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Assessment of Maternal and Perinatal Outcomes in Pregnancies Complicated by Epilepsy

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Abstract

Objective: The study was undertaken to assess the maternal outcomes of pregnancies complicated by epilepsy that is a common neurologic disorder of pregnancy, and to compare the perinatal outcomes of these pregnancies with healty controls.

Methods: Sixty-five pregnant women with epilepsy disorder and 69 healty controls who delivered at our clinic between April 2005 and March 2009 were included in this study. Age, number of previous pregnancies, administered anti epileptic treatments, disease duration and frequency of the seizures were examined in epileptic women. Birth weight and week, Apgar score at 5 minute, intensive care unit admission, perinatal complications, congenital anomalies and perinatal mortality were compared between two groups.

Results: Sixty-five pregnant women with epilepsy disorder and 69 healty controls were included in this study. Age, number of previous pregnancies, administered anti epileptic treatments, disease duration and frequency of the seizures were examined in epileptic women. Birth weight and week, Apgar score at 5 minute, intensive care unit admission, perinatal complications, congenital anomalies and perinatal mortality were compared between two groups.

Conclusion: Possible complications of pregnancies should be explained to epileptic women before conception, and perinatal outcomes should be improved with appropriate approach and follow-up strategies during pregnancy.

Keywords: Epilepsy, pregnancy, maternal and perinatal outcomes.

Epileptik gebeliklerde maternal ve perinatal sonuçların değerlendirilmesi

Amaç: Bu çalışmada, gebelikte sık rastlanan nörolojik bozukluklardan biri olan epilepsili gebelik olgularının maternal sonuçlarını değerlendirmek ve bu gebeliklerin perinatal sonuçlarını sağlıklı gebelerle karşılaştırmak amaçlandı.

Yöntem: Çalışmaya Nisan 2005-Mart 2009 yılları arasında hastanemizde doğum yapmış ve epilepsi hastalığı bulunan 65 gebe ile herhangi bir hastalığı olmayan 69 sağlıklı gebe alındı. Epileptik gebelerin yaşları, gebeliklerinin sayısı, alınan medikal tedaviler, hastalığın süresi ve gebelik boyunca geçirilen atakların sıklığı belirlendi. Perinatal sonuçlar olarak doğum ağırlıkları, doğum haftası, 5. dakikadaki APGAR skorları, yoğun bakımda ihtiyacı, perinatal komplikasyonlar, konjenital anomaliler ve perinatal mortalite oranları belirlendi ve bu sonuçlar iki grup arasında karşılaştırıldı.

Bulgular: Epileptik gebelerin yaş ortalaması 26.6+4.7/yıl, hastalık süresi 8.11+4.5/yıl olarak saptandı. Hastalardan 38'inin gebelikte atak geçirirken, en sık atak 1. trimesterde (%47.3) kaydedildi. Hastaların 53'ü (%81.5) gebelikte ilaç kullanırken, en sık kullanılan ilaç karbamazepin olarak tespit edildi. Doğum haftası ve ağırlığı, operatif doğumların oranı, yoğun bakım ihtiyacı, perinatal komplikasyon ve konjenital anomali oranı anlamlı olarak epileptik hastalarda yüksek bulundu ($p<0.05$).

Sonuç: Epileptik hastalar doğum öncesi dönemde gebelikte gözlenebilecek olası komplikasyonlar hakkında bilgilendirilmeli ve gebelik boyunca sağlanacak uygun yaklaşım ve takiplerle perinatal sonuçlar iyileştirilmelidir.

Anahtar Sözcükler: Epilepsi, gebelik, maternal ve perinatal sonuç.

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Introduction

Epileptic disorders are one of the major neurological complications affecting nearly 1% of society and observed most frequently in pregnancy after migraine. It was shown that approximately 0.3-0.5% of pregnancies have epilepsy.[1] Today, by means of developments in the diagnosis and treatment of epilepsy, many women with epilepsy have been able to maintain a normal life and get pregnant. Possible negative effects of antiepileptics on fetus used for epileptic pregnancies constitute a significant risk group associated with the increase of convulsion frequencies and malformations that may appear in their children. There are publications showing the increase in the frequency of epileptic attacks in pregnancy and teratogenic effects of anticonvulsants.[2] Also it is known that convulsions appeared during pregnancy pose threat in terms of mother and fetus.[3]

In many studies, it was shown that there was an increase in the risks of miscarriage, stillbirth, preterm delivery, lower birth weight, intrauterine growth retardation and low mental and motor retardation in newborns during epileptic pregnancies in the long period.[4-6] Besides, rates of maternal complications such as hypertensive diseases, antepartum hemorrhage, delivery by cesarean, intervened delivery were found as increased among epileptic pregnancies.[7] Therefore, epileptic pregnancies are the cases where convenient approaches and teamwork should be provided to obtain positive outcomes in terms of mother and fetus. The first condition to obtain positive outcomes in terms of pregnancy in epileptic women is to do pregnancy by planning. This enables to arrange antiepileptic drugs (AED), and to take required precautions by informing family in terms of fetal malformations and especially neural tube defects.

Our aim in this study is to evaluate maternal and fetal outcomes of epileptic pregnancies observed in our clinic which is a reference center and to compare their perinatal outcomes with healthy pregnants.

Method

65 pregnants who were diagnosed as epilepsy before or during their pregnancies as being followed-up in the Department of Obstetrics and Gynecology Department of Meram Medicine Faculty in between April 2005-March 2009 were included into the study. Also 69 healthy pregnants who were similar for age, gravida and parity but do not have epilepsy or any systemic disease were taken as control group to evaluate perinatal outcomes. Control group members were determined randomly among pregnants who delivered in our clinic during the period mentioned above. Those whose pregnancies were ended due to severe epileptic attacks or problems at early gestational weeks and those with suspected epileptic attack history were excluded from the study. Demographic characteristics of epileptic pregnants such as age, gravida, parity, abortus count as well as the duration of the disease, drugs used, whether they had epileptic attack or not during pregnancy and the rate of attacks as to trimesters were evaluated.

Neurological examination and obstetric ultrasonography were performed on each pregnant who had cardiac disease before delivery. Neurology Clinic decided the delivery type to be preferred according to disease rate of epileptic pregnants. Total hospitalization duration of these pregnants, delivery type and the existence of any accompanying medical disease were determined. Delivery type as perinatal outcomes, gestational weeks at delivery, birth weights, existence of any perinatal complication accompanying pregnancy such as oligohydramnios, intrauterine growth retardation and preeclampsia, antepartum neonatal death, fetal malformations, intense care requirement of babies and 5th minute Apgar score being below 5 were evaluated. Preterm delivery was defined as deliveries below 36th week and growth retardation was defined as deliveries below 10% according to delivery week. All these parameters were compared between epileptic pregnants and healthy pregnants.

Statistical analyses were done by evaluating in SPSS database. In the comparison of perinatal outcomes, chi-square test and Student T-test were used. P value being <0.05 was accepted as statistically significant.

Results

Maternal Results

Maternal results of the epileptic patients and the control group were shown in Table 1. No difference was observed between two groups in terms of mean age, gravida, parity and abortus (Table 1). On the other hand, hospitalization duration was found significantly high in epileptic group. Mean age of patients in epileptic group was found 26.6 + 4.77/year while mean disease period was found as 8.11 + 4.5/year. It was observed that 38 patients (58.4%) had epileptic attacks during pregnancy and that 47.3% of them were at first trimester. The gestational period with the least attack was third trimester. 53 of these patients (81.5%) used any AED during pregnancy and the most frequently used drugs were carbamazepine (41.4%) and sodium valproate (34%). The distribution of AEDs used during pregnancy was shown in Table 2. It was observed that 43 (66.2%) of epileptic pregnants were delivered by cesarean and 22 (33.8%) of them were delivered vaginally. 32.3% of patients had other medical diseases accompanying to epilepsy and the most frequently seen disease was diabetes mellitus. No maternal mortality was seen in any pregnant.

Table 1. Maternal characteristics of pregnancies with epilepsy and control group.

Maternal characteristics	Epileptic group (n=65)	Control group (n=69)	P value
Age* (year)	26.6±4.7	28.2±5.2	>0.05
Gravida*	2.4±1.31	2.7±1.23	>0.05
Parity*	1.2±1.09	1.4±1.17	>0.05
Abortus*	0.32±0.77	0.43±0.82	>0.05
Disease period (year)*	8.11±4.5	-	-
Week of attacks at pregnancy (n=38)		-	-
1st Trimester	18/38 (47.3%)	-	-
2nd Trimester	8/38 (21%)	-	-
3rd Trimester	12/38 (31.7%)	-	-
Medical treatment at pregnancy		-	-
Received	53 (81.5%)	-	-
Not received	12 (18.5%)	-	-
Delivery type		-	-
Cesarean	43 (66.2%)	28 (40.6%)	<0.05**
Vaginal	22 (33.8%)	41 (59.4%)	<0.05**
Hospitalization period (day)*	3.2±2.3	1.6±1.8	<0.05**
Accompanying medical disease	3.2±2.3	1.6±1.8	<0.05**
Exists	21 (32.3%)	-	
Does not exist	44 (67.7%)	-	
Maternal mortality	0	0	

:** *Mean ± SD (standard deviation);* *:** *Statistically significant*

Table 2. The distribution of AED used during pregnancy.

Drug	N=53	%
Carbamazepine	22	41.4
Sodium valproate	18	34
Oxycarbazepine	4	7.5
Lamotrigine	2	3.8
Levetiracetam	1	1.8
Carbamazepine + Sod. valproate	2	3.8
Carbamazepine + Levetiracetam	3	5.7
Oxycarbazepine + Sod. valproate	1	1.8

Perinatal Results

Results of epileptic and healthy pregnants were shown in Table 3. Delivery week and birth weights in epileptic pregnants (36.8 ± 2.7/week and 2758 ± 664/g) were lower than those in healthy pregnants (37.7 ± 1.4 week and 3122 ± 461 g) and the difference was statistically significant (p<0.036 and 0.01). While the rate of delivery by cesarean was 66.2% in epileptic pregnants, it was 40.6% in health pregnants and the difference was statistically significant (p<0.003).

Table 3. Perinatal outcomes of epileptic and healthy pregnants.

Perinatal outcomes	Epileptic (n=65)	Healthy (n=69)	P value
Delivery week*	36.8±2.7	37.7±1.4	0.036**
Birth weight	2758±664	3122±461	0.01**
Operative birth	43 (66.2%)	28 (40.6%)	0.003**
Perinatal mortality	4 (6.1%)	2 (2.8%)	0.062
Apgar 5th minute <5	13 (20%)	8 (11.6%)	0.18
Being taken to intense care	18 (27.7%)	9 (13%)	0.035**
Perinatal complication	22 (33.8%)	11 (15.4%)	0.043**
Congenital malformation	9 (13.8%)	3 (4.6%)	0.021**

:** *Mean ± SD (standard deviation);* *:** *Statistically significant*

Perinatal mortality was found in 4 pregnants within epileptic group and in 2 pregnants within healthy group. Perinatal mortality in epileptic group was caused by hydrocephaly in 1 case and by respiratory distress syndrome and accompanying anomalies due to prematurity in 3 cases. While the rate of those with 5th minute Apgar score <5 was 20% in epileptic group, it was found as 11.6% in healthy group. On the other hand, the difference was not statistically significant in terms of perinatal mortality and 5th minute Apgar score ($p>0.05$). The rate of pregnants who need intense care and found perinatal complication was again significantly higher than the epileptic group (27.7% vs 13%). It can be considered that the requirement of intense care by babies of healthy pregnants can be higher than normal society. However, this may be caused that pregnancies are chosen randomly though pregnants themselves are healthy. These complications in epileptic group were recorded as oligohydramnios in 7 patients, polyhydramnios in 5 patients and preeclampsia in 2 patients. Congenital malformation was found in 9 (13.8%) newborns within epileptic group and in 3 newborns (4%) within control group ($p<0.021$). These anomalies were detected as encephalocoele in 2 cases, hydrocephaly in 3 cases, ventriculomegaly in 2 cases, spina bifida in 1 case and phocomelia in 1 case within the first group. One cardiac anomaly, 2 hydrocephaly and meningocele were observed in other cases.

Discussion

Gestational periods of women with epileptic disorder are mostly non-problematic. Yet, some complications may be seen higher in epileptic pregnants than society.[8] It is known that the rates of fetal loss, congenital malformation and psychomotor growth disorder in epileptic pregnancies are higher compared to general population.[4,5,9] There are publications showing that extremity anomalies (distal phalanx and nail hypoplasia), craniofascial anomalies (lip-palate clefts), congenital cardiac diseases and NTD prevalence associated with valproic acid and carbamazepine increase.[10] It was shown in the studies of Richmond et al. that major congenital malformations (heart, orofacial defects, neural tube defects, intestinal atresia and urogenital anomalies) were approximately two times higher and minor anomalies were three times higher.[1]

AEDs, epileptic attacks and maternal genes that can cause epilepsy are considered as the factors which may cause congenital malformations. It is antiepileptic drug use among the factors mentioned which is clearly showed as having the most close relation with malformations.4 In a multi-centric study, 9.9% malformation rate was reported in living newborns. This rate was 11.5% in the group who did not have AED and 2.3% in the group who had the drug and the malfunction rate was reported as 5 times higher.[11] Again in the study of Katz et al. malformation rates with 2 times increased AED use were reported.[12] The classic AEDs used (carbamazepine, pheno-barbital, phenytoin, primadon, valproate) are in the D category in terms of their effects on fetus and they are the drugs which can be used during pregnancy since their benefits accepted as teratogenetically effective were more than their harms.[13] Nakane et al. showed that there was an increase in malformation rates as the number of used antiepileptic drugs increased. While the rate was less than 5% by monotherapy, malformation rate was shown as higher than 20% when drug number reaches four.11 In a study performed in our country found that anomaly rate in epileptic pregnancies were 5.09 times higher than the healthy group.[14] Congenital malformation risk proportionally increases by the number of antiepileptic drug used (polytherapy and monotherapy) and the increase in the dose.[15] In our epileptic patient group, we found 13.8% fetal malformation (2 encephalocele, 3 hydrocephaly, 2 ventriculomegaly, 1 spina bifida, 1 phocomely). A similar result was presented in the studies of Koch et al. and they reported that there was no difference in the malformation rate of mothers using single or multiple drugs.[16] There are publi-

cations reporting 3-5 times higher fetal loss rates associated with miscarriage and preterm delivery. In our case group, fetal loss rate was 6.1% (4/65) and it was observed that they were due to fetal malformation and prematurity. However, Hiilesmaa et al. showed in their studies that there was no difference between groups in terms of perinatal death.[17] Yerby et al. reported that there was increase in preeclampsia prevalence together with 2.79 times of increase in the rate of babies with low birth weight in epileptic women.[8] Similarly, Hvas et al. found in the study that birth weights of babies delivered by epileptic mothers were 208 gram lesser than those in the control group.[18] We found mean birth weight as 2758 ± 664 gram in epileptic pregnants. Preeclampsia developed in 2 epileptic patients and one of them also had hellp syndrome. None of the patients in control group had preeclampsia or hellp syndrome. While Hiilesmaa and Viinkainen found no evident difference in the gestational complications in epileptic women, preeclampsia and preterm delivery and perinatal death prevalence, Viinkainen et al. found SGA baby rate as considerably increased.[17,19] In our study, preeclampsia was found in the epileptic group while it was not found in the control group. These results support that preeclampsia risk is observed more in epileptic pregnants.

Although vaginal delivery is suggested to pregnants who have epileptic disorder, the uncertainty of complications which may develop in the management of delivery and attacks which may arise due to stress and sleeplessness associated with delivery increase cesarean rates in this group. The delivery is especially a risky period in terms of the formation of epileptic attack and there are publications showing that the possibility of having an attack is increased approximately 9 times.[20] In our follow-ups, we found that the rate of delivery by cesarean in epileptic group was high as 66.2% (43/65). This rate was significantly higher than cesarean rate (40.6%) in control group. Similarly, Katz et al. showed in their study that epilepsy is an independent risk factor for delivery by cesarean.12 However, Hiilesma et al. did not found increase in the operative delivery rates in this group.[17]

Today, by founding new anticonvulsants and the traceability of anticonvulsant levels, attack prevalence may stay same or decrease by patient compliance and close follow-up in the delivery period of many epileptic patients. Schmidt et al. indicated in their study that attack prevalence reduced or did not change in 63% of patients, and that attacks increased only in 37% of them.[21] It was observed that 58.3% of 65 epileptic pregnants consisting of our study group had epileptic attacks during their follow-up and these attacks were frequently at first trimester. One of the factors effective on attack prevalence is hormonal change. Increases and changes in estrogen and progesterone hormones affect the formation and prevalence of epileptic attacks.[22] One of the most important factors increasing epileptic attacks is the discontinuance of treatment by pregnants especially within first three months to minimize the risk of AED exposure by fetus. Similarly, in a study reported in our country indicated that epileptic attacks mostly observed in the first trimester[23] The pregnancy of an epileptic woman also should certainly be planned. Another benefit of a preconceptional advisor is the enablement of folic acid prophylaxis. It is reported that the use of 4 mg preconceptional folic acid decreases the formation of neural tube defect at a rate of 50%.24

Conclusion

The aim in follow-up of epileptic pregnants is to give folic acid prophylaxis by pre-gestational consultation, and the good control of epileptic attacks by monotherapy and the possible lowest drug dose. Also these patients should be informed before pregnancy about possible perinatal complications which may occur during these pregnancies. In order to improve perinatal results of these pregnancies, proper approaches and gestational follow-ups should be provided.

References

1. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. *Am J Obstet Gynecol* 2004; 190: 371.
2. Jeffrey MK, Orrin D. Primary generalized epilepsy: a risk factor for seizures in labor and delivery? *Seizure* 2003; 12: 217-9.
3. Crawford P. CPD Education and self-assessment. Epilepsy and pregnancy. *Seizure* 2001; 10: 212-9.
4. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia* 2003; 44: 11-20.
5. Gaily E, Kantola-Sorsa E, Granstrom ML. Intelligence of children of epileptic mothers. *J Pediatr* 1988; 113: 677-84.
6. Wide K, Winbladh B, Tomson T, Sarz-Zimmer K, Bergrenn E. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. *Dev Med Child Neurol* 2000; 42: 87-92.
7. Al Bunyan M, Abu Talib Z. Outcome of pregnancies in epileptic woman: a study in Saudi Arabia. *Seizure* 1999; 8: 26-9.
8. Yerby M, Koepsell T, Daling J. Pregnancy complications and outcomes in a cohort of woman with epilepsy. *Epilepsia* 1985; 26: 631-5.
9. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khosbin S, Hayes AM, et al. The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001 344: 1132-8.
10. Hanson JW, Smith DW. The fetal hydantoin syndrome. *J Pediatr* 1975; 87: 285.
11. Nakane Y, Okuma T, Takahashi R, Sato Y, Wada T, Sato T, et al. Multi institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: a report of a collaborative study group in Japan. *Epilepsia* 1980; 21: 663-80.
12. Katz O, Levy A, Wiznitzer A, Sheiner E. Pregnancy and perinatal outcome in epileptic woman: a population based study. *J Matern Fetal Neonatal Med* 2006; 19: 21-5.
13. Karceski S, Morrell M, Carpenter D. The expert consensus guidelines series: treatment of epilepsy. *Epilepsy Behav* 2001; 2: 1-50.
14. Ergeneli MH, Durukan T, Ciğerli A. Epileptik kadınlarda gebelik prognozu. *Perinatoloji Dergisi* 1995; 3; 51-3.
15. Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. *Seizure* 2002; 11: 512-8.
16. Koch S, Losche G, Jager-Roman E, Jakops S, Rating D, Deichl A, et al. Major and minor birth malformations and epileptic drugs. *Neurology* 1992; 42: 83-8.
17. Hiilesma VK, Bardy A, Teramo K. Obstetric outcome in woman with epilepsy. *Am J Obstet Gynecol* 1985; 152: 499-504.
18. Hvas CL, Henriksen TB, Ostergaard JR, Dam M. Epilepsy and pregnancy: effect of antiepileptic drugs and lifestyle on birthweight. *Br J Obstet Gynecol* 2000; 107: 896-902.
19. Viinikainen K, Heinonen S, Eriksson K, Kalviainen R. Community based, prospective controlled study of obstetric and neonatal outcome of 179 pregnancies in woman with epilepsy. *Epilepsia* 2006; 47: 186-92.
20. Bardy AH. Incidence of seizures during pregnancy, labor and puerperium in epileptic women: a prospective study. *Acta Neurol Scand* 1987; 75: 356-60.
21. Schmidt D, Canger R, Avanzini G, Battino D, Cusi C, Beck-Mannagetta G, et al. Change of seizure frequency in pregnant epileptic woman. *J Neurol Neurosurg Psychiatry* 1983; 46: 751-5.
22. Morrell MJ. Epilepsy in women: the science of why it is special. *Neurology* 1999; 53: 42-8.
23. Madazlı R, Öncül M, Albayrak M, Uludağ S, Eşkazan E, Ocak V. Gebelik ve epilepsi: 44 olgunun değerlendirilmesi. *Cerrahpaşa Tıp Dergisi* 2004; 35: 126-30.
24. Anonymous From the Centers for Disease Control and Prevention. Recommendations for use of folic acid to reduce number of spina bifida cases and other neural tube defects. *JAMA* 1993; 269: 1233-8.