Antiepileptic Drug Exposure during Pregnancy and Neonatal Birth Weight Outcomes: Protocol for a Systematic Review and Meta-analysis.

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Protocol

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Abstract

Background: The prevalence of epilepsy in pregnant women is estimated at 0.3- 1%. Antiepileptic drug (AED) exposure in-utero has been associated with various adverse health outcomes in neonates including adverse birth weight outcomes.

Methods: To summarize the evidence on the association between AED exposure in pregnancy and adverse birthweight outcomes. Studies assessing AED exposure in pregnancy and neonatal birth weight outcome including small for gestational age (SGA), low birth weight (LBW), birth weight (BW), length head circumference and cephalization index will be identified in MEDLINE, EMBASE, Cochrane Library, Scopus, CINAHL, IPA, and Global Health. Open grey, Theses Canada and ProQuest Dissertations will be used to locate grey literature. Eligible study designs include experimental and observational studies. Studies will be assessed for risk of bias using the Newcastle-Ottawa Scale and Meta-analysis will be conducted using a random-effects model.

Discussion: The results from this review could improve clinicians' prescribing decisions by highlighting the safest AEDs for women who are pregnant or planning to conceive based on the best evidence currently available.

Systematic review registration: submitted (19/08/2020))

Background

Epilepsy is a neurological condition that affects 50 million people worldwide.(1) The prevalence of epilepsy in pregnant women is estimated at 0.3- 1%.(2, 3) Antiepileptic drug (AED) exposure in-utero has been associated with various adverse health outcomes in neonates including congenital malformations, intrauterine growth restriction, neurological complications, and adverse birth weight outcomes.(4–7) Previous reports suggested that any AED exposure during pregnancy is associated with an increased risk of infants having a low birth weight (LBW) and being small for gestational age (SGA).(5, 8, 9) Infants with adverse birth weight outcomes like SGA are at a higher risk of stillbirth, impaired thermoregulation, and hypoglycemia at birth. Studies have also linked SGA with various long term health outcomes, including impaired neurodevelopment throughout childhood, as well as cardiovascular diseases and diabetes in adulthood.(10–15) The safety profile of AED varies based on the molecule, generation/class, and dose used. (16),(17) Evidence on the perinatal risk of old generation AED is relatively established when compared to new generation AED.(17) First-generation AEDs have been strongly associated with SGA compared to new generation AEDs; specifically, valproic acid exposure which has been associated with increased risk of SGA, whereas lamotrigine is believed to be comparatively safe.(16),(17)

Systematic reviews summarizing the published evidence on AEDs safety in pregnancy have mainly focused on malformations, and neurological outcomes, while birth weight outcomes were included as secondary outcomes. A limited number of systematic reviews had adverse birth weight outcomes as their primary focus.(18, 19) These studies show various methodological limitations. A recently published

systematic review by Chen et al. used fetal growth retardation (FGR) interchangeably with SGA for the definition of infants with > 10th percentile of the same gestational age. Using FGR as a substitute for SGA might have potentially excluded some of the studies which used SGA exclusively in the manuscripts.(19) Other published reviews are at least two decades old (Christian et al. 2000).(18) Moreover, several original reports were published on new generation AEDs in the past 20 years, hence the need for an up-to-date review to summarize and evaluate the risks involved with the use of AEDs in pregnancy, specifically adverse birth weight outcomes.

Objective

The objective of this systematic review will be to summarize the evidence on the association between AED exposure during pregnancy and neonatal birth weight outcomes.

Methods/design

A systematic review protocol was developed and submitted for registration in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) on 19/08/2020. Preparation of our systematic review protocol was done following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) checklist.(20,21)

Eligibility criteria

Inclusion criteria

This systematic review will include articles regarding pregnant women exposed to AEDs. No restrictions will be applied in terms of the comparison group, as we will include studies on women with epilepsy (WWE) on AED (active comparison), WWE not on AED, women without epilepsy (WWOE) on AED, and WWOE not on AED. Study designs that will be included in the review include experimental studies (RCTs and quasi-RCTs), observational studies (e.g. cohort and case-control), and grey literature (thesis and dissertations). Only studies published in English and French will be considered.

Exclusion criteria

Studies that include intrauterine growth restriction (IUGR) as an outcome but do not include any of the birth weight outcomes detailed below will be excluded. Studies with AEDs given exclusively to infants and not mothers during pregnancy will be excluded. Animal studies, studies containing no original research or data (e.g., reviews), conference abstracts, case reports, case series, and editorial letters will not be included. Studies that fulfill our eligibility criteria (Additional file 1) will be included in the review.

Outcome measures

Primary outcomes for this systematic review include:

a. Small for gestational age (SGA): A birth weight classified as small for gestational age within the study or when SGA is not named explicitly but defined as Infants ≤10th percentile in birth weight, based on birth weight, gestational age.
b. Low birth weight (LBW): A birth weight classified as low birth weight as defined within the study or birth weight less than 2500 grams (g).
c. Birth weight (BW): weight at birth in grams (g).

Secondary outcomes include head circumference, cephalization index, and birth length (height) defined as:

a. Head circumference: Head circumference at birth in centimeters (cm).
b. Length: Height of the infant in centimeters (cm),
c. Cephalization index: Ratio of the head circumference (HC) to body weight.

Studies that report any of the outcomes above with different terminology (e.g.,, neonatal growth restriction or intrauterine growth restriction to substitute for SGA) will be reclassified according to the definitions specified above.

Information sources and literature search

A systematic search strategy was developed with the assistance of a librarian (MLL). We will search MEDLINE, EMBASE, Cochrane Library, Scopus, CINAHL, IPA, and Global Health. See Additional file 2 for the search strategy that will be used in MEDLINE. The references from eligible publications will be reviewed for additional studies. Open grey, Theses Canada, EBSCO Open Dissertations, and ProQuest Dissertations will be searched using relevant keywords to locate additional studies and reports not published in the seven electronic databases previously stated.

The following key terms and subject headings (MeSH) will be used in various combinations and adapted according to each included database: anticonvulsants, convulsion, epilepsy, body weight, infant, low birth weight, small for gestational age, fetal growth retardation, body height, body size, cephalometry, fetal development, pregnancy outcome, pregnant woman, prenatal exposure.

Study selection process

Two authors (AL and CV) will independently screen titles and abstracts for studies that meet our inclusion criteria using Rayyan (22), as determined by our eligibility criteria. Selected studies will be

eligible for full-text review. Any disagreements will be resolved by consensus with a third reviewer. Two authors (SE and WS) will independently screen relevant studies in French.

Data collection process

Two team members (AL and CV) will independently extract information from eligible studies using a data extraction tool. A third member will revise the chart and help resolve any disagreements. Data will include study design, country, data source, drug exposure, sample sizes in exposure and control groups, control groups definitions, birth weight outcomes, and effect estimates including crude and adjusted odds ratios, prevalence ratios, relative risks and mean differences, as well as their confidence intervals and p-values.

Methodological quality/risk of bias appraisal

We will use the Newcastle-Ottawa Scale to assess the methodological quality of observational studies. Funnel plots will be used to assess publication bias and kappa value will be calculated to assess the agreement between the reviewers' screening and methodological quality scores. The risk of bias of experimental and quasi-experimental studies will be appraised using the Cochrane risk-of-bias tool for randomized trials (RoB 2).(23) The risk of bias analysis will be conducted individually, by two reviewers, and any disagreement will be resolved by consensus.

Synthesis of included studies

Characteristics of the included studies for primary and secondary birth weight outcomes will be presented both descriptively and in tables. Pooled estimates of SGA, LBW, BW, head circumference, height, and cephalization index will be presented. Statistical, clinical, and methodological heterogeneity will be examined before conducting the meta-analysis. We will also assess the strength of the evidence and combine the results quantitatively. Whenever methodological homogeneity is considered sufficient for an outcome, a meta-analysis will be conducted. We will conduct a random-effects meta-analysis to calculate pooled odds ratios for dichotomous data and pooled mean differences for continuous data.(24),(25) The study weights, size of the effect, effect consistency, and direction of effect will be represented in each forest plot. (24)

Funnel plots will be depicted for primary and secondary outcomes, including at least ten studies to explore asymmetry that might be explained by clinical, statistical, and methodological heterogeneity.(26) When the individual peculiarities of the studies under investigation are identified, sensitivity analysis will be done accordingly and reported in a summary table.(24) Projected sensitivity analyses include subgroup analysis by dose, AED exposure period during pregnancy (first trimester, second trimester, and third trimester) and therapy type (monotherapy and polytherapy).

Discussion

It is essential to understand how AEDs in pregnancy affects birth weight outcomes in offspring. This is particularly important due to the increased prescribing rates of new-generation AEDs, and the limited evidence of their fetal safety. Cautious prescribing practices of AEDs in women of reproductive age is crucial, as more than 30% of pregnancies are not planned, and some AEDs can potentially reduce contraceptives' efficacy.(27, 28) Therefore, placing women of childbearing age on AEDs should be based on recommended care, with sufficient evidence on neonates' safety. Clinicians must make medication choices by balancing the risk of increased seizure frequency in mothers versus the potential of adverse fetal outcomes caused by AED exposure.(29)

There is a need for a well constructed systematic review focusing on an array of adverse birth weight outcomes potentially caused by AED exposure during pregnancy. We anticipate the presence of fewer published reports on new generation AEDs and new versus old generation AEDs. This review will locate reports from numerous sources – including grey literature – and summarize, pool, and evaluate the methodological quality of the studies in a systematic approach.

This will help us expand the knowledge on how the safety of AED during pregnancy varies based on the type of AED and combination of prescribed AEDs. It will also help physicians make a careful decision regarding the safety of AED use in pregnancy and choose the safest treatment regimen. The knowledge generated through this project will also help in the pre-counseling of women who plan to be pregnant and will help them make rational evidence-based choices along with their physicians.

Abbreviations

AEDs: Anti-epileptic drugs; SGA: Small for gestational age; LBW: Low birth weight; BW: Birth weight; WWE: Women with epilepsy; WWOE: Women without epilepsy.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AL conceived and designed the study. AL, CV, WS, SAS, and SE have contributed to the concept and design of the study. AL, CV, and WS drafted the first protocol. CV registered the protocol in the PROSPERO database. AL and WS drafted the additional files. AL, CV, WS, SAS, and SE contributed to drafting and revising of the full manuscript and have approved the manuscript as submitted. AL, CV, WS, SAS, and SE have met the criteria of authorship, and take public responsibility for the manuscript contents. AL is the first author and SE is the corresponding author of the review.

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