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Obstetric Outcome and Predictors of Pregnancy Loss in Pregnant Women with Epilepsy: A Five-Year Prospective Observational Study

Emarh M[1], Hosni N[1], Nofal A[1], Al-Ahmar I[2] and El-Sayed H[3]*

[1]Department of Obstetrics and Gynecology, Menoufia University, Menoufia Governorate, Egypt

[2]Department of Neuropsychiatry, Menoufia University, Menoufia governorate, Egypt

[3]Department of Pediatrics, Menoufia University, Menoufia Governorate, Egypt

Abstract

Objective: To ascertain prospectively the maternal and fetal outcome in women with epilepsy who were on antiepileptic drugs compared to women who stopped medical therapy and to find out predictors of pregnancy loss.

Methods: A five-year prospective study was conducted on 412 patients with epilepsy who were allocated into two groups, group 1 (active disease) which included 234 patients on antiepileptic drugs and group 2 (non-active disease) which included 178 patients who stopped medications before pregnancy. Patients were followed to record maternal and fetal outcome. Data was statistically analyzed.

Results: Higher patients in group 1experienced spontaneous miscarriage ($p<0.05$), antepartum hemorrhage ($p<0.05$), pre-eclampsia ($p<0.001$), delivery by cesarean section ($p<0.05$), peripartum saizures ($p<0.001$), postpartum hemorrhage ($p<0.05$), admission to ICU ($p<0.001$), venous thromboembolism ($p<0.05$) and defective lactation ($p<0.001$) with higher babies suffered congenital malformations ($p<0.001$), prematurity ($p<0.001$), low Apgar scores ($p<0.001$), low birth weight ($p<0.05$) and admission to NICU ($p<0.001$) compared to those in group 2. The use of antiepileptic therapy, older maternal age (>33 years), peripartum seizures and admission to ICU were independent predictors of pregnancy loss ($p<0.05$).

Conclusion: patients with epilepsy even those with non-active disease, experienced higher odds of maternal and fetal complications which are increased with the use of antiepileptic drugs.

Keywords: Epilepsy; Antiepileptic Drugs; Maternal Outcome; Fetal Outcome; Obstetric Outcome

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Correspondence:
Mohamed Emarh, Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, 25 Yasin Abdelghafar Street, Shibin El-Kom City, Menoufia Governorate, Egypt, Tel: +201146256413, +201006237186; E-mail: mohemarh@yahoo.com

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Introduction

Epilepsy is considered as the most common neurological disorder that affect women during the childbearing period and has been considered as high risk pregnancy [1].

Adverse maternal outcome in terms of higher rates of abnormal bleeding, preterm labour, development of preeclampsia and delivery by cesarean section have been reported in some studies [2,3] and refuted by others [4,5].

Adverse fetal outcome in terms of congenital anomalies with the use of antiepileptic drugs [6]. Some studies report higher rates of stillbirth and neonatal death [7,8] which are not proved by others [9,10].

The most common major congenital malformations associated with AEDs are neural tube defects, congenital heart disorders, urinary tract and skeletal abnormalities and cleft palate. Sodium valproate is associated with neural tube defects, facial cleft and hypospadias; phenobarbital and phenytoin with cardiac malformations; and phenytoin and carbamazepine with cleft palate in the fetus [11-13]. Among AEDs, lamotrigine, and carbamazepine monotherapy at lower doses have the least risk of major congenital malformation in the offspring [13].

The aim of this study was to ascertain prospectively the maternal and fetal outcome in women

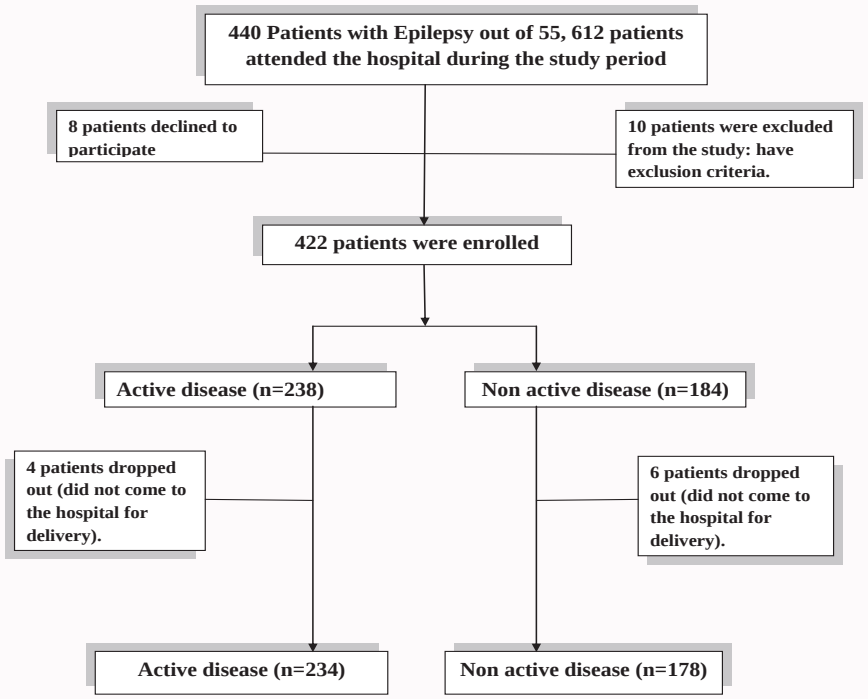

Figure 1: Flow diagram of recruitment and retention of patients in the study.

Table 1: Patients' characteristics.

	Group 1 on Therapy (n=234)	Group 2 Without therapy (n=178)	Student t-test	P-Value
Age (years)	31.6±4.2	30.9±4.5	1.62	>0.05
Parity	1.4±2.3	1.2±2.2	0.89*	>0.05
Body mass index (Kg/m²)	25.2±3.4	24.8±3.7	1.14	>0.05
Gestational age at inclusion (weeks)	6.4±2.2	6.6±2.1	0.93	>0.05
Periconception folate use	156	82	16.75	**<0.001**
Folate use in pregnancy	222	160	3.02	>0.05
Antenatal hospital admissions to control seizures	42	14	7.91	**<0.05**

*Mann Whitney test

with epilepsy who were on antiepileptic drugs compared to women who stopped medical therapy and to find out predictors of pregnancy loss.

Materials and Methods

This was a prospective five-year observational study that was conducted at the department of Obstetrics and Gynecology in collaboration with the Neuropsychiatry and Pediatrics departments at Menoufia University Hospital, Menoufia governorate, Egypt in the period between the beginnings of November 2012 and November 2017 which is the date of the end of follow-up of the last enrolled patient.

The Medical ethical committee for research at Menoufia faculty of medicine and the local review board approved the study protocol which was explained to all participants who signed informed consent before the study.

Pregnant women in the first trimester previously diagnosed with epilepsy (either on drug therapy or stopped medications) who attended the outpatient clinic or referred from other hospitals for antenatal care and further management were included in the study (Figure 1: The flow diagram).

Criteria of exclusion included patients with other medical disorders, multiple pregnancies or received any drug therapy other than folic acid.

Enrolled patients were followed up regularly every 1-3 weeks in the outpatient clinic from the start of pregnancy till the end of the puerperium Patients were seen every visit by Obstetrician and Neurologist.

Patients were divided into two groups:

Group 1 (Active disease): included 234 patients who were on antiepileptic drug therapy (single or multiple). Drugs taken during pregnancy included carbmazepine, phenytoin, phenobarbitone and sodium valproate.

Group 2 (Non-active disease): included 178 patients who stopped medical therapy for more than 3 months before the start of pregnancy secondary to absence of seizure activity for more than 2-3 years prior to pregnancy based on recommendations by their neurologists.

Outcome measures

Maternal outcome: Miscarriage, anemia during pregnancy (Hb< 11 gm%), antepartum hemorrhage, development of pre-eclampsia, mode of delivery, development of peripartum seizures, venous

Table 2: Maternal outcome.

	Group 1 on Therapy (n=234)	Group2 Without therapy (n=178)	Chi square test	P-Value	Odd's ratio at 95%CI
Miscarriage: **-All** **-Spontaneous** **-Threatened** **-Missed**	 68 (29%) 32 16 18	 30 (16.8%) 12 8 10	 7.65 4.39 0.63 0.4	 **<0.05** **<0.05**>0.05 >0.05	 2.02(1.25-3.28) 2.19(1.09-4.39) 1.56(0.65-3.73) 1.4(0.63-3.11)
Anemia during pregnancy	98 (41.8%)	82 (46.1%)	0.56	>0.05	0.84(0.57-1.25)
Antepartum hemorrhage	56 (23.9%)	22 (12.4%)	8.08	**<0.05**	2.23(1.3-3.82)
Pre-eclampsia: **-All** **-Mild** **-Severe**	 76 (32.5%) 24 52	 28 (15.7%) 10 18	 14.15 2.29 9.67	 **<0.001** >0.05**<0.05**	 2.58(1.58-4.2) 1.92(0.89-4.13) 2.54(1.43-4.52)
Mode of delivery **-Vaginal** **-Vacuum** **-CS**	 130 (55.5%) 24(10.3%) 80 (34.2%)	 128 (71.9%) 18(7.9%) 36 (20.2%)	 10.86 0.01 9.07	 **<0.001** >0.05 **<0.05**	 0.49(0.32-0.74) 1.02(0.53-1.94) 2.05(1.3-3.23)
Peripartum seizures	46 (19.6%)	8 (4.5%)	19.1	**<0.001**	5.2(2.39-11.33)
Postpartum hemorrhage	28 (11.9%)	8 (4.5%)	6.17	**<0.05**	2.89(1.28-6.5)
Admission to ICU	32 (13.7%)	6 (3.4%)	11.62	**<0.001**	4.54(1.85-11.12)
VTE	26 (11.1%)	6 (3.4%)	7.41	**<0.05**	3.58(1.44-8.91)
Defective lactation	84 (35.8%)	32 (17.9%)	15.18	**<0.001**	2.55(1.6-4.07)

ICU=Intensive care unit; VTE=Venous thromboembolism

Table 3: Fetal and neonatal outcome.

	Group 1 on Therapy (n=234)	Group 2 Without therapy (n=178)	Chi square test	P-Value	Odd's ratio at 95%CI
Congenital malformations	34 (14.5%)	6 (3.4%)	13.12	**<0.001**	4.87(2-11.89)
Intrauterine fetal demise	18 (7.7%)	6 (3.4%)	2.7	>0.05	2.39(0.39-6.15)
Prematurity	96 (41.1%)	34 (19.1%)	21.5	**<0.001**	2.95(1.87-4.65)
Low Apgar scores	134 (57.3%)	58 (32.6%)	23.77	**<0.001**	2.77(1.85-4.16)
Low birth weight	56 (23.9%)	20 (11.2%)	10	**<0.05**	2.49(1.43-4.32)
NICU admission	84 (35.9%)	28 (15.7%)	19.77	**<0.001**	3(1.85-4.87)
Neonatal death	20 (8.5%)	8 (4.5%)	2.02	>0.05	1.99(0.85-4.62)

thromboembolism (VTE), postpartum hemorrhage (PPH), defective lactation and admission to intensive care unit (ICU).

Fetal and neonatal outcome: Congenital malformations, low birth weight defined as a birth weight < 5th percentile, prematurity or preterm labour (delivery < 37 weeks), intrauterine fetal demise (IUFD), low Apgar scores (<7), admission to neonatal intensive care unit (NICU) and neonatal death (defined as death during the first four weeks after delivery).

Predictors of pregnancy loss at any gestational age or after birth

Statistical analysis: The data collected were tabulated & analyzed by SPSS (statistical package for the social science software) statistical package version 22 on personal compatible computer. Quantitative data was analyzed by applying student t-test or Mann-Whitney test as required while qualitative data was analyzed by applying Chi-square test with a significance level of P value less than 0.05.

Logistic regression was used to assess the crude association between pregnancy loss and maternal risk factors using univariate and multivariate logistic regression analyses.

Results

Table 1 depicts patients' characteristics. There was no significant difference between both groups regarding age, parity, body mass index, gestational age at inclusion and folate use during pregnancy (p>0.05). The use of folate during the peri-conception period and antenatal hospital admissions to control seizures were higher among patients on therapy (p<0.05).

Table 2 reveals maternal outcome. More patients in group (1) experienced spontaneous miscarriage (p<0.05), antepartum hemorrhage (p<0.05), pre-eclampsia (p<0.001), delivery by cesarean section (p<0.05), peripartum saizures (p<0.001), postpartum hemorrhage (p<0.05), admission to ICU (p<0.001), venous thromboembolism (p<0.05) and defective lactation (p<0.001) compared to patients in group (2).

Table 3 shows fetal and neonatal outcome. More babies in group (1) suffered congenital malformations (p<0.001), prematurity (p<0.001), low Apgar scores (p<0.001), low birth weight (p<0.05) and admission to NICU (p<0.001) compared to those in group (2).

Table 4 depicts predictors of pregnancy loss in the whole study participants. The use of antiepileptic therapy (single or multiple drugs), older maternal age (>33 years), peripartum seizures and admission to ICU were independent predictors of pregnancy loss (p<0.05).

Discussion

Patients with epilepsy who were using single or multi-drug therapy in the current study, have higher odds of adverse maternal outcome in terms of antepartum hemorrhage (OR 2.23 with 95% CI:

Table 4: Predictors of pregnancy loss by univariate and multivariate analysesin the whole study participants.

Risk factor	Crude Odd's ratio	Upper and lower limit (Confidence interval 95%)
-Multiple antiepleptic drug use	1.57	1.32– 1.86
-Single antiepleptic drug use	1.29	1.09– 1.53
-Old maternal age (>33 years)	1.25	1.02– 1.54
-Peripartum seizures	1.74	1.63– 1.86
-Admission to ICU	1.73	1.64 – 1.84

1.3-3.82), pre-eclampsia (OR 2.58 with 95% CI: 1.58-4.2), delivery by cesarean section (OR 2.05 with 95% CI: 1.3-3.23), peripartum seizures (OR 5.2 with 95% CI: 2.39-11.33), postpartum hemorrhage (OR 2.89 with 95% CI: 1.28-6.5), admission to ICU (OR 4.54 with 95% CI: 1.85-11.12), venous thromboembolism (OR 3.58 with 95% CI: 1.44-8.91) and defective lactation (OR 2.55 with 95% CI: 1.6-4.07).

In a previous hospital-based retrospective study, women with epilepsy using antiepileptic drugs had an increased risk of severe pre-eclampsia (OR 5.0 with 95% CI: 1.3-19.9), bleeding in early pregnancy (OR 6.4 with 95% CI: 2.7-15.2), induction (OR 2.3 with 95% CI: 1.2-4.3) and caesarean section (OR 2.5 with 95% CI: 1.4-4.7) after adjustment for maternal demographic data [14].

In contrast to previous studies [5,10,15,16], patients with epilepsy had an increased risk of severe pre-eclampsia in this study.

A previous study has suggested that the use of carbamazepine during pregnancy is associated with increased risk of pre-eclampsia [17]. However, in the current study, patients with epilepsy on or without drug therapy had an increased risk of developing pre-eclampsia which may alleviate the effect of drug use.

Although most of our patients use folate during pregnancy, the risk of pre-eclampsia was still high. This may be explained by folate antagonism by antiepileptic drugs as carbamazepine and phenytoin or abnormal maternal folate-homocysteine metabolic defect which leads to placental microvascular disease [18].

Development of seizures around delivery with maternal admission to ICU was noticed in this study which could be explained partially by irregular intake of antiepileptic drugs and/or stress of labour.

Increased seizure frequency during pregnancy and increased maternal mortality had been reported [4,19].

The majority of women under therapy (about 67%) do not experience a seizure in pregnancy [20]. In women who were seizure free for at least 9 months to 1 year prior to pregnancy, 74–92% continued to be seizure free in pregnancy [20,21].

Adverse fetal and neonatal outcome has been demonstrated in this study, in the form of higher odds of congenital malformations (OR 4.87 with 95% CI: 2-11.89), prematurity (OR 2.95 with 95% CI: 1.87-4.65), low Apgar scores (OR 2.77 with 95% CI: 1.85-4.16), low birth weight (OR 2.49 with 95% CI: 1.43-4.32) and admission to NICU (OR 3 with 95% CI: 1.85-4.87).

These complications had been reported in a previous community-based, prospective, controlled study of 179 pregnancies in women with epilepsy (WWE) [15] and in another controlled study of 277 WWE [22]. Both have reported increased risks of congenital malformations, low birth weight and the need for care in the neonatal ward and neonatal intensive care.

The strength of this study resides in being prospective and explored the obstetric outcome in patients with active and non-active epilepsy.

Lack of reporting the seizure type and severity with emphasis only on seizure frequency with dividing our patients into active and non-active groups, constitutes unintended limitation of this study.

Future research should explore the implementation of proper peri-conception counseling and antenatal programs with follow up of patients with epilepsy.

In conclusion, patients with epilepsy experienced higher odds of maternal and fetal complications which are increased with the use of antiepileptic drugs.

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