INPLASY PROTOCOL

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None to declare.

Higher risk of hypertensive disorders of pregnancy and preeclampsia in singleton pregnancies following frozen embryo transfer: a systematic review and meta-analysis

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Review question / Objective: **In women with singleton pregnancies conceived after in vitro fertilization (IVF), do frozen embryo transfer (FET) cycles increase the risk of hypertensive disorders of pregnancy (HDP) compared to fresh embryo transfer (ET)?**
Condition being studied: **The primary outcome measure was hypertensive disorders in pregnancy (HDP). According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), HDP includes chronic hypertension, white-coat hypertension, masked hypertension, gestational hypertension and preeclampsia. HDP, which occurs in 10% of pregnancies, is one of the leading causes of prematurity, maternal and neonatal morbidity and mortality. Therefore, studies focused exclusively on this outcome are warranted.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 May 2020 and was last updated on 30 May 2020 (registration number INPLASY202050113).

INTRODUCTION

Review question / Objective: **In women with singleton pregnancies conceived after in vitro fertilization (IVF), do frozen embryo transfer (FET) cycles increase the risk of hypertensive disorders of pregnancy (HDP) compared to fresh embryo transfer (ET)?**

Rationale: **Recent studies have reported that following FET, a higher rate of hypertensive disorders in pregnancy (HDP) is obtained. Hence, the association between FET and HDP warrants further investigation and a conservative attitude as regards the use of FET. In addition, since additional data concerning obstetric outcomes from randomized controlled**

trials (RCT) have been published, better-quality evidence from meta-analyses is required.

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METHODS

Search strategy: An electronic search was developed and approved by all authors. PubMed, Embase and Cochrane databases were searched for published RCTs in the English language to identify studies that assessed HDP and adverse perinatal outcomes after FET, through December 2019. The combined search terms were used: (Fresh Embryos) OR (Frozen Embryos OR Cryopreserved Embryos OR Cryopreservation of Embryos OR Frozen Thawed Embryos OR Cryopreserved-thawed Embryos) OR (Embryo Transfer OR Embryo Transfers OR Tubal Embryo Transfer OR Tubal Embryo Stage Transfer) OR (Vitrification OR Slow Freeze OR Slow Frozen OR Slow Freezing) with (In Vitro Fertilizations/IVF OR Fertilization in Vitro) OR (ICSI OR Injections, Sperm, Intracytoplasmic OR Injections, Intracytoplasmic Sperm OR Intracytoplasmic Sperm Injection OR Sperm Injection, Intracytoplasmic OR Intracytoplasmic Sperm Injections) AND (Pregnancy induced hypertension OR Preeclampsia). We also searched the references of the relevant articles.

Participant or population: Women with singleton pregnancies conceived after in vitro fertilization.

Intervention: Frozen embryo transfer (FET).

Comparator: Fresh embryo transfer (ET).

Study designs to be included: Randomized clinical trials.

Eligibility criteria: The review included RCTs reporting perinatal outcomes for singleton pregnancies after IVF that compared FET to fresh ET cycles.

Information sources: PubMed, Embase and Cochrane databases were searched for published RCTs in the English language to identify studies that assessed HDP and adverse perinatal outcomes after FET, through December 2019.

Main outcome(s): The primary outcome measure was hypertensive disorders in pregnancy, which includes chronic hypertension, white-coat hypertension, masked hypertension, gestational hypertension and preeclampsia. The articles included in the current study mostly refer to gestational hypertension and preeclampsia. Gestational hypertension is defined as hypertension arising de novo after 20 weeks' gestation in the absence of proteinuria and without biochemical or haematological abnormalities. Preeclampsia is diagnosed by the presence of de novo hypertension after 20 weeks' gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, and/or fetal growth restriction.

Quality assessment / Risk of bias analysis: Risk of bias for RCT was evaluated according to the Cochrane Handbook recommendations. The quality of the studies was assessed by two investigators independently in five categories: adequate sequence generation; allocation concealment; blinding of the outcome assessors; handling of missing data (intention-to-treat or per-protocol analysis); selective outcome reporting.

Strategy of data synthesis: In a first screening, two independent authors (J.M, P.S) assessed all of the abstracts retrieved

from the search, and then they obtained the full manuscripts of citations that fit the inclusion criteria. They judged study eligibility, assessed quality, and extracted data solving discrepancies by agreement, and if needed, reaching a consensus with a third author (M.C). The summarized results were critically appraised and referred to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to evaluate the quality of evidence for each outcome.

Subgroup analysis: No subgroup analysis.

Sensibility analysis: Sensitivity analysis will be performed to investigate the effect of a single study on the results by omitting one study at a time.

Language: English and Spanish.

Country(ies) involved: Spain, Chile.

Keywords: Hypertensive disorders of pregnancy, Preeclampsia, Frozen embryo transfer, In vitro fertilization, Cryopreservation.

Contributions of each author:
Author 1 - Jose Moreno-Sepulveda - JM worked on study concept and design, acquisition of data, analysis and interpretation of data and drafting the article.
Author 2 - Pamela Santucci - PS worked on study concept, acquisition and interpretation of data.
Author 3 - Miguel Checa - MC participated in the interpretation of data, critical revision of the article and the final draft.