metaPreg

Maternal and fetal consequences of use of medicines during pregnancy.

A live systematic review and meta-analysis of observational studies

Master Protocol

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www.metaPreg.org

Contents

1 Introduction

This platform protocol is part of an ambitious ongoing project to build a comprehensive knowledge base covering all the study of consequence of drug use during pregnancy (metaPreg.org).

The present protocol is being reported in accordance with the reporting guidance provided the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement(1). A populated checklist for this review protocol has been provided in appendix 15, page 10.

The systematic review and meta-analysis presented in this protocol will be reported in accordance with the reporting guidance provided in the PRISMA statement (2) and the MOOSE reporting guideline(3). Any amendments or modifications made in the protocol will be outlined and reported in the final paper.

2 Objectives

Assess the safety of a drug or therapeutic class use during pregnancy by synthesizing the available evidence derived from controlled observational studies and randomized controlled trials (RCTs) about the safety of the fetus, the newborn, the infant and the mother.

3 General methods

The procedure for this systematic review will follow established best methods and Cochrane standards used in the evolving science of systematic review research in general.

This meta-analysis will be performed accordingly to this present protocol established before the beginning of the trial search and the data analysis. It will be reported accordingly to the suggested PRISMA guidelines standards when appropriate.

4 Endpoints

All the adverse pregnancy outcomes will be systematically considered:

- Congenital malformations (limited to major malformations as coded by EUROCAT. Minor malformations and malformations not registered by EUROCAT are not considered in MetaPreg, except the whole group of minor malformations)
- Growth parameters and prematurity
- Maternal consequences
- Neonatal disorders
- Long-term consequences
- Intrauterine deaths
- Neurodevelopmental disorders

For treatment specific of pregnancy pathologies, the efficacy criteria are not considered except when a deleterious effect was observed (in a majority of the studies).

The treatment effect will be measured as the difference between treatment groups for these endpoints

5 Criteria for considering studies

Eligible studies will be studies reporting specific data for pregnancy outcomes after in utero exposition to the considered drug(s) (during pregnancy and/or during birth) with a comparator group.

Prospective cohort studies, historical cohort studies (also known as retrospective cohort studies), case–control studies and, possibly, randomized clinical trials will be included. Studies will be included regardless of publication status or language of publication. We will assess all potentially relevant published articles and abstracts for inclusion. Information from on-going studies and interim analyses will be included. There will be no restriction by study setting.

We will exclude studies with inappropriate design (case reports, case series, cross-sectional studies, disproportionate analysis, adverse drug reactions reports…), studies without original data (review, letter to editor, comments…) or animal studies.

Studies in which drugs exposure during pregnancy (at any time of the pregnancy) is not the exposure of interest, and adverse pregnancy outcome is not reported as the outcome of interest will also be excluded

Observational studies not presenting quantitative results (e.g., odds ratio, hazard ratio, relative risks, 95% confidence intervals, numbers of cases/population, observed and expected cases) or sufficient data for an outcome measure to be calculated will be also excluded. Only most recent publication of iterative study on the same database was included and in case of overlapping studies, only the one with larger sample size was kept or otherwise, with a methodology that provides a better consideration of the confounding factors.

6 Search methods for identification of studies

Relevant studies were identified using several methods in different electronic databases to ensure that all relevant literature, both published and unpublished, is identified.

When an abstract of a proceeding and a full paper refer to the same trial, we will only include the full article in the analysis. There are no date restrictions on the search

6.1 Bibliographic database

We will search the following sources using appropriate, comprehensive search strategies:

- Medline/PubMed
- SCOPUS
- Web of science (Science direct)

6.2 Published systematic reviews will be sought as a source of studies. Search strategy

The search strategy is composed of two parts. The first part is dedicated to the drugs of interest and is specific of each project. The second part is the methodological filter and is intended to seek the relevant type of studies. This part is generic and will be the same for each project.

A standardized search strategy for PUBMED including keywords and Medical Subject Heading (MeSH) terms was defined.

The following search strategy will be used for Pubmed and will be modified for performing searches in SCOPUS (Embase), Web of Science to account for differences in syntax and thesaurus headings:

(<<<drug of interest search strategy>>>) AND ("birth defects" OR "birth defects-drug exposure" OR "teratogenic risk" OR "teratogenicity" OR "prenatal exposure" OR "prenatally exposed" OR "fetal exposure" OR "congenital anomaly" OR "fetal anomalies" OR "congenital anomalies" OR "congenital malformation" OR "congenital malformations" OR "congenital major malformations" OR "congenital disorders" OR "cardiovascular defects" OR "preterm birth" OR "stillbirth" OR "miscarriage" OR "spontaneous abortion" OR "use during pregnancy" OR "exposure in pregnancy" OR "exposure during pregnancy" OR "exposed in utero" OR "first-trimester exposure" OR Teratogens OR "Birth

defect"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Death/chemically induced"[Mesh] OR "Fetal Development/drug effects"[Mesh] OR "Fetal Diseases/chemically induced"[Mesh] OR "Fetus/drug effects"[Mesh] OR "Stillbirth"[Mesh] OR "Teratogens"[Mesh] OR "Abortion, Spontaneous"[MESH]) AND ("cohort study" OR "prospective study" OR "prospective observational study" OR "case-control study" OR "prospective follow-up study" OR "prospective follow-up" OR "meta-analysis" OR "systematic review" OR "retrospective study" OR "registry" OR "birth register" OR "observational study" OR "populationbased health datasets" OR "population health data" OR "Cohort Studies"[MESH] OR "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Observational Study"[ptyp] OR "Meta-Analysis"[ptyp] OR "Longitudinal Studies"[MESH] OR "Registries"[MESH] OR "Retrospective Studies"[MESH] OR "Randomized Controlled Trial"[ptyp] OR "matched controls" OR "matched control" OR "case and control" OR "compared with controls" OR "case-control" OR "healthy controls" OR disproportionality OR "proportional reporting ratio" OR "odds ratio" OR "hazard ratio")

6.3 Conference proceedings

In addition to the search of the published literature, a search will be conducted of abstracts and presentations made at appropriate conferences to identify studies still ongoing or unpublished. We will search the abstracts from conference proceedings with the Web of science and other databases that indexe conference proceedings.

A cited reference search, of reports of all included studies, will be conducted on the Web of Science to identify any outstanding reports of trials.

The following conference proceedings will be searched:

- The Teratology Society and
- European Teratology Society

All abstracts selected from conference proceedings will be traced to full-text publications.

6.4 Others searches

Additional efforts to locate potentially relevant studies will be performed using Reference lists of all available primary studies and review articles (systematic review or meta-analysis) will be reviewed to identify potentially relevant citations.

7 Selection of studies

A two-step procedure will be used for the study selection.

The first step will be a selection using title and abstract of bibliographic records of all found references. Abstracts of all studies identified in the above search will be screened by one biocurator assisted by automation tools based on artificial intelligence.

For the second step, we will obtain the full text reports of studies that are potentially relevant. Studies under consideration will be assessed for whether they fulfill the inclusion criteria and methodological quality without regard to their results.

In case of doubt about inclusion of a study, the matter will be discussed with the scientific directors of the project until agreement is reached.

The process of study selection will be documented and reported using a PRISMA flow diagram.

8 Data extraction

Data will be extracted from the included studies using a standardized electronic data collection form on our proprietary platform (metaPreg admin).

The following information will be collected:

- **Study description**: information on first author, year of publication, focus, country of study, source of data, study period, population description, exposure definition, non-exposure definition, type of control, case description, control description , sample size
- **Method**: type of study, exposition measure, outcome measure, follow-up period, confounding factors that were taken into consideration
- **Results**: for each adverse outcome a maximally adjusted relative risk (reported as odds ratio for case–control studies and hazard ratio or standardized incidence/mortality ratio for cohort studies), and 95% confidence intervals and exposition period
- Risk of bias assessment using ROBINS -I for the observational studies and ROB-2 for the RCTs

Attempts will be made to obtain full-text translations and/or evaluations of all relevant non-English articles.

8.1 Handling of discrepant data

For studies published in multiple articles, reports or presentations, we will extract the most recent or most comprehensive data.

If adjusted and unadjusted results will be available from the same study, we will use the maximally adjusted data.

8.2 Data management

The results of the literature search and all relevant data will be extracted and managed using our proprietary meta-analysis platform (metaPreg-admin).

The project director and the data manager will be responsible for the master copy.

8.3 Indirectness

When the exact endpoint sought was not present in a study but quite a similar one was reported, the data of this last were used according to the indirectness principle.

9 Assessment of methodological quality

9.1 Observational studies

Risk of bias will be assessed with the Cochrane Risk of Bias Tool for Randomized Trials or with the Risk of Bias Tool for Non-Randomized Studies of Interventions (ROBINS-I)(4) adapted to our purpose by the scientific committee of the metaPreg project.

Adapted ROBINS-I will be used to assess the risk of bias due to confounding and others aspects of methodological quality such as participant selection, measurement of intervention, missing data, measurement of outcomes and selection of the reported result included non-randomized studies (see https://sites.google.com/site/riskofbiastool/).

Each study will be rated as critical, serious, moderate or low risk of bias based on a judgment of the gathered information. The overall assessment is based on the responses to individual domains. If there is insufficient detail reported in the study, the risk of bias will be classified as 'unclear' .

A summary table presenting risk of bias assessments for each study will be included in the review.

Data on risk of bias will be presented for all included studies, and results will be interpreted in light of risk of bias; studies will not be excluded on the grounds of risk of bias.

9.2 RCTs

Risk of bias for all randomized studies will be assessed using the Cochrane Collaboration's tool for assessing risk of bias (5). This tool addresses the following domains:

- selection bias (random sequence generation, allocation concealment);
- performance bias (blinding of participants and personnel);
- detection bias (blinding of outcome assessment);
- attrition bias (incomplete outcome data);
- reporting bias (selective outcome reporting);
- other sources of bias.

We will judge each of the six risk of bias domains using the categories "low risk", "high risk" or "unclear risk" of bias. Assessment of risk of bias will be performed by one biocurator. In case of doubt about risk of bias assessment, the matter will be discussed with the scientific directors of the project until agreement is reached.

10 Data analysis

The meta-analysis will be performed by using only the summary data. No attempt will be done to obtain the individual patient data.

10.1 Methods

Given the need to control for confounding factors in observational studies, we will use adjusted measures as the primary effect measures when reported by the authors. Odds ratio (OR) is an appropriate effect measure for both cohort and case‐control studies and is commonly provided when adjusted analyses are obtained using logistic regression models. However, we will also consider other effect measures if an appropriate adjusted OR was not available from the report. The effect measure may be an odds ratio, risk ratio, or hazard ratio.

Investigators used a variety of adjustment strategies. We will specify whether confounding was considered in the design (e.g., matching, stratification). We will provide the confounding factors considered in the design and analysis when presenting results.

If no adjusted measures were given as part of the primary analysis, we will use unadjusted measures. If data will available for unadjusted dichotomous outcomes, we will calculate the OR with 95% confidence interval (CI).

Data from primary observational studies will be used to perform random-effects meta-analyses. We will estimate the summary effect size and its 95% confidence interval using the inverse variance method based on the DerSimonian and Laird random effects model. The random-effects model is selected a priori to synthesize the epidemiological data, as it considers both within-study and between-study variation by incorporating the heterogeneity of effects into the overall analyses.

If all arms in a multi-arm trial are to be included in the meta-analysis and one treatment arm is to be included in more than one of the treatment comparisons, then we will divide the number of events and the number of participants in that arm by the number of treatment comparisons made. This method will avoid the multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial. It will compromise the precision of the pooled estimate slightly.

10.1.1 Dealing with multiple controls

Some studies considered different comparator groups and provided estimates for each comparator group (i.e., unexposed disease-free, unexposed-sick, and sick exposed to other treatments). As "sick comparator" take into consideration the potential impact of the disease, their estimates were preferentially used for the main analysis, if it is not exposed to other treatments, when available. Otherwise, disease-free controls were used.

In the main analysis, the use of control groups is done in the following preferred order:

- unexposed sick
- unexposed not otherwise specified
- unexposed disease free
- exposes to other treatment, sick

Thus, only one estimate from each study was used for the meta-analysis of each study outcome. A subgroup analysis using all included studies and according to different groups controls will be available.

10.1.2 Dealing with multiple period of exposure

Some studies considered different period of exposure for the same outcome (for instance, first trimester, late pregnancy, ...). In the main analysis, we reported the estimate corresponding to the more relevant period of exposure according to the outcome (for instance, the first trimester for the malformations ; the late pregnancy for neonatal withdrawal, ...).

Thus, for the meta-analysis, only one estimate was used by outcome.

10.1.3 Assessment of heterogeneity

We will assess heterogeneity of treatment effect visually from the forest plot. This will help determine whether the differences between the results of trials were greater than would be expected by chance alone.

We will also assess heterogeneity by means of the I-squared statistic(6). When considerable heterogeneity is present (>50%), an attempt will be made to explain the differences based on the clinical and methodological differences of the included studies.

Clinically and methodologically dissimilar studies will not be statistically combined. When statistically heterogeneous studies are not too clinically and methodologically heterogeneous, they will be combined using a random-effect model.

10.1.4 Dealing with missing data

Attempts will be made to contact study authors to obtain missing data (e.g. adjusted results, participants, intervention or outcome details) on the main endpoints or on the endpoint of interest (e.g. endpoints that appear modified from the other available studies (in order to limit the selective reporting bias).

Analyses will be conducted on an intention-to-treat basis where possible; alternatively, data will be analyzed as reported.

Loss to follow-up will be reported and assessed as a potential source of bias in our risk of bias assessment.

10.1.5 Dealing with zeros

In case of zero number of events in one or both groups, a continuity correction will be used by replacing the zeros by 0.5 (equivalent to arguments `incr=0.5, allincr=F, addincr=F` in metabin function of meta package in R).

10.2 Publication bias

We will test for publication bias using the funnel plot visually and quantitatively with the rank correlation test(7), the graphical test with or without heterogeneity(8), or the trim and fill method(9), depending on the number of trials included in the review.

10.3 Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses to assess the degree to which clinical and methodological differences between trials might have systematically influenced differences observed in the outcomes. These by subgroup analysis will also serve as sensitivity analysis to determine the robustness of our conclusions to methodological assumptions made in conducting the meta-analysis, including inclusion/exclusion of particular studies and the choices regarding analysis methods used.

We will group the trials according to the following clinical sources of heterogeneity (if the number of trials permitting):

- Exposition period (e.g. pregnancy trimester(s) of exposition)
- Type of control groups
- Risk of bias
- Study design

All analyses will be conducted in our proprietary meta-analysis platform metaPreg.org. Cross validation with R script using standard meta-analysis package (meta) will be performed.

11 Living systematic review and meta-analysis

We will perform a living systematic review and meta-analysis which will be continually updated, incorporating relevant new evidence as it becomes available. We will realize an actively continuously monitoring of new evidence that will be immediately included in the meta-analysis to update it.

In a dynamic meta-analysis, the research approach of the studies is somewhat different from that used in a classical meta-analysis. Emphasis is placed on the real-time detection of new results, which may come from publication channels different from traditional biomedical journals (preprints, press releases, etc.).

The following electronic bibliographic databases were continuously searched for relevant published literature using appropriate, comprehensive search strategies:

- Pubmed
- Scopus
- Web of Science

Each database was incrementally searched as far back as possible (last 24 hours), using automatic software robots. Detected hits are pushed to biocurators that manually selected relevant evidence.

Pre-publication manuscripts (aka preprints) were searching in preprint servers: Medrxiv, SSRN, research Square, arXiv, RePEc, research Gate, bioRxiv, preprints.org, JMIR, OSF preprints, Authorea, SciELO, Zenodo, , F1000, Qeios, PeerJ, and ChinRxiv).

To instantly detect new results and to update immediately after the availability of new results, automatic RSS and Tweeter feed screening tools have been implemented. Each item published through these channels is subject to text analysis to detect those announcing new clinical trial results. These tools use a self-learning algorithm based on a Naive Bayes classifier.

The searched RSS feeds encompass biomedical journals, preprints archives, stored Pubmed Query run daily and web sites dedicated into medical or pharma news.

The Twitter accounts to follow were determined by an algorithm using the presence in their history of known posts about drugs and pregnancy.

This list will be updated in future by searching Tweeter account posting about the new trials when there is available.

12 Protocol amendments

Any protocol amendments will be clearly documented and justified with an addendum made to the protocol specifying the changes and their justification. In addition, any such changes and their justification will be included in the final report of the review.

13 Funding

This project is funded by a grant of the French Drug Agency (ANSM) and self-funded by Hospices civils de Lyon and University Lyon 1 (LBBE laboratory).

14 Availability of data and materials

All the data used and analyzed are available on the metaPreg.org site.

15 Appendix Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	✓
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA

Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	✓
Sponsor	5b	Provide name for the review funder and/or sponsor	✓
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	NA
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	✓
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other gray literature sources) with planned dates of coverage	✓
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	✓
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	✓
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	✓
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	✓
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	✓
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

16 Authors and Contact

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(also see http://metapreg.org/About.aspx)

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