Variation in the reporting of outcomes among pregnant women with epilepsy: a systematic review

Al Wattar, Bassel H.; Placzek, Anna; Troko, Joy; Pirie, Alexander M.; Khan, Khalid S.; Mccorry, Dougall; Zamora, Javier; Thangaratinam, Shakila

DOI:
10.1016/j.ejogrb.2015.10.017

Title: Variation in the reporting of outcomes among pregnant women with epilepsy: a systematic review

Author: Bassel.H.Al Wattar Anna Placzek Joy Troko Alexander.M. Pirie Khalid.S. Khan Dougall McCorry Javier Zamora Shakila Thangaratinam<ce:collaboration id="colb0005"></ce:collaboration>

PII: S0301-2115(15)00376-0
DOI: http://dx.doi.org/doi:10.1016/j.ejogrb.2015.10.017
Reference: EURO 9166

To appear in: *EURO*

Received date: 18-9-2015
Revised date: 18-10-2015
Accepted date: 20-10-2015

Please cite this article as: Wattar BlHA, Placzek A, Troko J, Pirie ArM, Khan KdS, McCorry D, Zamora J, Thangaratinam S, for the EMPIRE Collaborative Network., Variation in the reporting of outcomes among pregnant women with epilepsy: A systematic review, *European Journal of Obstetrics and Gynecology and Reproductive Biology* (2015), http://dx.doi.org/10.1016/j.ejogrb.2015.10.017

Variation in the reporting of outcomes among pregnant women with epilepsy: A systematic review

Bassel.H.Al Wattar MD,[1]Anna Placzek BA,[1] Joy Troko MBBS,[2] Alexander.M.Pirie FRCOG,[2,3] Khalid.S.Khan MSc,[1,4] Dougall McCorry MD,[3] Javier Zamora PhD,[1] Shakila Thangaratinam PhD,[1,4] for the EMPIRE Collaborative Network.

[1]Women's Health Research Unit, Barts and the London School of Medicine, Queen Mary University London, London, UK

[2]Birmingham Women's Hospital, Mindelsohn Way, Birmingham, UK

[3]University of Birmingham, Birmingham, UK

[4]Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and the London School of Medicine, Queen Mary University London, London, UK

Corresponding Author:

Professor Khalid Khan

Barts and the London School of Medicine and Dentistry

Queen Mary University London, London

E-Mail: k.s.khan@qmul.ac.uk

Condensation:

There is large variations in outcomes reporting in clinical studies on pregnant women with epilepsy; there is need to identify a set of core outcome to harmonise reporting in future clinical studies.

Abstract:

Studies on pregnant women with epilepsy should evaluate both neurological and pregnancy outcomes. We undertook a systematic review of the literature of studies on pregnant women with epilepsy to collate the outcomes reported, and the quality of outcomes report in these studies.

We searched major electronic databases (from 1999 until January 2015). Two independent reviewers selected studies and extracted data on study design, the risk of bias of the studies, journal impact factor and the quality of reported outcomes. We assessed the quality outcomes report using a six items standardised tool (score range 0-6).

There were 70 different outcomes reported in 232 studies (maternal neurological (13/70, 19%), fetal and neonatal (28/70, 40%), and obstetric outcomes (29/70, 41%)). Most studies reported on major congenital fetal abnormalities (103/232, 44%), followed by live birth (60/232, 26%). Quality of the reported outcomes was poor (mean 1·54, SD 1·36). It was associated with journal impact factor (p=0·007), but not with study design (p=0·60), or risk of bias (p=0·17).

The outcomes reported in studies on pregnant women with epilepsy varied widely, and the quality of the outcomes report was poor. There is a need to identify a set of core outcome to harmonise reporting in future clinical studies.

Key words: Epilepsy, pregnancy, maternal, fetal, neurological, outcomes.

Introduction

Epilepsy in pregnancy is one of the major contributory factors to maternal morbidity and mortality.(1,2) About a third of women with epilepsy experience seizure deterioration in pregnancy. (3) Often they are exposed to anti-epileptic drugs (AED) before and during pregnancy. Both uncontrolled seizures, and exposure to AEDs contribute to maternal complications (4), and adverse offspring outcomes. (5)

Existing studies on epilepsy in pregnancy tend to focus on evaluation of fetal and childhood outcomes related to AED exposure.(6) The proportion of studies that report on important and clinically relevant outcome such as seizure control in pregnancy, and obstetric complications is not known. Given the relative rarity of epilepsy as a pre-existing medical condition in pregnancy, we can ill afford heterogeneity in reported outcomes. Standardised and consistent reporting leads to meaningful evidence synthesis. Identifying gaps in outcome reporting is crucial to adequately plan future studies.
Before standardising core outcome sets for studies on pregnant women with epilepsy, there is a need to map the various outcomes reported in primary studies. We undertook a systematic review to assess the range and the quality of the outcomes reported in clinical studies on pregnant women with epilepsy.

Material and methods:

We undertook a systematic review in line with current recommendations using a prospective protocol (7), and reported to comply with PRISMA guidelines (Appendix 1).

Literature search:

We searched major electronic databases MEDLINE, Embase, CINAHL, AMED and Cochrane Library (1999-January 2015) for studies on women with epilepsy. We combined the Mesh terms for "pregnancy", "anti-epileptic drugs", and "epilepsy" using the Boolean operators AND or OR as appropriate (Appendix 2). There were no language restrictions. We manually searched the bibliographies of relevant articles to identify papers that were not captured by electronic searches. We contacted the authors for additional data where required.

Study selection:

Two independent reviewers (BHA and JT) selected the studies. We screened the abstracts and obtained the full copies of all relevant articles. Then, we evaluated the retrieved manuscripts in detail to identify studies that may be eligible for inclusion. Any discrepancies were resolved by discussion with a third reviewer (ST). We excluded studies on non-pregnant population, only on pharmacodynamics of AEDs, surveys, case series, case reports, and animal studies.

Quality assessment of the included studies:

Two independent reviewers (BHA and JT) assessed the risk of bias in the included studies using the Newcastle-Ottawa Scale (8) for study selection, comparability and outcome assessment. The studies were allocated stars according to the rating. A study was awarded a maximum of four stars for selection, two for comparability, and three for ascertainment of exposure. Studies were considered to have a low risk of bias if they scored 4 stars for selection, 2 stars for comparability, and 3 stars for assessment of outcomes (8). Studies with only 1 or no stars for selection, comparability, or outcome assessment were considered to have high risk of bias. The risk of bias was considered to be medium in studies with 2 or 3 stars for selection, 2 or 1 for comparability, and 2 stars for outcome assessment. For

randomised studies we planned to assess the risk of bias using the Cochrane risk of bias assessment tool.(9)

Quality assessment of reported outcomes:

We assessed the quality of the outcomes reported using a standardised six items tool.(10) One point was awarded if each of the following items were met: primary outcome stated; clearly defined primary outcome; authors stated whether there were any secondary outcomes; clearly defined secondary outcomes; authors stated the rationale for choosing the reported outcomes; methods were used to enhance the quality of outcomes measurement such as the repeating measures or training in the use of measurement tools. A maximum score of 6 could be awarded for a study. We considered a score above 4 to be of high quality, 2 to 4 as moderate quality, and less than 2 as low quality.

Data extraction and analysis:

Two independent reviewers (BHA, JT) extracted data on study design (cohort studies, case control studies, and randomised controlled trials), the outcomes reported, country of the study, type of journal (general vs. specialist), impact factor of the journal, and year of publication using pre-designed forms. Journals with an impact factor above the 95th percentile of all included studies were considered to have high impact.

We categorised the reported outcomes into three main domains: Maternal neurological, obstetric, and fetal and neonatal outcomes. We grouped similar outcomes together, and estimated the proportion of these grouped outcomes that were reported in each domain. In the maternal neurological domain, outcomes related to AED such frequency of AED use in pregnancy, AED serum levels, and AED maternal toxicity were categorised as AED related

outcomes; and postnatal depression and psychosis were grouped as mental health related outcomes. In the fetal and neonatal domain, outcomes such as birth weight, neonatal height, and head circumference were categorised as anthropometric outcomes; and neonatal conditions such as acute respiratory distress syndrome, hypotonia, feeding problems, and hypoglycemia as neonatal clinical complications. In the obstetric domain, pregnancy viability outcomes included live birth, miscarriage, ectopic pregnancy, and termination; pregnancy specific complications included pre eclampsia and gestational diabetes; and placenta praevia and accreta were grouped as placental abnormalities.

We estimated the rates of reporting for various outcome categories in each domain, and also for individual outcomes. Due to the variation in reported outcomes, we refrained from summarising the overall rates. We used the Mann-Whitney test to determine the significance of comparative statistics for non-parametric data. Multiple linear regression analysis was done to assess the association between the quality of outcomes' report and the journal impact factor, and the risk of bias. We did not assess publication bias, as it was not appropriate. All analyses were undertaken in Microsoft Excel and SPSS (Version 20.0. Armonk, NY: IBM Corp).

Results

From 482 potentially relevant citations, we included 232 studies in our review, Figure (1), Appendix (3). Nine studies were excluded due to inappropriate study design (2 focus groups, 6 surveys, 1 case report) and 241 studies did not report primary data in a pregnant population.

Study characteristics and risk of bias:

All the included studies were observational in design. Over 80% were cohort studies (218/232, 94%), of which 171(78%) were prospective and 47 (22%) were retrospective cohorts. Only six per cent (14/232) were case-control studies. The majority of the studies were conducted in mainland Europe (120/232, 52%) followed by the USA (41/232, 18%) and the UK (35/232, 15%). Countries from Asia (31/232, 13%) and South America (8/232, 3%) published the least number of studies in this field. Nine tenth of all studies (209/232, 90%) were published in specialist journals, and only a tenth (23/232, 10%) were published in general medical journals. Less than 5% of studies (11/232) were published in journals with high impact factor.

The mean star rating for the risk of bias assessment using the Newcastle-Ottawa Scale was 4·7 (SD 2·0) out of a maximum of nine stars. Over half of the included studies had a medium risk of selection bias (131/232, 56%) and a quarter had low risk of selection bias (61/232, 26%) (Figure 2). The risk of comparability bias was high in half of the studies (117/232, 50%) and medium in a third (75/232, 32%) of studies. More than half of the included studies had high risk of outcome assessment bias (130/232, 56%), and a quarter had a medium risk (52/232, 22%).

Variation in the reported outcomes:

Overall, 70 different individual outcomes were reported in 232 clinical studies on pregnant women with epilepsy (Figure 3, Table 1). The studies reported 13 different categories of maternal neurological, 29 obstetric, and 28 fetal and neonatal outcomes. AED related outcomes (70/232, 30%) were the most commonly reported from maternal neurological domain, followed by seizure control in 24% of studies (55/232). About 80% of all studies reported on congenital abnormality in the baby (189/232), followed by newborn

anthropometric outcomes (102/232, 44%). Outcomes related to viability of pregnancy (137/232, 59%) were frequently reported from the obstetric domains.

Seizure control in pregnancy was the most commonly reported individual neurological outcome (56/232, 24%), followed by the rate of AED use (53/232, 23%). All other neurological outcomes were reported in less of 5% of all included studies. A quarter of studies reported live birth rates (60/232, 26%), the most commonly reported obstetric outcome, followed by pre term birth (42/232, 18%). Mode of delivery, miscarriage and termination of pregnancy were reported in about 15%, and other obstetric outcomes were reported in less than 10% of all studies. In the newborn, major and minor congenital abnormalities were the most commonly reported individual outcomes in 44% (103/232) and 36% (86/232) of studies. A fifth of studies evaluated birth weight (46/232), stillbirth (41/232) and neurodevelopment of the offspring (49/232), and 13% reported on intra uterine growth restriction (31/232). Neonatal mortality and admission to NICU (neonatal intensive care unit) were reported in less than 5% of the all studies.

Quality of the reported outcomes:

The mean quality of the reported outcomes across all studies was 1.5 (SD 1·4). Primary outcomes were not stated in two third (148/232, 64%) of the studies, and not clearly defined in three quarter (171/232, 74%) of them (Figure 4). Secondary outcomes were not stated in over 95% of the studies (222/232, 96%) and clear definitions of secondary outcomes were absent in 97% of them (225/232).The authors did not explain the use of the reported outcomes in three quarter (171/232, 74%) of the studies and no methods were used to enhance the quality of measuring outcomes in 41% (96/232).

There were no differences in the mean scores for outcome reporting quality for cohort and case control studies (p=0·60), and for prospective and retrospective cohort studies (p=0·24). Multiple linear regression analysis showed a significant association between the outcome reporting quality and the impact factor of the journal (β= 0.037, SE= 0.014, p= 0.007). There was no association between the quality of the studies and the outcome reporting quality (β= -0.059, SE= 0.043, p= 0.17).

Comments:

Studies on pregnant women with epilepsy have not employed randomisation, have a high risk of bias, and vary widely in the reporting of outcomes. They focus on fetal and neonatal outcomes, particularly on congenital abnormalities and viability of pregnancy, with less focus on other clinical outcomes.

Our review is the first to look at the outcomes reported in clinical studies on pregnant women with epilepsy. We used a structured comprehensive search strategy with no language restrictions. Although we aimed to capture all relevant outcomes, it is possible that studies in non-Medline indexed journals may have not been captured. We assessed the methodological quality of all included studies, and used a well-defined standardised tool to evaluate the quality of the outcomes reported (10). We categorised outcomes into three relevant domains and estimated the frequency of grouped and individual outcomes.

Assessment of risk related to congenital abnormalities appears to be the main focus in most studies. Given the significance of this finding, relative ease of obtaining relevant data, and growing evidence on association of AED and epilepsy, and congenital abnormalities, most studies have reported this finding. National and international registries appear to be the main

source for these outcomes. Anthropometric outcomes such as the birth weight of the newborn have also been widely reported, possibly due to the easy availability of such data. Despite uncontrolled seizures being the main contributor of maternal deaths in women with epilepsy, seizure related outcomes were evaluated in less than half of the studies. Furthermore, there is wide variation in the measurement of seizure deterioration in pregnancy, with no validated tool for use in pregnancy. Very few studies assessed or reported obstetric outcomes such as pre term birth, pregnancy related complications, and mode of delivery. Although women with epilepsy, particularly those on AED, are at increased risk of depression, mental health related outcomes were not the main focus in most studies.

Most of the outcomes reported appeared to be driven by clinicians, and very few were patient oriented, such as quality of life. Few studies evaluated the effect of epilepsy and AED exposure on symptoms and functional ability of the mother in pregnancy and afterwards. Involvement of patients in the study design may have resulted in the inclusion of above outcomes in studies. The input from research groups that are founded to collect evidence on Patient-Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) (11) may improve the current situation.

Identifying a set of core outcomes for assessment in studies on pregnant women with epilepsy will allow studies to focus on those outcomes that are considered to be clinically relevant to both healthcare professionals and patients. Furthermore, it will facilitate robust evidence synthesis for key outcomes. Any effort to generate a set of core outcomes for clinical trials on pregnant women with epilepsy requires a consensus between different stakeholders involved in the management of epilepsy in pregnancy such as obstetricians, specialist midwives, neurologists, epilepsy nurses, neonatologists, and patient representatives. This will provide

guidance for future researchers to evaluate outcomes that are relevant to clinical practice, but less reported in the literature. Internationally the COMET (12) and The CROWN (13) initiatives have reemphasised the importance of developing core outcome sets for clinical studies. Such endeavour requires active engagement between healthcare professionals, researchers, policy makers, and patients using a robust consensus methodology. (13)

Our work has highlighted the wide variation in outcomes that are currently reported, and their poor quality in clinical studies on pregnant women with epilepsy. Development of a core outcome set to be minimally reported will address the current deficiencies.

Acknowledgment:

None

Role of the funding source:

We received funding from NIHR HTA (No. 09/55/38) to identify clinically important outcomes to be reported in clinical studies on epilepsy in pregnancy. This work was undertaken as part of the on-going EMPIRE trial (Antiepileptic drug (AED) management in Pregnancy: An evaluation of effectiveness, cost effectiveness and acceptability of dose adjustment strategies). The funders did not play a role in the planning and execution of this work or in drafting of the manuscript.

Declaration of interests

All authors disclose no conflict of interest.

Authors' contribution:

ST conceived the idea for the paper, and gave input into all stages of the manuscript. BW wrote the first manuscript, JZ undertook the analysis. All authors provided critical input into the manuscript.

References:

1. Freedman RL, Lucas DN. MBRRACE-UK: Saving Lives, Improving Mothers' Care–implications for anaesthetists. Int J Obstet Anesth. Elsevier; 2015;24(2):161–73.

2. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJE. Saving Lives, Improving Mothers' Care Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-2012. University of Oxford; 2014;

3. Battino D, Tomson T, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. Epilepsia. United States; 2013 Sep;54(9):1621–7.

4. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Lancet Neurol. Elsevier; 2012;11(9):803–13.

5. Shorvon SD, Adab N, Kini U, Vinten J, Ayres J, Baker G, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. England: BMJ Publishing Group Ltd; 2004 Nov;75(11):1575–83.

6. Fatemeh M, Nazanin EB. Pregnancy complications and outcomes in women with epilepsy. Open J Obstet Gynecol. Scientific Research Publishing; 2012;2:230.

7. Comet-initiative. Defining core outcomes for clinical trials in pregnant women with epilepsy (E-core): A Delphi surveyle. 2013.

8. Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.

9. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. 2008.

10. Harman NL, Bruce IA, Callery P, Tierney S, Sharif MO, O'Brien K, et al. MOMENT–Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. Trials. BioMed Central Ltd; 2013;14(1):70.

11. University of Oxford. Patient-reported outcome measures group. (http://phi.uhce.ox.ac.uk/). Accessed online 18/09/2015

12. Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) initiative: its role in improving cochrane reviews. Cochrane Database Syst Rev. 2012;5:ED000041.

13. Khan, Khalid, and Peter O'Donovan. "The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health." *BMC pregnancy and childbirth* 14.1 (2014): 199.

Condensation:

There is large variations in outcomes reporting in clinical studies on pregnant women with epilepsy; there is need to identify a set of core outcome to harmonise reporting in future clinical studies.

Table (1): Frequency of reported individual maternal neurological, obstetric, fetal and neonatal outcomes in 232 studies on pregnant women with epilepsy

Maternal neurological outcomes	No. of studies (n)	% (n/N)	Obstetric outcomes	No. of studies (n)	% (n/N)	Fetal and neonatal outcomes	No. of studies (n)	% (n/N)
Seizure control in pregnancy	56	24.1%	Live birth[3]	60	25.9%	Major congenital abnormalities[8]	103	44.4%
AED use in pregnancy[1]	53	22.8%	Preterm birth[6]	42	18.1%	Minor congenital abnormalities[8]	86	36.6%
AED serum levels[1]	7	3.0%	Miscarriage[3]	39	16.8%	Neurodevelopment of offspring	49	21.1%
Folic acid intake in pregnancy	6	2.6%	Termination of pregnancy[3]	36	15.5%	Birth weight[9]	46	19.8%
Postnatal depression[2]	6	2.6%	Mode of delivery	35	15.1%	Stillbirth[10]	44	19.0%
AED compliance in pregnancy[1]	5	2.2%	Pre-eclampsia[4]	18	7.8%	Intra-uterine growth restriction[9]	31	13.4%
AED maternal toxicity[1]	4	1.7%	Pregnancy induced hypertension[4]	13	5.6%	Apgar scores	25	10.8%
Anxiety[2]	2	0.9%	Vaginal bleeding[4]	10	4.3%	Neonatal head circumference[9]	12	5.2%
Eating disorders[2]	1	0.4%	Induction of labour	9	3.9%	Neonatal height[9]	12	5.2%
Fear of Child birth[2]	1	0.4%	Postpartum haemorrhage[4]	9	3.9%	Admission to neonatal intensive care unit	9	3.9%
Quality of life	1	0.4%	Placental abruption[5]	7	3.0%	Fetal distress	8	3.4%
Sudden unexpected death in epilepsy	1	0.4%	Placenta previa[5]	7	3.0%	Neonatal death[10]	7	3.0%
Postpartum psychosis[2]	1	0.4%	Gestational diabetes[4]	6	2.6%	Neonatal haemorrhagic disease[11]	7	3.0%
			Premature rupture of membrane[6]	6	2.6%	Neonatal withdrawal syndrome[11]	6	2.6%
			Hyperemesis gravidarium[4]	3	1.3%	Acute respiratory distress syndrome in neonates[11]	4	1.7%
			Breech presentation	3	1.3%	Neonatal anaemia[11]	4	1.7%
			Eclampsia[4]	3	1.3%	Autism spectrum disorder[12]	3	1.3%
			Polyhydramnios[7]	3	1.3%	Neonatal icterus/convulsions[11]	2	0.9%
			Urinary tract infection[4]	3	1.3%	Attention deficit hyperactivity disorder[12]	1	0.4%
			Ectopic pregnancy[3]	2	0.9%	Fetal anti convulsant syndrome	1	0.4%
			Blood transfusion	2	0.9%	AED cord levels	1	0.4%
			Oligohydramnios[7]	2	0.9%	Cephalheamatoma[11]	1	0.4%
			Perineal tears[4]	2	0.9%	Feeding problems[11]	1	0.4%
			Antepartum haemorrhage[4]	1	0.4%	Neonatal hyperglycemia[11]	1	0.4%
			Endometriosis in pregnancy	1	0.4%	Neonatal hypoglycemia[11]	1	0.4%
			Maternal mortality	1	0.4%	Neonatal hypocalcemia[11]	1	0.4%
			Placental retention[5]	1	0.4%	Neonatal hypotonia[11]	1	0.4%
			Prolonged labour	1	0.4%	Sedation syndrome[11]	1	0.4%
			Twin Pregnancy	1	0.4%			

[1] AED related outcomes; [2]Mental health; [3] Viability of pregnancy; [4]Pregnancy related clinical complications; [5]Placental abnormalities; [6]Pre term birth; [7]Amniotic fluid abnormalities; [8]Congenital abnormalities; [9]Anthropometric outcomes; [10]Perinatal mortality; [11]Neonatal clinical complications; [12]Autism spectrum disorder

Table (1): Frequency of reported individual maternal neurological, obstetric, fetal and neonatal outcomes in 232 studies on pregnant women with epilepsy

Maternal neurological outcomes	No. of studies (n)	% (n/N)	Obstetric outcomes	No. of studies (n)	% (n/N)	Fetal and neonatal outcomes	No. of studies (n)	% (n/N)
Seizure control in pregnancy	56	24.1%	Live birth[3]	60	25.9%	Major congenital abnormalities[8]	103	44.4%
AED use in pregnancy[1]	53	22.8%	Preterm birth[6]	42	18.1%	Minor congenital abnormalities[8]	86	36.6%
AED serum levels[1]	7	3.0%	Miscarriage[3]	39	16.8%	Neurodevelopment of offspring	49	21.1%
Folic acid intake in pregnancy	6	2.6%	Termination of pregnancy[3]	36	15.5%	Birth weight[9]	46	19.8%
Postnatal depression[2]	6	2.6%	Mode of delivery	35	15.1%	Stillbirth[10]	44	19.0%
AED compliance in pregnancy[1]	5	2.2%	Pre-eclampsia[4]	18	7.8%	Intra-uterine growth restriction[9]	31	13.4%
AED maternal toxicity[1]	4	1.7%	Pregnancy induced hypertension[4]	13	5.6%	Apgar scores	25	10.8%
Anxiety[2]	2	0.9%	Vaginal bleeding[4]	10	4.3%	Neonatal head circumference[9]	12	5.2%
Eating disorders[2]	1	0.4%	Induction of labour	9	3.9%	Neonatal height[9]	12	5.2%
Fear of Child birth[2]	1	0.4%	Postpartum haemorrhage[4]	9	3.9%	Admission to neonatal intensive care unit	9	3.9%
Quality of life	1	0.4%	Placental abruption[5]	7	3.0%	Fetal distress	8	3.4%
Sudden unexpected death in epilepsy	1	0.4%	Placenta previa[5]	7	3.0%	Neonatal death[10]	7	3.0%
Postpartum psychosis[2]	1	0.4%	Gestational diabetes[4]	6	2.6%	Neonatal haemorrhagic disease[11]	7	3.0%
			Premature rupture of membrane[6]	6	2.6%	Neonatal withdrawal syndrome[11]	6	2.6%
			Hyperemesis gravidarium[4]	3	1.3%	Acute respiratory distress syndrome in neonates[11]	4	1.7%
			Breech presentation	3	1.3%	Neonatal anaemia[11]	4	1.7%
			Eclampsia[4]	3	1.3%	Autism spectrum disorder[12]	3	1.3%
			Polyhydramnios[7]	3	1.3%	Neonatal icterus/convulsions[11]	2	0.9%
			Urinary tract infection[4]	3	1.3%	Attention deficit hyperactivity disorder[12]	1	0.4%
			Ectopic pregnancy[3]	2	0.9%	Fetal anti convulsant syndrome	1	0.4%
			Blood transfusion	2	0.9%	AED cord levels	1	0.4%
			Oligohydramnios[7]	2	0.9%	Cephalheamatoma[11]	1	0.4%
			Perineal tears[4]	2	0.9%	Feeding problems[11]	1	0.4%
			Antepartum haemorrhage[4]	1	0.4%	Neonatal hyperglycemia[11]	1	0.4%
			Endometriosis in pregnancy	1	0.4%	Neonatal hypoglycemia[11]	1	0.4%
			Maternal mortality	1	0.4%	Neonatal hypocalcemia[11]	1	0.4%
			Placental retention[5]	1	0.4%	Neonatal hypotonia[11]	1	0.4%
			Prolonged labour	1	0.4%	Sedation syndrome[11]	1	0.4%
			Twin Pregnancy	1	0.4%			

[1] AED related outcomes; [2]Mental health; [3] Viability of pregnancy; [4]Pregnancy related clinical complications; [5]Placental abnormalities; [6]Pre term birth; [7]Amniotic fluid abnormalities; [8]Congenital abnormalities; [9]Anthropometric outcomes; [10]Perinatal mortality; [11]Neonatal clinical complications; [12]Autism spectrum disorder

Figure (1): Study identification and selection process in the systematic review of variation in outcomes reported in studies on pregnant women with epilepsy

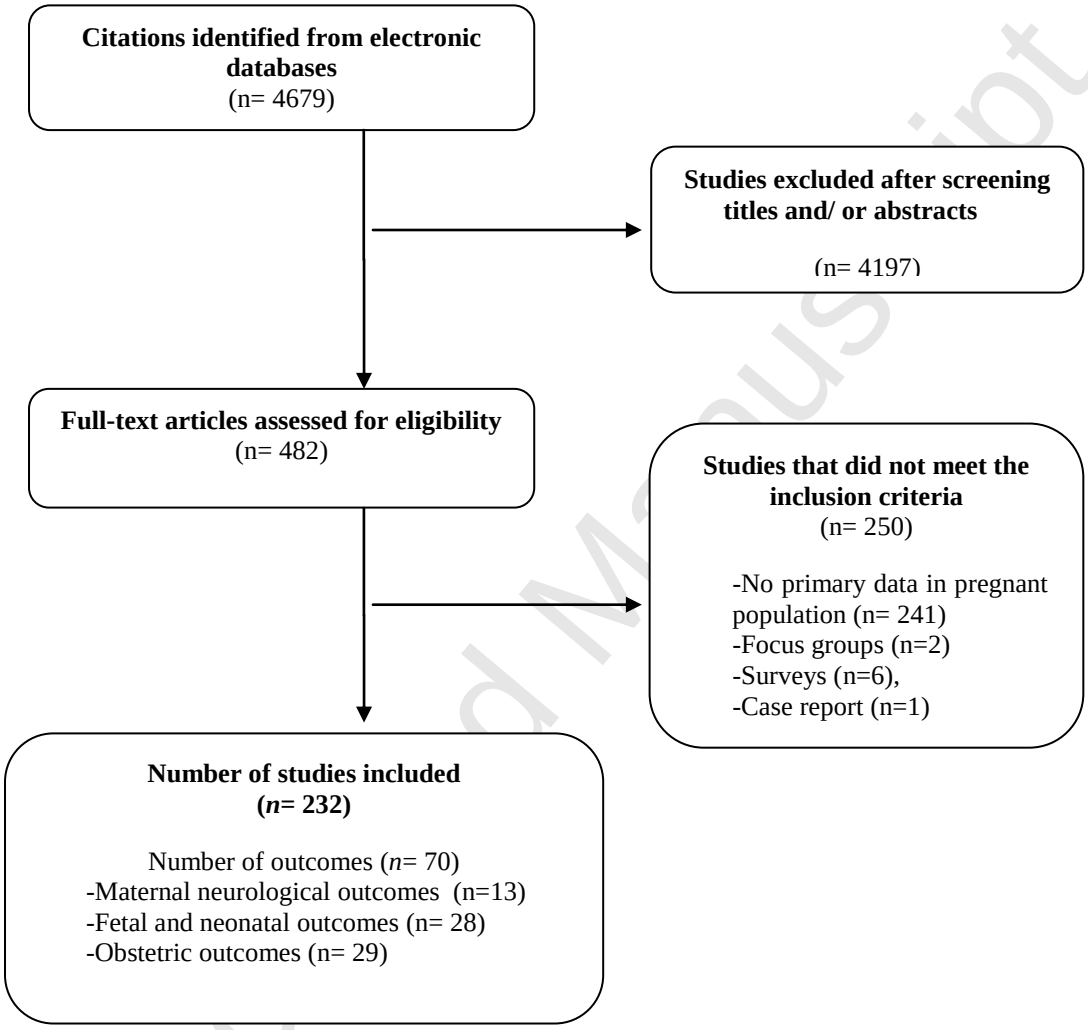


Figure (2): Risk of bias in studies of pregnant women with epilepsy assessedusing the Newcastle-Ottawa Scale

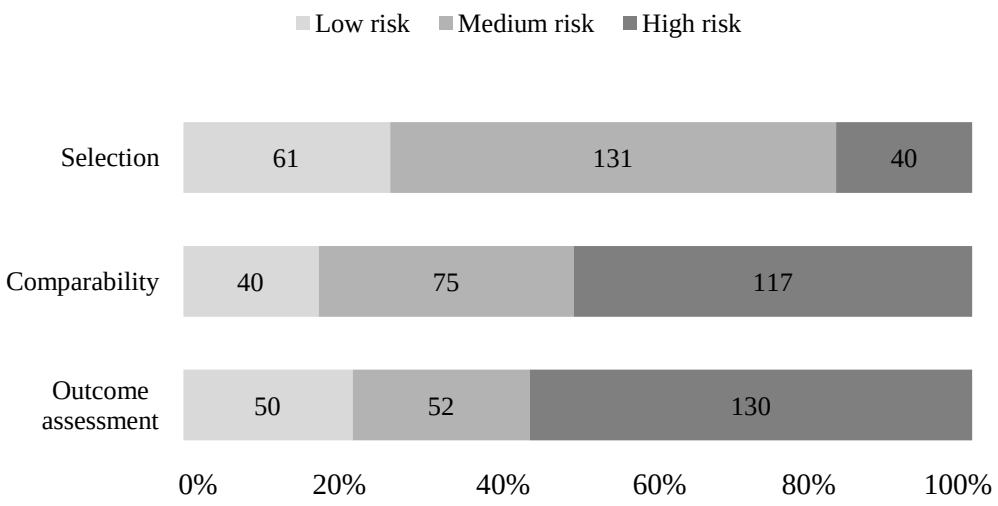
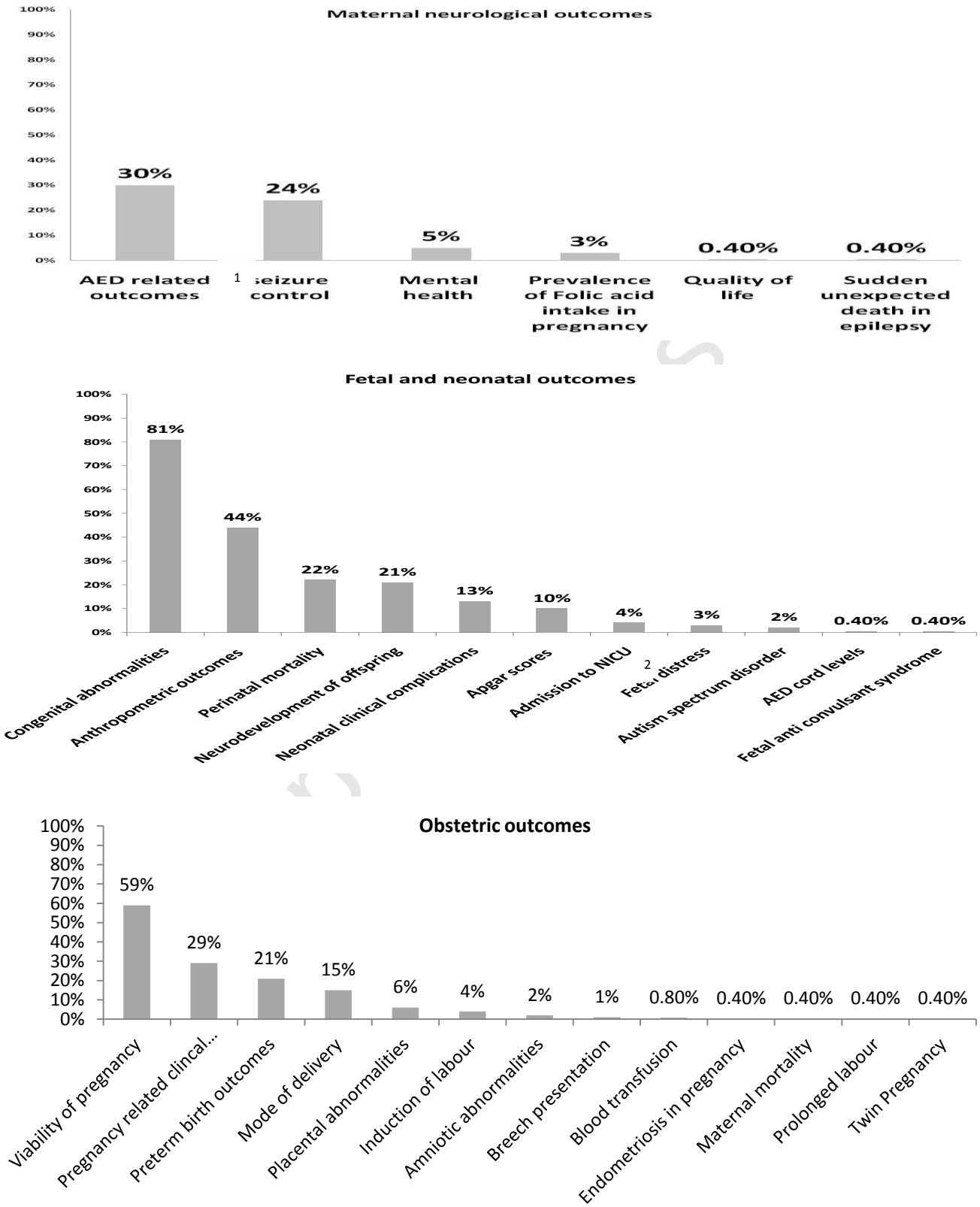


Figure (3): Frequency of reported outcomes in studies of pregnant women with epilepsy



[1]AED: Anti epileptic drug
[2]NICU: Neonatal intensive care unit

Figure (4): Quality of outcomes report in studies on pregnant women with epilepsy