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EFFECT OF ANTI-EPILEPTIC DRUGS IN PREGNANCY AND TERATOGENESIS

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ABSTRACT

Epilepsy raises special concern in women during pregnancy. Antiepileptic drugs are known to induce major and minor malformations in the foetus. Aim of the study was to find an association between maternal serum alpha fetoprotein levels, foetal abnormalities and antiepileptic drugs mediated teratogenicity. Maternal serum alpha feto protein levels, kidney and liver function tests in age matched normal pregnant women and seizure free epileptic pregnant women during 12 - 14 weeks of gestation were estimated. Cases were subjected to ultrasonography at 11th -14th week of pregnancy and again at 20th week of pregnancy. maternal serum alfa feto protein was assayed by a specific Electro Chemiluminescence Immuno Assay test. There was no significant difference in kidney and liver function tests in cases as compared to controls. There were elevated levels of alpha feto protein in cases as compared to controls but this was not statistically significant. No anomalies were detected in ultrasound reports. Most women had normal full term delivery with healthy children but of low birth weight. No correlation was seen between maternal serum alfa feto protein levels and antiepileptic drug leading to teratogenesis.

KEY WORDS

Alpha feto proteins, Antiepileptic drugs, Teratogenic effects, Chemiluminescence.

INTRODUCTION

Epilepsy represents a heterogeneous group of disorders of neuronal excitability arising from inherited and acquired disturbances. Prevalence of epilepsy among women in India is estimated to be 2.5 million (1),52% of them in their reproductive age group(2). Women experience gender related physical and social problems and are at the risk of seizures during labor. A complex interaction between epileptic seizures during pregnancy, antiepileptic drugs (AED), its adverse impacts on the developing fetus, congenital malformations are all being related. The risk of congenital malformation and teratogenic effect of AED is of great concern.

Many studies have shown that children born to epileptic mothers have malformations twice as often as children born to non epileptic mothers (3, 4). The data often varies and is controversial (5). Some studies show that there is increased frequency of seizures during pregnancy (6, 7), while others have shown that there is no increase in seizure frequency during pregnancy and puerperium (8). Seizure activity or seizure types do not appear to increase the risk of fetal malformations (9, 10).A complex congenital malformation are high in epileptic women who are on medication than among offspring of untreated patients (8, 11-13).

Risk increases as the number of anti epileptic drugs increased due to additive teratogenic effects. The risk of malformation being higher in women on polytherapy as compared to monotherapy (14-17). Excess risk was seen in patients using sodium valproate either as monotherapy or sodium valporate on poly therapy (13, 18), higher doses implicate with increased risk. Children exposed to sodium valporate have significantly lower IQ as compared with those with exposure to other AEDs (13, 19). Infants born to mother with epilepsy on AEDs in utero have increased risk of birth defects (10-12).

Major anomalies may affect CNS, CVS and GI systems with neural tube defects, anencephaly, spina bifida (20, 21), Chromosomal abnormalities (22, 23) and neurophysiological effect (19). However, recent studies have shown that there

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was no significant difference in pregnancy complication in cases as compared to controls in the incidence of perinatal mortality, congenital malformations, except low birth weight babies in cases (18,24,25) Recent reports have also shown the possibility of AEDs to cause selective developmental language deficits and Fetal Anti Convulsant Syndrome in children.(3,19,23, 26-28).

There has been increased interest to establish biochemical mechanisms and genetic factors in teratogenesis. Prenatal diagnostic tests can identify the fetus with common major malformations. Alfa Feto Protein (AFP) as a marker, aids in detecting fetus with neural tube defects. Increase in AFP is well known in hepatocellular carcinoma. (21), multiple pregnancy and neural tube defects (29, 30). Low levels of AFP are associated with molar pregnancy (31) and Down's syndrome (32).

Teratogenic effect of AED may be mediated by the formation of free radicals or by antifolate effects. Folic acid supplementation helps to protect from congenital malformations (17, 33) including neural tube defects (34). Indian Registry of Epilepsy and Pregnancy (IREP) have recommended 5mg folic acid per day throughout the pregnancy.

AFP is a glycoprotein with molecular weight of 70,000 D formed in yolk sac and non-differentiated liver cells, secreted to amniotic fluid and into mother's blood. It reaches maximum in about 13 – 14 week of pregnancy and falls continuously (35).

Table 1 : Age wise distribution and obstetric history of cases and controls

	Cases (n=30)		Controls(n=50)	
	N	%	N	%
Age in years				
20 – 25	17	56.67%	31	62%
26 – 30	11	36.67%	18	36%
> 30	02	6.67%	01	2%
Obstetric History				
Primigravida	18	60%	29	58%
Gravida 2	11	36.67%	17	34%
Gravida 3	01	3.33%	04	8%
Outcome of pregnancy				
FTND	26	86.67%	44	88%
LSCS	02	6.67%	04	8%
Preterm delivery	01	3.33%	00	–
IUD	00	–	01	2%
Abortion	01	3.33%	01	2%

Abbreviations: FTND=Full term normal delivery;
LSCS=Lower segment caesarian section; IUD= Intra uterine death.

AED are known to induce cytochrome P_{450} enzyme system in the liver, leading to the formation of rapid hepatic metabolites of AED which may impair the normal liver functions. Renal functions normally increases during pregnancy, AEDs may further add on to aggravate the condition.

The study has been taken, to estimate maternal serum AFP (MSAFP) levels, liver function tests and kidney function tests in 12^{th} -14^{th} week of epileptic pregnant women and controls. They were subjected to ultrasonography at 11^{th}-14^{th} week of pregnancy and again at 20^{th} week of pregnancy, to determine the obstetric and neonatal outcome in epileptic pregnancy as compared to controls. Reports helps to identify the anomalies, for timely information regarding AED mediated teratogenicity, so that major birth defects can be taken care of in early stages.

MATERIALS AND METHODS

The present study was undertaken in the Department of Biochemistry, Bowring and Lady Curzon Hospital attached to Bangalore Medical College in collaboration with OBG department. Thirty epileptic pregnant women below 35 years of age served as cases and fifty age matched pregnant women formed the control group, from middle and lower class families. Both cases and controls were non-smokers, non-alcoholic and they were on folate supplementation from the day of confirmation of pregnancy. Folic acid of 0.4 mgs/day for controls and 5mg/day for cases was prescribed.

The cases were seizure free for the last one-year but were on the base line monotherapy except for two cases who were on drug combination (Table 2). None of them were on sodium valporate, as its induced risk of teratogenicity is well established either as monotherapy or as polytherapy.

Gestational age was calculated by counting the number of complete weeks after last menstrual period. Diabetic and hypertensive controls and cases were excluded from the study. Cases and controls of 12 to 14 weeks of gestation were subjected to various biochemical parameters. Maternal serum was used to find the levels of glucose, total proteins, albumin, bilirubin, SGOT, SGPT, alkaline phosphatase, cholesterol, urea and creatinine. AFP was assayed by chemiluminisence assay (ECLIA) method, which is a highly innovative detection technology with enhanced sensitivity and specificity. The method combines the conventional antigen antibody – reaction on surface of a Magnetic Microbead with Ruthenium complex.

Table 2 : Particulars regarding onset of seizures and AED Protocol

Age of Onset	**Number**	**Percentage**	
< 5 years	08	26.67%	
5-10 years	18	60%	
11-20 years	04	13.33%	
AED protocol			
Drugs			**Dosage**
Carbamazepine(CBZ)	14		400mg/day
Phenytoin	07		200mg/day
Phenobarbital (PB)	07		120mg/day
	28	93.33%	
PB+CBZ	02	6.67%	6mg/day(PB)+ 400mg/day(CBZ)

ECLIA is a process in which highly reactive species are generated from stable precursors at the surface of an electrode. Congenital abnormalities were assessed by detailed ultrasonography targeting foetal organogenesis, between 11^{th} -14^{th} week of pregnancy and again at 20^{th} week of pregnancy. Neonatologist's service was taken to detect congenital abnormalities.

Student's 't' test was used to find the statistical significance.

The protocol of the study was to refer women to amniocentesis for estimation of amniotic fluid AFP levels, chromosomal study and 3 D ECHO in the following conditions-1. When the MSAFP levels were more than normal levels? 2. When skeletal and soft tissue anomalies were detected? 3. When the heart chambers and the out flow track of fetus was abnormal. This is to narrow down the group of women of high risk, for further higher invasive diagnostic tests, so that AED mediated teratogenesis can be detected early which aids in effective management by counseling the parents for selective termination and to confirm the diagnosis on the aborted fetus.

RESULTS AND DISCUSSION

The results obtained in the present study are presented in Tables 1-5. Epidemiological study has shown 2.5 million women with epilepsy in India (1). The findings of the complications during pregnancy and its outcome are controversial. Some studies have shown increase in seizures during pregnancy with epilepsy(6,7) while some studies have shown no increase in seizure during pregnancy and perpeurim (8).Chances of risk with AEDs are more, the risk being higher with polytherapy as compared to monotherapy (14-17). Sodium valporate either as monotherapy or as poly therapy increases the risk of foetal malformations (13, 18). Recent studies have shown no significant difference between cases and controls in pregnancy complications and perinatal mortality (18, 24, 25).

There was no significant difference in liver function tests and kidney function tests in cases as compared to controls (Table 3 and 4). There was increase in MSAFP levels in cases as compared to controls but not statistically significant and its levels were found to be independent of the type of AED used. No congenital abnormalities were seen in the newborn. There were no complications either during pregnancy or during labor with no difference in neonatal outcome in cases as compared with controls (Table 1) except low birth weight babies in cases (Table 5) in accordance to the finding of others (18, 24, 25). The beneficial effect may be due to folic acid supplementation (5mg/day) through out pregnancy. Folic acid is needed for DNA replication. It is an important vitamin involved in one carbon transfer and has a major role in amino acid, purine and pyrimidine metabolism. Any interference in this metabolism may affect normal development especially in rapidly proliferative embryonic tissues including post transcriptional modification. Folic acid is known to reduce the incidence of neural tube defects (34), congenital defect can be reduced by perioconceptual folate supplementation (16, 33, 34). Low birth weight in children may be due to intrauterine growth retardation by AED.

Most of the patients (93.33%) in this study were on base line monotherapy (Table 2), the children born to cases were normal, without any congenital malformations in agreement with other studies. Monotherapy was found to reduce the overall prevalence of malformation, as the additive teratogenic effects of AED (polytherapy) are considerably reduced (14-17). Teratogenic effect of AED may be mediated by the formation of free radicals or by antifolate effects. The relationship

Table 3 : Liver function tests of cases and control

Group	Total Protein	Albumin	Bilirubin	SGOT	SGPT	Alk.Phosphatase
Cases (n=30)	5.68±0.36*	3.14±0.36*	0.6±0.16*	20.6±3.38*	22.56±2.8*	125.66± 21.33*
Controls (n=50)	6.41±0.34	3.5±0.45	0.4±0.14	25.54±54	22.26±4.7	117.0±21.89

Results are expressed as mean ±SD; *Not Significant

Table 4 : Plasma levels of sugar, urea, creatinine, cholesterol and MSAFP levels in cases and controls

Group	Sugar	Urea	Creatinine	Cholesterol	MSAFP
Cases (n=30)	87.48±5.5*	25.22±5.5*	0.71±0.15*	164.0±6.9*	29.95±8.7**
Controls (n=50)	83.02±7.15	22.76±4.2	0.6±0.17	163.0±17.5	25.72±5.19

Results are expressed as mean ± SD; * Not Significant ** P < 0.1

between AFP levels, epileptic pregnancy and congenital malformations is therefore unclear.

Epilepsy raises special concern in women especially during pregnancy. AED are known to induce major and minor malformation in the fetus. The study was aimed in detecting AED mediated teratogenesis. No congenital abnormalities were seen in the newborn except they were low birth weight. The beneficial effect may be due to folic acid supplementation, which plays a major role in nucleic acid metabolism.

Table 5 : Birth weight of new born children of cases & controls

Birth Weight	Cases(n=30)		Controls(n=50)	
	N	%	N	%
< 2.5 kg	26	86.67%	05	10%
2.5 – 3 kg	03	10%	27	54%
3 – 3.5 kg	–	–	16	32%

The study was on small number of epileptic patients on baseline monotherapy. Further research must be aimed in multivariate analysis of risk factors on large population. Several other factors unrelated to AEDs such as consanguinity, genetic factors, socioeconomic status and nutritional factors have to be correlated before coming to conclusion. Epidemiological data along with retrospective study of data of epileptic pregnant women is essential to correlate the effect of monotherapy/ polytherapy, dosage of drugs to congenital malformations. Large population study and long term prospective follow up for neurological development of the children is needed before coming to any conclusion. Estimation of Red cell folate along with the measure of proportions of unbound AED to bound AED in different AED regime is our plan for future study to elucidate the role of drugs and its dosage in implicating fetal anomalies.

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