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Original article

# Patterns of antiseizure medication prescription in pregnancy and maternal complications in women with epilepsy: A retrospective study in Saudi Arabia

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ABSTRACT

*Aim:* To evaluate patterns of antiseizure medication (ASM) prescription in pregnancy and changes over a 16-year period: 2005–2020, and to investigate maternal complications in pregnant women with epilepsy (WWE).

*Method:* Data of pregnant WWE was retrospectively reviewed at the King Faisal Specialist Hospital and Research Centre, Riyadh and Jeddah, Saudi Arabia.

*Results:* Out of 162 pregnancies, 81.5% were prescribed ASMs. During the study period, the prescription rate increased from 68.8% to 93.5%. Between 2005 and 2020, the use of new ASMs increased from 15.4% to 75.5% ($p < 0.0001$). Furthermore, valproate use markedly decreased from 23.08% to 2.04%. The rate of maternal and delivery complications was 29.6%; the most frequent was gestational diabetes (5.6%), followed by bleeding during pregnancy (4.9%). Furthermore, preeclampsia and eclampsia were documented in 3.7% and 1.8%, respectively. ASMs use and other factors were not found to be associated with maternal complications ($p > 0.05$). However, first generation ASMs, i.e. carbamazepine (38.71%) and valproate (41.67%), were associated with higher maternal complication rates than new ASMs, i.e. levetiracetam (25%) and lamotrigine (20%), but the difference was not statistically significant ($p = 0.4403$).

*Conclusion:* ASM prescription in pregnancy is increasing as is the use of new ASMs. The rate of maternal and delivery complications was relatively low, particularly preeclampsia and eclampsia. ASMs use was not found to associated with these complications. However, exposure to first generation ASMs seemed to be a predictor of adverse pregnancy outcomes.



## 1. Introduction

Epilepsy is considered among the commonest neurological conditions that needs medication throughout pregnancy, and antiseizure medications (ASMs) are used in 34 to 95% of pregnant women with epilepsy (WWE) (Veiby et al., 2009; Borthen et al., 2011; Artama et al., 2013; Yeh et al., 2017). In Saudi Arabia, it has been estimated that 88% of pregnant WWE received ASMs (Al Bunyan and Abo-Talib, 1999; AlSheikh, 2020). Most studies have focused on adverse drug effects on children who exposed in utero to ASMs such as congenital malformations and neurodevelopmental delay (Hernandez-Diaz et al., 2012; Meador et al., 2013; Bromley et al., 2014; Campbell et al., 2014; Tomson et al., 2018). However, few studies have examined the effects of epilepsy and ASMs use on maternal and delivery outcomes. For the optimal management of epilepsy in pregnancy, a balance between control seizures by ASMs and adverse drug effects on the mothers and their fetuses is required.

Furthermore, there are contradicting data on the risks of pregnancy and delivery complications in WWE. Some studies have demonstrated that maternal epilepsy is not significantly associated

ASMs, Antiseizure medications; WWE, Women with epilepsy.

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with these complications (Thomas et al., 2009; Borthen et al., 2011), while in other studies, WWE using ASMs had an increased risk for some maternal and delivery complications including of pre-eclampsia, vaginal hemorrhage, induction of labor and caesarean section (Veiby et al., 2009; Borthen et al., 2011; Viale et al., 2015). Therefore, the effects of epilepsy and ASMs on pregnancy outcomes indeed need further investigation (Kaplan et al., 2007; Borthen et al., 2010).

Despite the expanded use of new ASMs such as lamotrigine and levetiracetam in pregnant WWE (Meador et al., 2018), there are limited and inconsistent evidence on the effects of specific ASMs on maternal and delivery outcomes. Some studies have demonstrated that WWE who received first generation ASMs such as carbamazepine and valproate at higher risks for pregnancy complications, including pre-eclampsia (Veiby et al., 2009; Danielsson et al., 2018), while new ASMs such as lamotrigine and levetiracetam did not precipitate pre-eclampsia (Danielsson et al., 2018). Other studies showed that lamotrigine is associated with increased risks of pre-eclampsia and early bleeding (Borthen et al., 2011). The preferred ASMs and ASMs that should be avoided in pregnancy, therefore, need to be identified.

The aim of the present study was to examine ASM prescription patterns in pregnancy and changes over a 16-year period: 2005–2020. This study also aimed to evaluate maternal complications in pregnant WWE.

## 2. Method

### 2.1. Patients and setting

Data of pregnant WWE was retrospectively reviewed at the King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh and Jeddah, Saudi Arabia. The data included all pregnancies with a confirmed diagnosis of maternal epilepsy (n = 162) from July 1, 2005, to October 30, 2020.

### 2.2. Data collection

As previously described (Alsfouk et al., 2021), data was obtained from patient records and included sociodemographic information of the mothers (age at pregnancy, educational level, and employment status); history of epilepsy risk factors (family history of epilepsy, birth problem, febrile convulsion, head injury, central nervous system [CNS] tumor, CNS surgery, CNS infection, and cerebrovascular disease); results of investigations (electroencephalography [EEG], magnetic resonance imaging [MRI] and computed tomography [CT] scan); type of epilepsy and seizure according to the latest International League Against Epilepsy (ILAE) classification (Fisher et al., 2017; Scheffer et al., 2017); and epilepsy duration.

Data collection on each pregnancy included parity, the expected date delivery, results of ultrasound scans, ASMs and daily doses in milligrams, frequency and type of seizures, comorbidities and concomitant medications, folic acid supplementation, mode of delivery, and obstetrical history of previous pregnancies (maternal age, parity, delivery method, pregnancy complications). Any pregnancy and/or delivery complications were documented.

The fetal complications including congenital malformation have been previously described (Alsfouk et al., 2021). In the analysis, the main outcome was maternal complications during pregnancy and/or delivery including bleeding during pregnancy, gestational hypertension, eclampsia, preeclampsia, gestational diabetes, cervical cerclage, placenta abruption, prolonged labor, pre-mature rupture of membranes, seizure on day of delivery or during delivery, and post-partum hemorrhage.

Investigated potential risk factors for maternal complications were maternal age, parity, folic acid use during pregnancy, ASMs use during pregnancy, exposure to ASM polytherapy, exposure to first generation ASMs, uncontrolled seizure during pregnancy, chronic hypertension, chronic diabetes, psychiatric comorbidity, and other comorbidities.

### 2.3. Definitions

Hypertension was defined as persistent increased blood pressure to a value of 140/90 mmHg or higher. Chronic hypertension was defined as hypertension that was diagnosed prior to conception or before 20 weeks of gestation while gestational hypertension was hypertension that was present after the 20th week of gestation with no proteinuria. Pre-eclampsia was defined as hypertension associated with proteinuria ($\geq$0.3 g in 24 h) developing after the 20th week of gestation. Eclampsia was defined as generalized tonic-clonic seizures occurring with pre-eclampsia and without other reasons (American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy, 2013).

Seizure status during pregnancy was categorized as controlled and uncontrolled. Controlled was defined as being seizure-free throughout pregnancy, while uncontrolled was defined as patients experiencing seizures during pregnancy.

Exposure to an ASM regimen during pregnancy was classified as either a monotherapy (i.e., single ASM) or a polytherapy (i.e., combination of two or more ASMs). First generation ASMs were those introduced before 1980 whereas new ASMs were those developed after 1980. In five pregnancies, the ASM regimens had been changed during the second or third trimesters. The regimen which was received in the first trimester was used in the analytical stage for those pregnancies. Because some patients received both first generation and new ASMs, they were classified as a separate category. In the analysis, to recognize exposure to first generation ASMs, a binary code was assigned for those who received first generation and those who did not.

To evaluate the change in ASM prescription in pregnancy over time, the study period was divided into five epochs according to the ASM prescription date, i.e., 2005–2008, 2009–2011, 2012–2014, 2015–2017, and 2018–2020.

### 2.4. Statistical analysis

Descriptive data are presented as count and percentage (%) for categorical variables. A Pearson chi-squared ($\chi^2$) test was applied to evaluate the associations between proportions; Fisher's exact test was performed when expected counts were < 5. A chi-squared ($\chi^2$) test for trend was used to assess the linear associations between ordered variables (i.e., prescription rate of first generation vs. new ASMs in each year interval). IBM Statistical Package for the Social Sciences (SPSS) and GraphPad Prism were used for data analysis.

This study was approved by the Institutional Review Board at KFSHRC (RAC # 2191-047).

## 3. Results

### 3.1. Clinical characteristics

This study cohort included 162 pregnancies of 97 WWE. During the majority of pregnancies (n = 132, 81.48%), the mothers were taking ASMs while the remaining were off medication. As demonstrated in Table 1, there were no significant differences in clinical characteristics between WWE with ASMs and those without ASMs. The majority (93.83%) of WWE were aged between 21 and 39 years and more than half of pregnancies were multiparous (i.e., had more

**Table 1**
Characteristics of women with epilepsy pregnancies (n = 162).

| | | Pregnancies of all WWE n=162 n (%) | Pregnancies of WWE with ASMs n=132 n (%) | Pregnancies of WWE without ASMs n=30 n (%) | P-value |
|---|---|---|---|---|---|
| Maternal age (years) | ≤ 20 | 1 (0.62) | 1 (0.76) | 0 (0) | 0.6295 |
| Age group | 21–29 | 64 (39.51) | 50 (37.88) | 14 (46.67) | |
| | 30–39 | 88 (54.32) | 73 (55.3) | 15 (50) | |
| | ≥ 40 | 9 (5.56) | 8 (6.06) | 1 (3.33) | |
| Parity | 0 (Nulliparous) | 36 (22.22) | 27 (20.45) | 9 (30) | 0.5091 |
| | 1 (Primiparous) | 39 (24.07) | 33 (25) | 6 (20) | |
| | >1 (Multiparous) | 87 (53.7) | 72 (54.55) | 15 (50) | |
| Folic acid use during pregnancy | Yes | 92 (56.79) | 78 (59.09) | 14 (46.67) | 0.2276 |
| | No | 70 (43.21) | 54 (40.91) | 16 (53.33) | |
| Seizure control during pregnancy | Controlled | 103 (63.58) | 80 (60.6) | 23 (76.67) | 0.1405 |
| | Uncontrolled | 59 (36.41) | 52 (39.4) | 7 (23.33) | |
| Chronic hypertension | Yes | 15 (9.26) | 13 (9.85) | 2 (6.67) | 0.7398 |
| | No | 147 (90.74) | 119 (90.15) | 28 (93.33) | |
| Chronic diabetes | Yes | 9 (5.56) | 7 (5.3) | 2 (6.67) | 0.6729 |
| | No | 153 (94.44) | 125 (94.7) | 28 (93.33) | |
| Psychiatric comorbidity | Yes | 20 (12.35) | 18 (13.64) | 2 (6.67) | 0.3734 |
| | No | 142 (87.65) | 114 (86.36) | 28 (93.33) | |
| Other comorbidities | Yes | 50 (30.86) | 38 (28.79) | 12 (40) | 0.2746 |
| | No | 112 (69.14) | 94 (71.21) | 18 (60) | |

Abbreviations: ASMs, antiseizure medications; WWE, women with epilepsy. Chi-square test/Fisher's exact test were used.

than one previous pregnancy). Approximately 36.4% had at least one seizure during pregnancy. Comorbidities included chronic hypertension, chronic diabetes, psychiatric disorders, and other comorbidities (Table.1). During 50 pregnancies, the mothers had at least one other comorbidity included systemic lupus erythematosus (n = 19), chronic kidney disease (n = 15), hypothyroidism (n = 9), other autoimmune disease (n = 8), asthma (n = 7), other cardiovascular disease (n = 7), anemia (n = 3), MTHFR [methylenetetrahydrofolate reductase] heterozygous (n = 3), and chronic myelogenous leukemia (n = 2).

### *3.2. Antiseizure medication prescription patterns in pregnant women with epilepsy*

Overall, the prescription rate of ASMs was 81.48% (n = 132) either as monotherapy (n = 85, 64.39%) or as polytherapy (n = 47, 35.60%). The pattern of ASM prescription (no ASM, monotherapy, and polytherapy) was observed over a period of 16 years and shown in Fig. 1. Changes over the study period showed that prescription of ASMs in pregnancy had steadily increased from the first to the fourth epoch in which rate of "no ASM" reduced from 31.25% to 6.45%, respectively. Monotherapy remained predominant through the study period, though considerable proportions used polytherapy (up to 35.48%).

Out of 132 pregnancies of WWE with ASMs, 48 (36.36%) received regimens of first generation ASMs, 52 (39.39%) used regimens of new ASMs, and 32 (24.24%) received regimens of both first generation and new ASMs. A total of 193 ASMs were prescribed either as monotherapy or as part of polytherapy, of which 88 were first generation ASMs while 105 were new ASMs. First generation ASMs were carbamazepine (n = 54), valproate (n = 23), phenytoin (n = 8), phenobarbital (n = 2), and clonazepam

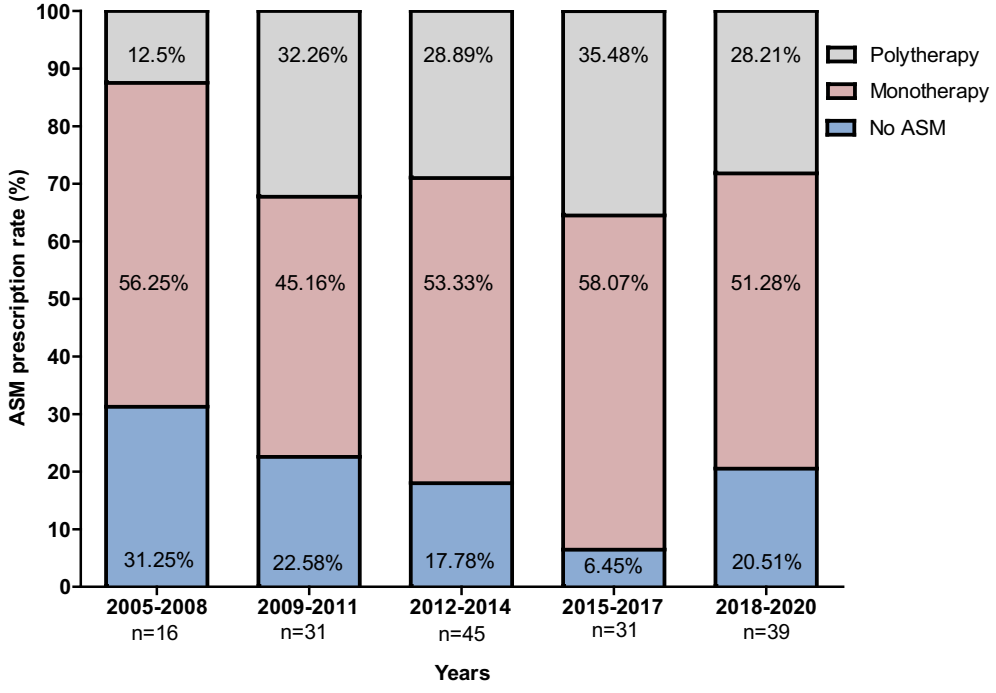


**Fig. 1.** Polytherapy, monotherapy and no antiseizure medication prescription rate in women with epilepsy (n = 162). ASM; antiseizure medication.

(n = 1). New ASMs were levetiracetam (n = 55), lamotrigine (n = 37), topiramate (n = 8), lacosamide (n = 3), and oxcarbazepine (n = 2).

Trends of prescription of first generation and new ASMs in pregnant WWE over the study period were observed (Fig. 2). The prescription rate of new ASMs steadily increased from 15.38% in the first epoch to 75.51% in the fifth epoch while the use of first generation reduced significantly ($p < 0.0001$, $\chi^2$ test for trend). Furthermore, the valproate prescription rate markedly decreased over the study period from 30.77% in the first epoch to 2.04% in the fifth epoch (Fig. 3).

### 3.3. Maternal complications in women with epilepsy

Out of 162 pregnancies, 48 (29.63%) had at least one maternal and/or delivery complication. As demonstrated in Table 2, the most common maternal complication was gestational diabetes, followed by bleeding during pregnancy.

The association between several factors and maternal complications was evaluated. Potential factors were maternal age, parity, folic acid use during pregnancy, ASMs use during pregnancy, exposure to ASM polytherapy, exposure to first generation ASMs, uncontrolled seizure during pregnancy, chronic hypertension, chronic diabetes, psychiatric comorbidity, and other comorbidities. As shown in Table 3, exposure to first generation ASMs and chronic diabetes were associated (but not statistically significant) with increased maternal complications. Other factors were not found to be associated with maternal complications.

Maternal complication rates associated with the most commonly prescribed ASMs as monotherapy were compared, as shown in Fig. 4. First generation ASMs, i.e. carbamazepine (38.71%) and valproate (41.67%), were associated with higher maternal complication rates than new ASMs, i.e. levetiracetam (25%) and lamotrigine (20%), although the difference was not significant (P = 0.4403, $\chi^2$ test).

## 4. Discussion

The purpose of this study was to evaluate ASM prescription in pregnancy and changes over a 16-year period from 2005 to 2020.

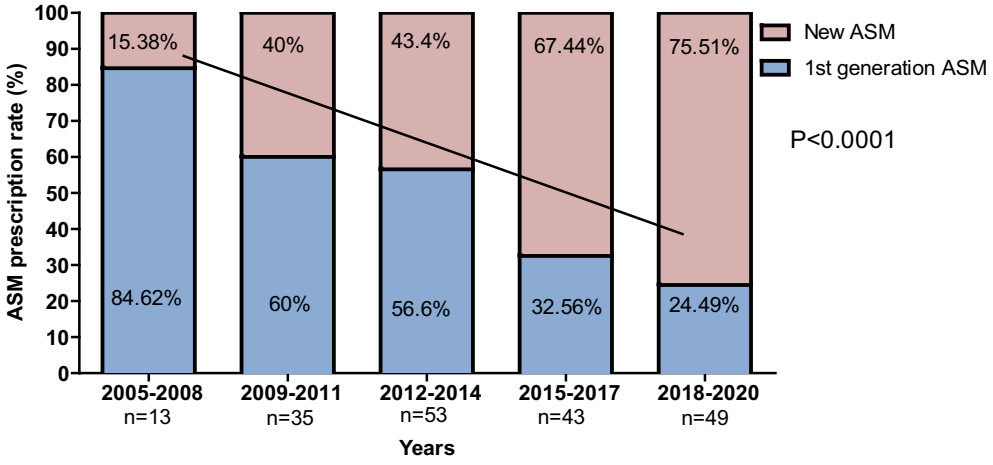


**Fig. 2.** Prescription rate of first generation vs. new antiseizure medication by years from 2005 to 2020 in women with epilepsy (total ASMs prescribed: n = 193). ASM; antiseizure medication. Chi-square ($\chi 2$) test for trend was used.

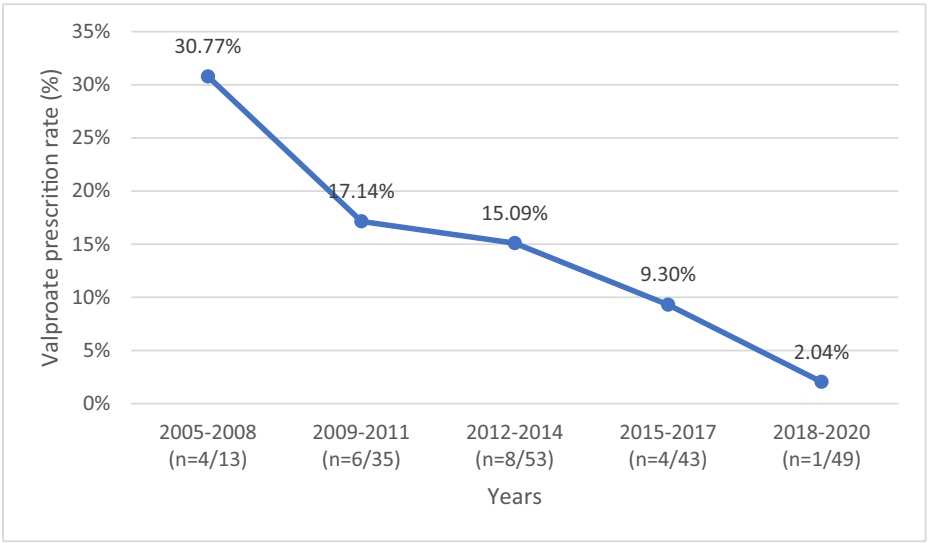


**Fig. 3.** Valproate prescription rate by years from 2005 to 2020 (total valproate prescribed: n = 23/ total ASMs prescribed: n = 193).

**Table 2**
Maternal and delivery complications in women with epilepsy (n = 162).

| | |
|---|---|
| Gestational diabetes | 9 (5.56) |
| Bleeding during pregnancy | 8 (4.94) |
| Pre-mature rupture of membrane | 6 (3.7) |
| Preeclampsia | 6 (3.7) |
| Seizure on day of delivery or during deliver | 6 (3.7) |
| Cervical cerclage | 6 (3.7) |
| Placenta abruption | 3 (1.85) |
| Post-partum hemorrhage | 3 (1.85) |
| Eclampsia | 3 (1.85) |
| Prolong labor | 2 (1.23) |

Data in number (%).

**Table 3**
Association between several factors and maternal complications in women with epilepsy (n = 162).

| | | Maternal complications (n=48) n (%) | P-value |
|---|---|---|---|
| Maternal age (years) | <35 (n = 116) | 34 (29.31) | 1 |
| | ≥35 (n = 46) | 14 (30.43) | |
| Parity | 0 (n = 36) | 11 (30.56) | 1 |
| | ≥1 (n = 126) | 37 (29.36) | |
| Folic acid use during pregnancy | Yes (n = 92) | 29 (31.52) | 0.6044 |
| | No (n = 70) | 19 (27.14) | |
| ASMs use during pregnancy | Yes (n = 132) | 38 (28.78) | 0.6603 |
| | No (n = 30) | 10 (33.33) | |
| Exposure to ASM polytherapy | Yes (n = 47) | 12 (25.5) | 0.5704 |
| | No (n = 115) | 36 (31.3) | |
| Exposure to 1st generation ASMs | Yes (n = 80) | 27 (33.75) | 0.303 |
| | No (n = 82) | 21 (25.6) | |
| Seizure control | Yes (n = 103) | 30 (29.1) | 0.8599 |
| | No (n = 59) | 18 (30.51) | |
| Chronic hypertension | Yes (n = 15) | 4 (26.67) | 1 |
| | No (n = 147) | 44 (29.93) | |
| Chronic diabetes | Yes (n = 9) | 4 (44.44) | 0.4521 |
| | No (n = 153) | 44 (28.76) | |
| Psychiatric comorbidity | Yes (n = 20) | 6 (30) | 1 |
| | No (n = 142) | 42 (29.58) | |
| Other comorbidities | Yes (n = 50) | 10 (20) | 0.0937 |
| | No (n = 112) | 38 (33.93) | |

Fisher's exact test was used.

In this cohort of WWE, the overall prescription rate of ASMs was 81.5%. The prescription rate reported in the presented work was slightly lower than that observed in other national studies. In two hospital-based studies in Saudi Arabia, 88% of pregnant WWE received ASMs (Al Bunyan and Abo-Talib, 1999; AlSheikh, 2020). However, the reported prescription rates varied greatly across studies conducted in other countries. ASMs were used in 34% of pregnant WWE in a population-based study in Norway (Veiby et al., 2009). Furthermore, a study from Taiwan that used national databases found that only 14% of WWE took ASMs during pregnancy (Lin et al., 2009), in contrast, the prescription rate was 91% in a hospital-based study in India (Thomas et al., 2009). The differences in the reported prescription rates across studies may reflect variations in healthcare systems, study designs, and periods of investigation.

In the present study, the prescription rate of ASMs gradually increased during the study period from 68.8% in the first epoch to 93.5% in the fourth epoch. The same pattern was observed in other studies (Bobo et al., 2012; Cohen et al., 2020). In a Norwegian registry, the ASM prescription rate in pregnant WWE increased from 34% in 1999–2005 (Borthen et al., 2009; Veiby et al., 2009) to 38% in 2004–2012 (Danielsson et al., 2018). This is probably due to the increased recognition of the importance of controlling seizures by ASMs during pregnancy to avoid the risks of uncontrolled seizures on mothers and fetuses (Chen et al., 2009; Borthen, 2015; Kusznir Vitturi et al., 2019). The seizure control rate in this study was 63.6%. This was comparable to that in EURAP (European and International Registry of Antiepileptic Drugs and Pregnancy), in which 66.6% of WWE with ASMs remained seizure-free during pregnancy (Battino et al., 2013). Further possible explanations for the increasing prescription rate could include improved knowledge about the safety profiles of ASMs particularly some new ASMs.

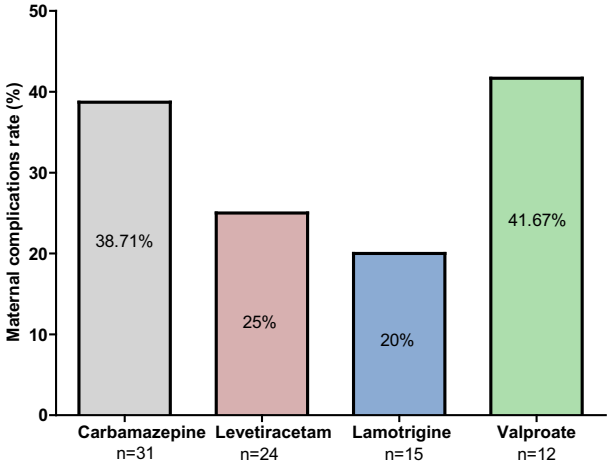


**Fig. 4.** Maternal complication rates of the most commonly prescribed monotherapies. P = 0.4403, Chi-square ($\chi 2$) test was used.

Monotherapy (64.4%) was prescribed more than polytherapy (35.6%) in this cohort of pregnant WWE. The same trend of a high prescription rate of monotherapy was observed in other studies (The EURAP Study Group, 2009; Artama et al., 2013; AlSheikh, 2020). There is indeed consistent evidence that monotherapy is associated with a reduced risks to fetuses, including congenital malformations, compared to polytherapy (Morrow et al., 2006; Artama et al., 2013; Kilic et al., 2014; Thomas et al., 2017). However, data were contradicting regarding the effect of polytherapy on obstetric outcomes (Thomas et al., 2009; Borthen et al., 2011; Yeh et al., 2017; Danielsson et al., 2018; Kusznir Vitturi et al., 2019). In this study, polytherapy was not associated with increased risks of maternal and delivery complications.

Between 2005 and 2020, the use of new ASMs increased significantly from 15.4% to 75.5%, while first generation ASM use decreased during this period. This is in line with other studies that demonstrated a gradual reduction of older ASMs prescription and an increase in newer ASM use in pregnant WWE. A study conducted in Taiwan demonstrated that, between 2004 and 2015, first generation ASM use decreased from 73% to 8% (Yeh et al., 2017). Furthermore, a study from the United States that included 2,405 WWE found that newer ASMs use during pregnancy increased from 21.2% in 2001 to 24.7% in 2007 (Bobo et al., 2012). The EURAP study, which evaluated the use of ASMs between 1999 and 2005 in 4,798 epilepsy pregnancies from 38 countries, showed an increase in newer ASM use (The EURAP Study Group, 2009). The use of lamotrigine particularly increased from 10% before 2001 to 20% after 2003 in EURAP. A similar pattern of a reduction in older ASM prescription and an increase in prescribing of newer ASMs in pregnancy was observed between 1999 and 2007 in the Australian Register of Antiepileptic Drugs in Pregnancy (Vajda et al., 2010). These trends may be explained by the better safety profiles of many newer ASMs. A low risk of major congenital malformation has been observed with new ASMs such as lamotrigine, levetiracetam, and oxcarbazepine (Hernandez-Diaz et al., 2012;

Mawhinney et al., 2013; Campbell et al., 2014; Weston et al., 2016; Tomson et al., 2018). Likewise, the neurodevelopmental risks are low with many ASMs including lamotrigine and levetiracetam (Meador et al., 2009; Shallcross et al., 2011; Bromley et al., 2016; Blotière et al., 2020). However, there is limited evidence of the reproductive risks of other new ASMs.

Over the study period of 2005–2020, valproate prescription in pregnant WWE markedly reduced (from ~ 31% to 2%). This is consistent with the findings of other studies (Vajda et al., 2010; Hurault-Delarue et al., 2019; Cohen et al., 2020). There is indeed robust evidence that valproate has the greatest risks among all ASMs for congenital malformations and for adverse effects on cognition and behavior (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). Therefore, valproate should be avoided, whenever possible, in women who can become pregnant (Tomson et al., 2019).

The rate of maternal and delivery complications in this cohort of WWE was 29.6%; the most frequent was gestational diabetes (5.6%), followed by bleeding during pregnancy (4.9%). Furthermore, preeclampsia and eclampsia were documented in 3.7% and 1.8%, respectively. The rate of complications in this study was lower that documented in other studies. In a study of 220 WWE, the rate of gestational diabetes and hypertensive disorders was 9.1% and 7.7%, respectively (Katz et al., 2006). Additionally, the rate of hypertensive disorders including preeclampsia and eclampsia was 8.9% in a study of 1,778 WWE (Danielsson et al., 2018). With regard to the risks of maternal epilepsy on maternal and delivery outcomes, the data are inconsistent. A large study that included 5,373 births of WWE reported that WWE had higher pregnancy and delivery complications, including preeclampsia, induction of labor, placental abruption, cesarean section, and infection compared to women without epilepsy (Razaz et al., 2017). Furthermore, a systematic review and *meta*-analysis comparing reproductive outcomes of WWE with those without epilepsy from 38 studies conducted in different countries showed that WWE were at increased risk of spontaneous abortion, antepartum and post-partum bleeding, hypertensive conditions, caesarean section, and induction (Viale et al., 2015). On the other hand, several studies found that maternal epilepsy was not significantly associated with most of these complications (Thomas et al., 2009; Borthen et al., 2011).

The association between several factors and the incidence of maternal and delivery complications was examined in the present work. The use of ASMs during pregnancy was not found to be associated with maternal complications. Previous studies showed no increased risk of adverse pregnancy outcomes in WWE on ASMs (Razaz et al., 2017; Danielsson et al., 2018), but this was not confirmed by other studies (Veiby et al., 2009; Borthen et al., 2011; Viale et al., 2015). However, exposure to first generation ASMs, i.e. carbamazepine and valproate, was associated with more adverse pregnancy outcomes than newer ASMs, i.e. levetiracetam and lamotrigine, but this was not statistically significant. This positive but statistically non-significant association was observed in other small studies (Yeh et al., 2017). Additionally, Danielsson et al. (2018) have found that women on valproate were at increased risk of pre-eclampsia, whereas levetiracetam and lamotrigine did not predispose for pre-eclampsia. The statistically non-significant result may be because of the small sample size of the present study, yet the findings may be of clinical significance. This emphasizes the requirement for larger studies to examine and compare the effects of different individual ASMs, particularly newer ASMs, on maternal and pregnancy outcomes.

The lack of a control group, i.e. women without epilepsy, was a limitation of the present study. Therefore, the maternal and delivery outcomes of WWE were not compared to those without epilepsy.

In conclusion, the prescription of ASMs in pregnancy is increasing, possibly due to increased recognition of the importance of controlling seizures by ASMs to avoid the risk of seizures on the mother and fetus. Moreover, the use of new ASMs has increased, which may be explained by the improved safety profiles of many newer ASMs. The rate of maternal and delivery complications was relatively low (~30%), particularly preeclampsia and eclampsia. ASMs use was not found to be associated with these complications. However, exposure to first generation ASMs was potentially associated with increased risk of adverse pregnancy outcomes. Nevertheless, these findings need further confirmation by larger comparative studies.

## CRediT authorship contribution statement

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