Evaluation of antiepileptic drugs in pregnancy in a Jordanian army hospital

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تقييم الأدوية المضادة للصرع لدى الحوامل في مستشفى عسكري أردني

رفيق برقاوي

الخلاصة: كان هدفنا هو تحديد بروتوكول علاجي للحوامل المصابات بالصرع. وقد قمنا باختيار خمسين حاملاً، كن يراجعن عيادة رعاية الحوامل في مركز الملك حسين الطبي، ممَّنْ كنَّ يُعالجن من الصرع قبل الحمل. وقد قُسِّمن ثلاث مجموعات، المجموعة أ (عددهن 16)، تلقّين علاجاً أحادياً بعقار الكاربامازيبين، والمجموعة ب (عددهن 16) تلقّين علاجاً مشتركاً بعقاري الكاربامازيبين والفينيتوين، والمجموعة ج (عددهن 18) لم يتلقّين أي علاج لرفضهن ذلك خشية حدوث ضرر للجنين. و لم تُصَبْ سوى إمرأة واحدة من المجموعة التي تلقت علاجاً أحادياً، بنوبات صرعية. أما المجموعة ب، فلم تتعرض أيٌّ منهن لأية نوبات، إلا أن الحمل أُنهي لدى اثنتين منهن بسبب عيوب في الأنبوب العصبي. وفي المجموعة ج، أصيبت خمس سيدات بنوبة أو نوبتين صرعيتين. و لم يُصَبْ أيٌّ من الأطفال الذين وُلدوا لسيدات المجموعة ج بأية شذوذات خلقية، أما الأطفال الذين وُلدوا للأمهات من المجموعتين ب و ج فقد كان لدى 25٪ منهم شذوذات خلقية طفيفة، الأمر الذي يمثل فارقاً يُعتَدُّ به إحصائياً.

ABSTRACT We aimed to determine a treatment protocol for pregnant women with epilepsy. We selected 50 pregnant women from the antenatal clinic, King Hussein Medical Centre, who had been treated for epilepsy prior to pregnancy. They were divided into 3 groups. Group A (***n*** = 16) received monotherapy with carbamazepine, group B (***n*** = 16) received combined therapy with carbamazepine and phenytoin, and group C (***n*** = 18) received no drugs because they refused treatment for fear of harming the fetus. Only 1 woman on monotherapy had seizures**.** In group B, no one had seizures, but 2 pregnancies were terminated because of neural tube defects. In group C, 5 patients had 1–2 seizures. No babies delivered to women in group C had congenital anomalies but 25% of babies born to mothers in groups A and B had minor congenital anomalies, a statistically significant difference.

Évaluation des médicaments antiépileptiques pendant la grossesse dans un hôpital militaire jordanien

RÉSUMÉ Notre objectif était de définir un protocole thérapeutique pour les femmes épileptiques enceintes. Nous avons sélectionné 50 femmes enceintes au dispensaire de surveillance prénatale du centre médical Roi Hussein, qui avaient traitées pour l'épilepsie avant la grossesse. Elles ont été réparties en trois groupes : le groupe A (n = 16) a reçu une monothérapie à base de carbamazépine, le groupe B (n = 16) a reçu une association de carbamazépine et phénytoïne et le groupe C (n = 18) n'a reçu aucun médicament car les femmes ont refusé le traitement de peur de nuire au fœtus. Une seule femme dans le groupe de monothérapie a eu des crises. Dans le groupe B, aucune n'a eu de crises, mais 2 grossesses ont été interrompues en raison d'anomalies du tube neural. Dans le groupe C, 5 patientes ont eu 1 à 2 crises. Aucun bébé né dans le groupe C ne présentait d'anomalies congénitales mais 25 % des bébés nés dans les groupes A et B présentaient des malformations congénitales mineures, ce qui constitue une différence statistiquement significative.

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Introduction

Epilepsy is the most common neurological disorder that the obstetrician encounters in pregnancy, as about 1% of the population is affected [*1*]. Seizures in pregnancy have an incidence of 0.15%–10% [*2*].

During recent years, many antiepileptic drugs have been approved for preconception in different countries. Some promising drugs are in various stages of development and many are being tested to determine which drug or combination of drugs is safest for the fetus.

The majority of women with epilepsy who become pregnant have uncomplicated pregnancies and healthy babies. Nonetheless, pregnancy management must include folic acid before pregnancy and awareness of the teratogenic effect of the drugs, obstetric complications and contraception.

The primary objective of our study was to evaluate the safety of available antiepileptic drugs for the fetus and simultaneously to reduce the incidence of seizures, so as to deliver a healthy baby with the fewest complications possible.

Methods

We enrolled 50 pregnant women in our study, each with a history of epilepsy. They were aged 25–35 years, multiparous, with known past history of epilepsy for the last 5 years, and with no obvious cause of the disease. All women were regular attenders of the internal medicine clinic at King Hussein Medical Centre, Amman, Jordan, and were receiving various drug therapies for epilepsy management. They were followed in the antenatal clinic from their initial visit through to delivery and during each visit a detailed history of seizures was taken. Each woman had had at least 3–4 seizures during the 12 months prior to pregnancy while on treatment. The poor control was mainly due to lack of patient compliance with the antiepileptic medication. Vital signs were recorded, especially blood pressure, and a detailed ultrasound examination was done at 16–18 weeks gestation.

The women were randomly classified into 3 groups: Group A had monotherapy with carbamazepine. Group B had combined therapy of carbamazepine and phenytoin and group C had no antiepileptic medication. The benefits and side-effects of the drugs were explained to the women at their first antenatal visit. Those assigned to group C were aware of the possibility of an increased frequency of seizures. A few women refused medication and were assigned to Group C. All the women signed consent forms.

All patients were on treatment before pregnancy and the serum level of the drugs was taken at each visit and the dose was adjusted accordingly for those in groups A and B. We asked the women to attend the antenatal clinic fortnightly during the first 2 trimesters and then weekly in the third trimester: they all attended regularly. The course of the pregnancy and the neonatal outcome were identified and compared between the groups. Statistical analysis was done using Fisher exact test.

Results

In group A (n = 16), 1 of 16 patients (6%) had 2 seizures between 30–34 weeks gestation. We continued giving her the same treatment, keeping the serum level of carbamazepine at its optimal level. All patients in group A reached term and had normal vaginal deliveries. The neonates of 4 women in this group had minor congenital anomalies (incidence 25%); these anomalies included distal digital hypoplasia and ear flap abnormalities.

No patients in group B (n = 16) had seizures, but the babies of 6 women (37.5%) developed congenital anomalies. Of these, 4 neonates had minor anomalies and 2 women underwent pregnancy terminations at 14-weeks and 16-weeks gestation with the diagnosis of anencephaly with open spina bifida, i.e. not compatible with life.

In group C (n = 18), 5 patients (27%) had at least 1 seizure during the prenatal period. All refused medical treatment for the fear of harming the fetus. Moreover, some were not even aware of the occurrence of the seizure and we would verify events with their relatives. All the patients in this group had normal vaginal deliveries. Unfortunately 1 patient had a seizure just after delivery, which was managed appropriately and the patient and her child remained in good general condition. No congenital abnormalities were detected among the offspring of this group (Table 1).

Major fetal malformations were detected in group B, although none occurred in groups A and C but the difference was not statistically significant (P = 0.07). The malformations were not associated with seizures. No seizures occurred in the combined therapy group compared with both group A and group C but again the difference was not statistically significant (P = 0.03). However, minor congenital anomalies were noted in both groups A and B compared with group C which was a statistically significant (P = 0.01).

Discussion

Pregnancy may be problematic for epileptic woman because obstetric complications tend to be more frequent and seizure control may be affected. The risk of seizures is high: during labour the risk is almost 10-fold higher. There is a 2-fold or 3-fold increase in the risk of birth defects with the use of antiepileptic drugs [*3*]. Anticonvulsants to prevent the occurrence of seizures are recommended during pregnancy, even if they are potential teratogens [*3,6,8*].

One area of controversy involves the effect of pregnancy on seizure frequency, as approximately one-third of patients will have an increase in frequency, although the remainder will have no change or a decrease [*4,5*]. The effect of pregnancy on epilepsy may be inferred from the woman's

Table 1 **Seizures and neonatal congenital anomalies with monotherapy, combined therapy and without medication**

Outcome	Group A (n = 16) Monotherapy with carbamazepine		Group B (n = 16) Combined therapy with carbamazepine and phenytoin		Group C (n = 18) No seizure control medication		P-value
	No.	%	No.	%	No.	%	
Seizures	1	6	0	0	5	27	0.03
Minor congenital anomalies	4	25	4	25	0	0	0.01
Major congenital anomalies	0	0	2	12.5[a]	0	0	0.07

[a]***Pregnancies terminated at 14 weeks and 16 weeks.***
Significance at: P ***< 0.01 (Fisher exact test).***

seizure frequency before pregnancy. As a rule, the fewer seizures in the 9 months before conception, the lower the risk of epilepsy worsening during pregnancy [*1*].

In our study, the incidence of seizures increased in the group with no treatment (Group C). Similarly, in Germany the frequency of seizures increased for patients who were not on medication [*6*].

The increase in seizure frequency during pregnancy is the result of a quicker rate of clearance of antiepileptic drugs. One study concluded that sub-therapeutic serum levels of antiepileptic drugs correlated highly with increased frequency of seizures in epileptic pregnant women [*7*]. The state of seizure control in epileptic pregnant women should therefore be monitored regularly during the course of the pregnancy.

The effects of antiepileptic drugs on the fetus are complex [*8*]. The four most commonly used drugs—carbamazepine, phenobarbital, phenytoin and valproic acid—are known to cross the placenta and have teratogenic effects. The rate of congenital malformations in patients using these drugs is approximately 2–3 times that of non-epileptic mothers [*9*]. An estimated 6%–8% develop congenital malformations; thus, more than 90% of mothers taking antiepileptic drugs during pregnancy will deliver normal children [*9*].

Additional factors have been linked to the increased rate of anomalies in the fetuses of patients taking antiepileptic drugs. Multiagent therapy appears to enhance the malformation rate [*10*]. In addition, phenytoin and carbamazepine have been associated with patterns of malformation that are quite similar [*11,12*]. Common anomalies include mildly dysmorphic face and fingers with stubby distal phalanges and hypoplastic fingernails, suggesting a "fetal antiepileptic drug syndrome" [*9*].

Despite the etiologic uncertainty, individual drugs have been associated with specific anomalies. Cleft lip and palate and cardiac and urogenital defects are reported with phenytoin [*13*]. Spina bifida occurs in 1%–2% of the fetuses of patients taking valproic acid [*14*]. The malformation pattern associated with phenobarbital is similar to that seen with phenytoin. Carbamazepine was thought to be the safest of the antiepileptic drugs, but recently it too has been associated with spina bifida at a rate of approximately 1% [*15*].

The management of a pregnant woman with epilepsy should start during the prepregnancy period. We recommend that the physician optimize control of seizures with the lowest possible dose of a single agent; give folic acid supplementation; and counsel the patient about risks. In the prenatal period, serum anticonvulsant levels should be regularly checked to adjust the dose to control seizures. The fetus should also be regularly checked. Finally, during delivery and the postpartum period, the physician should strive to avoid occurrences of convulsions.

References

1. Devinsky O, Yerby MS. Women with epilepsy. Reproduction and effects of pregnancy on epilepsy. ***Neurologic clinics***, 1994, 12:479–95.
2. O'Brein MD, Gilmour-White S. Epilepsy and pregnancy. ***British medical journal***, 1993, 307:492–5.
3. Tomson T, Danielssen BR, Winbladh B. Epilepsi och graviditet. En balansgang mellan risker for mor och barn. [Epilepsy and pregnancy, balancing between the risks to mother and child.] ***Lakartidningen***, 1997, 94(34):2827–32.

4. Yerby MS, Devinsky O. Epilepsy and pregnancy. ***Advances in neurology***, 1994, 64:45–64.

5. Yerby MS. Pregnancy and epilepsy. ***Epilepsia***, 1991, 32:51–9.

6. Klinger W. Antikonvulsive Therapie und Komplikationen der Schwangerschaft bei Epileptikerinnen [Anticonvulsant therapy and complications of pregnancy in epileptic women]. ***Psychiatrie, Neurologie, und medizinische Psychologie***, 1989, 41(7):400–5.

7. Al-Bunyan MA. Random total antiepileptic drug level and seizure control during pregnancy. ***Saudi medical journal***, 2001, 22(4):355–9.

8. Samren EB et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. ***Epilepsia***, 1997, 38:981–90.

9. Delgado-Escueta AV, Janz D. Consensus guidelines preconception counselling, management and care of pregnant women with epilepsy. ***Neurology***, 1992, 42:12–6.

10. Lindhout D, Hoppener RJ, Meinardi H. Teratogenicity of antiepileptic drug combinations with special emphasis on epoxidation of carbamazepine. ***Epilepsia,*** 1984, 25:77–83.

11. Hansson JW, Smith DW. The fetal hydantoin syndrome. ***Journal of pediatrics***, 1975, 87:258–90.

12. Jones KL et al. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. ***New England journal of medicine***, 1989, 320: 1661–6.

13. Annegers JF et al. Congenital malformation and seizures disorders in the offspring of parents with epilepsy. ***International journal of epidemiology***, 1978, 7:241–7.

14. Lindhout D, Omzigt JGC, Cornel MC. Spectrum of neural tube defects in 34 infants prenatally exposed to antiepileptic drugs. ***Neurology***, 1992, 42(suppl. 5): 111–8.

15. Rosa F. Spina bifida in infants of women treated with carbamazepine during pregnancy. ***New England journal of medicine***, 1991, 324:674–7.