BMJ Open

Low-dose aspirin prophylaxis to prevent hypertensive disorders of pregnancy after in vitro fertilisation: a scoping review protocol

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To cite: Collee J, Vervier J, Vandenput S, *et al*. Low-dose aspirin prophylaxis to prevent hypertensive disorders of pregnancy after in vitro fertilisation: a scoping review protocol. *BMJ Open* 2024;**14**:e080353. doi:10.1136/bmjopen-2023-080353

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-080353).

Received 28 September 2023
Accepted 27 May 2024

Check for updates

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ABSTRACT

Introduction Pregnancies resulting from in vitro fertilisation are associated with an increased risk of developing hypertensive disorders of pregnancy, such as preeclampsia, when compared with naturally conceived pregnancies.

Objective The efficacy of aspirin prophylaxis to reduce the incidence of preeclampsia is well established in naturally conceived pregnancies identified as high risk for developing preeclampsia. However, the efficacy of aspirin to reduce the rate of preeclampsia for all pregnancies resulting from in vitro fertilisation remains uncertain, although in vitro fertilisation conception is a well-known risk factor for preeclampsia. Therefore, the purpose of this scoping review is to provide a comprehensive overview of the current literature regarding the use of low-dose aspirin to prevent hypertensive disorders of pregnancy after in vitro fertilisation.

Inclusion criteria This review will identify all peer-reviewed published articles including pregnant women who underwent embryo transfer after in vitro fertilisation and were prescribed low-dose aspirin to reduce the risk of hypertensive disorders of pregnancy.

Methods We have devised a comprehensive search strategy to systematically identify pertinent studies published from January 2000 until May 2024, within the Medline (PubMed interface), Embase and Scopus databases. The search strategy is based on the keywords 'aspirin,' 'pregnancy-induced hypertension,' and ('in vitro fertilization' OR 'oocyte donation' OR 'embryo transfer' OR 'donor conception'). Two reviewers will independently screen the titles, abstracts and full-text articles to select the relevant articles, using the Covidence software.

Ethics and dissemination No patients are involved in this study. This study aims to be published in a peer-reviewed journal and could be presented at a conference.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The subject of this review is really specific.
⇒ The conclusion of the study could be interesting.
⇒ There was a lack in the literature concerning this subject.
⇒ The research will be exhaustive on different database.
⇒ This research could help the clinicians to treat patients for the prevention of preeclampsia.
⇒ Due to this specific subject, number of studies could be limited and the studies could be heterogeneous.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) include gestational hypertension, preeclampsia (PE), eclampsia and haemolysis, elevated liver enzymes and low platelet syndrome. The overall incidence of HDP is between 10% and 13%.[1–3] HDP, as opposed to chronic hypertension, is characterised by the new onset of hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic) after 20 weeks' gestation.[4]

According to the International Society for the Study of Hypertension in Pregnancy, PE is defined by the association of gestational hypertension with one or more of the following new-onset conditions: proteinuria, other maternal organ dysfunction (renal, liver, neurological or haematological complications) and/or uteroplacental dysfunction leading to fetal growth restriction.[4 5] PE is an important cause of severe maternal and fetal complications,[6] including acute renal failure, hepatic failure, thrombocytopenia and eclampsia on the maternal side and prematurity, intrauterine growth restriction and stillbirth on the fetal side.[1 7] PE can only be cured after delivery of the fetus and the placenta. However, a timely diagnosis and a preventive treatment could help decreasing maternal and fetal morbidity and mortality.[8 9]

Since 1979, aspirin has been used for its antiplatelet properties to prevent PE.[10] In the following decades, numerous trials have attempted to enhance the benefit of low-dose aspirin for the prevention of PE.[11–13] In 2017, the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based

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Preeclampsia Prevention) trial demonstrated that the daily administration of 150 mg of aspirin, starting from 11 to 14 weeks until 36 weeks of gestation, reduces the incidence of PE by 62% in singleton pregnancies identified at high risk for developing PE by the first-trimester Fetal Medicine Foundation combined algorithm.[8]

The incidence of PE is increased among women who conceived through assisted reproductive technology (ART) when compared with those who conceived naturally.[14] The underlying mechanisms are not well-established and are currently widely investigated. Among ART techniques, in vitro fertilisation (IVF) and especially frozen embryo transfer (FET) with hormone replacement therapy (HRT) have been identified as the principal risk factors for developing PE.[14] A potential mechanism is the absence of corpus luteum which secretes vasoactive substances (such as vascular endothelial growth factor and relaxin), after FET with HRT.[15] Altered angiogenic balance is the precursor to the molecular basis of PE.[16] Relaxin is involved in the creation of a low-resistance vascular system, reducing arterial stiffness and peripheral vascular resistance. It helps maintain normal blood pressure and vascular compliance during pregnancy.[17] Indeed, maternal vascular maladaptation appears to be the cornerstone of the development of PE. IVF with oocyte donation is also a risk factor of PE[18] because of the absence of corpus luteum. Preventing PE after IVF is therefore an important issue, particularly with the rising number of pregnancies resulting from IVF.[19]

To the best of our knowledge, the existing reviews studying the use of aspirin to prevent PE have only focused on naturally conceived pregnancies.[20] However, there is a lack of a comprehensive literature review assessing the effectiveness of aspirin to prevent HDP after IVF pregnancies. Therefore, the overarching aim of this scoping review is to identify all published studies concerning the use of aspirin for the prevention of HDP, including PE, in IVF pregnancies. This review will also investigate the optimal dose, timing and duration of treatment in the specific case of IVF when the date of conception is known. To achieve our objectives, this scoping review will address the following key inquiries within the context of pregnancies resulting from IVF:

- Does aspirin prevent the development of HDP in IVF pregnancies?
- What are the recommended dosage, the optimal timing and the optimal duration for the administration of aspirin in IVF pregnancies?

METHODS

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews[21] and Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews guidelines for literature research.[22] The protocol was registered with the Open Science Framework (https://osf.io/pk2n3/).

Patient and public involvement

None.

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Participants

This scoping review will consider all studies that describe pregnancies obtained by embryo transfer after IVF or oocyte donation without restrictions concerning maternal age, ethnicity, comorbidities or multiple pregnancies.

Concept

The intervention is the prescription of prophylactic aspirin alone regardless of the dosage, the onset and the duration of treatment. The included outcomes are both maternal and/or neonatal. The maternal outcomes are the incidence of HDP including gestational hypertension, chronic hypertension, PE, eclampsia and haemolysis, elevated liver enzymes and low platelet syndrome. The fetal outcomes are intrauterine growth restriction, preterm birth and intrauterine demise.

Context

The review will consider all relevant studies that were conducted in any geographical location and any setting (such as hospital, primary care or at home), between 2000 and May 2024. All studies written in English or French will be included.

Study designs

This scoping review will consider both experimental and quasi-experimental study designs including randomised controlled trials, analytical observational studies (prospective or retrospective cohort studies, case-control studies), descriptive studies (case series or case reports) and reviews (narrative, scoping, systematic and meta-analysis).

Search strategy

An exploratory search in Medline (PubMed interface) will be undertaken to provide the research strategy using identified keywords and subject headings (MeSH) and will be validated against benchmark articles, in consultation with a research librarian (SV). This will be followed by the analysis of text words contained in the abstracts and titles of the retrieved papers, and index terms used to describe these articles. This will inform the development of a research strategy, which will be tailored for each information source (Embase (Elsevier interface, 1974 onwards) and Scopus (Elsevier interface, 1974 onwards)) (online supplemental appendix 1). The research string is 'aspirin' AND 'pregnancy-induced hypertension' AND ('in vitro fertilization' OR 'oocyte donation' OR 'embryo transfer' OR 'donor conception'). We will apply no language or other limitations on any of the databases searches.

Selection process

All identified records will be uploaded into Covidence software (Veritas Health Information, Melbourne, Australia) and duplicates will be removed. The entire process of selection will be performed by two independent reviewers

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(JC and JV). Disagreement between the reviewers will be resolved through discussion and if necessary a third author (LN) will be involved. Titles and abstracts will be screened for assessment against the eligibility criteria. Potentially relevant studies will be retrieved in full and will be assessed in detail against the inclusion criteria. All reasons for exclusion will be reported in the final manuscript. After screening and identifying the studies, the reference list of included studies will be hand-searched for relevant citations.

Data collection process

Data will be extracted from papers included in the scoping review by two independent reviewers (JC and JV) into Covidence. The extracted data will include specific details about the participants, concept, context, study methods and key findings relevant to the review.

A draft extraction form is provided (online supplemental appendix 2): we will extract the study ID, study design, the total number of patients or the total number of studies considered (in case of review), the type of assisted reproductive treatment, the study period, the study location, the daily Aspirin dosage investigated, the tested treatment duration, the outcome(s), the clinical conclusion(s) and the limitation(s). If the draft data extraction tool is modified and revised during the process of extracting data, modifications will be detailed in the scoping review.

Data analysis and presentation

Analysis will be focused on the aspirin dosage and optimal timing for the administration of aspirin. Efficacy of aspirin to prevent HDP and the outcomes measures to evaluate the effect of aspirin will be analysed. In addition, the conclusions of the articles will be reported. All results will be presented in a narrative summary. Bias will be described.

ETHICS AND DISSEMINATION

No patients are involved in this study. This study aims to be published in a peer-reviewed journal and could be presented at a conference.

Contributors JC conceptualised the ideas and assured the evolution of overarching research goals and aims. JC and SV developed the methodology. JC and JV will independently select the articles. JC, JV and SV wrote the original draft of the paper. LN, LH and FC revised the manuscript and realised the critical review of the draft. The oversight and leadership responsibility of this research was done by MN, LN, FC and LH.

Funding The first author (JC) and the second author (JV) are Medical Doctors Applicant to an MSc and a PhD of the Fonds National de la Recherche Scientifique – FNRS (Belgium) (40017857).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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