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Outcome of pregnancies in epileptic women: a study in Saudi Arabia

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We studied the outcome of 79 pregnancies in 44 Saudi women who had epilepsy. Their mean age was 28 ± 6.5 years and the number of pregnancies studied varied from one to six. Nineteen subjects had generalized seizures, 16 had partial seizures and nine were unclassified. The commonest drug prescribed was carbamazepine and the majority of the women (61%) were on monotherapy. The seizures were controlled in 53 pregnancies (67%). Spontaneous vertex deliveries were the commonest. The indications for intervention by lower segment Caesarean section, forceps or ventouse were foetal distress, pre-eclamptic toxemia (PET), eclampsia, breech presentation and prolonged labour. The most frequent adverse outcome in the babies was low birth weight (<2.5 kg) in nine pregnancies. The frequency of congenital malformation was 2.5%. Low birth weight was associated with prematurity, PET, congenital malformation and polytherapy. Avoidance of polytherapy appears to be the most feasible intervention in reducing the frequency of low birth-weight children by epileptic mothers.

Key words: epilepsy; pregnancy; malformations; outcome; drug therapy.

INTRODUCTION

Successful management of epilepsy in pregnancy incorporates seizure control, maintenance of good health of the mother and delivery of a healthy baby. The possible problems and complications that may arise and could compromise the outcome include: increased risk of maternal seizures due to altered drug pharmacokinetics, risk of bleeding, toxemia and prematurity^{1–3}. Additionally, exposure to antiepileptic drugs (AED) in utero could be associated with congenital malformations in the baby^{1–6}. We reviewed the course of pregnancy in a group of female epileptic patients followed up in the neurology clinics to document the outcome of pregnancy and the factors associated with adverse outcome.

MATERIALS AND METHODS

The study took place at the King Khalid University Hospital, Riyadh (KKUH) which is a teaching hospital with approximately 600 beds. The hospital provides

secondary and tertiary care services. It attracts referral from all over the Kingdom. Health care is provided free for all Saudis; however, there is no special bias for delivery in KKUH.

Methodology

The antenatal and perinatal records of the pregnant epileptic patients followed up in the neurology clinics compiled by M. A. Bunyan (MAB) between 1985 and 1994 were examined. The information obtained on each patient included: the duration of epilepsy, the seizure type, seizure frequency during the index pregnancy, the AED prescribed, compliance and serum drug levels. We documented the previous obstetric history including parity, mode of delivery and adverse outcomes like congenital anomalies or stillbirth if any. For the index pregnancies we recorded: the last menstrual period and the expected delivery date. The gestational age of the baby at delivery was determined from these dates and ultrasound scan findings. The type of delivery (i.e. whether spontaneous vertex, Caesarean section, ventouse or others) was recorded.

In patients who underwent surgical intervention the indications for operative delivery were noted. The Apgar scores of the babies at 1 and 5 minutes were derived from the quality of heart rates, respiratory effort, muscle tone and reflexes determined in the standard way.

The following measurements were made: occipito-frontal head circumference, length and weight of each baby. The weights were measured on electronic baby scales (BSL 20A, FCG, Japan) with automatic resetting to zero. The baby lengths were measured using an infantometer supplied by Holtian Ltd (Crymych, Dyfed, Wales UK). These methods have been previously described⁷. The post-partum examinations were carried out by a paediatrician who documented any congenital anomalies present. The reasons for admission of any baby to the neonatal intensive care units were recorded where applicable.

Data analysis

We used frequency counts for all the variables. We tested for association between pregnancy outcome and the following: maternal age, duration of epilepsy, mode of therapy using cross-tabulations, determination of the odds ratio and chi-squared test statistics. We compared the anthropometric measurements of the babies with those from published literature on Saudi birth weights (historical controls)⁷⁻⁹. Birth weights less than 2.5 kg were regarded as low birth-weight infants⁷.

RESULTS

A total of 79 pregnancies occurred in 44 women with varying parity from one to 10 during the study period. Twenty-four patients had one pregnancy each, 12 had two, three had three and four had four pregnancies in the hospital. One woman had six pregnancies during the study period. The ages of the women ranged between 17 and 48 years with a mean of 28 years (SD = 6.5 years). The mean age at onset of epilepsy was 18 years (SD = 6.4 years). Nineteen patients (43.2%) had generalized seizures of whom 10 were of the myoclonic type and the remaining nine had tonic-clonic seizures. Sixteen subjects (36.4%) had partial seizures, of whom 10 were complex, five were secondarily generalized and one was simple. The remaining nine cases were not classifiable. The seizures remained controlled during 53 pregnancies (67%).

Table 1 shows the drug therapy during the pregnancies. The most frequently prescribed drug was carbamazepine which was used as monotherapy during 31 pregnancies, and in combination with other drugs in 15 other pregnancies. In 10 pregnancies, the mothers did not take AED because their seizures were in remis-

Table 1: Pattern of drug prescription.

Drug	Monotherapy	Polytherapy ^a	Total
Carbamazepine (CBZ)	31	15	46
Phenytoin (PHT)	9	12	21
Valproate (VAL)	5	6	11
Phenobarbitone (PHB)	2	8	10
Clonazepam (CLO)	1	2	3
No drugs ^b	—	—	10
Total ^c	48	21	79

^aCombinations: PHT + CBZ = 8; CBZ + PHB = 4; PHT + PHB = 3; LBZ + Val = 2; Val + PHB, Val + PHT, Val + CLO, Val + CBZ + CLO of 1 each.

^b Seizures in remission for a long time.

^c Monotherapy + Polytherapy + No drugs.

Table 2: Outcome of pregnancies—post-partum data.

	Epileptic mothers <i>n</i> = 79	Non-epileptic ^a	Statistics
Gestational age (weeks)			
Mean	39.4 ± 2.0	39.2 ± 2.0	ns ^b
Mean Apgar score			
1 minute	7.5 ± 1.3	n/a ^c	
2 minutes	8.9 ± 0.8	n/a	
Mean birth weight ^d (kg)	3.2 ± 0.6	3.3 ± 0.5	ns
Number < 2.5 kg	9 (11.5%)	338 (7.4%)	ns
Number > 2.5 kg	69 (88.5%)	4578 (92.6%)	
Mean birth length (cm)	48.8 ± 2.9	49.7 ± 2.5	ns
Mean head circumference (cm)	33.7 ± 1.7	34.4 ± 1.4	ns

^a Ref: 8–10;

^b ns = not significant;

^c n/a = not available;

^d excludes one stillbirth.

sion and as a personal preference for fear of an adverse outcome in their babies.

Spontaneous vertex deliveries for 63 pregnancies (79.7%) were the most frequent. Lower segment Caesarean section was performed for 10 pregnancies and there were three deliveries each by ventouse and forceps. The indications for intervention were: foetal distress (five cases), pre-eclamptic toxemia (three cases), elective procedure by a particular patient (three cases), eclampsia (two cases) and one case because of breech presentation, prolonged labour and obstructed labour due to cephalopelvic disproportion. A summary of the anthropometric measurements and Apgar scores of the babies tabulated against the data for historical controls in Saudi Arabia is presented in Table 2.

Two babies had congenital malformations. One of them was delivered by a 39-year-old, gravida 11, whose seizures were controlled by a combination of phenytoin and carbamazepine. That baby had dextrocardia and oesophageal atresia. In addition, the baby had a low birth weight and a low Apgar score. The second baby had hydronephrosis and a low birth weight. The second mother was controlled on carbamazepine only. A third child with cardiomegaly was recorded, though

there was no clinical evidence of congenital heart disease. His mother was a 35-year-old, gravida nine, who had pre-eclamptic toxemia. The same woman had a previous baby with congenital heart disease. She was on polytherapy of valproate, clonazepam and carbamazepine. The frequency of congenital malformation in this study was 2.5%. One woman with juvenile myoclonic epilepsy on carbamazepine and phenytoin had a stillbirth. That pregnancy was terminated at 32 weeks. Two babies needed observation in a neonatal intensive care unit because of meconium-stained liquor, and were later discharged with no complications.

Low birth weight (lbw) was recorded in a total of nine babies including two premature deliveries, three cases of pre-eclamptic toxemia, two babies born with congenital malformations; the stillbirth at 32 weeks and the baby of one 40-year-old, gravida eight, mother who was not on AED. Out of the 10 pregnancies that had obstetric or neonatal problems (including lbw), six of them involved AED polytherapy (carbamazepine and phenytoin in three cases; carbamazepine and phenobarbital in two cases and a combination of valproic acid, clonazepam with carbamazepine in the last case). Three others were associated with monotherapy (i.e. carbamazepine two cases and phenytoin one case). The 10th one involved a woman who was no longer on any medication. There was a statistically-significant association between polytherapy and low birth weight (odds ratio = 6.0; $\chi^2 = 6.62$; $P \leq 0.001$).

When the obstetric and neonatal complications were analysed according to the ages of the mothers, the two babies that had congenital malformations were born to mothers older than 30 years. There was no association between adverse pregnancy outcome and the duration of epilepsy in the mothers. Six complications in 37 pregnancies occurred in women who had been epileptic for less than 10 years compared with four out of 32 in women whose duration of epilepsy was more than 10 years (odds ratio = 1.35; $\chi^2 = 0.16$; $P \geq 0.1$).

DISCUSSION

The high standard of living, absence of smoking, absence of hard physical work during pregnancies and adequate energy reserves at confinement are some of the factors which have been reported to account for the documented favourable outcome of pregnancies in Saudi mothers⁷⁻¹⁰. In addition, hospital care is free, so patients have access to drugs and investigations deemed necessary. However, epilepsy constitutes a medical constraint which can disturb the expected favourable outcome, more so, when seizures are either uncontrolled or if complications arise as a result of the use of AEDs. In fact, some authors consider women with epilepsy as having high-risk pregnancies⁵. Our

study served to highlight the favourable outcome of many pregnancies in epileptic women with seizure control, approximately 67% of them. The complications of pregnancies in this study group are no different from results of other studies in non-epileptic mothers in this environment. Our study, however, emphasized the aspect of congenital malformations.

The type of seizure influences the choice of AED although studies have shown that there is no appreciable difference in the effectiveness of the major AEDs¹¹. The predominant use of carbamazepine during pregnancies in our patients, because of its proven efficacy in both secondarily generalized and partial seizures, is similar to the other reports^{5,12,13}. The distribution of AED use in our cases is similar to other studies. The high frequency of myoclonic seizures warranted the use of valproic acid in spite of its known association with congenital malformations especially neural tube defects^{1,2,4-6,14}. Although the use of valproic acid is not absolutely contra-indicated in pregnancy, especially when the seizures are well-controlled or there is no alternative, however, such women would require examination for markers of dysraphism and ultrasonography before the 20th week of gestation^{6,15}. These were done routinely in our patients and none of the babies had spina bifida. Despite the regular follow-up and compliance of these women, seizures were uncontrolled in about a third of them. This is not an unusual proportion, as seizures may be uncontrolled in up to 64% of patients with major seizures in one series¹³. The breakthrough attacks are more likely to be due to sleep deprivation or deliberate non-compliance during pregnancy. Another reason could be altered drug pharmacokinetics in pregnancy related to plasma protein binding^{1,2,5,16}. In such instances, the usually measured total plasma-drug concentration may be misleading but the active free-drug concentration may be abnormal which might cause confusion as regards adjustment of drug dosages¹³.

The pattern of obstetric management in this study is no different from the experiences of others^{1,2}. The commonest neonatal problem was: intra-uterine growth retardation or low birth weight which was associated with prematurity, pre-eclamptic toxemia, congenital malformations, maternal old age and polytherapy. Maternal age in Saudis of more than 35 years was associated with a doubled increase in the risk of low birth weight compared with Swedish mothers in another study⁹. Intra-uterine growth retardation and developmental delay are well-documented as minor anomalies associated with the use of phenytoin, carbamazepine and phenobarbital⁵. None of the women were treated with trimethadone which is also associated with intra-uterine growth retardation⁵. The higher proportion of babies with intra-uterine growth retardation born by epileptic mothers was the only feature that

appeared different from the data on the historical controls in earlier studies⁷⁻⁹. However, the difference was not statistically significant.

The frequency of congenital malformations of 2.5% in this study group is within the range of 1-6% reported previously². However, we could not have encountered all the possible congenital malformations because of the small sample size. In spite of this limitation, the association of polytherapy with adverse pregnancy outcome was apparent. Polytherapy is associated with enhanced formation of active metabolites which overtake the capacity for their elimination and could result in malformations¹⁶. Other possible considerations include genetic predisposition and reduced folate levels¹⁶.

In conclusion, our results showed a slightly higher frequency of low birth-weight children born by epileptic mothers which was associated with prematurity, older maternal age and multiple AED usage. The frequency of congenital malformation was within the range reported in other studies. The use of AED as monotherapy during pregnancy is a feasible intervention which is essential for reducing the frequency of prematurity and congenital malformations.

REFERENCES

1. Waters, C. H., Belai, Y., Gott, P. S., Shen, P. and De Gioglio, C. M. Outcome of pregnancy associated with antiepileptic drugs. *Archives of Neurology* 1994; **51**: 250-253.
2. Dalessio, D. J. Seizure disorders and pregnancy. *New England Journal of Medicine* 1985; **312**: 559-563.
3. Commission on Genetics, Pregnancy and the Child. International League Against Epilepsy. Guidelines for the care of women of childbearing age with epilepsy. *Epilepsy* 1993; **34**: 588-589.
4. Lindhout, D. and Omtzigt, J. G. G. Teratogenic effects of anti-epileptic drugs: implications for the management of epilepsy in women of childbearing age. *Epilepsia* 1994; **35** (Suppl. 4): S19-S28.
5. Yerby, M. S., Leavitt, A., Erickson, D. M., McCormick, K. S., Loewenson, R. B., Sells, C. J. and Benedetti, T. J. Antiepileptics and the development of congenital anomalies. *Neurology* 1992; **42** (Suppl. 5): 132-140.
6. Penry, J. K. (Ed.). *Epilepsy: Diagnosis, Management, Quality of Life*. New York: Raven Press, 1986: pp. 28-30.
7. Al-Eissa, Y. A., Ba'aqueel, H. S. and Hague, K. N. Low birth-weight in Riyadh, Saudi Arabia: incidence and risk factors. *Annals of Tropical Paediatrics* 1991; **11**: 75-82.
8. Taha, S. A., Abdullah, M. A., Jowda, M. S. and Akbar, J. U. Size at birth of live-born Saudi infants. *British Journal of Obstetrics and Gynaecology* 1984; **91**: 1197-1202.
9. Serenius, F., Edressee, A. W. and Swaillem, A. R. Size at birth of infants in a Saudi maternity hospital. *Acta Paediatrica Scandinavica* 1988; **346** (Suppl.): 44-56.
10. Serenius, F., Edressee, A. W. and Swaillem, A. R. Characteristics of the obstetric population in a Saudi maternal hospital. *Acta Paediatrica Scandinavica* 1988; **346** (Suppl.): 29-43.
11. Mattson, R. H., Cramer, J. A., Collins, J. F., Smiths, D. B., Delgado-Escueta, A. U., Brown, T. R., Williamson, P. D., Treiman, D. M., McNamara, J. O. and McCutchen, C. D. Comparison of carbamazepine, phenobarbital, phenytoin and primidone in partial and secondarily generalized tonic-clonic seizures. *New England Journal of Medicine* 1985; **313**: 145-151.
12. Gjerde, I. O., Strandjord, R. E. and Ulstein, M. The course of epilepsy during pregnancy: a study of 78 cases. *Acta Neurologica Scandinavica* 1988; **78**: 198-205.
13. Tomson, T., Lindbom, U., Ekqvist, B. and Sundqvist, A. Epilepsy and pregnancy: a prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. *Epilepsia* 1994; **35**: 122-130.
14. Battino, D., Binelli, S., Caccamo, M. L. *et al.* Malformations in offsprings of 305 epileptic women: a prospective study. *Acta Neurologica Scandinavica* 1992; **85**: 204-207.
15. Hillesmaa, V. K. Pregnancy and birth in women with epilepsy. *Neurology* 1992; **42** (Suppl. 5): 8-11.
16. Kaneko, S., Otani, K., Kondo, T. *et al.* Malformations in infants of mothers with epilepsy receiving antiepileptic drugs. *Neurology* 1992; **42** (Suppl. 5): 68-74.