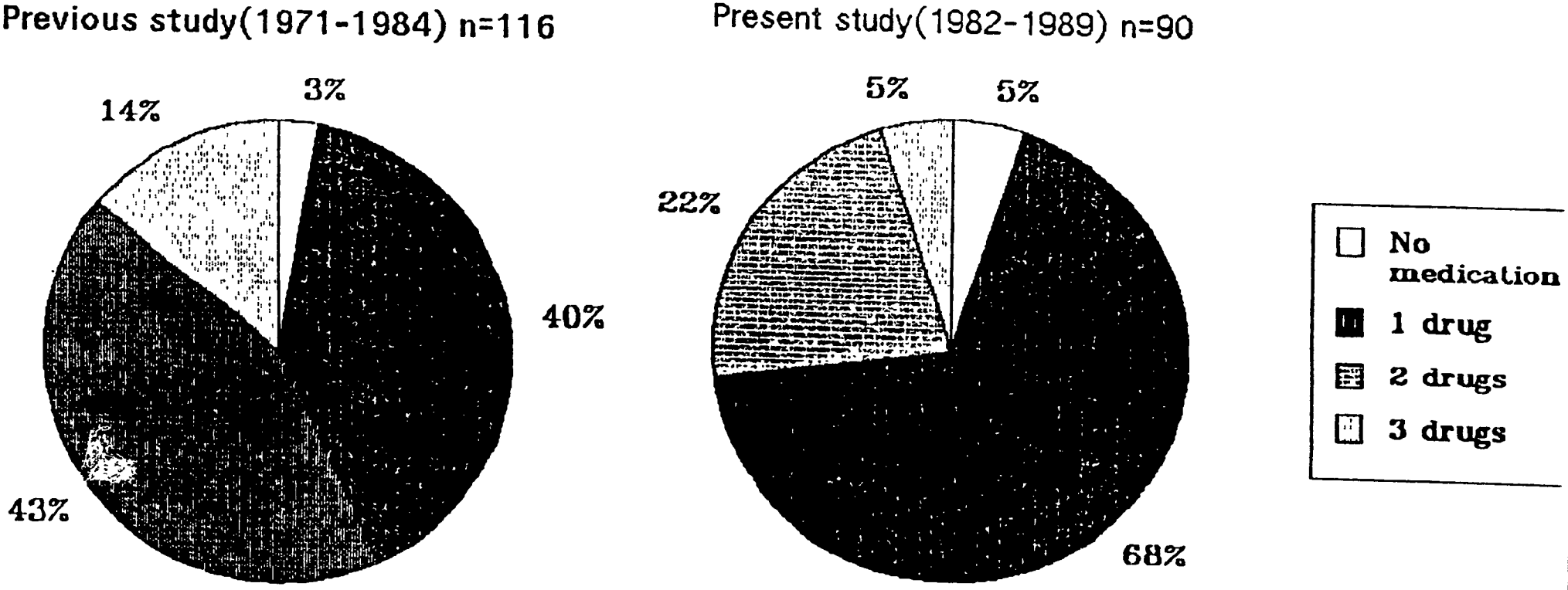

Previous study(1971-1984) n=116
3%
14%
40%
43%
Present study(1982-1989) n=90
5%
5%
22%
68%
No medication
1 drug
2 drugs
3 drugs

Fig. 8

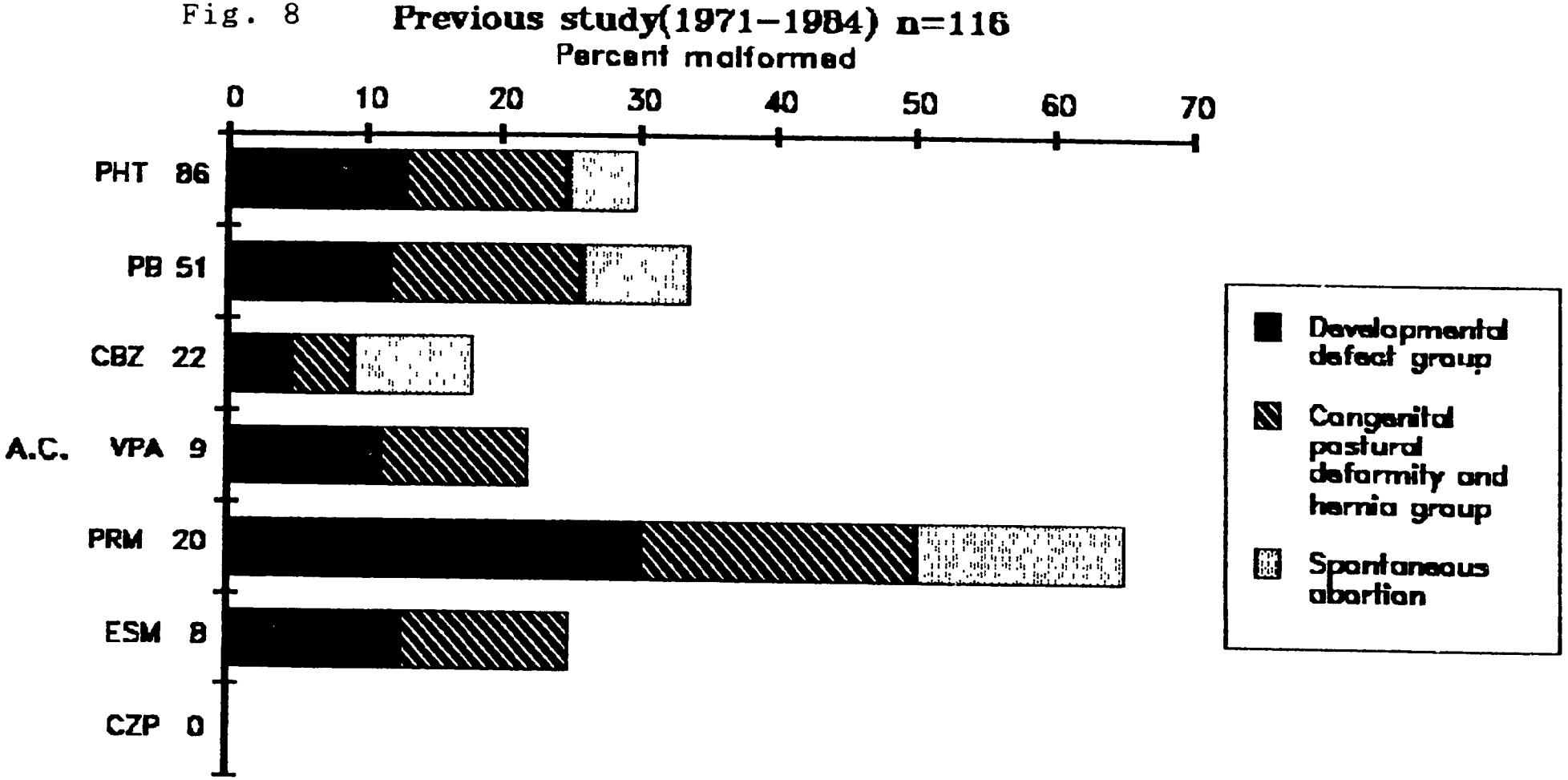

Previous study(1971–1984) n=116
Percent malformed
0
10
20
30
40
50
60
70
PHT 86
PB 51
CBZ 22
A.C. VPA 9
PRM 20
ESM 8
CZP 0
Developmental defect group
Congenital postural deformity and hernia group
Spontaneous abortion

Fig. 9 **Present study(1982–1989) n=90**

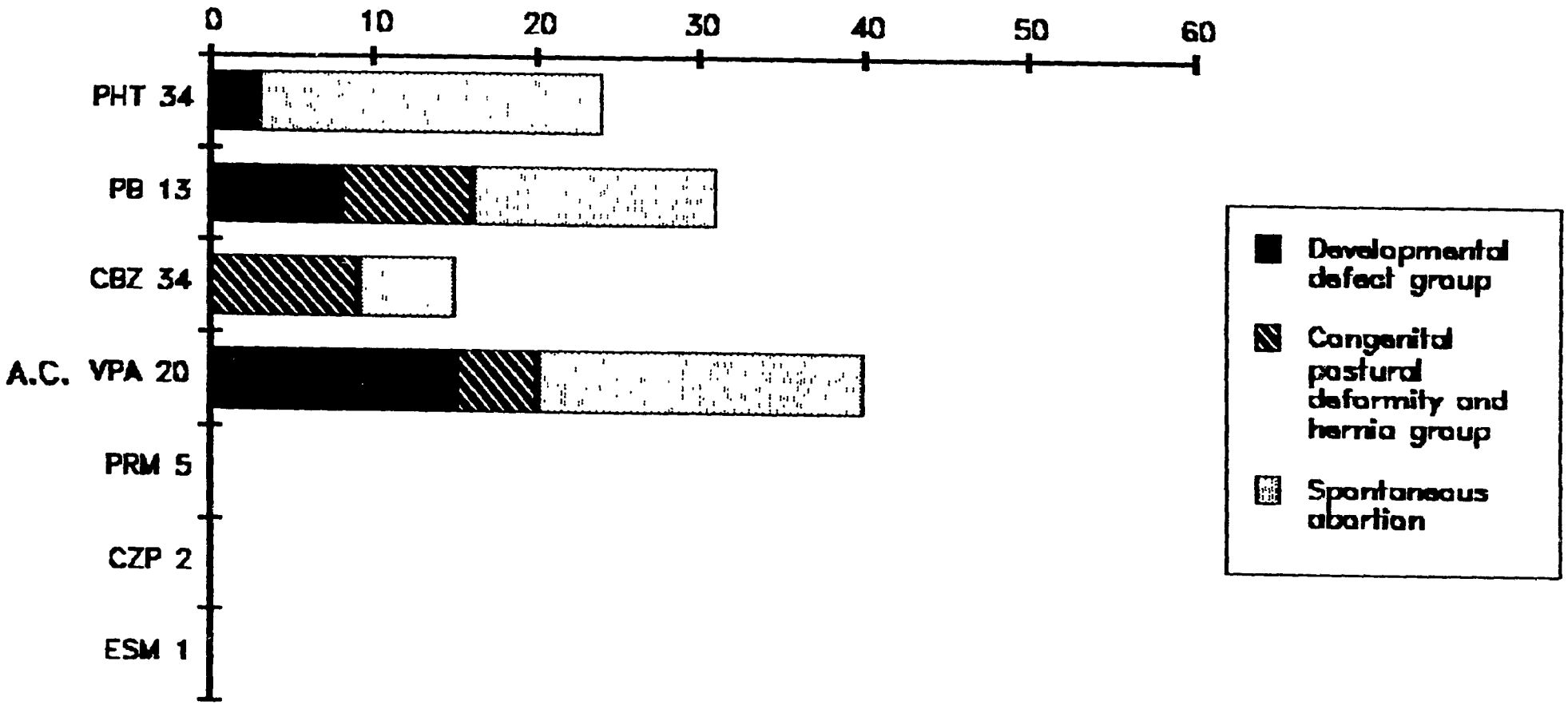
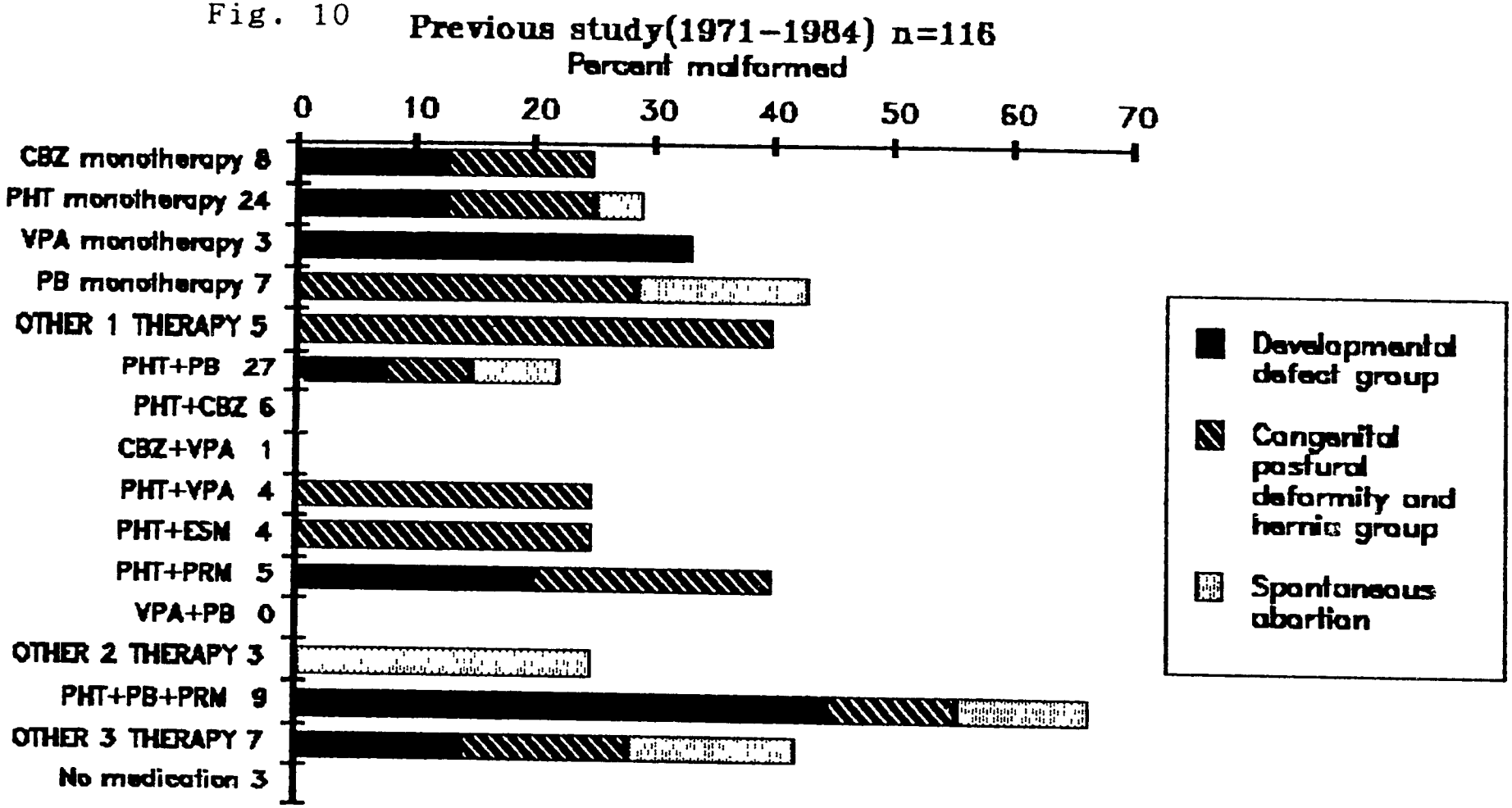
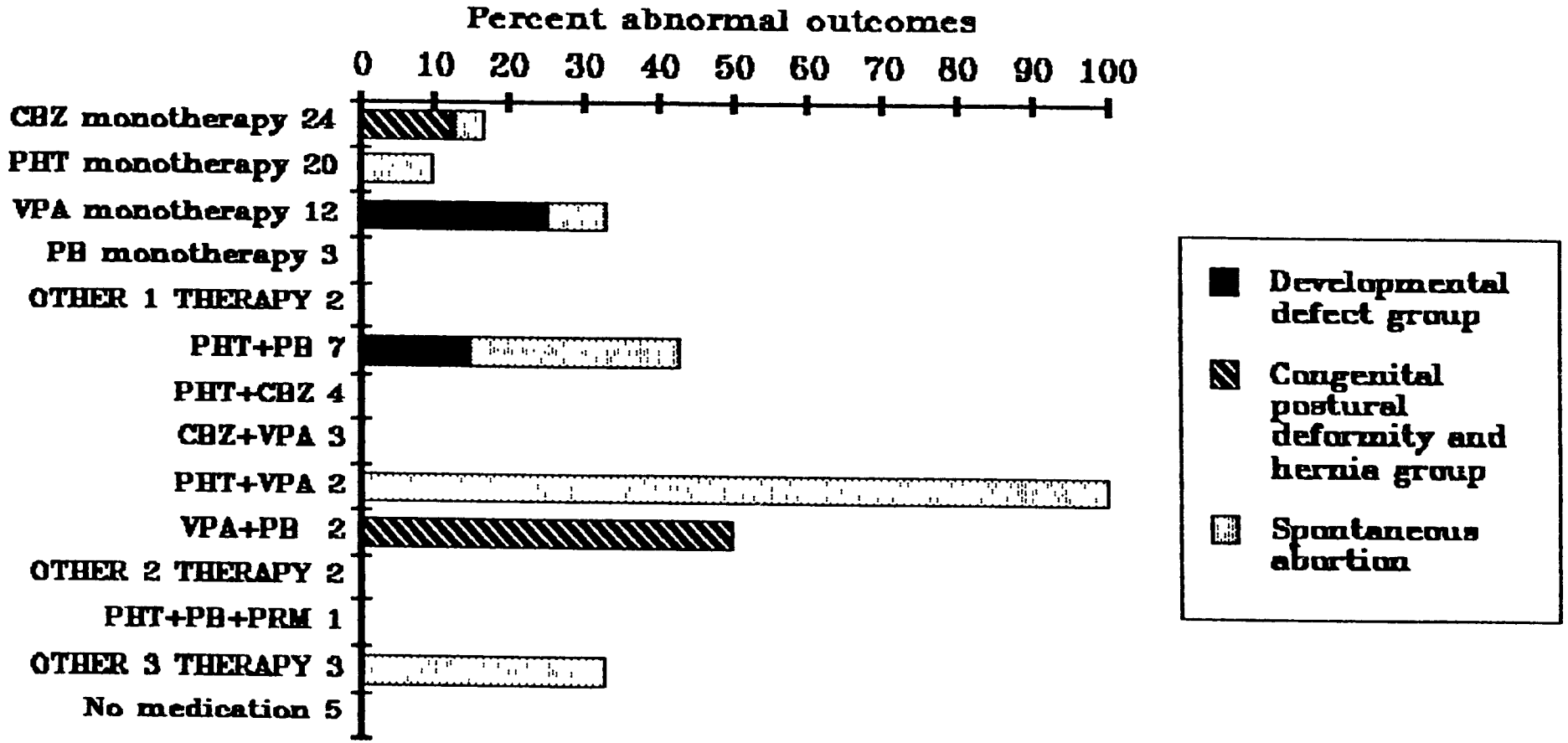


Fig. 10


Previous study(1971-1984) n=116
Percent malformed
0
10
20
30
40
50
60
70
CBZ monotherapy 8
PHT monotherapy 24
VPA monotherapy 3
PB monotherapy 7
OTHER 1 THERAPY 5
PHT+PB 27
PHT+CBZ 6
CBZ+VPA 1
PHT+VPA 4
PHT+ESM 4
PHT+PRM 5
VPA+PB 0
OTHER 2 THERAPY 3
PHT+PB+PRM 9
OTHER 3 THERAPY 7
No medication 3
Developmental defect group
Congenital postural deformity and hernia group
Spontaneous abortion

A.C.

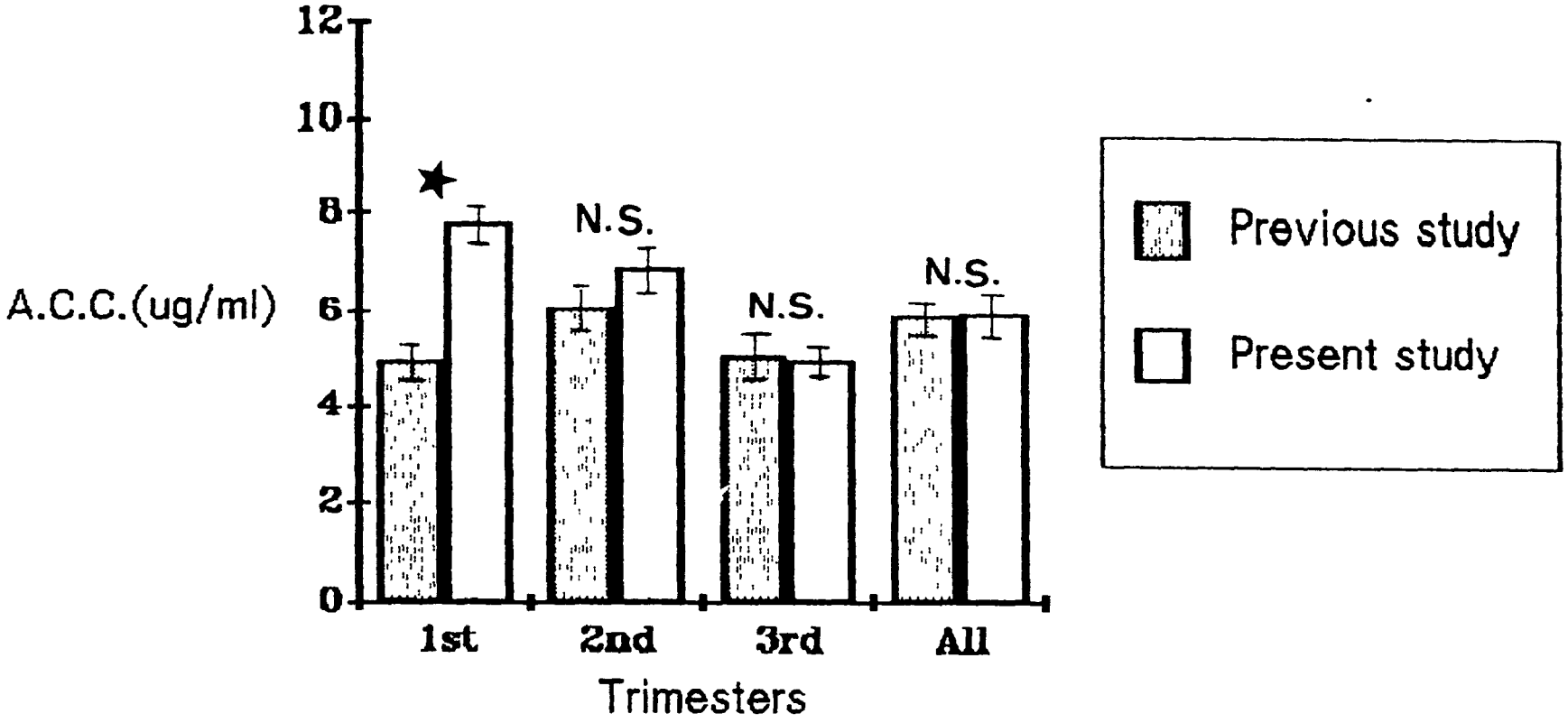
Fig. 11 **Present study(1982–1989) n=90**



A.C.

Fig. 12

Comparison of the plasma PHT level between previous and present studies (PHT monotherapy)



★ P<0.05

Fig. 13

Comparison of the plasma CBZ level between previous and present studies (CBZ monotherapy)

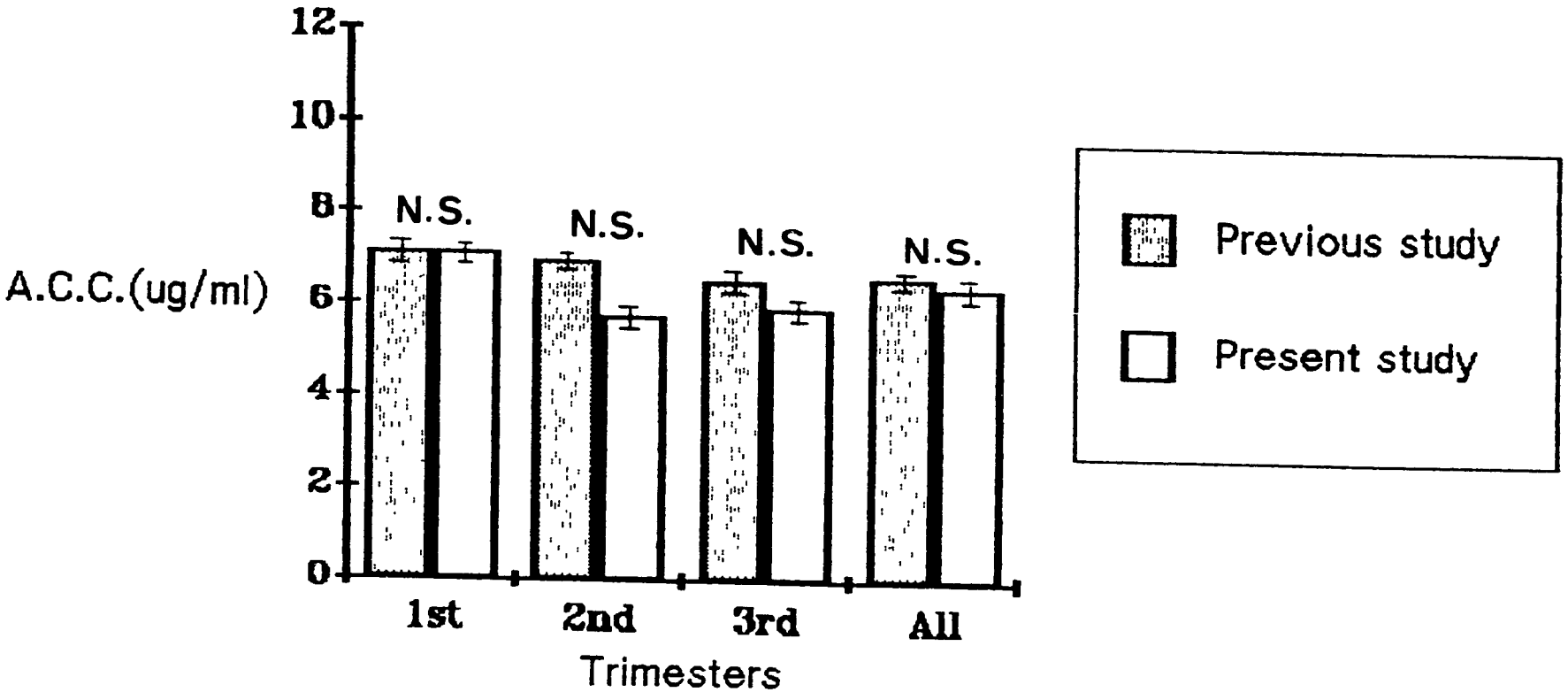


Fig. 14

Comparison of the plasma VPA level between previous and present studies (VPA polytherapy)

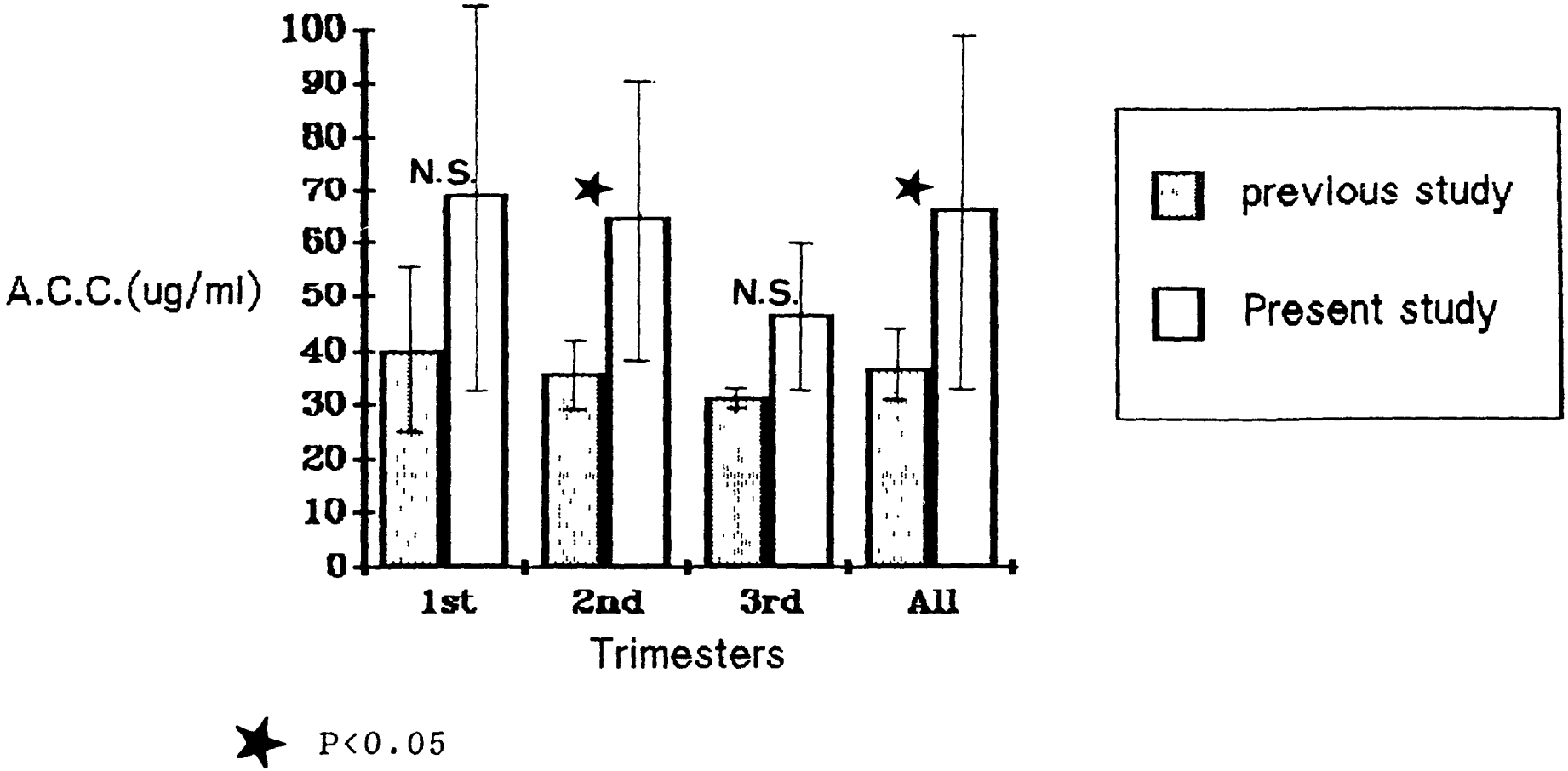
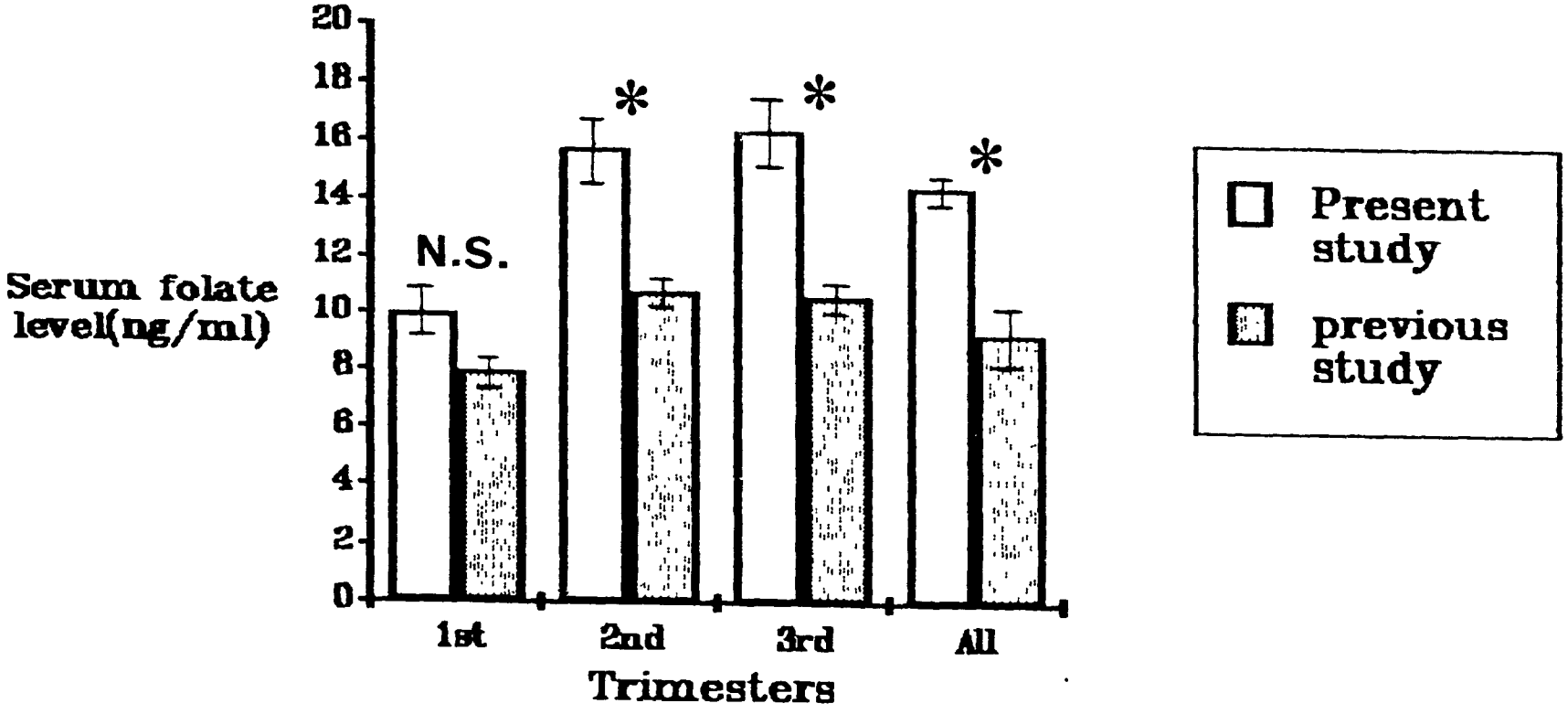


Fig. 15 **Comparison of serum folate levels between the present and the previous studies**



* P<0.01

Fig. 16

Frequency of major congenital malformations in the offspring in relation to maternal anticonvulsants (isolated and in combination) during the first trimester of pregnancy: combined data from previous and present studies (n=206)

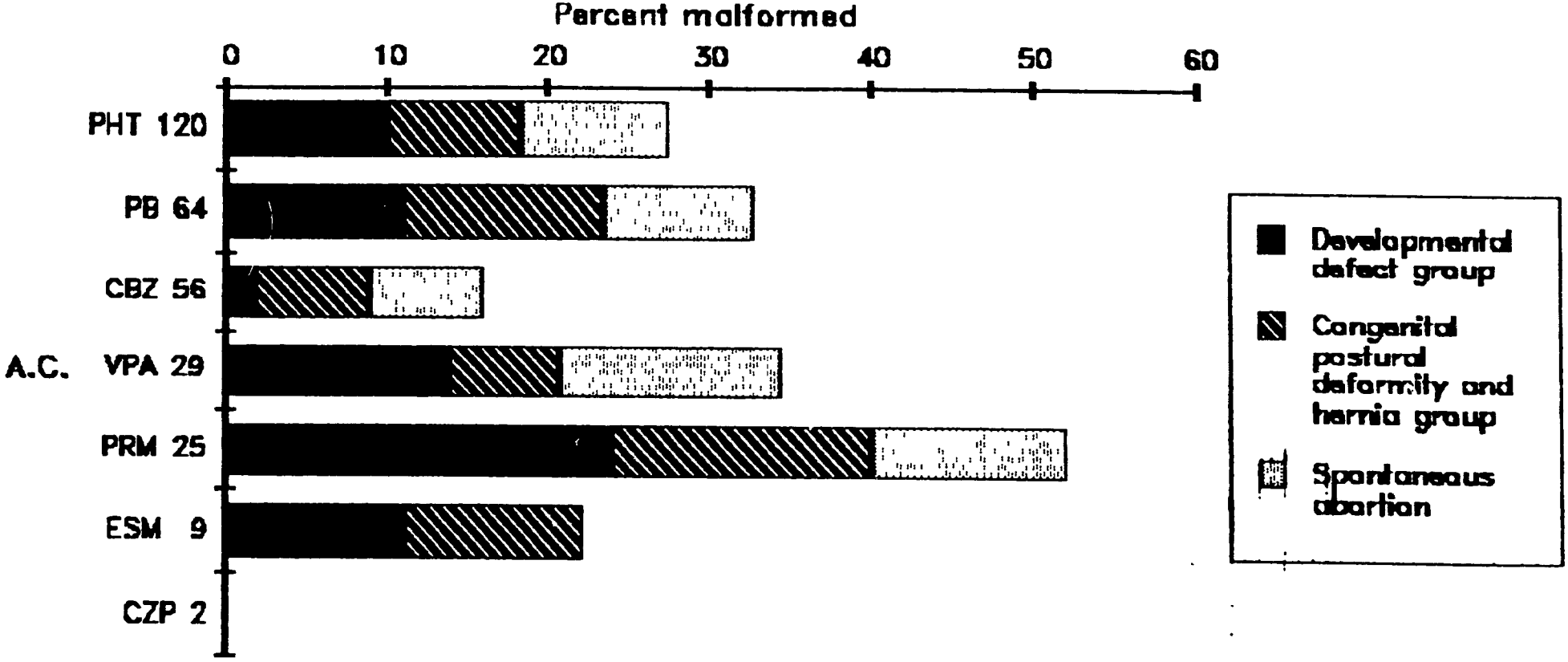
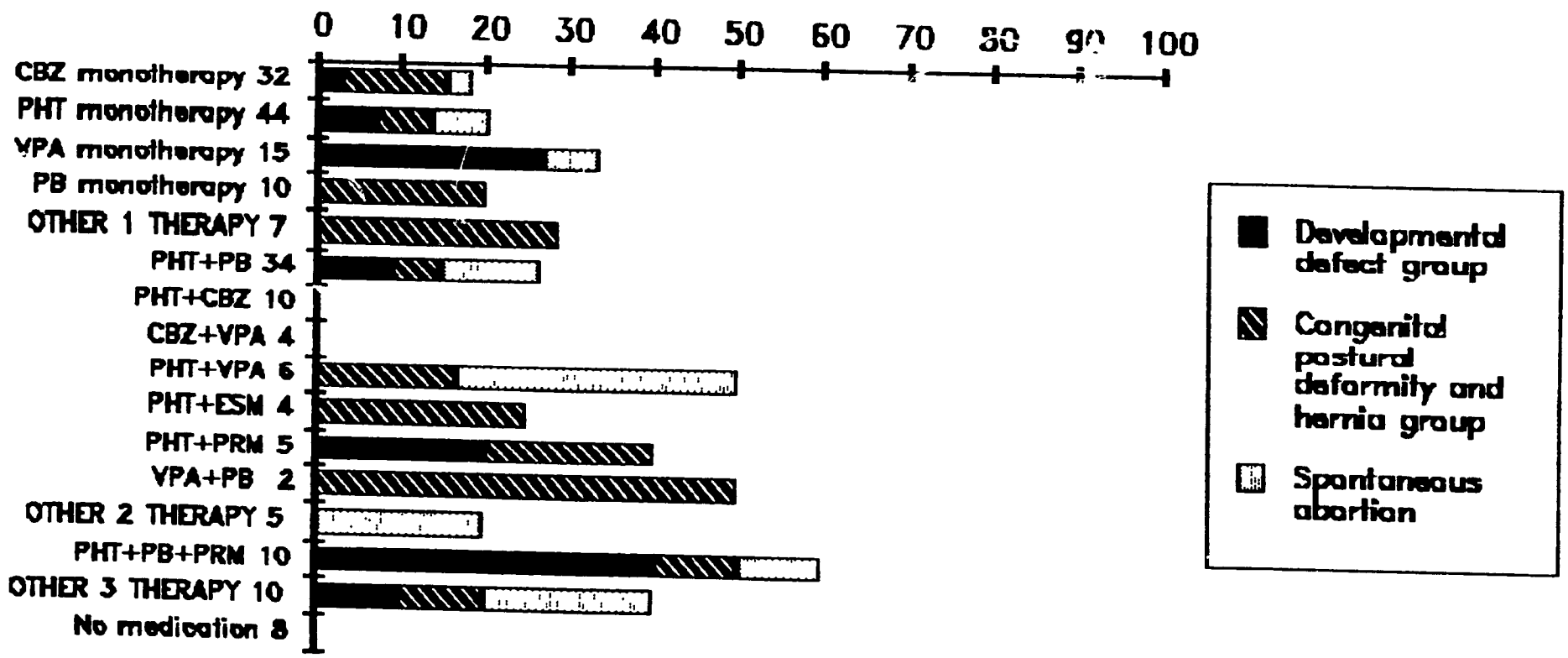


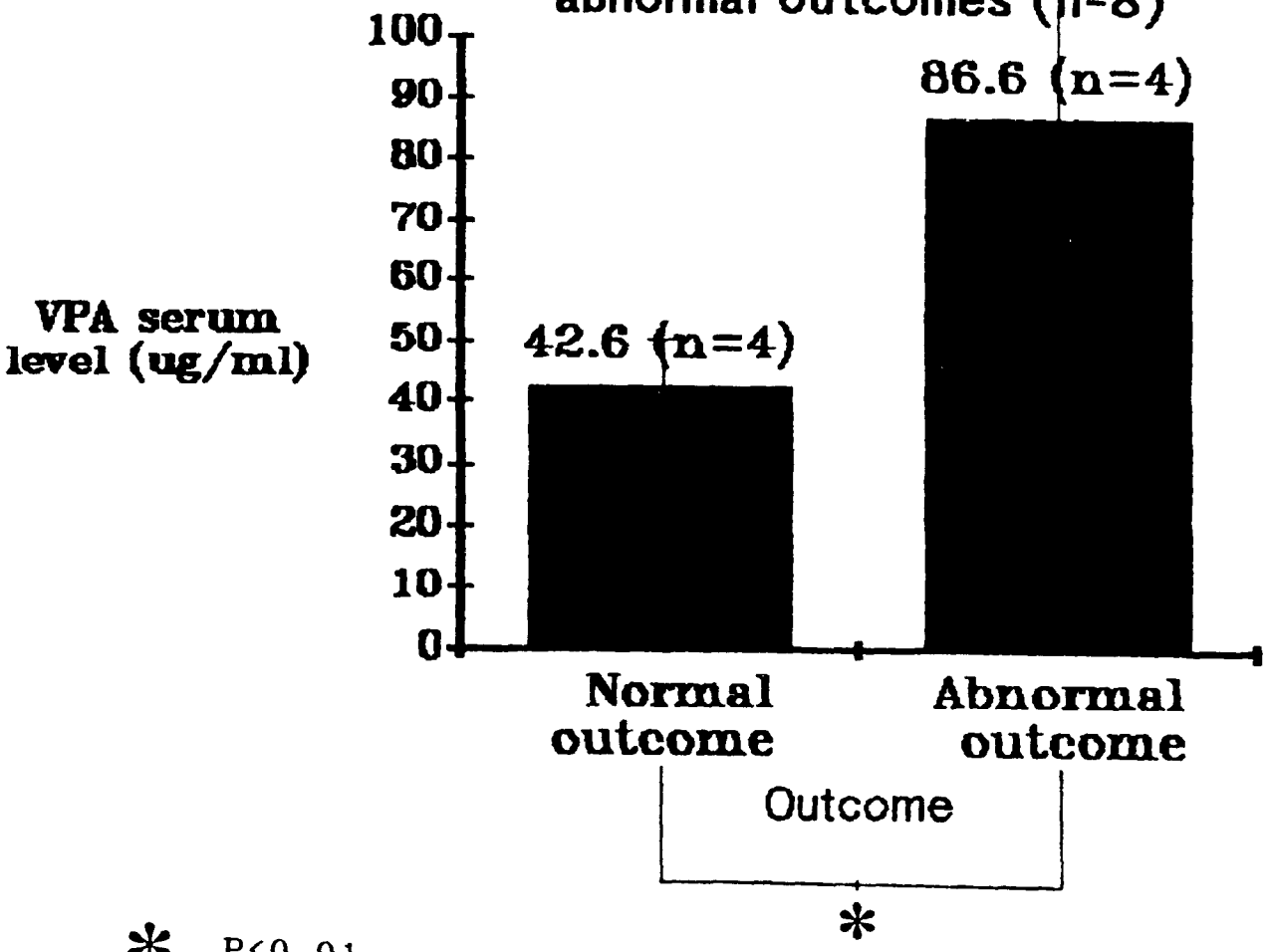
Fig. 17

Frequency of major congenital malformations in the offspring in relation to maternal anticonvulsants during the first trimester of pregnancy combined data from previous and present studies (n=206)



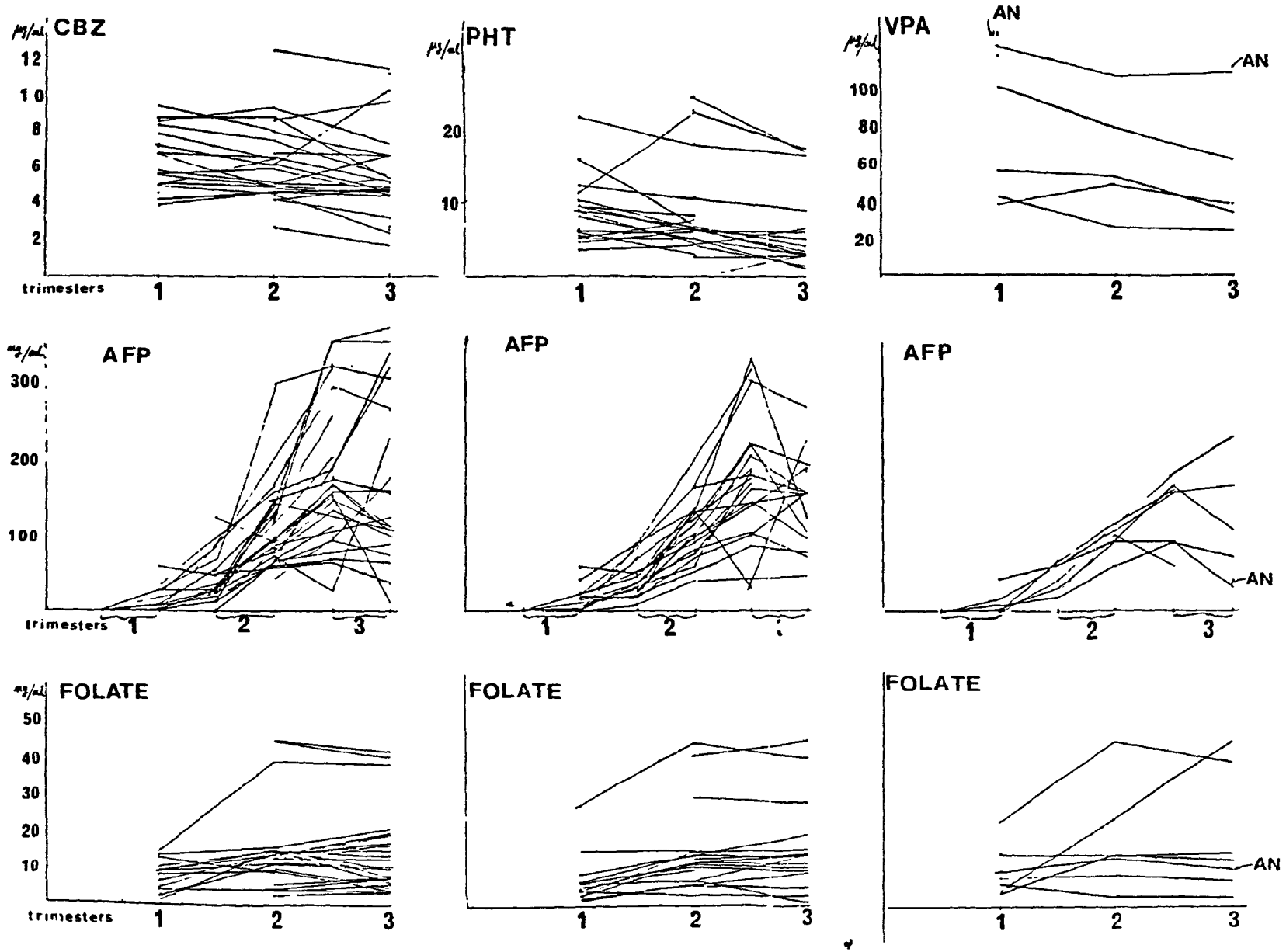
A.C.

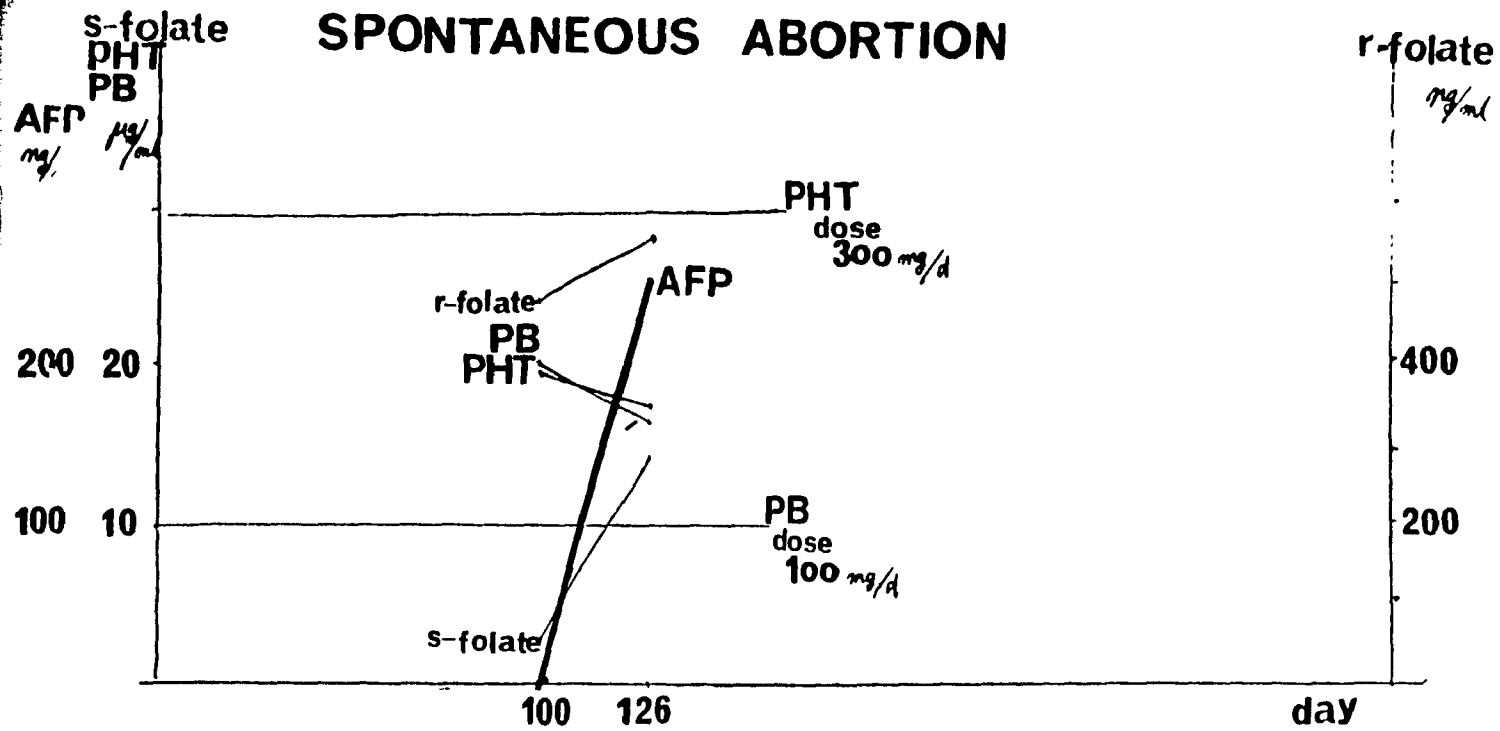
Fig. 18 Comparison of the mean VPA serum level in monotherapy between pregnancies with normal and abnormal outcomes (n=8)



* P<0.01

Fig. 19 SERUM LEVELS OF AC DRUGS, MS-AFP & S-FOLATE




s-folate
PHT
PB
AFP
SPONTANEOUS ABORTION
r-folate
PHT
dose
300 mg/d
AFP
r-folate
PB
PHT
200 20
400
100 10
PB
dose
100 mg/d
200
s-folate
100 126
day

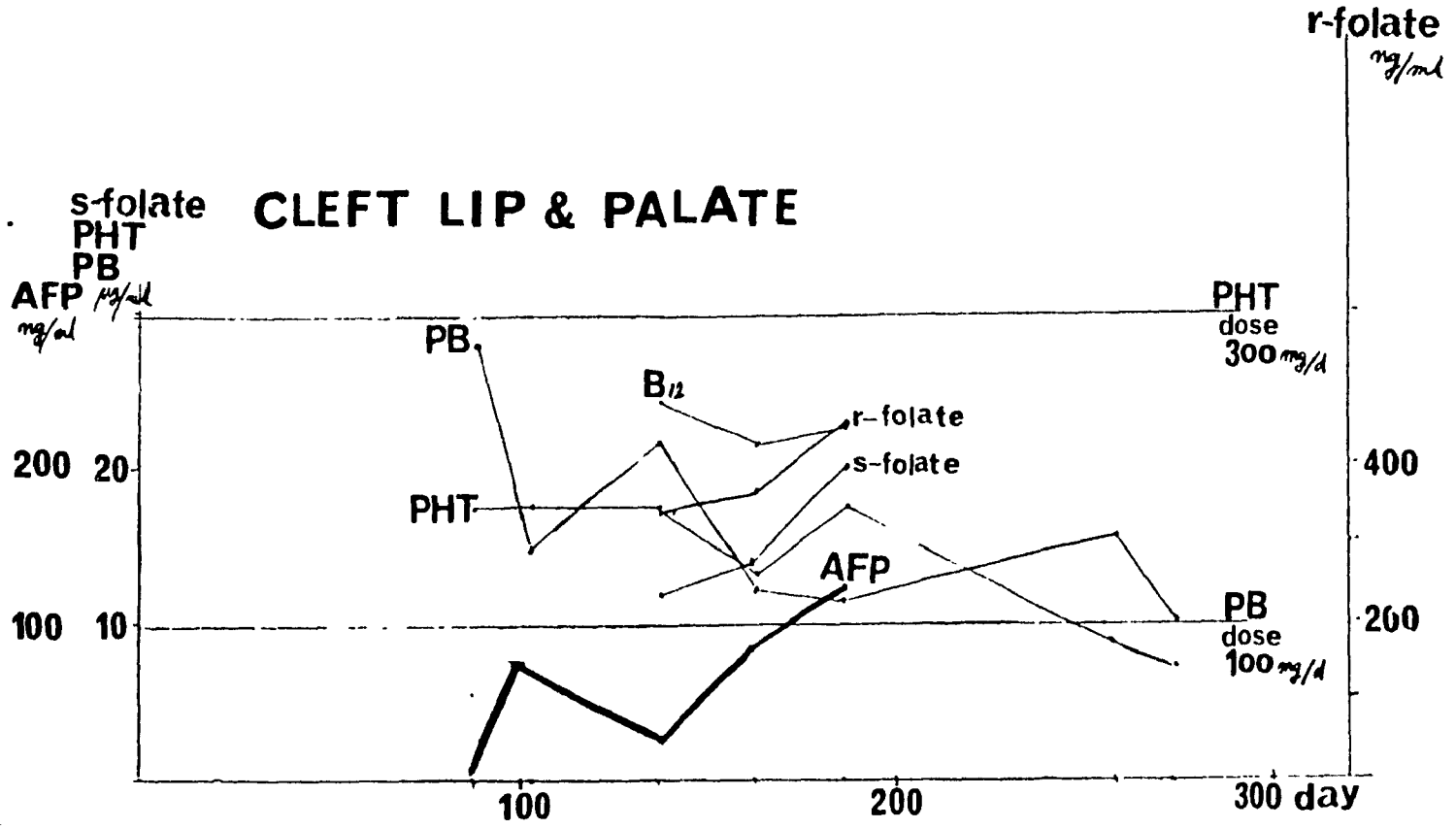
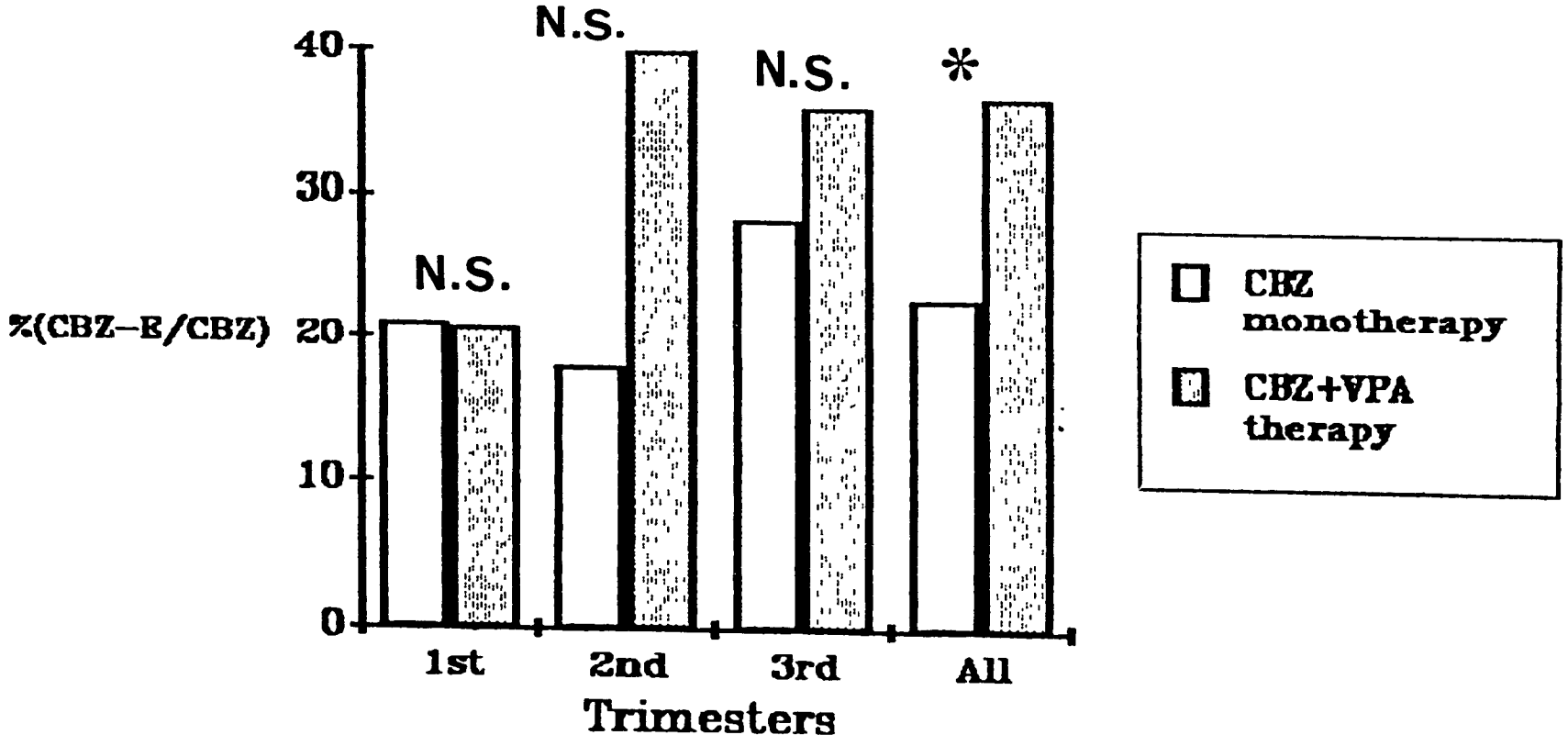
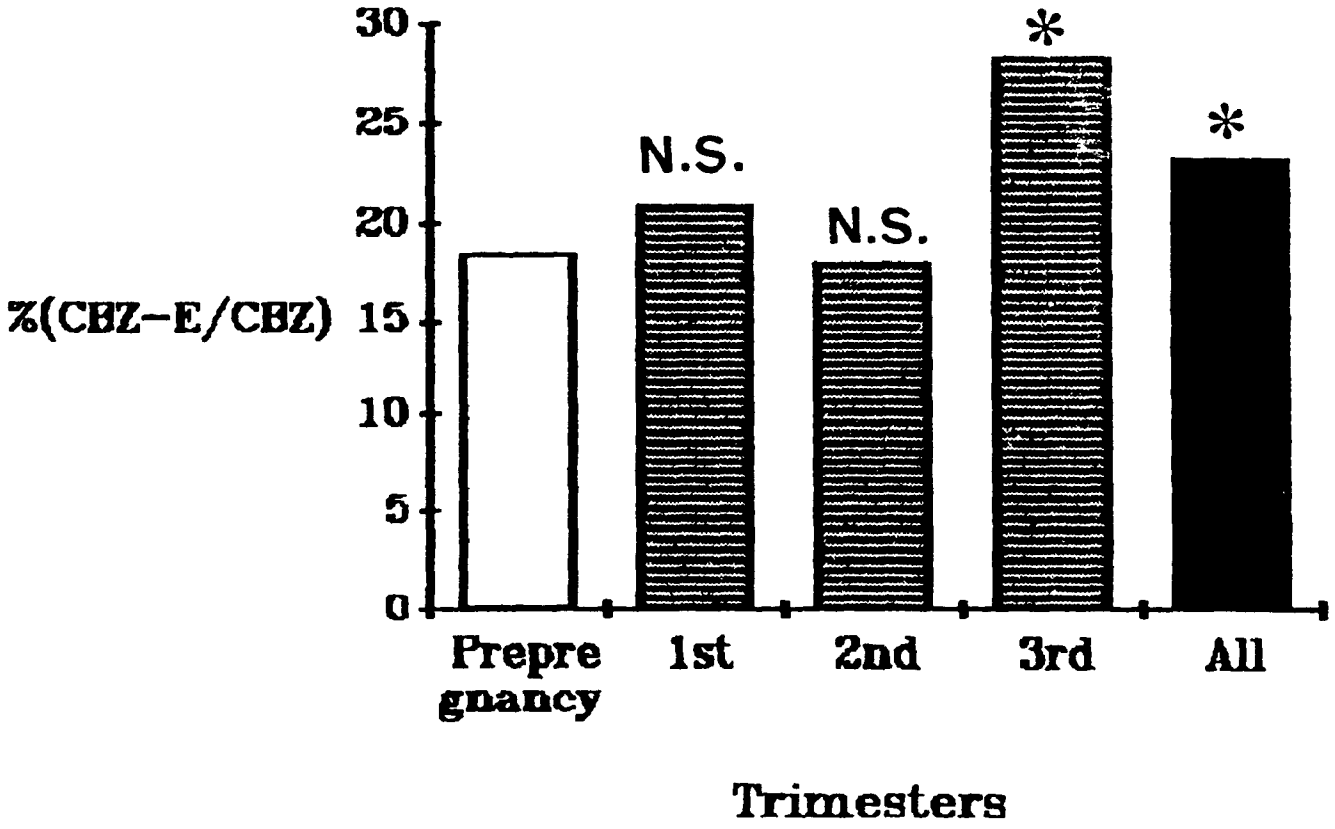

r-folate
s-folate
PHT
PB
AFP
CLEFT LIP & PALATE
PHT
dose
300 mg/d
PB
B12
r-folate
s-folate
200 20
PHT
400
AFP
100 10
PB
dose
100 mg/d
200
100
200
300 day

Fig. 21 **Comparison of % CBZ-E/CBZ between CBZ monotherapy and combined CBZ and VPA therapy groups**



* P<0.01

Fig. 22 **Comparison of % CBZ-E/CBZ between prepregnant and pregnant periods in the CBZ monotherapy group**



* P<0.01