Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis

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Summary

Background Antenatal care of women with epilepsy is varied. The association of epilepsy and antiepileptic drug exposure with pregnancy outcomes needs to be quantified to guide management. We did a systematic review and meta-analysis to investigate the association between epilepsy and reproductive outcomes, with or without exposure to antiepileptic drugs.

Methods We searched MEDLINE, Embase, Cochrane, AMED, and CINAHL between Jan 1, 1990, and Jan 21, 2015, with no language or regional restrictions, for observational studies of pregnant women with epilepsy, which assessed the risk of obstetric complications in the antenatal, intrapartum, or postnatal period, and any neonatal complications. We used the Newcastle-Ottawa Scale to assess the methodological quality of the included studies, risk of bias in the selection and comparability of cohorts, and outcome. We assessed the odds of maternal and fetal complications (excluding congenital malformations) by comparing pregnant women with and without epilepsy and undertook subgroup analysis based on antiepileptic drug exposure in women with epilepsy. We summarised the association as odds ratio (OR; 95% CI) using random effects meta-analysis. The PROSPERO ID of this Systematic Review’s protocol is CRD42014007547.

Findings Of 7050 citations identified, 38 studies from low-income and high-income countries met our inclusion criteria (39 articles including 2,837,325 pregnancies). Women with epilepsy versus those without (2,809,984 pregnancies) had increased odds of spontaneous miscarriage (OR 1·54, 95% CI 1·02–2·32; P=0·06), antepartum haemorrhage (1·49, 1·01–2·02; P=0·037), post-partum haemorrhage (1·29, 1·13–1·49; P=0·004), hypertensive disorders (1·37, 1·21–1·55; P=0·01), induction of labour (1·67, 1·31–2·11; P=0·01), caesarean section (1·40, 1·23–1·58; P=0·006), any preterm birth (<37 weeks of gestation: 1·16, 1·01–1·34; P=0·031), and fetal growth restriction (1·26, 1·20–1·33; P=0·001). The odds of early preterm birth, gestational diabetes, fetal death or stillbirth, perinatal death, or admission to neonatal intensive care unit did not differ between women with epilepsy and those without the disorder.

Interpretation A small but significant association of epilepsy, exposure to antiepileptic drugs, and adverse outcomes exists in pregnancy. This increased risk should be taken into account when counselling women with epilepsy.

Funding EBM CONNECT Collaboration.

Introduction Epilepsy is one of the common chronic disorders affecting women of reproductive age. Maternal mortality is ten-times higher in women with epilepsy than in those without the disorder. Care of women with epilepsy is fragmented, with few units providing joint obstetric–epilepsy care. The Confidential Enquiries into Maternal and Child Health in the UK emphasised that epilepsy was not always perceived as a high-risk disorder in pregnancy. Adequate engagement with women with epilepsy is needed during preconception and pregnancy to plan appropriate management.

Quantification of the risks associated with pregnancy in women with epilepsy is essential for appropriate counselling and provision of care. Evidence tends to be focused on fetal harm from in-utero exposure to antiepileptic drugs or on severity of maternal seizures, with less emphasis on other pregnancy outcomes. Individual studies provide varied and imprecise estimates of the association between epilepsy and pregnancy complications such as miscarriage, preterm delivery, antepartum and post-partum bleeding, caesarean section, fetal growth restriction, and admission to neonatal intensive care unit (NICU). Existing guidelines on women with epilepsy have suggested a possible association between epilepsy and pregnancy complications on the basis of a few small studies.

We did a systematic review of medical literature by collating the available evidence to generate precise estimates of the association between epilepsy in pregnancy, with or without exposure to antiepileptic drugs, and reproductive outcomes.

Data collection Search strategy and study selection criteria We followed the present methods recommendations and used a prospective protocol to enable compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting this systematic review.

We searched MEDLINE, Embase, Cochrane, AMED, and CINAHL from Jan 1, 1990, to Jan 21, 2015, without language or regional restrictions, for observational studies of pregnant women with epilepsy, which assessed the risk of obstetric complications in the antenatal, intrapartum, or postnatal period, and any neonatal complications. We used the Newcastle-Ottawa Scale to assess the methodological quality of the included studies, risk of bias in the selection and comparability of cohorts, and outcome. We assessed the odds of maternal and fetal complications (excluding congenital malformations) by comparing pregnant women with and without epilepsy and undertook subgroup analysis based on antiepileptic drug exposure in women with epilepsy. We summarised the association as odds ratio (OR; 95% CI) using random effects meta-analysis. The PROSPERO ID of this Systematic Review’s protocol is CRD42014007547.
Quality assessment and data extraction

We used the Newcastle-Ottawa Scale to assess the methodological quality of the included studies, risk of bias in the selection and comparability of cohorts, and outcome. Two independent reviewers (LV and JA) undertook quality assessment and allocated stars for adherence to the prespecified criteria. Studies that scored four stars for selection, two stars for comparability, and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability, and two for outcome ascertainment were deemed to have a medium risk of bias. Any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains, was deemed to have a high risk of bias.

Data were extracted in duplicate (LV and JA) with predesigned data extraction forms. Dichotomous data were extracted as 2x2 tables and continuous data as means and SDs. We contacted authors of potentially eligible manuscripts by email for relevant data. When the same cohort was reported twice, we extracted data from the most recent study with the largest sample size for relevant outcomes.

Outcomes

The main outcomes were maternal, fetal, and neonatal complications.

Statistical analysis

We compared the odds of maternal and perinatal complications in pregnant women in the following groups: women with epilepsy versus women without epilepsy, antiepileptic drug treatment versus no treatment in women with epilepsy, and antiepileptic drug polytherapy versus monotherapy in women with epilepsy. Pregnancy was the unit of analysis. We reported the results obtained after pooling individual study estimates with a random effects meta-analysis as odds ratio (OR) with 95% CIs. Heterogeneity was assessed with the I² statistic.

We undertook subgroup analyses planned a priori for any differences in the association of epilepsy and pregnancy outcomes based on the following factors: economic status of the country (developed or developing countries according to International Monetary Fund), year of publication (before 2000 or in 2000 and after), study quality (high or low), and proportion of women with epilepsy who were exposed to antiepileptic drugs (<30% or ≥30%). We created funnel plots by plotting the natural logarithm of the ORs against the inverse of the standard error to assess publication and related bias. We statistically checked for the asymmetry of the funnel plot by using Egger’s method. All analyses were done using Revman statistical software and Stata 13.0. The PROSPERO ID of this Systematic Review’s protocol is CRD42014007547.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full responsibility for the decision to submit for publication.

Results

Of the 7050 citations identified, we selected 89 abstracts for detailed assessment (figure 1). 38 studies published in 39 articles, including 2837325 pregnancies, met our inclusion criteria. 31 studies (2809984 pregnancies) provided rates of adverse outcomes for women with epilepsy compared with those without epilepsy.
11 studies (934,443 pregnancies) provided relevant outcome data for pregnant women with epilepsy exposed to antiepileptic drugs compared with those not exposed to antiepileptic drugs, and eight studies (839,380 pregnancies) provided data for women with epilepsy exposed to antiepileptic drug polytherapy compared with those exposed to antiepileptic drug monotherapy. Of the 38 primary studies, 13 studies were prospective and 25 were retrospective. Data were obtained from population-based cohorts in 21 studies and from registry data in 17 studies.

The definition of epilepsy and the type of exposure to antiepileptic drugs varied between the studies. 32 (84%) of the 38 studies included women exposed to antiepileptic drugs such as carbamazepine, topiramate, lamotrigine, valproate, and phenytoin. Very few studies provided rates of maternal and fetal outcomes for the individual drugs. 29 (76%) of the 38 included studies were published after 2000 and 28 (74%) were done in a developed country setting (appendix).

Quality assessment by the Newcastle-Ottawa Scale showed that 23 (61%) of the 38 included studies had low or medium risk of bias (figure 2, appendix). 33 (87%) of the 38 studies had low risk of bias for study selection, one had high risk of bias. For comparability of the cohorts, 15 (40%) studies had low risk, seven (18%) had medium risk, and 16 (42%) had high risk of bias. The risk of bias for outcome assessment was low in 35 (92%) studies, medium in one (3%) study, and high in two (5%) studies.

The odds of the following maternal outcomes were increased in pregnant women with epilepsy compared with those without epilepsy: spontaneous miscarriage, antepartum haemorrhage, post-partum haemorrhage, hypertensive disorders, induction of labour, caesarean section, and any preterm birth before 37 weeks of gestation. No differences were reported between the two groups for early preterm birth or gestational diabetes.

Fetal and neonatal outcomes were assessed in 21 studies. The odds of delivering a baby with fetal growth restriction were increased in women with epilepsy compared with women without epilepsy (figure 3). Other infant outcomes such as fetal death, perinatal death, and admission to the NICU were not increased.

11 studies (934,443 pregnancies) examined the association between antiepileptic drug exposure in pregnant women with epilepsy and maternal and fetal outcomes (figure 4A). The odds of post-partum haemorrhage and induction of labour were significantly higher in pregnant women with epilepsy exposed to antiepileptic drugs compared with those not given drugs. No significant differences were reported.
### Maternal outcomes

<table>
<thead>
<tr>
<th>Studies (n)</th>
<th>Events (n)</th>
<th>Pregnancies (n)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous miscarriage</td>
<td>6</td>
<td>110340</td>
<td>842610</td>
<td>1.54 (1.02–2.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>10</td>
<td>8090</td>
<td>670100</td>
<td>1.49 (1.01–2.20)</td>
<td>0.04</td>
</tr>
<tr>
<td>Post-partum haemorrhage</td>
<td>7</td>
<td>107905</td>
<td>952477</td>
<td>1.29 (1.13–1.49)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Induction of labour</td>
<td>9</td>
<td>67474</td>
<td>473006</td>
<td>1.67 (1.31–2.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>20</td>
<td>162937</td>
<td>1126069</td>
<td>1.40 (1.23–1.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any preterm birth (&lt;37 weeks)</td>
<td>19</td>
<td>100104</td>
<td>1525237</td>
<td>1.16 (1.01–1.34)</td>
<td>0.03</td>
</tr>
<tr>
<td>Early preterm birth (&lt;34 weeks)</td>
<td>3</td>
<td>12392</td>
<td>422421</td>
<td>1.96 (0.97–3.99)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>17</td>
<td>57870</td>
<td>1131629</td>
<td>1.37 (1.21–1.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5</td>
<td>12004</td>
<td>322790</td>
<td>0.99 (0.53–1.83)</td>
<td>0.96</td>
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</tbody>
</table>

### Fetal and neonatal outcomes

<table>
<thead>
<tr>
<th>Studies (n)</th>
<th>Events (n)</th>
<th>Pregnancies (n)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal death or stillbirth</td>
<td>8</td>
<td>4473</td>
<td>569231</td>
<td>1.27 (0.73–2.20)</td>
<td>0.39</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5</td>
<td>2633</td>
<td>261345</td>
<td>1.83 (0.79–4.25)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>18</td>
<td>123386</td>
<td>1508306</td>
<td>1.26 (1.20–1.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission to neonatal intensive care unit</td>
<td>3</td>
<td>37810</td>
<td>411375</td>
<td>1.06 (0.97–1.17)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

### Fetal and neonatal outcomes

<table>
<thead>
<tr>
<th>Studies (n)</th>
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<th>Pregnancies (n)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal death or stillbirth</td>
<td>4</td>
<td>39</td>
<td>3888</td>
<td>0.98 (0.37–2.64)</td>
<td>0.97</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>6</td>
<td>1103</td>
<td>9649</td>
<td>3.51 (1.23–10.01)</td>
<td>0.02</td>
</tr>
<tr>
<td>Admission to neonatal intensive care unit</td>
<td>1</td>
<td>164</td>
<td>2861</td>
<td>1.42 (1.13–1.78)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

### Figure 3: Association between maternal epilepsy diagnosis and adverse maternal and fetal outcomes

- Favours women with epilepsy
- Favours women without epilepsy

### Figure 4: Association between exposure to antiepileptic drugs and pregnancy outcomes

(A) Exposure to antiepileptic drugs versus no exposure. (B) Exposure to antiepileptic drug polytherapy versus monotherapy.
between the two groups for caesarean section, antepartum haemorrhage, spontaneous miscarriage, any preterm births before 37 weeks of gestation, and hypertensive disorders.

No differences were noted between the two groups of women with epilepsy, exposed or not exposed to antiepileptic drugs, for fetal death or stillbirth (figure 4A). Admission to the NICU was reported in one study, which showed an increase in the odds in women exposed to antiepileptic drugs. The odds of fetal growth restriction were significantly higher in pregnant women with epilepsy exposed to antiepileptic drugs than in those not exposed.

Eight studies (839,380 pregnancies) assessed the association between exposure to more than one antiepileptic drug in pregnancy (polytherapy) and maternal and fetal complications, compared with monotherapy (figure 4B). Caesarean section was increased in women given polytherapy compared with those given monotherapy. No differences were noted between the two groups in the odds of induction of labour, any preterm births before 37 weeks of gestation, antepartum haemorrhage, and post-partum haemorrhage.

Polytherapy was not associated with any fetal or neonatal outcomes such as fetal death, admission to the NICU, or fetal growth restriction (figure 4B).

Subgroup analysis based on country economic status, publication year, risk of bias, and proportion of women with epilepsy exposed to antiepileptic drugs did not show significant differences between women with epilepsy and those without epilepsy for caesarean section, antepartum haemorrhage, induction of labour, early preterm births before 34 weeks of gestation, hypertensive disorders, gestational diabetes, and fetal growth restriction (table). Significant differences were reported between the groups based on the risk of bias for admission to the NICU ($p<0.0001$) and any preterm birth before 37 weeks of gestation ($p=0.01$), publication year for post-partum haemorrhage ($p=0.007$), admission to the NICU ($p<0.0001$), and fetal death or stillbirth ($p=0.001$), the country status for perinatal death ($p=0.04$), and exposure to antiepileptic drugs for spontaneous miscarriage ($p=0.002$).
We noted no differences in the odds of any adverse outcome between the subgroups based on risk of bias, country status, or year of publication for exposure to antiepileptic drugs in pregnant women with epilepsy and for polytherapy with antiepileptic drugs (table).

Funnel plot asymmetry was assessed for the outcomes that had at least ten studies. We did not observe evidence of small studies effect for any of the outcomes and epilepsy, except for any preterm birth, which showed a slightly asymmetrical funnel plot (p=0.039; table).

**Discussion**

Our meta-analysis has provided precise quantitative estimates of the magnitude of association between epilepsy in pregnancy, exposure to antiepileptic drugs, and various maternal and fetal outcomes. In pregnant women, a diagnosis of epilepsy is associated with a small but significant increase in adverse pregnancy outcomes such as antepartum and post-partum haemorrhage, spontaneous miscarriage, hypertensive disorders, induction of labour, caesarean section, any preterm birth, and fetal growth restriction. In women with epilepsy, exposure to antiepileptic drugs is associated with an increase in the odds of post-partum haemorrhage, induction of labour, fetal growth restriction, and admission to the NICU. Our review has provided much needed information about epilepsy and obstetric outcomes and will help in the counselling of women with epilepsy and their partners, during the preconceptual and antenatal period.

To our knowledge, our review is the first comprehensive assessment of the association between epilepsy and antiepileptic drug exposure and pregnancy outcomes by meta-analyses. We did a detailed literature search without language restrictions, thereby increasing our potential to capture all relevant studies. The review was done with a prospective protocol, and we prespecified the relevant subgroups to explore the sources of heterogeneity. We assessed study quality in detail and the effect of study quality on the results. We were able to provide results with high precision for epilepsy and outcomes owing to the large sample size.

The studies varied in characteristics of the population; cause of epilepsy; details of antiepileptic drugs therapy such as type, dose, and compliance; and the definition of outcomes. Because of the inconsistency and paucity of reporting, we were unable to explore the effects of seizures, parity, smoking status, congenital abnormalities in the fetus, type and dose of antiepileptic drug, and underlying medical disorders on the results. Fewer studies were published about exposure to antiepileptic drugs than epilepsy and pregnancy outcomes, which contributed to a reduced precision in the findings for this group. Evidence to provide estimates of adverse outcomes for various individual antiepileptic drugs and their dosage is insufficient.

Recommendations for the care of mothers with epilepsy are based on few observational studies. In the UK, the National Institute for Health and Care Excellence guidance reported on the increased risk of preterm delivery, caesarean section, and induction of labour, and no changes in the rates of perinatal deaths in women with epilepsy based on the findings of three individual studies. In the USA, the American Academy of Neurology recommendations have suggested a probable increase in the rates of caesarean section and fetal growth restriction in women with epilepsy and in those exposed to antiepileptic drugs. All guidelines have consistently emphasised the absence of robust evidence in this field.

A diagnosis of epilepsy and exposure to antiepileptic drugs were significantly associated with increased risk of induction of labour and caesarean section. The proportion of women with substantial seizure deterioration needing delivery is too low to account for this occurrence. Many other factors such as the perception of epilepsy as a chronic disease, uncertainty in management, an increase in rates of antepartum haemorrhage, hypertensive disorders and fetal growth restriction, and a low threshold for intervention might have contributed to this rise. The observed increase in hypertensive disorders in pregnant women with epilepsy was consistent with the findings of the individual studies that adjusted for maternal education, smoking, diabetes, underlying medical disorder, and maternal age.

We did not note any association between the presence of epilepsy or antiepileptic drug exposure with fetal and neonatal mortality, despite including pregnancies with congenitally malformed fetuses. The odds will probably be even lower if these pregnancies with congenital malformation of the fetus were excluded. The increased complications such as stillbirth and NICU admission in the pre-2000 published studies could be attributed to the adverse effects of older antiepileptic drugs, improvements in clinical care since then, or to the poor quality of reporting in studies published before 2000.

On the basis of our findings, women with epilepsy, and those given antiepileptic drugs, should be informed that a small but significant risk of obstetric complications can occur. Regular monitoring of pregnant women with epilepsy in the antenatal period is essential for early detection of hypertensive disorders and growth-restricted fetuses.

Prospective studies and registries need to focus on pregnancy outcomes in addition to congenital malformations. Further assessment is needed on the relation between seizure control in pregnancy, individual antiepileptic drugs and their dosage, and pregnancy complications.

Health-care professionals should incorporate the estimates for various reproductive outcomes quantified by our review, when counselling women with epilepsy.
Contributors

ST was involved in the conception of the research question and designed the protocol. JZ and JA did the literature search, study selection, and data extraction, with the help of FC-S. JZ and DA-M did the statistical analysis. The tables, figures, and appendices were designed by JA and IV. The initial drafts of the manuscript were prepared by ST, JA, and IV, with additional input from KSK, DM, and MB. All authors contributed to the drafts and final version of the manuscript.

Declaration of interests

MB reports grants and personal fees from Eisai and personal fees from UCB, outside the submitted work. All other authors declare no competing interests.

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