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Uterine Artery Pulsatility Index in Singleton Pregnancies Conceived via Assisted Reproductive Technology versus Spontaneous Conception

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ADMINISTRATIVE INFORMATION

Support - The investigators have obtained no external funding.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - The investigators have obtained no external funding and declare no conflicts of interest relevant to the research question.

INPLASY registration number: INPLASY202560104

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 June 2025 and was last updated on 25 June 2025.

INTRODUCTION

Review question / Objective Our primary objective will be to systematically synthesize and quantitatively assess trimester- and method-specific differences in the uterine artery pulsatility index between singleton pregnancies conceived via assisted reproductive technology and those conceived spontaneously. We will also aim to examine how these observed uterine artery pulsatility index differences align with the associated risks for adverse perinatal outcomes, such as preeclampsia and small-for-gestational-age neonates, within the same populations.

Rationale The uterine artery pulsatility index serves as a critical non-invasive biomarker for placental function, with elevated values typically indicating impaired placentation and an increased risk of adverse pregnancy outcomes like preeclampsia and fetal growth restriction. Pregnancies conceived through assisted reproductive technology are recognized to carry a higher risk of placental dysfunction and related complications, including a significantly increased incidence of preeclampsia and small-for-gestational-age neonates.

However, the interpretation of uterine artery pulsatility index measurements in assisted reproductive technology pregnancies remains uncertain, and existing literature often presents conflicting results, frequently due to a lack of stratification by specific assisted reproductive technology techniques. This meta-analysis will address this gap by providing a comprehensive, systematic assessment of uterine artery pulsatility index variations across different assisted reproductive technology modalities. By contextualizing uterine artery pulsatility index findings with associated perinatal outcomes, we aim to understand whether observed differences in uterine artery pulsatility index truly reflect placental perfusion or are influenced by the specific assisted reproductive technology methods and protocols.

This deepened understanding may contribute to the development of assisted reproductive technology-specific uterine artery pulsatility index assessment strategies, which could potentially inform clinical management and improve maternal-fetal outcomes for this growing population.

Condition being studied The primary condition being studied will be the uterine artery pulsatility index. This will specifically involve comparing uterine artery pulsatility index values between singleton pregnancies conceived via various assisted reproductive technology methods and those conceived spontaneously.

METHODS

Search strategy PubMed search string: "((uterine artery) OR (UtA)) AND (((((((assisted reproductive techniques) OR (ART)) OR (assisted reproduction)) OR (IVF)) OR (in vitro fertilization)) OR (ICSI)) OR (intracytoplasmic injection)) OR (embryo transfer))".

Participant or population Our study population will comprise women with pregnancies conceived via assisted reproductive technology. The control population will consist of spontaneously conceived pregnancies. Both groups will have undergone uterine artery Doppler measurements. Studies involving participants under 18 years of age will be excluded.

Intervention No intervention is investigated. Only observational studies will be included.

Comparator Not applicable.

Study designs to be included Observational studies.

Eligibility criteria Study Design: Observational studies investigating differences in uterine artery pulsatility index measurements between spontaneously and assisted reproductive technology conceived singleton pregnancies.
Measurements: Studies must include uterine artery pulsatility index Doppler measurements from either the first or second trimester.
Population: The study population will comprise women who conceived via assisted reproductive technology, while the control population will comprise spontaneously conceived pregnancies. Pregnancies should be singletons and both groups should have uterine artery Doppler measurements.
Age: Studies involving participants under 18 years of age will be excluded.
Exclusions: Case reports, small case series, letters to the editor, animal studies, conference proceedings, abstracts, and review articles will not be included.

Information sources A comprehensive literature search will be conducted to identify studies comparing mean uterine artery pulsatility index Doppler measurements between spontaneously conceived pregnancies and those achieved through various assisted reproductive technology methods and protocols. The search will cover MEDLINE (via PubMed), Scopus, and the Cochrane Central Register of Controlled Trials from inception up to a defined end date. Search strategies will be customized for each database. Additional sources will be identified through Google Scholar, and the reference lists of eligible studies and relevant review articles will be manually screened. Only studies published in English will be considered for inclusion.

Main outcome(s) The primary outcome of this review will be the standardized mean difference in uterine artery pulsatility index between spontaneously conceived pregnancies and those resulting from assisted reproductive technology during the first and second trimesters.

Additional outcome(s) To ensure the robustness of our findings and account for potential confounding, additional analyses will be performed:
Gestational Age-Adjusted Indices: Analyses will utilize gestational age-standardized indices, specifically multiples of the median, for the first or second trimester, based on the availability of the data.
Multivariable Model Coefficients: Inverse-variance weighted meta-analyses will be performed using regression coefficients from multivariable models reported in individual studies (either for uterine artery pulsatility index or log base 10 uterine artery pulsatility index) as a supplementary analysis to assess the consistency of associations.

Quality assessment / Risk of bias analysis The methodological quality of each included study will be evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies. Risk of bias within individual studies will be assessed using the Quality In Prognosis Studies (QUIPS) tool. Each domain will be categorized as low, moderate, or high risk of bias, and discrepancies will be resolved through discussion or consultation with a third reviewer.

Strategy of data synthesis This will be an aggregate data meta-analysis based on study-level summary statistics. In cases where studies report

outcomes at multiple time-points or from overlapping cohorts, only one observation per analysis will be included to prevent double counting. However, when studies provide data for distinct, non-overlapping assisted reproductive technology subgroups (e.g., fresh versus frozen embryo transfer), each subgroup will be included separately within the relevant stratified analysis.

Uterine artery pulsatility index will be analyzed as a continuous variable. When heterogeneous continuous variables are included in an analysis, the results will be presented as standardized mean differences, which express effect sizes in units of the pooled standard deviation across studies. When the same type of continuous measurements are analyzed, the results will be presented as mean differences. For continuous variables, the inverse variance will be employed as the statistical method. For categorical outcomes, the effect measure will be risk ratio, and the statistical method used will be Mantel-Haenszel.

Given the expected variability among studies, a random-effects model (DerSimonian and Laird method) will be employed for all meta-analyses. Between-study heterogeneity will be assessed using the Cochrane Q test (with $p<0.1$ indicating significant heterogeneity) and quantified with the I^2 statistic.

Publication bias will be assessed visually via funnel plots and statistically using Egger's test for primary analyses if more than ten studies are included.

Subgroup analysis To thoroughly investigate method-specific vascular profiles, we will conduct comprehensive subgroup analyses for all outcomes that will be investigated. These analyses will involve stratifying pregnancies by specific assisted reproductive technology methods and protocols, including cases of ovulation induction/intrauterine insemination, the use of donor or autologous oocytes, fresh or frozen embryo transfers, and natural or artificial endometrial preparation cycles. Pregnancies resulting from in vitro fertilization/intracytoplasmic sperm injection for which more detailed information regarding oocyte origin, specific protocol, or other relevant factors is unavailable will be grouped into a broader, common in vitro fertilization/intracytoplasmic sperm injection category.

Sensitivity analysis A risk of bias sensitivity analysis for our primary analyses will take place, excluding those studies deemed as high risk based on QUIPS.

Language restriction No language limits will be imposed on the search but we will consider for inclusion only studies written in English.

Country(ies) involved Greece.

Keywords Assisted Reproductive Technology, Uterine Artery Pulsatility Index, Placental Function, Preeclampsia, Small for Gestational Age.

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