Evaluation of seizures in pregnant women in Kerman – Iran

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Abstract

Background and Objectives: Seizure occurs in 0.5 to 1 percent of pregnant women, marking it as one of the most prevalent serious neurological disorders during pregnancy. Women with epilepsy face a greater threat of pregnancy-related adverse effects. The effects of seizures on pregnancy and its maternal and fetal adverse effects, necessitates the study of the prevalence of pregnancy seizures, an issue ignored by previous studies conducted elsewhere.

Method: The present study is a descriptive-analytical research. The participants included women who were referred to delivery centers of Kerman (public and private) for childbirth. The exclusion criteria were lack of cooperation and consent of the subjects for sitting the interviews.

Results: Among 3,807 admitted pregnant women, 38 cases (1%) experienced epileptic seizures. Among the participants, 2,125 subjects were admitted to public hospitals and 1,682 subjects to private hospitals. Seizure recurrence remained constant in 58% of the subjects, declined in 21%, and increased in 21%. Twenty four cases (0.63%) had a history of prepartum seizures, and 14 cases (0.36%) experienced seizures for the first time during pregnancy, with eclampsia as the most prevalent cause. Patients of public hospitals had lower levels of education and higher number of epileptic seizures. Average age of patients experiencing epileptic seizures was lower than the non-epileptic cases. Seizures were observed more in nulliparous women.

Conclusion: More than 6 in 1,000 pregnant women suffer from epilepsy. Eclampsia is the most prevalent cause. Epileptic seizures increased in 21% of epileptic pregnant women, and declined in 21% of the cases.

Key words: seizure, epilepsy, pregnant, women

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Introduction

Seizures are referred to as the temporary physiological dysfunction of the brain, caused by the abnormal electrical and excessive discharges of cortical neurons, and epilepsy is the unexplained and unpredicted repetition of these attacks (1-5). Women with epilepsy have a greater risk of pregnancy-related adverse effects, including cesarean section, preeclampsia, pregnancy-induced hypertension, premature contraction or preterm labor, postpartum hemorrhage, possibility of stillbirth, and microcephaly. Also, the risks of mental retardation and afebrile seizures are increased in their infants. Women with a history of pregnancy seizures are likely to experience epilepsy-related adverse effects including status epilepticus and increased epileptic seizures(2). Uncontrolled seizures influence maternal and fetal mortality and morbidity; tonic-clonic seizures may cause physical damage and spontaneous abortion , hypoxia, acidosis and intracranial hemorrhage in the fetus; also fetal bradycardia is possible during the mother's seizures. The etiology of epileptic seizures in pregnancy includes epilepsy of unknown cause, metabolic disorders, eclampsia, and cerebral sinus thrombosis, causing pregnancy and postpartum seizures(4, 6). Convulsion has occurred in 0.5-1% of pregnancies(6), and is one of the serious neurologic disorders in pregnancy(6, 7).

The most seizure attacks occurred in pregnant women, who have history of epilepsy (8). Another study reported that 1 in 200 pregnant women experience seizures(9).

In India, 2.5 million women are experiencing epileptic seizures, almost half of whom are at fertility ages(10). Approximately 1 million women of childbearing age in the US have seizures, among whom 20 thousand go into labor, annually (2, 3, 5, 11, 12).

In a study in the US on 45,000 pregnant women, 21.4 cases per 1,000 experienced non-eclamptic seizures before or during pregnancy(13). According to estimations, 3 to 5 per 1,000 births are related to women with epilepsy (2-4, 11) . Another study in Europe in 2013 reported that pregnant women comprise 25% of all epileptic patients, and most of these women are in need of long-term treatment with antiepileptic medications. Approximately 3-4 out of 1,000 pregnancies concern women with a history of epilepsy and 1,800-2,400 infants in Britain are born from women with a history of epilepsy, most of whom have healthy pregnancies and infants(14).

In a study conducted between 1991 and 2000, at Vali-Asr Hospital of Tehran, out of 21,000 admitted pregnant women, 53 cases had epilepsy; of these women 55% were nulliparous and 45% multiparous; 82% had generalized epilepsy, 14% had focal epilepsy, and 4% had other types. Epileptic attacks occurred in 34 subjects (70%) during pregnancy, and the number of attacks increased in only 15 patients (32%) and declined in 9.5%; 58.6% showed no change in the seizure frequency. This study reported that the cause of increased epileptic attacks may be due to the discontinuation of anti-epileptic medication and pharmacokinetic and pharmacodynamic changes of these medications during pregnancy, as well as, insomnia, stress, and anxiety(10) .

Epilepsy control must be handled adequately, as the frequency of attacks increases in 15 to 30% of the cases. Pregnancy-induced changes of anti-epileptic medications are an important agent(8). Due to reduced serum albumin and increased hepatic and renal clearance, and increased emission volume, the blood level of anti-epileptic drugs falls in pregnancy(5, 8, 9, 12, 15), causing a changed control over epileptic attacks in pregnancy. Mother's compliance and acceptance is, however, another important factor (5, 15).

Fear of fetal adverse effects is a major issue in pregnancy(12), accompanied by nausea, vomiting, and sleep disorders of the mother(5). One of the most important predicting factors is the frequency of attacks in pregnancy versus the prepartum years(16).

It has been shown that sex hormones influence epileptic attacks, as estrogen decreases the threshold and progesterone increases it (17).

Nearly 1-2% of epileptic women are afflicted with status epilepticus, which causes mortality and morbidity (8).

Preconception counseling, as well as monitoring drug serum levels, along with drug and dosage adjustment and providing patients with the information concerning their condition, can help decrease the frequency of attacks (10).

Seizures are the most probable to appear in the first trimester of pregnancy and upon delivery (8). Women with epilepsy who take anti-epileptic medication are likely to suffer from an increased risk of caesarean and hemorrhage(12, 15), yet they do not experience increased risks of premature contractions or preterm labor (2).

The present study was conducted in Kerman with regard to the prevalence of pregnancy seizures and the importance of maternal and fetal adverse effects. It must be mentioned that this study is unprecedented.

Methods

Patient Selection: This is a descriptive-analytical study. The participants of the study were women who referred to delivery centers of Kerman (public and private) for childbirth. The patients were initially asked to fill out the questionnaire developed by Placencia et al (18-20) for screening, containing 9 questions. The questionnaires were also filled out by Hospital obstetricians, who had previously received the required instructions by a faculty member neurologist. Suspicious patients were then examined by a neurologist who filled out the complementary questionnaire, including the demographic information of the patients, type of epilepsy, history of attacks, pregnancy condition, and medications used. A case of epilepsy was approved by

biography, physical examination, and EEG. Patients with approved epilepsy underwent lab assessment, imaging, including MRI and CT scan, and lumbar puncture, when required.

Sample Size: Considering the fact that epileptic seizures are reported in 1% of all pregnancies (5), the population of this study comprised 3,800 cases admitted to public and private hospitals. Since the cause of epileptic seizures in pregnant women is different from others and certain types are more frequent in pregnancy, there was no need for a control group in this study.

Exclusion Criteria: The exclusion criteria were non-cooperation and dissent of participants to sit interviews or non-cooperation of the pertaining delivery wards for patient screening. This study aimed at determining different types of epilepsy (idiopathic or secondary causes) and comparing epilepsy prevalence in nulliparous and multiparous cases, as well as between pregnant women with a prepartum history of seizures and those with no such history. Furthermore, the comparison of epilepsy prevalence according to the admitted medical centers (public and private hospitals) was determined according to the prevalence of seizures in pregnant women in each subgroup and a 95% confidence interval.

Comparison of prevalence between the groups was carried out using chi-squared test.

This study was conducted subsequent to obtaining informed consent from the participants, describing the study objectives, and commitment to confidentiality.

Results

Out of 3,807 pregnant women who were admitted to public and private hospitals of Kerman in the last month of their pregnancy, 38 subjects had experienced seizures (epileptic patients and those who experienced their first seizure in pregnancy).

Age of the epileptic patients ranged from 15 to 33 years, at an average age of 28.1274 ± 5.60687 years; it was 24.6579 ± 6.14267 for patients with epileptic attacks, and 28.1624 ± 5.60687 for patients without epileptic attacks, and the difference was significant (P=0.001).

In this study, out of the epileptic patients (a total of 24), 11 cases were nulliparous and 13 cases were multiparous, while, a total of 901 subjects were nulliparous which was statistically significant (P=0.017). A number of 2,125 cases were admitted to public hospitals and 1682 cases referred to private hospitals. Incidence of epileptic attacks was 31 cases among those admitted to public hospitals and 7 cases in those admitted to private ones, indicating a significant difference (P=0.001). (Table 1).

The degree of gravidity and parity in customers of public and private hospitals showed no significant difference, yet, the number of abortions was higher in public hospitals, which was statistically significant (P=0.000) (Table 2). In total pregnant women these factors are shown in Table 3.

Customers of public hospitals had lower education. The majority of pregnant women in the public sector were less than high school diploma, while, those in the private sector held higher than high school diploma (P=0.000). In this study, the number of epileptic patients was directly associated with the education level (P=0.039) (Table 1).

Out of the 24 epileptic pregnant women, 20 were receiving antiepileptic medications (7 patients under multi-drug and 13 under single-drug regimens); in 2 cases, the epilepsy was controlled and the treatment was discontinued, and 2 cases did not take any medications. Epileptic attacks were controlled in only 1 case among the multi-drug patients (%14), while they were controlled in 7 cases of single-drug patients (54%), approximately 4 times the former group. The frequency of attacks declined in 5 cases (21%), increased in 5 (21%), and was unchanged in 14 cases (58%).

Of all the patients experiencing epileptic attacks, 24 had epilepsy (2 cases did not take antiepileptic medications, and 2 cases had discontinued their medications after controlling seizures), 13 cases were non-epileptic, and 1 case had a childhood experience of febrile seizure.

Among the 38 cases with a history of seizures, 27 cases had seizures in pregnancy, and the remaining 11 cases experienced no seizures in pregnancy; 6 cases had a family history of epilepsy.

Out of the 27 women with pregnancy seizures, 13 subjects had a history of epilepsy, 14 cases experienced seizures for the first time in their pregnancy; out of 11 cases without pregnancy seizures, 8 cases had a history of active epilepsy. In 2 cases who did not take medications seizures were controlled, and one subject had an experience of seizures once in her childhood.

Out of 22 patients with active epilepsy, 5 had a history of myoclonic jerk. No myoclonic jerks were reported in patients with inactive epilepsy or those experiencing their first epileptic seizure in pregnancy. Table 4 portrays the occurrence of different epileptic seizures in the patients.

Concerning the anti-epileptic medications, 13 cases received single-drug regimens (9 cases, carbamazepine; 2 cases, lamotrigine; 2 cases sodium valproate) and 7 subjects received multi-drug regimens (3 cases, lamotrigine and levetiracetam; 2 cases, carbamazepine and levetiracetam; 1 case, carbamazepine and sodium valproate; and 1 case, carbamazepine and lamotrigine).

In the present study, 11 cases had a history of abortion, out of whom: 2 cases experienced cerebral vein thrombosis (CVT) and 1 case, eclampsia; 6 cases had epilepsy; 1 case had Arterio-Venous Malformation (AVM), and 1 case had brain tumor. Six cases of epileptic patients (24%) had a history of abortion, whereas, in the remaining participants, 654 cases out of the total 3783 subjects (17%) had

Table 1: Relationship between education and seizures in pregnant women and type of Hospital

	Hospital	School + Illiterate	High School	Bachelor	Ms +PhD
Patients	Public	864	744	463	54
	Private	183	834	621	44
Seizures	No	1032	1562	1079	96
	Had	15	16	5	2

Table 2: Relationship between seizures and some pregnancy factors

		Sum of Squares	Df	Mean Square	F	Sig (ANOVA)
Gravidity	Between Groups	375.190	3	125.063	78.839	0.000
	Within Groups	6032.727	3803	1.586		
	Total	6407.917	3806			
Parity	Between Groups	339.484	3	113.161	82.263	0.000
	Within Groups	5231.442	3803	1.376		
	Total	5570.926	3806			
Abortion	Between Groups	0.862	3	0.287	2.007	0.111
	Within Groups	544.064	3803	0.143		
	Total	544.926	3806			

Pregnant women with higher levels of education referred to private hospitals more (P=0.000). The pregnant women with higher education have lower number of seizures (P=0.039).

Table 3: Relationship between hospital type and a number of pregnancy factors

	Hospital	N	Mean	Std. Deviation	P value
Gravidity	Public	2125	2.6551	1.37611	
	Private	1682	2.5470	1.18858	0.009
Parity	Public	2125	1.4442	1.29802	
	Private	1682	1.3603	1.08685	0.030
Abortion	Public	2125	1.1934	0.39507	
	Private	1682	1.1474	0.35465	0.000

Table 4: Type of seizures in pregnant women

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Tonic-Clonic	29	0.8	76.3	76.3
	F-G	1	0.0	2.6	78.9
	JME	5	0.1	13.2	92.1
	CPS	3	0.1	7.9	100.0
	Total	38	1.0	100.0	

experienced abortion previously, indicating a significant difference (P=0.000). However, there was no significant difference in the increasing cases of epilepsy, between pregnant women with a history of abortion and those without such history (P=0.111). The difference between the degree of parity and gravidity between women with a history of seizures and those with no such history was significant (P=0.000) (Table 2).

For all the patients with a history of eclampsia, epilepsy, CVT, and AVM, pregnancy seizures occurred in the third trimester (except for a CVT patient who experienced seizures in month 2).

Only 5 out of 38 patients (total number of patients) had an abnormal neurological examination. According to the assessments, one case was caused by AVM, another case by trauma, one case by tumor; epilepsy in 24 cases had unknown etiology. The causes of the first seizures in pregnancy were eclampsia in 7 cases, CVT in 3 cases, and TTP in one case.

Discussion

In the present study, out of 3807 pregnant women admitted to public and private hospitals of Kerman in their last month of pregnancy, 38 cases (0.99%) had previously experienced seizures. In a study in the US on 45,000 pregnant women, 21.4 cases per 1,000 individuals were reported to have experienced one non-eclamptic seizure during or before pregnancy(2). A study in Vali Asr Hospital of Tehran in 1991, reported 53 epileptic cases out of 21,000 pregnant women (10). The pregnancy prevalence in a study in London was reported at 0.5-1%(21). An Australian study claimed that 1 in 200 pregnant women experience seizures(9).

Out of the total referrals, 2,125 women were admitted to public hospitals and 1,682 women to private hospitals. The prevalence of seizures was significantly higher in patients admitted to public hospitals (P=0.001). Numerous causes to this are: 1. Patients with complications who are more likely to experience epilepsy are referred to teaching (public) hospitals; 2. Patients of private hospitals hold higher education, and according to studies in this region, lower education is directly associated with epilepsy; 3. This study, also, revealed that the education of pregnant women in public hospitals is lower, matching the results of a 2011 study in Kerman, indicating a significant relationship between the incidence of epilepsy and lower education (22). Our findings were similar to those of studies conducted in the US (23), Vietnam(24), and Turkey (25), whereas, in his study in England, Ferro did not report such a relationship (26); 4. The degrees of gravidity and parity and abortion were higher in women admitted to public hospitals, which was only significant in case of abortion. This may have caused the increased cases of epilepsy. In a study in Canada on 55 pregnant epileptic women, it was shown that 42 patients were admitted to public hospitals and 13 patients to private hospitals (P=0.000)(27).

The age of our patients ranged from 15 to 33. A study in Italy reported the age of pregnant epileptic patients between 15.3 to 43.5 years (28). The decline of the childbearing age in Iran is due to cultural conditions. The important point is that, the age of pregnant women who experienced epileptic seizures was lower than others (24.6 years compared to 28.1 years). A study in England reported the average age of epileptic patients (38 cases) at between 11 to 35 years old(29). The average age of pregnant epileptic patients is reported at 26 years by a study in India (30). This difference arises from cultural conditions.

Among our patients, 6 cases (15.7%) had a family history of epilepsy. This rate was 17.3% in a study in Kerman, in 2011 (22), close to that of a study in Turkey (14.3%) (25).

In the present study, out of patients with a history of epilepsy (24 cases), 14 patients were multiparous and 10 cases were nulliparous, while, 901 women in the population were nulliparous, indicating a significant difference. A study in England reported 12 multiparous cases out of 38 participants (P=0.000) (29).

In another study in Canada it was observed that there was no relationship between worsening of seizures and the childbearing age, parity, toxemia, a family history of epilepsy, age at onset of pregnancy, and preterm labor. The most prevalent complication in these patients was preterm labor, occurring in 8 cases (27). Preterm labor or abortion occurred in 2.6% of the cases in a study in Italy (28).

Eleven of our cases had a history of abortion, out of whom: 2 cases experienced cerebral vein thrombosis (CVT) and 1 case, eclampsia; 6 cases had epilepsy; 1 case with Arterio-Venous Malformation (AVM), and 1 case had brain tumor. Six cases of the epileptic patients (24%) had a history of abortion, while, for the remaining participants, 654 cases, out of the total 3,783 subjects (17%), had previously experienced abortion, indicating a significant difference (P=0.000). However, there was no significant difference in the increasing cases of epilepsy, between pregnant women with a history of abortion and those without such history (P=0.111).

We observed a significant difference between the degree of parity and gravidity between women with and without a history of seizures (P=0.000).

None of our patients experienced status epilepticus, similar to our Canadian counterpart(27), however, in the study conducted in Italy, 21 in 3,415 cases (0.6%) experienced status epilepticus (28). The similar study in England reported 2 patients with status epilepticus (29).

For all the patients with a history of eclampsia, epilepsy, CVT, and AVM, pregnancy seizures occurred in the third trimester (except for a CVT patient who experienced seizures in month 2).

The study in Canada reported exacerbation of seizures in early pregnancy (27). In England, the frequency of seizures rose in the first trimester (29). Yet, in Italy, the exacerbation of seizures was reported in 29% of the cases in the first trimester, 32% in the second trimester, and 39% in the third trimester (28). We have no explanations for these differences.

Seizure recurrence declined in 5 cases (20%), increased in 5 cases (20%), and remained constant in 15 cases 60% of the subjects.

In the study in England, out of 38 pregnant women with idiopathic epilepsy, seizure frequency increased in 45.2% of the cases, remained constant in 50%, and declined in 4.8% (29).

Pregnancy in the Australian study increased seizures in 24% of the subjects(9). Seizure frequency in the Canadian study increased in 9, remained constant in 14, declined in 4 cases, and was unknown for the rest of the participants(27). In Italy, pregnancy seizures were unchanged in 70.5% of the patients, declined in 12%, and increased in 15.8% of the cases(28). A study in Texas reported a decline in

the seizures in 3-24% of the subjects, a rise in 14-32%, and no change in 54-80%; 84-92% of the patients were pregnancy seizure-free (4). The study in England showed a positive relationship between seizure frequency 2 years prior to pregnancy and increased seizure frequency in pregnancy. Patients with more than one seizure per month had a higher risk of exacerbation in pregnancy, whereas, only 25% of patients whose seizure intervals were more than 9 months, got worse (29). However, in the study by Rosciszewka and Grudzinska in 1970, no such relationship was reported (21).The average age of onset of seizures was lower in subjects with increased seizures (12.6 years old), compared to others (16.1 years), yet, insignificant. In the present study we did not take into account the age of onset of seizures in epileptic patients.

Of the referrals, 24 cases were epileptic, with 2 cases of inactive and 22 cases of active epilepsy.

Out of the total patients, 25 cases had a history of seizures, while 13 cases did not. Out of the total 27 cases with pregnancy epilepsy, 13 cases already had epilepsy, while, 14 cases experienced seizures for the first time in their pregnancy. From the 38 cases with previous seizures, 11 cases had no pregnancy seizures (8 cases had a history of active epilepsy, 2 cases had non active epilepsy, and one of the patients experienced epilepsy in her childhood only once), while, 27 cases experienced pregnancy seizures. Six cases had a family history of epilepsy and 32 had no such history. In a study in England, in 1974, 59 pregnant women had epilepsy, out of whom, 14 cases experienced their first seizure in pregnancy: 7 cases in the first pregnancy, 5 cases in the second, one case in the third, and one case in the fifth pregnancy. Thirty eight cases had idiopathic and 7 cases had symptomatic epilepsy. In the former group, 11 cases had only one seizure, and 5 cases had recurrent seizures in the very same pregnancy (29). In Canada, 55 patients had a history of idiopathic epilepsy and 3 cases experienced seizures in pregnancy for the first time (27).

In our study seizure attacks occurred in the third trimester of pregnancy, except one case of CVT, which was in the second month. The 8 cases who were epileptic had frequent attacks.

The England study reported pregnancy seizures from week 10 to 38, one case upon delivery, and one case postpartum (29). None of the cases had seizures upon delivery in the study in Australia and seizure recurrence in pregnancy was reported between 30 and 50% in the study conducted in Australia (9).

Incidence of different seizures is portrayed in Table 4 (76.3% GTC (generalized tonic-clonic), 13.2% Juvenile Myoclonic Epilepsy (JME), and 2.6% Focal-Generalized, and 7.9% Complex Partial Seizures (CPS). In the 22 patients with active epilepsy, 5 cases had myoclonic jerks, and 17 cases did not. No myoclonic jerks was reported in patients with inactive epilepsy or those experiencing their first epileptic seizure in pregnancy. In Australia, in a study on 75 pregnant epileptic women, the majority of the cases (82.7%) had GTC (9). The study in Canada reported most patients with GTC; two cases had absence, and 4 cases had focal or psychomotor epilepsy (27). In Italy, GTC was observed in 39.3% of the cases, localized in 47.1%, and unknown in the rest (28).

Etiology of Epilepsy in the Present Study: Only 5 out of our total 38 patients had abnormal neurological examination. According to the assessments, one case was caused by AVM, another case by head trauma, one case by tumor; epilepsy in 24 cases had unknown etiology. The causes of the first seizures in pregnancy were eclampsia in 7 cases, CVT in 3 cases, and TTP in one case. The English study reported the etiology of symptomatic epilepsy as including meningitis, brain abscess, encephalitis, meningioma, and head trauma, none of which was observed in the present study (29). Epilepsy in the study in Canada was caused by head trauma in 5 cases, and brain aneurysm in 4 cases (27). In a study done in Africa, prevalence of eclampsia was reported at 1.02% (31).

In this study, epileptic patients mostly used Carbamazepine, in addition to a few cases of Lamotrigine, Levetiracetam, and Sodium Valproate. Seven cases received multi-drug regimens (2 drugs), and 13 cases received single-drug regimens. Seizures were seen in 1 case of single-drug patients (14%), and 7 cases of multiple-drug cases (54%), almost four times the single-drug patients.

In Australia, 70.7% of pregnant women with a history of epilepsy received anti-epileptic medications prior to pregnancy. Epilepsy was controlled in 46 patients with only one or two drugs. The most common anti-epileptic medication was Phenytoin (81%), followed by Phenobarbital 29.3%, Primidone 20.7%, Carbamazepine 13.8%, and Sodium Valproate 5.2%. Out of the said patients, 39.6% received only one medication, 39.6% two medications, 17.4% three, and 3.4% more than three medications (9).

In Italy, recurrence of seizures, mostly GTC seizures, was higher in those receiving Lamotrigine (58.2%), and there was no seizure recurrence in 75% of Valproate users, 67.3% of Carbamazepine users, and 73.4% of Phenobarbital users (28).

Conclusion

More than 6 in 1,000 pregnant women have epilepsy. Though without a history of epilepsy, less than 4 in 1,000 pregnant women are afflicted with seizures, mostly caused by eclampsia. Seizures increased in 21% of epileptic pregnant patients, and declined in 21% of the cases.

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