The Association Between Non-prescription Analgesic Drug Use in Pregnancy and Neurodevelopmental Disorders: Protocol for an Umbrella Review

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Protocol

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Abstract

Background

Maternal prenatal health has been shown to bean important influence on children's developmental outcomes, which has led to an increased emphasis onprovidingmore information to supportclinical decisions in pregnancy. Several systematic reviewssuggest that analgesic drug use during pregnancy may haveneurodisruptive properties. However, no firm conclusions have yet been drawn onthe associations between prenatal analgesic drug use and children's long-term development of neurodevelopmental disorderssuch as Autism Spectrum Disorder (ASD) or Attention-Deficit Hyperactivity Disorder (ADHD). Therefore, an umbrella review is proposed for the purpose of examining the associations between maternal analgesic drug use during pregnancy and diagnoses of neurodevelopmental disorders.

Methods

Included systematic reviews will consist of studies examining the effect of maternal prenatal non-prescription analgesic drug use on children's neurodevelopmental disorder status. Examined drugs will be restricted to those readilyaccessible and frequently used by pregnant women, and with characteristics that allow them to cross the placenta and directly affect fetal development. Outcomes will be restricted to formal clinical diagnoses of ASD and/or ADHD. Two reviewers will independently identify eligible reviews from six databases and a manual search of reference lists, consultation with field experts, and scan of pre-print archives.A third researcher will be consulted when consensus cannot be reached.Search strategy and data extraction will be based on the preferred reporting items for systematic review and meta-analysis (PRISMA) protocol and PRISMA-P checklist. Extracted data will also include short qualitative summaries by both reviewers. As part of quality assessment, astandardised measurement tool to assess systematic reviews (AMSTAR 2) will be used. A narrative synthesis is proposed to integrate findingsfrom different, potentially methodologically heterogeneousstudies.

Discussion

This umbrella review of associations between maternal prenatal use of non-prescription analgesic drugs andchildren's neurodevelopmental disorders could allow for firmer conclusions to be drawn through the synthesis of all relevant published research. The synthesis of findings using high-quality evidence couldprovide more accurate healthcare information on the long-term effects of analgesic drugs on neurodevelopment, to better guide future clinical decisions during pregnancy. This review will also allow gaps and methodological differences in the literature to be identified, informing recommendations for future research.

Systematic review registration

PROSPEROregistration number CRD42020179216.

Background

Recent years have shown an increased emphasis on the effects of maternal prenatal health onchildren's long-term development. Decisions made during pregnancy should be as well-informed as possible tounderstand possible long-term effects, such ason children's neurodevelopment.Since 1990, there has been global increased awareness ofneurodevelopmental disorders such as autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder(ADHD), withthe worldwide prevalence of ASD being 0.17-0.62% [1] and 5.29-7.20% for ADHD[2,3].Currently, 56% of pregnant women useanalgesic drugs[4]. With this prevalence rate, it is worthwhile to examine the effects of prenatal drug use on a child's long-term development.An umbrella review is proposed for the purpose of looking at the associations betweenwomen's non-prescriptive analgesic drug useduring pregnancy and children's diagnoses of neurodevelopmental disorders.

With increased cardiac output and blood flow that occur as part of the physiological changes during pregnancy, drug absorption also increases [5]. This bioavailability creates complex chemical changes in both the mother and fetus. Studies on pharmacokinetic changes in pregnancy show how placenta transfer occurs between maternal and fetal blood circulatory systems[6]. Some pharmacological characteristics of drugs that cross the placenta include soluble lipids, unbound drugs that are lower of degree of ionization, and have a molecular weight of less than 500g/mol [7]. Drugs that fall under this category include aspirin, ibuprofen, naproxen, and acetaminophen (paracetamol). With hormonal changes in pregnancy and increased lipid levels diminishing the binding capacity of drugs[8], a fetusmay experience large concentrations of drug doses, directly effectingthe developing brain.

During pregnancy, drugs may be used for a wide variety of reasons, such as to alleviate pain, improve health, or increase well-being. While previous research hassuggestedneurodisruptive properties of certain drugs on the fetus, some of these drugs are still not recognized as human teratogensand arereadily accessible to the public.Current studies show that prenatal use of drugs is frequent in pregnant women, with around 90% them taking some form of medication during pregnancy [9]. Withanalgesic drugs recorded asthe most commonlyrecommended class of drugs to be used during pregnancy, it is possible that pregnant women are engaging in this type of drug use without being aware ofpotential long-term effects on theirchild.

Recognising that there was not enough information to guide clinical decisions, the United States Food and Drug Administration (FDA) established new pregnancy exposure registries in 2002 in order to encourage use of prospective studies to obtain relevant data[10]. This registry is similar to those in other countries, such as the Swedish Medical Birth Register, which was established in 1973, and hascollected information on drugs used during pregnancy since1995 [11]. However, at the time of writing, neither of these registers have produced research withfirm conclusions regarding prenatal exposure to analgesicdrugs and their influence onchildren's neurodevelopmental outcomes.

Since January 2016, the FDA also proposed changing medication labels in order to provide more information for pregnant women. Despite having shown that analgesic drugs cross the placenta, most of

them havebeen placed under either FDA categories B:

‘Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or animal studies have shown adverse effects, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester’,

Or category C:

‘Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks’,

Or categoryD:

‘There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease in which safer drugs cannot be used or are ineffective)’[12, 13].

This illustrates thatcurrent clinical guidelines are still based on limited and inconsistent evidence regarding the long-term effects of these drugs on the fetus.

Research has suggested that prenatal drug use is associated with increased behavioural symptoms such as conduct problems and hyperactivity at age 7 [14]. Further, a systematic review of nine studies suggested that prenatal exposure to analgesic drugs such as acetaminophen was associated with an increased risk of neurodevelopmental disorders between 18 months and 3 years [15]. The results are consistent with another systematic review of seven retrospective cohort studies[16] that found significantly increased risk of ASD and ADHD in children with age ranges of 3 to 12 years old, in relation to prenatal acetaminophen use.

The above studies and national registries imply thatcurrent research or government initiatives are not yet sufficient in nature to understandlong-term effects of prenatal non-prescriptionanalgesic drug use on a child’s development.Many systematicreviews show that outcomes are limited to age ranges up until middle childhood (12 years old), consistentwith the latest version of the American Psychiatric Association’s*Diagnostic and Statistical Manual of Mental Disorders*(DSM-5)[17],where symptoms of ADHD have to have had emerged before the age of 12 years for a diagnosis to be given. However, recent evidence hasshown that symptoms of a neurodevelopmental disorder such as ADHD can either persist or have a late-onset[18]; some studies even arguing for an emergence of a distinct ADHD diagnosis only in adulthood [19, 20]Therefore, in order for this umbrella review to provide more comprehensive information for future clinical decisions in healthcare, examinedoutcomes will include adulthood.

Systematic reviews have long been held as the gold-standard in contributing to evidence-based healthcare by informing decision-making processes[21]. The next step in conducting an umbrella review

offers valuable insight through providing an overall summary of multiple systematic reviews; effectively comparing and contrasting results of published systematic reviewsand meta-analyses[22]. The topic ofassociations between maternal prenatal use of non-prescriptive analgesic drugs andchildren's neurodevelopmental disorders has reached a level of maturity where it can benefit from this form ofsynthesis, further allowing for firmer conclusions to be drawn through an overall examination of published research. Therefore, the aims of this umbrella review are to a) summarise and synthesise findings from systematic reviews or meta-analyses on links between non-prescription analgesic drug use in pregnancyand children's diagnoses of neurodevelopmental disorders, specifically ASD and ADHDb) use high-quality evidence to provide firm conclusions from current literature, in order to inform healthcare guidance for pregnant women c) identify gaps and methodological weaknesses in the literature to inform recommendations for future research in this area.

Inclusion criteria

Included studies will be based on the following eligibility criteria:

Population

Study populations will includepregnant women and the children resulting from their pregnancies. No age limit is set for the pregnant women.

Predictors

Only systematic reviews or meta-analyses examining the effects ofnon-prescription analgesic drugswill be included in this review. Drugs reviewedwill fulfil the criteria of easy access and common usage[23],and havecharacteristics that allow them to cross the placenta and directly affect development of the fetus[6]. Healthcare settings will include both hospital and community data. The study will cover the analgesic drugs taken during the period of pregnancy only.

Outcomes

Only reviews which draw on previous clinical diagnoses of ASD, ADHD or co-occurring ASD and ADHD as outcomeswill be included, as will gender-specific reviews.No upper age limit restrictions will be applied for studyoutcomes.

Study Design

Only reviews of studies which include human female/male offspring will be considered for this review. Only reviews of quantitative studies will be included. The review will be restricted to systematic reviews and meta-analyses but will not be restricted to reviews of studies of a particular design (e.g. longitudinal or cross-sectional).Methodologicaldifferences will be discussedin the umbrella review.

Language

In order for search results to be both selective and relevant to this umbrella review, limits will be set to only meta-analysis and systematic reviews in the English language.

Exclusion criteria

Excluded studies will be based on the following criteria:

Population

Studies on non-human mammals only will be excluded.

Predictors/Outcomes

Reviews focusing on non-analgesic drugs, prescription drugs or illegal drugs will not be included in this review. Neither will studies examining neurodevelopmental disorders other than ASD or ADHD.

Study Design

Articles that are not relevant to the review's scope of prenatal use ofanalgesic drugs or children's ASD or ADHDwill be excluded. Types of articles which will be excluded are: primary or original research,non-systematic reviews (e.g. narrative or scoping reviews), non-review articles (e.g. experimental studies, randomised control trials and empirical studies), case studies or qualitative reviews, and reviews that incorporated published opinion or theoretical studies as a primary source of evidence.Non-peer reviewed articles will also be excluded.

Two reviewers will assess studies against the inclusion and exclusion criteria.

Search strategy

A search will be performed throughmajor repositories of systematic reviews and meta-analyses, namely the following databases: Embase, Maternity and Infant Care, PsycINFO, PsycARTICLES, PubMed and

Medline. Boolean operators of “AND” and “OR” will be used for search terms and adapted for different databases. Search filters will be employed and presented sequentially for the databases with key terms searched for in the title or abstract fields. Search details are listed in Table 1, where the number of citations from each database will be recorded in the final umbrella review. Search periods will extend from the inception dates of the respective databases to the date of data extraction, with duplicated studies removed based on comparing full texts. Searches will be independently repeated if necessary. Article selection will be based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 protocol, with the PRISMA Flow Diagram attached (Figure 1) [24]. In order for a comprehensive search, reference lists of selected reviews, reviewsin-press (derived from scanning pre-print archives or discussion with field experts), will formpart of the supplementarysearch strategy under PRISMA andrecorded under “additional records”.

Data extraction and harmonisation

Data extractionand coding will be independently carried out by two researchers. Information extracted from eachstudy will include authors’ names, publication date, independent and dependent variables, categorisation of data analysis methods,reported effect sizes and significance (if applicable), andshort qualitative summaries written by both reviewers(for a full list, see Appendix1). Researchers involved in data extraction will store data in separate spreadsheets, which will then be compared for agreement. The manuscript will provide asynthesisedsummary of included studies.Any discrepancies will be solved through discussion until consensus is achieved.If a consensus cannot be achieved through discussion, a third researcher will be consulted to help achieve consensus.Includedstudies with missing essential informationsuch as participant data or search strategies will not be included in the final review.

Quality assessment

A proposed quality assessment, the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews-2) [25] will be used for this umbrella review (Appendix 2). This updated version of a critical appraisal tool was chosen for rapid quality assessments of systematic reviews in healthcare. The AMSTAR 2 not only allows for future replicability, but also provides reviewers with little epidemiological training with a standardised template, in order for a more in-depth appraisal of the literature. It consists of detailed questions addressing search strategies, data extraction techniques, bias risk, appropriate methodology, and interpretation and discussion of results. This tool is in line with advised guidelines on assessment of systematic reviews based on identifying methodological featuressuch as how well the research question is defined, use of a systematic search strategy, possible publication or funding bias, selective reporting,previous quality ratings, and presence of information synthesis and conclusion[26].This study protocol has been registered in the international prospective register of systematic reviews (PROSPERO registration number CRD42020179216).

Synthesis method

A narrative synthesis method is proposed for this umbrella review. Results fromstudies that pass the quality check will be tabulated with an overall summary. This method was primarily chosen due to the lack of firm conclusions onprenatal analgesic drug use and potential heterogeneity of data from multiple systematic reviews and meta-analyses. A narrative synthesis provides flexibility due to its qualitative rather than quantitative nature of analysis.The purpose of this narrative synthesisis to examine and integrate ideas from multiple different reviewsin order to provide a clear overview of the effects of analgesic drugs on neurodevelopmental diagnoses.

Discussion

The purpose of this umbrella review is to elucidate the associations between prenatal use of non-prescription analgesic drugs and children's neurodevelopmental disorder diagnoses through synthesis of relevant published research. Findingsfrom this review will provide clearer direction for clinical decisions made during pregnancy in relation to the use of non-prescriptionanalgesic drugs. A potential limitation of this review could involve difficulties in synthesising information due to methodological differences of original studiesleading to heterogenous results in the selected reviews. However, this also offers an opportunity to discuss these methodological differences and provide clear suggestions for future research. Using synthesised information on analgesic drugs and their association with neurodevelopmental outcomes, there are several strengths of this paper. These strengths include a novel approach to studying factors that may impact long-term neurodevelopment, refining clinical practices during the prenatal period, and increasing the quality of available information which future decisions in healthcare policy are based on.

List Of Abbreviations

ASD: Autism Spectrum Disorder

ADHD: Attention-Deficit Hyperactivity Disorder

AMSTAR 2: A MeaSurement Tool to Assess systematic Reviews (2nd edition)

DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5thedition)

FDA: Food and Drug Administration (United States)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: international prospective register of systematic reviews

Declarations

Ethics approval and consent to participate

No informed consent or ethical approval is required for the purpose of this protocol.

Consent for publication

Not applicable.

Availability of data and materials

Data available in a public (institutional, general or subject specific) repositories that issues datasets with DOIs (non-mandated deposition). Repositories include Embase, Maternity and Infant Care, PsycINFO, PsycARTICLES, PubMed and Medline.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JK and HAH conceptualised, designed and drafted the protocol and will analyse and interpret data. ALM and BA designed the protocol and will aid in analysis and interpretation of data.

Acknowledgements

Not applicable.

Authors' information (optional)

None.

Footnotes

Not applicable.

Appendix

1. Data extraction form items.

ESSENTIAL INFORMATION

1. ID
2. Authors
3. Title
4. Publication Year
5. Database names
6. Search Type
7. Search terms
8. Fulfils inclusion criteria
   (1= Yes, 2= No, 3= Not sure)
9. Fulfils exclusion criteria
   (1= Yes, 2= No, 3= Not sure)
10. Number of participants category
    (1= ≥100,000, 2 = 10,000-99,999, 3 = 1,000-9,999, 4 = 100-999, 5 < 100)
11. Number of Participants (n)
12. Data extraction approach (free text)
13. Data synthesis method (1= quantitative, 2= qualitative, 3= mixed, 4= Not sure)
14. Data synthesis method (description)
15. Missing essential information?
    (1= Yes, 2 = No, 3 = Not sure)
16. What essential information is missing?
    (If none, state NA)
17. Additional comments (Essential Information)

PRESENTATION

18. Presentation format [select all applicable] (1= Descriptive, 2 = Graphical, 3 = Table, 4 = Others (state)
19. Additional comments (Presentation)

STUDY DESIGN

20. Study Design A
    (1= Meta-analysis, 2= Systematic Review, 3 = Others (state))
21. Study Design A1 (Meta-analysis) Publication Bias Present? (1 = Yes, 2 = No, 3 = Not sure)
22. Study Design A2 (Systematic Review)
    Publication Bias Present? (1 = Yes, 2 = No, 3 = Not sure)
23. Study Design A3 (Others) Publication Bias Present? (1 = Yes, 2 = No, 3 = Not sure)
24. Study Design A1 (Meta-analysis) Analysis Method(s)
25. Study Design A2 (Systematic Review) Analysis Method(s)
26. Study Design A3 (Others) Analysis Method(s)
27. Study Design B [Select all applicable] (1= Cross-sectional, 2= Longitudinal, 3 = Randomised Control Trial, 4 = Quasi-experimental, 5 = Mixed, 6 = Others (state))
28. Additional comments (Study Design)

SELECTION

29. Include for final analysis? (1= Yes, 2= No, 3 = Not sure)
30. If 2= no, why not included in final analysis? (text)

FINDINGS/SUMMARY

31. Results A Effect Size [State NA if not applicable i.e. systematic review]
32. Significance (p-value) [State NA if not applicable i.e. systematic review]
33. Outcome Findings
34. Other findings
35. Short summary (text)
36. Additional comments (Findings/Summary)

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Figures

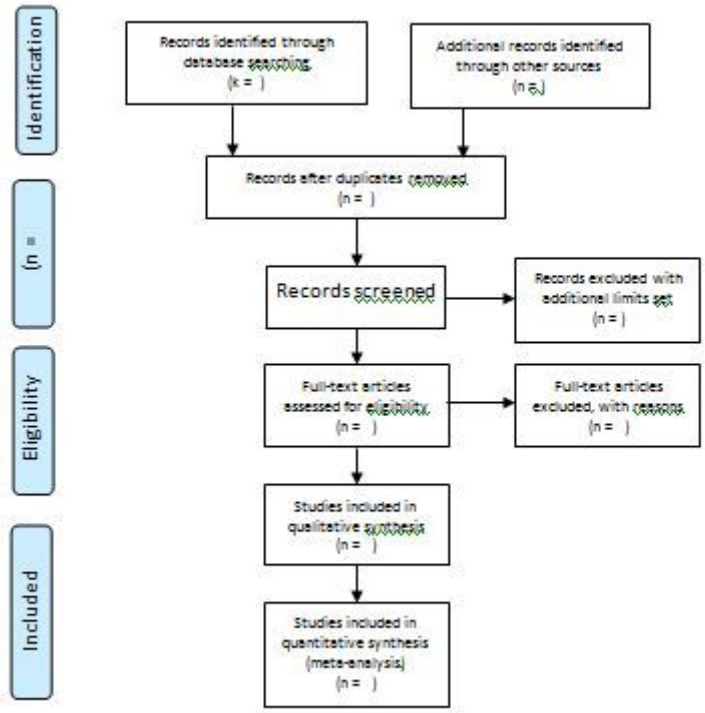

Figure 1

PRISMA Flow Diagram

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix2AMSTAR2.pdf
- Appendix1DataExtractionForm.xlsx
- PROSPEROregistrationCRD42020179216.pdf
- NEOPRISMCFundingDetails.pdf