Comparison of maternal and fetal outcomes, in epileptic and non-epileptic women

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ABSTRACT

الهدف: تقييم نتائج الأمهات والأجنة لدى النساء الحوامل المصابات بالصرع وغير المصابات بالصرع.

الطريقة: تمت مراجعة ما مجموعه ١٦٥٠٨ ملف لحالات ولادة حية خلال الفترة من يناير ٢٠٠٥ إلى ديسمبر٢٠٠٦ كما تمت مقارنة نتائج الأمهات والحوامل والأجنة بين النساء ضمن المجموعة الأولى المصابة بالصرع (عددهن ٥٣ امرأة) والنساء ضمن المجموعة الثانية غير المصابات بالصرع (عددهن ٦٠امرأة).

النتائج: لم يكن هناك اختلاف ذو دلالة في مضاعفات الحمل (سكر الحمل وارتفاع الضغط المحفز بالحمل) بين المجموعتين. كما لم تكن هناك اختلافات ذات دلالة بين المجموعتين في طول مدة المخاض وتحفيز المخاض وتعزيز الأوكستوسين والحاجة للمسكنات أثناء المخاض وإجمالي فقدان الدم والحاجة لإعطاء الدم ووضع الولادة وطول مدة البقاء في المستشفى. ولم تكن هناك اختلافات ذات دلالة في المضاعفات على جميع الأمهات بين المجموعتين (نسبة الخطأ =٠,٨) إلا أنه كانت هناك زيادة في متوسط الأدوية المضادة للصرع اللازمة أثناء الحمل. ومع ذلك تعرضت أربع نساء (٥,٧٪) من المجموعة المصابة بالصرع لنوبات رئيسية أثناء مدة الحمل. وقد احتاجت جميع هؤلاء النساء لإضافة دواء ثاني إلى مضادات الصرع. وقد حدث تشوه خلقي رئيسي لدى مولودين (٥,٣٪) من مواليد النساء المصابات بالصرع ولم تحدث أي تشوهات خلقية بين مواليد النساء في المجموعة الضابطة. وقد كان هذان المولودان لامرأتين تناولتا عدة أدوية.

خاتمة: لاتتعرض النساء المصابات بالصرع لزيادة خطر التعرض للمضاعفات لهن أو لمواليدهن شريطة توفير الرعاية المناسبة أثناء العلاج المشترك من قبل أخصائي الأعصاب وأخصائي الولادة. وقد تساعد المحافظة على مستويات العقاقير العلاجية المضادة للصرع أثناء الحمل على منع نوبات الصرع.

Objective: To assess maternal and fetal outcomes, in epileptic and non-epileptic pregnant women.

Methods: A retrospective case-control study was conducted from January 2005 - December 2006 at Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia. A total of 16508 live birth charts were reviewed. Maternal, obstetrical, and fetal outcomes were compared between women with epilepsy Group 1 (n = 53) and women who did not have epilepsy (controls) Group 2 (n = 60).

Results: There were no significant differences between either group in total length of labor, labor induction and oxytocin augmentation, need for labor analgesia, total blood loss and the need for blood transfusion, mode of delivery, and the length of hospital stay. There were no significant differences in all maternal complications between either group (p=0.8, 95% CI: 0.3-2.1). There was an increase in the mean dose of the antiepileptic medications needed during pregnancy. However, 4 women (7.5%) in the epileptic group had major seizures during pregnancy. All of these women needed addition of a second antiepileptic medication. Major congenital malformations occurred in 2 newborns (3.8%) of epileptic women, and none occurred in the control group. Both newborns were from women who received polytherapy.

Conclusions. Women with epilepsy are not at increased risk for obstetric and neonatal complications, provided there is a combined team management approach by a neurologist and an obstetrician.

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Epilepsy is a chronic neurological disease characterized by a tendency for 2 or more recurrent seizures unprovoked by any known proximate insult with a prevalence of 4-10 per 1000 population, and affecting one in 200 pregnant women.[1,2] It may result from central nervous system lesion caused by trauma, abscess, tumor or perinatal factors.[3,4] Over 90% of women with epilepsy will have good outcomes, however, it can affect the course of pregnancy, labor, delivery, and fetal development.[5,6] The major threats to women with epilepsy are an increase in seizure frequency in about a third of women during pregnancy and pregnancy complications, pre-eclampsia and eclampsia, abruptio placenta, and increased risk of cesarean delivery.[7,8] Several studies have focused on a possible worsening of epilepsy during pregnancy, especially an increase in the frequency of seizures. Increased seizure frequency is often associated with subtherapeutic anticonvulsant levels, low seizure threshold, or both. It is well established that the offspring of epileptic women carry a 2-7 fold higher risk of specific congenital malformations than the general population, that can be caused by the disease itself, the anticonvulsant medications, or a combination of both.[9-11] Kelly et al[12] reviewed 750000 pregnancies from 13 cohort studies, they reported that the malformation rate of 70/1000 infants of epileptic mothers compared with 30/1000 for controls. The most common congenital defects, whether or not mothers take anticonvulsant medication include orofacial clefts, congenital heart defects, neural-tube defects, microcephaly, mental subnormality, hypertelorism, Palmer creases, and digital hypoplasia.[13-15] Several studies reported that antiepileptic drugs are class D drugs, which are known to be associated with congenital anomalies, and adverse fetal outcomes.[12-15] Fetal malformations are more prevalent with antiepileptic monotherapy occurring in 3-4%, and even more with polytherapy occurring in 5-9%, when used during pregnancy.[11-13] Recent guidelines for the care of pregnant women with epilepsy emphasize the need for preconception counseling for women with epilepsy, who are contemplating pregnancy.[14] Women of child bearing age should be informed about risks associated with epilepsy and pregnancy, the importance of planned pregnancy, use of lowest effective monotherapy dose that controls seizures, and the use of 5 mg/day folic acid supplement.[14] Accordingly, our current obstetrical practice at our center for pregnant epileptic women is to see them at combined neurology and obstetrical clinics, for close follow up and monitoring of their seizure activity and antiepileptic drug levels. There are fewer studies that evaluate the effect of epilepsy on pregnancy from the obstetrical and fetal prospective. This retrospective case-control study was conducted to assess the maternal morbidity, mode of delivery, fetal, and neonatal outcomes of pregnancy associated with epilepsy compared to women without epilepsy.

Methods. We performed a retrospective chart review for all singleton epileptic women who delivered at Riyadh Military Hospital from January 2005 to December 2006. We included all epileptic women who were diagnosed before pregnancy, and non-epileptic women. The study was approved by our Institutional Review Board. Both groups were followed up and delivered in our center during the study period. Patients with unconfirmed diagnosis, eclampsia, and hypoglycemia induced seizures or lacking prenatal care were excluded from analysis. A total of 16508 live births charts were reviewed. Of these, 53 births (0.3%) were to 53 epileptic women (Group 1) who fulfilled our inclusion criteria, and were matched with 60 births to non-epileptic women as control (Group 2), during the same study period. The type of epilepsy diagnosed at our center were generalized tonic-clonic (n=33), partial (n=9), post traumatic (n=5), post cerebral vascular accident (n=3), nocturnal (n=2), and juvenile myotonia (n=1). The duration of epilepsy, monitoring serum levels of antiepileptic drug(s) used, mean dose, number of years since diagnosis and last seizure attack, and the occurrence of seizure activity during pregnancy were recorded and analyzed. The characteristics of the study groups included women's age, parity, gestational age, height, weight, type of diabetes, use of preconception vitamin, history of previous one lower segment cesarean delivery, pregnancy induced hypertension, and postpartum complications are shown in **Tables 1** and **2**. Characteristics of labor, mode of delivery, total blood loss and length of hospital stay are shown in **Table 3**. The type and duration of epilepsy, number of years since diagnosis and last seizure attack, antiepileptic drug(s) used, mean dose used, and the occurrence of seizure activity during pregnancy were recorded and analyzed. Seizures were classified as major if they resulted in falling, or generalized motor activity with loss of consciousness. The latter may represent either primary or secondarily generalized seizures. The accoucheurs were all obstetric residents or registrars in training, supervised by an on-call senior registrar or consultant. Progress of labor was monitored on a regular basis, and when necessary labor was augmented with intravenous oxytocin. Continuous fetal heart monitoring by electronic cardiotocogram was used for all patients during labor. A diagnosis of non-reassuring fetal status was made in the presence of any of the following: prolonged deceleration, bradycardia, decreased variability, or thick meconium. Prolonged second stage of labor was considered in nulliparous women when lack of continuing progress for >2 hours in the absence of regional anesthesia, and for >3 hours

Table 1 - Demographic characteristics of the study population (n = 113). Group 1 epileptic women, and Group 2 non-epileptic women.

Maternal characteristics	Group 1 n = 53 (%)	Group 2 n = 60 (%)	*P*-value
Age (y)	31.3 ± 6.8	31.7 ± 5.0	0.9
Parity	4.6 ± 3.2	3.6 ± 3.0	0.4
0	6 (11.3)	8 (13.3)	0.8
1-3	18 (34.0)	20 (33.3)	0.9
> 4	29 (54.7)	32 (53.3)	0.9
Gestational age (weeks)	37.9 ± 6.2	38.8 ± 1.1	0.6
Maternal height (cm)	154.4 ± 6.9	154.9 ± 4.3	0.8
Maternal weight (kg)	68.8 ± 5.4	76.9 ± 4.3	0.05
Booked to antenatal clinics	45 (85)	57 (95)	0.11
Medical disease in pregnancy			
GDOD	6 (11.3)	8 (13.3)	0.8
GDOI	1 (1.9)	2 (3.3)	0.9
Pregnancy induced hypertension	1 (1.9)	4 (6.7)	0.4
Previous one LSCS	4 (7.5)	7 (11.7)	0.5

GDOD - gestational diabetes on diet, GDOI - gestational diabetes on insulin, LSCS - lower segment cesarean section, values expressed as means ± SD

Table 2 - Maternal complications for the study groups. Group 1 epileptic women, and Group 2 non-epileptic women

Complications	Group 1 n = 12 (%)	Group 2 n = 16 (%)	*P*-value
Second degree tear	6 (11.3)	4 (6.7)	0.5
Third degree tear	0	1 (1.7)	>0.5
Paraurethral tear	1 (3.8)	0	>0.5
Postpartum hemorrhage	2 (3.8)	3 (5.0)	>0.5
Women needing blood transfusion	1 (1.9)	0	>0.5
Fever	1 (1.9)	2 (3.3)	>0.5
Wound infection	0	1 (1.7)	>0.5
UTI	1 (1.9)	2 (3.3)	>0.5
URTI	0	1 (1.7)	>0.5
Endometritis	0	2 (3.3)	>0.5
Total	**12 (100)**	**16 (100)**	**0.8**

UTI - urinary tract infection, URTI - upper respiratory tract infection

with its presence, while in multiparous women when lack of continuing progress >1 hour in the absence of regional anesthesia, and for >2 hours with its presence. Epidural analgesia was available to all patients as needed. The senior pediatrician on call assessed the neonatal outcome immediately after delivery until discharge. All neonates received 1 mg of intramuscular vitamin K after delivery. Infants in need of close monitoring were transferred to the neonatal intensive care unit (NICU) or intermediate care nursery (ICN). Neonatal outcome: one and 5 minute Apgar scores, birth weight, infant gender, need for resuscitation or intubation, admission to NICU or ICN, neonatal complications, and length of hospital stay were compared between the 2 groups (**Table 4**). Congenital malformations were divided into minor and major. Major congenital malformations were defined as those malformations that caused major functional disturbance or disability that required medical or surgical intervention.

Table 3 - Characteristics of labor and mode of delivery of the study population (n = 113). Group 1 epileptic women, and Group 2 non-epileptic women.

Characteristics	Group 1 n = 53 (%)	Group 2 n = 60 (%)	*P*-value
Delivery			
Spontaneous	44 (83)	54 (90)	0.4
Induced	9 (17)	6 (10)	0.4
Analgesia/anesthesia used			
None	22 (41.5)	31 (51.7)	0.3
Entonox	15 (28.3)	11 (18.3)	0.26
Pethidine	9 (17.0)	12 (20.0)	0.8
Epidural	4 (7.5)	3 (5.0)	0.7
General anesthesia	3 (5.7)	3 (5.5)	0.9
Women needing oxytocin augmentation	13 (24.5)	20 (33.3)	0.4
First stage of labor (h)	6.3 ± 4.1	5.9 ± 1.9	0.8
Second stage of labor (min)	15.9 ± 2.2	23.3 ± 1.9	0.4
Third stage of labor (min)	5.4 ± 2.1	7.0 ± 1.8	0.07
Total blood loss (ml)	184 ± 135	171 ± 120	0.7
Women needing blood transfusion	1 (1.9)	0	>0.5
Dilatation and curettage	4 (7.5)	0	>0.5
Vaginal delivery			
SVD	44 (83.0)	55 (91.7)	0.7
Forceps /vacuum	2 (3.8)	2 (3.3)	0.9
Cesarean delivery			
Elective	1 (1.9)	2 (3.3)	0.9
Emergency	2 (3.8)	1 (1.7)	0.6
Hospital stay (day)	1.6 ± 1.3	1.7 ± 1.3	0.9

SVD - spontaneous vaginal delivery, values expressed as means ± SD

Data analyses. Statistical comparisons were performed with descriptive techniques, and 2-tailed t tests were used for continuous data. Fisher's Exact and Chi-Square tests were used for categorical data. A p value of <0.05 was considered statistically significant. We used the Statistical Package for Social Sciences Version 10.0.

Results. A total of 16508 live births charts were reviewed during the study period. Of these, 53 births (0.3%) were to 53 epileptic women (Group 1) who fulfilled our inclusion criteria, and were matched with 60 births to non-epileptic women as control (Group 2) during the same study period. **Table 1** shows the demographic characteristics of the women with epilepsy, and the women without epilepsy. There were no significant differences between both groups of patients' age, height, parity, mean gestational age at delivery, number of women booked to antenatal clinic, medical disease during pregnancy, and previous history of a cesarean delivery (**Table 1**). There was no significant difference in pregnancy complications (gestational diabetes and pregnancy induced hypertension) between both groups (**Table 1**). There were significant heavier weights in the control group versus the epileptic women group (p<0.05) (**Table 1**). There were no significant differences between either group in total length of labor, labor induction and oxytocin augmentation, need for labor analgesia, total blood loss and the need for blood transfusion, mode of the delivery, and the length of hospital stay (**Table 3**). There were no significant differences in instrumental and operative deliveries between either group (**Table 3**). The mean duration of epilepsy at the time of pregnancy was 14.7±8.6 years. There was increase in the mean dose of the antiepileptic drugs needed during pregnancy in 60% of epileptic women. However, 4 women (7.5%) needed addition of the second antiepileptic medication to control major seizures. No women reported to have status epilepticus. Folic acid 5 mg/day was used before and during gestation in 95% of the pregnancies, and prenatal vitamins in 97% for both groups. During the study period, 2 women had new onset seizures during pregnancy (one in the first trimester, and one in the

second trimester). We found the most common type of epilepsy in our study population was generalized tonic-clonic seizures (62.3%), followed by partial (17%), and post traumatic (9.4%). There was no evidence that any of the seizures were caused by hypoglycemia, eclampsia, or the effect of drugs and anesthetic agents. Major congenital malformation occurred in 2 newborns (3.8%) of epileptic women; one ventricular septal defect (VSD) and one multicystic kidney. Both newborns were from women who received polytherapy (valproate and phenobarbital) during pregnancy. No congenital malformation was reported in the nonepileptic women group. There were no significant differences in all maternal complications between either group (p=0.8, 95% CI: 0.3-2.1) (**Table 2**). There were no significant differences in the mean birth weight, gender, one and 5 minute Apgar scores, neonates needing resuscitation, and admission to NICU, preterm delivery, and mean hospital stay between either group (**Table 4**). There were no cases of stillbirth or neonatal deaths reported in either group.

Discussion. In this case-control study, we compared maternal morbidity, obstetrical, and neonatal outcomes of women with epilepsy and women of general obstetric population, within the same hospital and same time period. Of the 52 epileptic women, 4 women (7.5%) had major seizures during pregnancy. All of these women required admission for seizure control and needed addition of a second antiepileptic medication. The incidence of our major congenital malformation of infants exposed to polytherapy was 3.8%, and is lower than the 9.1% who were exposed to polytherapy, and 4.6% who were exposed to monotherapy reported by Richmond et al,[4] and others.[9] This emphasizes that the safest drug regimen is the regimen with optimal seizure control, and the least side effects with monotherapy being preferable to polytherapy.[4] In agreement with Richmond et al,[4] we found those women who had seizures during pregnancy had seizures within the 2 years before index pregnancy. Monitoring antiepileptic serum levels for each woman during pregnancy revealed that 60% of women in our studied population needed increased doses of their monotherapy medication, while the remaining 40% of women were maintained on their prepregnancy dosage. However, 4 women who had major seizures during pregnancy needed polytherapy treatment (more than one antiepileptic medication). Two of their offspring developed major congenital anomalies; one case had VSD, and one case had multicystic kidney, compared with women who received single antiepileptic medication and women with no epilepsy. Contrary to many published reports, we found no significant differences in the antenatal complications between women with epilepsy and women of general obstetric population.[3,5,6] Furthermore, no significant statistical differences were found in the rate of women who underwent induction of labor and oxytocin augmentation, analgesia needed during labor, length of first, second and third stages of labor, and post partum complications between both groups. We found in our study, that there were no significant statistical differences in the rate of operative deliveries; forceps and/or vacuum, and cesarean delivery rates between both groups. We found no significant differences in the rate of maternal complication and adverse neonatal

Table 4 - Neonatal outcomes for the study groups (n = 113). Group 1 epileptic women, and Group 2 non-epileptic women

Neonatal characteristic	Group 1 n = 53 (%)	Group 2 n = 60 (%)	*P*-value
Gender			
Male	29 (54.7)	41 (68.3)	0.2
Female	24 (45.3)	19 (31.7)	
Birth weight (g)	3153 ± 520	3178 ± 560	0.9
Apgar score at 1 minute	8.1 ± 1.6	8.1 ± 0.9	0.9
Apgar score at 5 minute	8.9 ± 0.8	9.1 ± 0.6	0.5
Resuscitation			
No	49 (92.5)	52 (86.7)	0.4
Yes	4 (7.5)	8 (13.3)	
Admission to NICU			
No	50 (94.3)	58 (96.7)	0.2
Yes	3 (5.7)	2 (3.3)	
Preterm delivery (<37weeks)	1 (1.9)	2 (3.3)	>0.5
Hospital stay (day)	1.1 ± 0.2	1.2 ± 1.0	0.5

NICU - neonatal intensive care unit, values expressed are means ± SD

outcomes between both groups. Due to close medication monitoring, and combined obstetrical and neurological care in our study, there were no maternal reports of status epilepticus and seizure-associated maternal mortality. In agreement with previous studies, this good outcome was attributed to adherence to management guidelines, and the combined care provided in our tertiary center by the neurologists and the obstetricians.[16-18] The limitation of this study was its retrospective nature, relatively small patient sample size, and no long-term follow-up.

In conclusion, this study supports that most women with epilepsy can be reassured that they are not at increased risk for obstetric and neonatal complications, comparable to that of the general population, provided that appropriate care is available during combined preconception and neurological clinics, labor, delivery, and postpartum. In addition, the patients should be placed on preconceptional folic acid supplementation, which should be continued throughout pregnancy. The appropriate dosage appears to reduce the risk of induced malformation and adverse outcome. Therefore we recommend that antiepileptic medication should be monitored with serial drug levels during pregnancy, and adjustment of ongoing treatment doses.

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