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Original article

Antiseizure medications use during pregnancy and congenital malformations: A retrospective study in Saudi Arabia

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ABSTRACT

Aim: To evaluate the incidence of congenital malformations in children exposed prenatally to antiseizure medications (ASMs), to assess other perinatal and fetal complications, and to determine the potential predictors for these complications.

Method: A retrospective review of pregnancy outcomes of women with epilepsy. Patients were followed up at the King Faisal Specialist Hospital and Research Centre, Riyadh and Jeddah, Saudi Arabia, between Dec 1993 and Oct 2020.

Results: Of 162 pregnancies included, 10 (6.17%) congenital malformations were observed, 6.82% in ASM-exposed babies versus 3.33% in babies of epilepsy-untreated mothers (P = 0.69). The overall incidence of perinatal and fetal complications was 53%; most frequent were low birth weight (24%), preterm birth (19%), transfer to neonatal intensive care unit (18%) and abortion (8%). These complications were higher in the untreated group (66.67%) than in the ASM group (50%). The use of other non-antiseizure medications during pregnancy was the only factor that significantly increased the risk of complications.

Conclusion: Prenatal exposure to ASMs was associated with increased risk of congenital malformations. However, overall perinatal and fetal complications were higher in the untreated group than in the ASM group, which could be explained by maternal seizures. Therefore, taking ASMs to control epilepsy and prevent perinatal complications may outweigh the risks of teratogenicity.

1. Introduction

Epilepsy is a common chronic disorder in women of childbearing potential (Hauser et al., 1993). Furthermore, epilepsy has been considered as a high-risk condition during pregnancy (Yerby et al., 2004). Maternal seizures can be exacerbated during pregnancy due to several factors, such as hormonal changes and altered drug pharmacokinetics (Khuda and Aljaafari, 2018). Epileptic seizures of mothers and prenatal exposure to antiseizure medications (ASMs) can increase risks of fetal complications. Adverse drug effects on the fetuses can occur, such as abortion, low birth weight, preterm birth, congenital malformations, delayed postnatal cognitive development and postnatal behavioral complications (Tomson and Battino, 2012). The estimated prevalence of congenital malformations in children of women with epilepsy in Saudi Arabia is 2.5–5.9% (AlBunyan and Abo-Talib, 1999, AlSheikh, 2020).

Management of epilepsy in pregnant women is often difficult, and the benefits of controlling maternal seizures during pregnancy by ASMs versus the risk to the fetus of prenatal exposure to ASMs needs balancing. There is indeed a need for national and international pregnancy registries to provide evidence-based clinical practice and enhance the management of epilepsy in pregnancy. Internationally, there have been three major registries operating for more than two decades: the UK Epilepsy and Pregnancy Registry (UKEPR) (Morrow et al., 2006, Campbell et al., 2014), the North American Antiepileptic Pregnancy Registry (NAAPR) (Hernandez-Diaz et al., 2012), and the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) (Tomson et al., 2011, Tomson et al., 2018). However, there is no national pregnancy registry in Saudi Arabia. In fact, there are only few studies in Saudi

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Arabia on outcomes in pregnant women with epilepsy (AlBunyan and Abo-Talib, 1999, Algahtani et al., 2020, AlSheikh, 2020).

This study aims to evaluate the rate of congenital malformations in children exposed to ASMs in utero and to assess other perinatal and fetal complications in pregnant women with epilepsy. It also aims to determine the factors that may affect perinatal and fetal complications.

2. Method

2.1. Study design and setting

This was a retrospective study of pregnant women with epilepsy conducted at the King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh and Jeddah, Saudi Arabia. We evaluated pregnancy outcomes in those mothers. Patients were followed up prospectively between 6th Dec 1993 and 30th Oct 2020 at the KFSHRC, a tertiary care hospital covering the central and western regions of Saudi Arabia. The inclusion criteria of the study were pregnancy and a confirmed diagnosis of epilepsy during the study period.

2.2. Data collection

The data was collected from both patients' electronic and paper-based medical records. Data obtained on each patient included demographic information (age at pregnancy, education, and employment); risk factors for epilepsy (family history of epilepsy, head trauma, febrile convulsion, central nervous system [CNS] infection, CNS surgery, and birth difficulties); epilepsy and seizure types according to the International League Against Epilepsy 2017 classification (Fisher et al., 2017, Scheffer et al., 2017); the duration of epilepsy; ASMs administered during pregnancy, including dose (mg/day) and adherence; previous obstetric history (parity, type of delivery and obstetric complications if any); other medications taken during pregnancy, their indications and doses; and folic acid use during pregnancy.

For each pregnancy, parity, the last menstrual period and the expected delivery date, ultrasound scan findings, and seizure frequency and type during pregnancy were collected. Type of delivery was also documented and categorized into spontaneous vertex, emergency Caesarian section, elective Cesarean section, and assisted vaginal delivery by forceps or vacuum suction. Any complications during pregnancy or delivery were documented. For baby health, gestational age at delivery, weight, length, occipitofrontal head circumference, and Apgar at 1, 5, and 10 min were recorded. Any fetal complications were recorded, particularly congenital malformations.

2.3. Study outcomes

The primary outcome in this study was congenital malformation. A major congenital malformation is recognized as a defect in body structure at birth that has functional, medical, surgical, or cosmetic significance (Tomson and Battino, 2012). Other adverse perinatal and fetal outcomes were also investigated, including spontaneous and medically induced abortions (before 20 weeks gestational age) or stillbirth (at 20 weeks gestational age or after), spontaneous and medically indicated premature birth (<37 weeks gestational age), low birth weight (<2.5 kg), transferred to neonatal intensive care unit (NICU), neonatal infection, neonatal convulsion or seizure, neonatal hypoglycemia, neonatal jaundice, and respiratory distress.

Investigated potential predictors were the mother's age at pregnancy, parity, folic acid use during pregnancy, ASMs used during pregnancy, use of other medications during pregnancy, and previous obstetric complications. Previous obstetric complications included abortion/stillbirth, emergency Caesarian section, birth defect, preterm, low birth, pre-eclampsia, eclampsia, gestational diabetes, and hemorrhage.

2.4. Statistical analysis

Categorical data was presented as frequency and percentage, while continuous data was summarized as mean (SD, standard deviation) or median (range). A chi-squared (x^2) test was performed for comparison of categorical data (when expected counts were less than five, Fisher's exact test was used). Univariate and multivariate logistic regression analyses were applied to evaluate the effect of the potential factors on fetal complications. IBM Statistical Package for the Social Sciences (SPSS) and GraphPad Prism were used for data analysis.

This research project was approved by the Institutional Review Board at KFSHRC (RAC # 2191–047).

3. Results

3.1. Clinical characteristics

The study included a total of 162 pregnancies born to 97 women. Number of pregnancies were ranging from one to four during the study period between 6th Dec 1993 and 30th Oct 2020. The ages of the women ranged between 19 and 43 years with a mean of 31.21 years (SD = 5.08 years). Types of epilepsy in those mothers were focal in 49 (50.52%), generalized in 36 (37.11) and unclassified in 12 (12.37). The seizures remained controlled during 103 pregnancies (63.58%). The mothers were taking folic acid during pregnancy in 92 pregnancies (65.79%).

The mothers were taking monotherapy in 85 pregnancies (52%) while in 47 (29.01%), they were taking polytherapy ranging from 2 to 4 ASMs. In the remaining 30 pregnancies (18.52%), the mothers did not take ASMs during pregnancies. The most frequently prescribed monotherapy was carbamazepine (n = 31), followed by levetiracetam (n = 24), lamotrigine (n = 15), and valproate (n = 12). Table 1 shows the drug monotherapies during pregnancy and their doses.

Spontaneous vertex was the mode of delivery for 70 pregnancies (43.21%). Emergency Caesarian section and elective Cesarean section was performed for 40 (24.69%) and 36 pregnancies (22.22%), respectively. In addition, there were three assisted vaginal births by vacuum extraction or forceps. Furthermore, there were 13 abortions (spontaneous or medically induced). Reasons for emergency Caesarian section were fetal distress, placental abruption, and mother's pre-eclampsia and eclampsia.

3.2. Perinatal and fetal complications

A total of 86 pregnancies were associated with at least one perinatal complication (53%; 86/162). Table 2 shows the perinatal

Table 1
Antiseizure drug monotherapy during pregnancy (n = 85).

	N (%)	Dose in mg/day as median (range)
Carbamazepine	31 (36.47)	600 (400–1400)
Levetiracetam	24 (28.24)	2000 (1000–4000)
Lamotrigine	15 (17.65)	300 (125–600)
Sodium valproate	12 (14.12)	1000 (500–1500)
Topiramate	2 (2.35)	125,125
Phenytoin	1 (1.18)	300

Table 2
Perinatal and fetal complications (n = 162).

Spontaneous or medically induced abortions	13 (8)
Medically indicated preterm (<37 weeks)	15 (9.26)
Spontaneous preterm (<37 weeks)	16 (9.88)
Low birth weight (<2.5 kg)	40 (24.69)
Transferer to neonatal intensive care unit	30 (18.51)
Birth defect	10 (6.17)
Others (7 respiratory distress, 3 jaundice, 2 infections, 1 hypoglycemia)	13 (8.02)

Data in number (%)

abnormalities. Out of 31 preterm deliveries, 10 were before 34 gestational weeks.

Ten babies had at least one congenital malformation (Table 3). Four cases were likely to be related to maternal epilepsy or antiseizure use. These including cardiac abnormalities, urogenital abnormalities, dysmorphic features, and retinopathy. The other detected congenital malformations including dextrocardia, strabismus, hearing impairments, and hereditary genetic disorders. All babies except one were exposed prenatally to ASMs. Seven mothers were taking monotherapy (five carbamazepine, and two lamotrigine) while two were taking dual ASM therapy. Mothers' ages ranged from 26 to 43 years, and 80% were taking folic acid (5 mg) during pregnancy. Parity ranged from zero to seven. Fifty percent of the mothers had experienced seizures during pregnancy. Three babies had other perinatal complications, such as preterm, low birth weight, and low Apgar. Furthermore, in four cases the mother had a history of obstetric or fetal complications. During three pregnancies, the mothers had comorbidities and were taking concomitant medications: one systemic lupus erythematosus and two uncontrolled gestational diabetes.

As shown in Fig. 1, ASMs were associated with increased birth defects (n = 9/132; 6.82%) compared to untreated epilepsy (n = 1/30; 3.33%), yet the difference was not significant (P = 0.6900, Fisher's exact test). However, total complications were higher in the untreated group (n = 20; 66.67%) than the ASM group (n = 66; 50%). In the ASM group, the rate of complications was higher in polytherapy (n = 24; 51.06%) than in monotherapy (n = 42; 49.41%).

3.3. Factors affect perinatal and fetal complications

The effects of several potential risk factors for fetal complications were evaluated. Factors included were the mother's age at pregnancy, parity, folic acid use during pregnancy, ASMs used during pregnancy, use of other medications during pregnancy, and previous obstetric complications. As demonstrated in Table 4, the only factor that significantly increased the risk of fetal complications was the use of other medications during pregnancy. In the adjusted model, the odds of complications in a fetus exposed to other medications in utero was approximately twice that for a fetus who was not exposed to other medications prenatally.

The most common drug (or drug class) of the concomitant medications used during pregnancy were immunosuppressants/corticosteroids (n = 25), followed by thyroxine (n = 20) and enoxaparin (n = 18). In addition, other medications such as antihypertensive medications (n = 12), aspirin (n = 10), insulin (n = 9), CNS medications (n = 6), gastrointestinal drugs (n = 4), frusemide (n = 3), antibiotics (n = 2), inhalers (n = 2), metformin (n = 2), hydroxyurea (n = 2) and interferon (n = 2) were used.

4. Discussion

The main objective of the present work was to assess the incidence of congenital malformations in babies exposed prenatally to ASMs. In this cohort of pregnant women with epilepsy, 10 birth defects were detected, which represented overall rate of 6.17%. The rate of congenital malformation was 6.82% in babies of treated mothers compared to 3.33% in babies of mothers untreated for epilepsy; however, the difference was not significant. The statistically non-significant finding is likely to be due to sample size, but the results may have clinical significance, as the rate of malformations in the treated group was twice that in the untreated group. This indicates the need for larger studies and a pregnancy registry at national level. The malformation rate observed in the presented study was comparable to that reported in other studies. In a recent study in Saudi Arabia which included 68 women of epilepsy, congenital malformation was observed in 4 (5.9%) neonates (AlSheikh, 2020). A study from the United Arab Emirates (UAE) that included 179 pregnancies of women with epilepsy observed 13 (7.26%) birth defects (Alsaadi et al., 2020). Likewise, a pregnancy registry in India that included 1688 fetuses reported a congenital malformation rate of 6.84% (Thomas et al., 2017). Furthermore, in another study, the congenital malformation rate was estimated to be 5% in the offspring of mothers taking ASMs and 3% in the offspring of untreated women (Artama et al., 2005). However, other studies reported lower rates than that detected in the present study. The rate of congenital malformation estimated by the UK pregnancy registry was 4.2% (Morrow et al., 2006), and 3.5% in updated results (Campbell et al., 2014). The incidence of malformation in women with epilepsy was 2.5% (2 out of 79 pregnancies) in a study from Saudi Arabia (AlBunyan and Abo-Talib, 1999). However, some studies have observed higher rates of congenital malformations. In a Canadian study, the rate of birth defects was reported to be 13% in 173 pregnant women with epilepsy (Kulaga et al., 2011). One possible explanation for variations in the reported rates of malformations across studies is a variation in the categorization of borderline cases of congenital malformation used (Tomson and Battino, 2012).

In this cohort, carbamazepine was the most commonly prescribed monotherapy. Likewise, carbamazepine was reported as the most frequently used ASM in pregnancy in many studies (Morrow et al., 2006, Kulaga et al., 2011, Artama et al., 2013). The EURAP registry, which evaluated the utilization of ASMs in 38 countries, showed that carbamazepine was the most frequently used ASM during pregnancy (The EURAP Study Group, 2009). Carbamazepine shows a favorable safety profile and is a rational choice for controlling seizures during pregnancy (Artama et al., 2005, Morrow et al., 2006, Hernandez-Diaz et al., 2012, Tomson and Battino, 2012, Campbell et al., 2014). However, the use of new ASMs in pregnancy has increased recently. In the updated results of the UK and EURAP registries, lamotrigine was the most commonly used ASM in pregnancy (Campbell et al., 2014, Tomson et al., 2018). In the NAAPR, lamotrigine, levetiracetam, and topiramate were the most frequently used ASMs in pregnancy (Hernandez-Diaz et al., 2012).

Although levetiracetam was the second most frequently used monotherapy in this cohort, no cases of malformation were detected. This is consistent with previous reports of a reduced risk of congenital malformations associated with levetiracetam monotherapy (Hernandez-Diaz et al., 2012, Mawhinney et al., 2013, Weston et al., 2016, Tomson et al., 2018). The risk associated with levetiracetam (2.9%) reported in the EURAP registry was comparable to that observed in the literature for babies unexposed prenatally to ASMs (Tomson et al., 2018). These results may help in the rational selection of levetiracetam for controlling seizures dur-

Table 3
Congenital malformations detected in 10 babies.

Congenital malformation	ASM used during pregnancy, dose mg/day	Mother's age at pregnancy (years)	Folic acid during pregnancy	Parity	Seizure control	Obstetric abnormality	Previous obstetric and fetal complications	Mother's comorbidity	Other medications used during pregnancy
Congenital malformations potentially related to maternal epilepsy/ASM use									
Hypospadias and cardiomegaly	CBZ, 400	34	Yes	4	No	Low weight	No	Systemic lupus erythematosus	Azathioprine Hydroxychloroquine Prednisone Aspirin
Mild dysmorphic features with coarse facial features and microcephaly. Multiple atrial septal defects which closed spontaneously, and upper limb rhizomelia	CBZ, 400 LTG, 400	28	Yes	0	No	No	Yes Stillbirth and miscarriages	No	No
Cardiac defect [Patent ductus arteriosus (PDA) and patent foramen ovale (PFO)]	LTG, 300	38	Yes	4	No	Low weight	No	No	No
Retinopathy [Retinal changes stage I zone 2]. Ambiguous genitalia	CBZ, 800	33	Yes	2	Yes	Preterm Low weight Low Apgar	No	No	No
Other congenital malformations									
Dextrocardia	No ASM	29	No	3	Yes	No	No	No	No
Congenital hip disconnection	CBZ, 400	36	Yes	6	Yes	No	No	Gestational diabetes and uncontrolled glucose	Metformin
Handicapped at birth and moderate bilateral hearing loss	CBZ, 400	39	Yes	7	Yes	No	Yes Congenital malformation	Diabetes mellitus and uncontrolled glucose	Insulin
Strabismus [large angle exotropia bilateral lateral rectus recession (comitant strabismus)]	VPA, 1500 PHT, 400	37	Yes	6	No	No	No	No	No
Hereditary disease (Morquio syndrome, abnormal bones, and mucopolysaccharidosis)	CBZ, 1400	26	No	1	No	No	Yes Same syndrome in sibling	Yes Mother is carrier for the defective gene	No
Congenital aplasia cutis	LTG, 200	43	Yes	5	Yes	No	Yes Hereditary disease	No	No

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; LTG, lamotrigine; PHT, phenytoin; VPA, valproate.

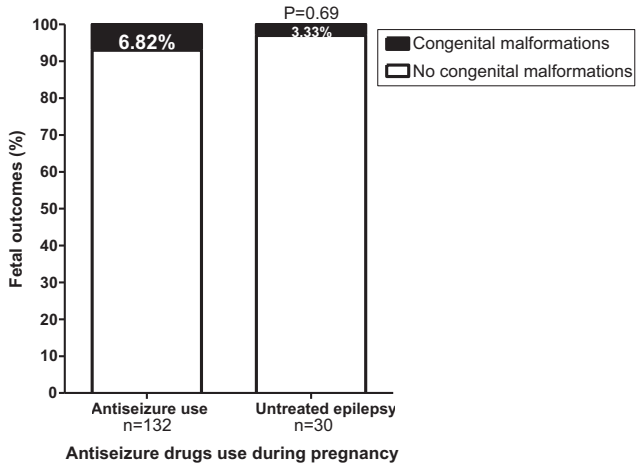

Fig. 1. Rate of congenital malformations in babies of women taking antiseizure drugs compared to children of those with untreated epilepsy. Fisher's exact test was used.

ing pregnancy. In fact, levetiracetam was the most frequently reported ASM used during pregnancy in recent national and domestic studies (Algahtani et al., 2020, Alsaadi et al., 2020).

On the other hand, valproate monotherapy was used infrequently in this study (in only 12 pregnancies). This is most probably due to the recognition of its high teratogenicity. Valproate has consistently demonstrated the highest teratogenicity risks among ASMs, including congenital malformations, postnatal neurodevelopmental delay, and behavioral problems. (Morrow et al., 2006, Hernandez-Diaz et al., 2012, Christensen et al., 2013, Cohen et al., 2013, Meador et al., 2013, Campbell et al., 2014, Tomson et al., 2015, Tomson et al., 2018). Consequently, prescribing valproate must be avoided for girls and women of childbearing potential where possible (Tomson et al., 2015). Moreover, studies showed that congenital malformation is dose-dependent, particularly for valproate (Tomson et al., 2011, Hernandez-Diaz et al., 2012, Campbell et al., 2014, Thomas et al., 2017, Tomson et al., 2018), which indicates the importance of using the lowest effective dose of ASM, which should be achieved in the pre-conception period.

The overall rate of perinatal and fetal complications in this cohort was high, at 53%; the most frequent were low birth weight (24%), preterm birth (19%), transfer to NICU (18%) and abortion (8%). Furthermore, Caesarian section was performed for 47% of deliveries. This is in line with other studies that demonstrated an association between epilepsy and adverse pregnancy outcomes (Borthen et al., 2010, Artama et al., 2013, Kilic et al., 2014, Razaz et al., 2017). A study comparing pregnancy outcomes of women with epilepsy to those without showed that epilepsy is an independent risk factor for preterm birth, low birth weight and small for gestational age (SGA) (Chen et al., 2009). Furthermore, a systematic review and *meta*-analysis of 38 studies showed that mothers with epilepsy had higher risks of premature birth, intrauterine growth retardation, Caesarian section and abortion compared to those without epilepsy (Viale et al., 2015). A recent study conducted in Saudi Arabia found that out of 600 babies of women with epilepsy, 2% had low birth weight, 0.7% had preterm birth, 17.7% were delivered by Caesarian section, and 0.17% had malformations. The rate of miscarriage was 15.6% (Algahtani et al., 2020). The rate of abortion in the present study was 8%, which may be an underestimate, as miscarriages in early pregnancy may not be well documented. Another study in Saudi Arabia demonstrated that out of 79 pregnancies 12% had perinatal or neonatal complications, including 11% low birth weight, and 2.5% malformation. Caesarian section was performed in around 12% of pregnancies (AlBunyan and Abo-Talib, 1999).

However, in this study the overall rate of complications was higher in mothers with untreated epilepsy (66.67%) than in the ASM group (50%). This is consistent with other findings (Kulaga et al., 2011, Razaz et al., 2017). In fact, 15–33% of women with epilepsy experience their seizures worsening during pregnancy (Battino et al., 2013). Therefore, the greater risk of complications in the unexposed group compared to those taking ASMs could be justified by epileptic seizures of the mothers. Chen et al. (2009) found that mothers with uncontrolled seizures during pregnancy had higher rates of fetal complications, including premature birth, SGA, and low birth weight compared to mothers with seizures controlled during pregnancy. This study also showed the rate of complications was slightly higher in polytherapy (51.06%) than in monotherapy (49.41%). Monotherapy has consistently demonstrated a reduced risk for fetal complications, including congenital malformations, compared to polytherapy (Morrow et al., 2006, Artama et al., 2013, Kilic et al., 2014, Thomas et al., 2017). These findings could indicate that the best strategy for controlling maternal seizures and protecting fetuses would be to use ASM monotherapy rather than polytherapy or not treating at all (Kulaga et al., 2011).

The present study investigated the association between a number of factors and the occurrence of perinatal and fetal complications. The adjusted regression model demonstrated that the use of concomitant medications during pregnancy was the only factor that significantly increased the risk for perinatal and fetal complications. The risk of complications in a fetus exposed to other medications in utero was approximately twice that for a fetus not exposed prenatally to other medications. In fact, in around 47%

Table 4
Univariate and multivariate logistic regression analysis for predictors of fetal complications.

		Fetal complications (n = 86), frequency (%)	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Mother's age at pregnancy (years)			0.998 (0.939–1.061)	0.949	0.99 (0.916–1.071)	0.803
Parity			1.034 (0.891–1.198)	0.662	1.049 (0.868–1.268)	0.619
Folic acid use during pregnancy	Yes (n = 92)	44 (48.8)	0.611 (0.326–1.147)	0.125	0.604 (0.314–1.163)	0.132
	No (n = 70)	42 (60)				
ASMs used during pregnancy	Yes (n = 132)	66 (50)	0.534 (0.231–1.23)	0.143	0.711 (0.291–1.738)	0.455
	No (n = 30)	20 (66.7)				
Other medications used during pregnancy	Yes (n = 77)	48 (62.3)	2.047 (1.092–3.839)	**0.026**	2.02 (1.023–3.989)	**0.043**
	No (n = 85)	38 (44.7)				
Previous obstetric complications	Yes (n = 90)	48 (53.3)	1.023 (0.55–1.903)	0.944	0.83 (0.429–1.606)	0.58
	No (n = 72)	38 (52.8)				

Abbreviations: ASMs, antiseizure medications; CI, confidence interval; OR, odds ratio.

(n = 77/162) of pregnancies, the mothers were taking other medications. This may contribute to the observed increased pregnancy complications in this cohort, as many mothers had comorbidities other than epilepsy and used concomitant medications during pregnancy other than ASMs. These maternal comorbidities may lead to congenital malformation. Some medical conditions pose teratogenic risks including gestational diabetes (Allen and Armson, 2007, Ornoy et al., 2015) and thyroid diseases (Temboury Molina et al., 2015) which were found to be associated with high risks of congenital malformations and other fetal complications. Likewise, other medication use during pregnancy could induce birth defects and other fetal complications. Some medications can cross maternal placental barrier and reach fetuses in an active form (Bermas and Hill, 1995). Drugs can cause teratogenicity by different mechanisms including antagonize folate, disrupt neural crest cells, disrupt endocrine or vascular systems, oxidative stress, and stimulate or inhibit specific receptors or enzymes (van Gelder et al., 2010). In addition, multivariate analysis showed that the presence of previous obstetric complications was a potential (but not statistically significant) factor in fetal complications. It has been demonstrated that mothers who already had an infant with a birth defect were associated with an increased risk of having others with congenital malformations. This may suggest a genetic involvement in the risk of teratogenicity of ASMs (Campbell et al., 2013).

The limitations of the present study were the tertiary care character of the KFSHRC and the relatively small sample size, which may limit the generalizability of the findings. This emphasizes the requirement for a national pregnancy registry.

In conclusion, the rate of congenital malformations was 6.17% in women with epilepsy. Prenatal exposure to ASMs was associated with an increased risk of congenital malformations. However, overall perinatal and fetal complications were higher in the untreated group than in the ASM group, which could be explained by uncontrolled maternal epilepsy. Therefore, taking ASMs to control seizures and prevent perinatal complications may outweigh the risk of teratogenicity. ASM-related teratogenicity can be reduced by pre-conception planning that aim to select an ASM with low risk, use of monotherapy with the lowest effective dose, and monitor the use of co-medications.

CRediT authorship contribution statement

Bshra Alsfouk: Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Manal Almarzouqi:** Data curation, Writing - review & editing, Project administration, Software. **Aisha Alsfouk:** Formal analysis, Writing - original draft, Writing - review & editing. **Saleh Alageel:** Formal analysis, Writing - review & editing, Project administration, Software. **Abdulaziz Alsemari:** Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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