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Doppler Ultrasound Assessment of Fetuses with Single Umbil-ical Artery (SUA): A Systematic Review of the Literature from the Past 15 Years

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INTRODUCTION

 $R^{\mbox{eview question / Objective}}_{\mbox{research question guiding this systematic}}$ review is:

How does Doppler ultrasound contribute to the prediction and management of complications in fetuses with SUA?

This central question includes the following subquestions:

• What Doppler indices are typically observed in SUA pregnancies, and how do they differ from those in normal gestations?

• What is the correlation between Doppler findings and fetal outcomes such as IUGR, SGA, and preterm birth?

• How does the diagnostic utility of Doppler ultrasound vary across different trimesters, and how can this information inform obstetric management? • What maternal or fetal factors (e.g., comorbidities or structural anomalies) may influence Doppler patterns and associated outcomes in SUA?

Addressing these questions will enhance our understanding of SUA and improve clinical decision-making in affected pregnancies. This review aims to provide clinicians and researchers with a consolidated body of evidence based on data from the past 15 years.

This systematic review aims to provide a comprehensive synthesis of the existing literature regarding the application of Doppler ultrasound in pregnancies affected by SUA. The objectives are: 1. Evaluation of Doppler Parameters:

To assess the effectiveness of Doppler indices, particularly RI and PI, in identifying adverse perinatal out-comes such as IUGR, SGA, and fetal hypoxia in pregnancies complicated by SUA.

2. Trimester-Specific Findings:

To evaluate the differences in Doppler findings across the first, second, and third trimesters, with

emphasis on the second and third trimesters as key periods for fetal development and placental assessment.

This review aims to address existing gaps in the literature and provide evidence-based recommendations for the clinical use of Doppler ultrasound in the monitoring of SUA pregnancies.

Rationale Single Umbilical Artery (SUA) is the most common umbilical cord abnormality, occurring in approximately 0.5–1% of singleton pregnancies and up to 5% of multiple pregnancies. SUA is associated with increased risks of intrauterine growth restriction (IUGR), small for gestational age (SGA) fetuses, fetal hypoxia, preterm delivery, and, in severe cases, intrauterine fetal demise (IUFD).

Doppler ultrasound offers a non-invasive, dynamic assessment of fetoplacental circulation and has become an essential tool in evaluating high-risk pregnancies. Parameters such as the Resistance Index (RI), Pulsatility Index (PI), and Systolic/ Diastolic (S/D) ratio provide critical insight into vascular resistance and perfusion status. However, despite widespread clinical use, there is a lack of consensus on the timing, interpretation, and prognostic value of Doppler findings specifically in SUA-complicated pregnancies.

This systematic review was conducted to synthesize the existing literature from the past 15 years on the utility of Doppler ultrasound in SUA pregnancies. The study aimed to clarify its diagnostic accuracy, predictive value for adverse outcomes, and role in guiding clinical management. Addressing this gap is essential for optimizing surveillance strategies and improving maternal-fetal outcomes in affected pregnancies.

Condition being studied Single Umbilical Artery (SUA) is the most common congenital abnormality of the umbilical cord, characterized by the absence of one of the two umbilical arteries. Instead of the typical two arteries and one vein, the umbilical cord in SUA cases contains only one artery and one vein. This vascular anomaly occurs in approximately 0.5–1% of singleton pregnancies and up to 5% in multiple gestations.

While SUA can be an isolated finding with no clinical consequences, it is frequently associated with a range of adverse fetal outcomes. These include intrauterine growth restriction (IUGR), small for gestational age (SGA) neonates, fetal hypoxia, preterm delivery, and increased perinatal morbidity and mortality. SUA is also correlated with structural anomalies, particularly in the cardiovascular, renal,

and central nervous systems, as well as chromosomal abnormalities such as trisomy 13 and 18.

Given these potential complications, early identification and close monitoring of fetuses with SUA are crucial. Doppler ultrasound is a noninvasive imaging modality that allows real-time assessment of fetal and placental hemodynamics. It measures parameters such as Resistance Index (RI), Pulsatility Index (PI), and Systolic/Diastolic (S/ D) ratio in key fetal vessels, including the umbilical artery. These indices reflect vascular resistance and can signal impaired placental perfusion, a precursor to many of the complications associated with SUA.

Despite widespread use, there remains variability in how and when Doppler ultrasound is applied in pregnancies affected by SUA. Moreover, the predictive value of Doppler findings for specific outcomes such as IUGR, IUFD, and preterm birth has not been comprehensively synthesized in the context of SUA.

This systematic review aims to fill that gap by critically evaluating and summarizing the literature from the past 15 years on the use of Doppler ultrasound in pregnancies complicated by SUA. It investigates the diagnostic utility of Doppler indices, their correlation with perinatal outcomes, and their role in guiding obstetric management. The ultimate goal is to support evidence-based clinical decision-making and improve outcomes in this high-risk population.

METHODS

Search strategy To ensure a comprehensive and high-quality synthesis of the literature, a systematic search strategy was developed based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The objective was to identify relevant studies published over the past 15 years that investigated the role of Doppler ultrasound in pregnancies complicated by Single Umbilical Artery (SUA), with a specific focus on fetal outcomes and Doppler indices.

Electronic Databases

The following three major bibliographic databases were systematically searched to capture peerreviewed journal articles across a broad spectrum of clinical, biomedical, and obstetric research:

PubMed (MEDLINE):

A comprehensive database of biomedical literature maintained by the U.S. National Library of Medicine. PubMed includes journals focusing on obstetrics, fetal medicine, imaging, and perinatal outcomes.

Scopus:

One of the largest abstract and citation databases of peer-reviewed literature, covering health sciences, life sciences, and clinical research. Scopus was used to retrieve studies not indexed in PubMed and to cross-reference multidisciplinary content.

Web of Science (WoS):

An international citation database indexing highimpact scientific literature, including medical, clinical, and epidemiological studies. Web of Science helped ensure inclusion of globally relevant and high-quality research.

These three databases were selected for their coverage of clinical and imaging-based research, their ability to index full-text and abstracted literature, and their compatibility with Boolean and MeSH (Medical Subject Headings) search strategies.

Search Terms and Strategy

A combination of Medical Subject Headings (MeSH), Emtree terms, and free-text keywords was employed to capture a wide range of relevant studies. Terms were selected to reflect both the condition of interest (SUA) and the diagnostic modality (Doppler ultrasound), along with relevant outcomes.

The primary keywords and Boolean search terms included:

"Single Umbilical Artery" OR "SUA"

"Doppler Ultrasound" OR "Color Doppler" OR "Fetal Doppler"

"Fetal Outcomes" OR "Pregnancy Outcomes" OR "Perinatal Outcomes"

"Resistivity Index" OR "RI"

"Pulsatility Index" OR "PI"

"Systolic/Diastolic Ratio" OR "S/D Ratio"

"IUGR" OR "Intrauterine Growth Restriction"

"SGA" OR "Small for Gestational Age"

"IUFD" OR "Intrauterine Fetal Demise"

"Preterm Delivery" OR "NICU Admission"

"Umbilical Artery" OR "Uterine Artery" OR "Middle Cerebral Artery"

These terms were combined using Boolean operators such as AND and OR to optimize both sensitivity and specificity. Sample search strings included:

"Single Umbilical Artery" AND "Doppler Ultrasound" AND ("RI" OR "PI" OR "S/D Ratio")

"SUA" AND "Fetal Outcomes" AND "Pregnancy Complications"

"Single Umbilical Artery" AND "Umbilical Artery Doppler" AND ("Growth Restriction" OR "Hypoxia")

Search Filters Applied

To enhance the quality and relevance of the included studies, the following filters were applied during the database searches:

Publication Date: January 2008 to December 2023

Language: English only

Article Type: Peer-reviewed original research articles (including cohort, case-control, and prospective observational studies)

Case reports, review articles, editorials, conference abstracts, and non-human studies were excluded. Only studies that included quantitative data on Doppler parameters and fetal or perinatal outcomes in SUA pregnancies were considered eligible for inclusion.

Additional Search Methods

Manual Reference List Screening: Reference lists of included articles were reviewed to identify additional studies that may have been missed during database searches.

Forward Citation Tracking: Citation networks were analyzed through Google Scholar and Scopus to identify studies that cited or were cited by key papers.

Grey Literature: No unpublished studies, theses, or government reports were included due to concerns about variability in methodological quality and lack of peer review. This structured approach ensured a comprehensive and unbiased selection of relevant literature, capturing both foundational studies and recent advances in the field. The search strategy was designed to be transparent and reproducible, allowing future researchers to replicate or expand upon this review.

Participant or population This systematic review focuses on pregnant individuals diagnosed with Single Umbilical Artery (SUA) and the fetuses affected by this condition, across various gestational stages. The included studies were selected based on well-defined criteria that ensured clinical relevance, methodological quality, and direct relevance to the use of Doppler ultrasound in evaluating SUA pregnancies.

Inclusion Criteria:

Pregnant Women Diagnosed with SUA:

Participants included were pregnant individuals carrying fetuses diagnosed prenatally with SUA via routine obstetric ultrasound, with or without associated fetal anomalies.

Singleton and Multiple Gestations:

Both singleton and multiple pregnancies were considered, although most studies focused primarily on singleton gestations due to the higher rate of isolated SUA in this population.

Gestational Age at Diagnosis:

Participants were included regardless of the trimester at which SUA was diagnosed. However, particular attention was given to those assessed in the second and third trimesters, as this is when Doppler ultrasound is most frequently employed and relevant outcomes (e.g., IUGR, SGA, IUFD) begin to manifest.

Live Pregnancies Monitored with Doppler Ultrasound:

Only studies that conducted Doppler evaluation of umbilical or other fetal vessels (e.g., middle cerebral artery, uterine artery) in SUA pregnancies were included. These Doppler assessments needed to be linked to measurable fetal or perinatal outcomes.

Fetuses With or Without Additional Anomalies:

The review encompassed SUA cases both with isolated findings and those accompanied by additional fetal anomalies or syndromic diagnoses (e.g., trisomy 13, trisomy 18), as long as Doppler indices and outcomes were explicitly reported.

Exclusion Criteria: Pregnancies without confirmed SUA diagnosis Studies lacking Doppler ultrasound data

Animal models or in vitro studies

Case reports or studies without clear clinical outcome data

Participants with only postnatal SUA diagnosis (i.e., not identified prenatally)

This inclusion framework ensures that the review comprehensively addresses the population most relevant to clinical practice: pregnant individuals with prenatally diagnosed SUA, with a focus on understanding how Doppler ultrasound contributes to fetal surveillance, risk stratification, and obstetric decision-making.

Intervention The primary intervention evaluated in this systematic review is the use of Doppler ultrasound to assess fetoplacental circulation in pregnancies complicated by Single Umbilical Artery (SUA).

Description of the Intervention:

Doppler ultrasound is a non-invasive imaging modality used to evaluate the velocity and pattern of blood flow within fetal and placental vessels. In the context of SUA, Doppler assessments are employed to monitor vascular resistance, placental sufficiency, and fetal well-being.

The review specifically focuses on Doppler evaluation of the following key vessels and parameters:

Umbilical Artery Doppler

Resistance Index (RI)

Pulsatility Index (PI)

Systolic/Diastolic (S/D) Ratio

These indices reflect vascular resistance and are used to detect early signs of placental insufficiency, which is common in SUA pregnancies.

Additional Vessels (as applicable in included studies):

Middle Cerebral Artery (MCA): Assesses fetal cerebral redistribution in response to hypoxia

Uterine Artery Doppler: Evaluates maternal blood flow to the placenta

Ductus Venosus: Reflects fetal cardiac function and central venous pressure

Timing of the Intervention:

The review includes studies where Doppler ultrasound was performed in any trimester, though most data derive from the second and third trimesters, when abnormal flow patterns are more predictive of adverse outcomes such as intrauterine growth restriction (IUGR), small for gestational age (SGA), fetal hypoxia, or intrauterine fetal demise (IUFD).

Purpose of the Intervention:

The Doppler ultrasound assessments aim to:

Identify fetuses at increased risk of adverse outcomes

Guide decisions regarding increased surveillance, hospitalization, or early delivery

Support clinical management by informing timing and mode of delivery (e.g., induction vs. cesarean section)

This review evaluates the effectiveness, predictive value, and clinical utility of Doppler ultrasound as an intervention in the management of SUA pregnancies. It also explores how Doppler findings influence obstetric decisions and contribute to improved maternal and neonatal outcomes.

Comparator In this systematic review, the primary focus is on assessing the use of Doppler ultrasound in pregnancies complicated by Single Umbilical Artery (SUA). While many of the included studies are observational and do not use a formal control arm, several studies include or compare with the following:

Comparative Groups (if applicable):

SUA Pregnancies Without Doppler Monitoring:

Some studies compare outcomes in SUA pregnancies monitored with Doppler ultrasound to those without Doppler evaluation, allowing assessment of the added clinical value of Doppler surveillance.

Normal (Three-Vessel Cord) Pregnancies with Doppler:

Doppler indices and fetal outcomes in SUA pregnancies are compared with those from pregnancies with a normal three-vessel cord. This comparative approach helps distinguish whether abnormal Doppler findings are specific to SUA-related placental dysfunction.

SUA Pregnancies with Isolated Findings vs. SUA with Structural/Chromosomal Anomalies:

In some studies, SUA fetuses are divided into those with isolated SUA and those with additional anomalies. Doppler findings are compared between these subgroups to evaluate whether associated anomalies influence vascular resistance and outcomes.

Purpose of Comparative Interventions: These comparisons allow for the evaluation of:

The incremental value of Doppler ultrasound in monitoring SUA pregnancies

Whether intervention with Doppler alters management or outcomes

How Doppler findings in SUA differ from normal pregnancies

Whether SUA should be managed more aggressively when Doppler abnormalities are detected

While randomized controlled trials are limited in this area, these comparative analyses provide meaningful clinical insights into the diagnostic and prognostic utility of Doppler imaging in high-risk obstetric care.

Study designs to be included The review will include observational study designs such as prospective and retrospective cohort studies, case-control studies, and cross-sectional studies that report on Doppler ultrasound findings in pregnancies complicated by Single Umbilical Artery (SUA). Only studies providing quantitative Doppler indices and associated fetal or perinatal outcomes will be considered. Case reports, reviews, and animal studies will be excluded.

Eligibility criteria In addition to the criteria defined by the PICOS framework, the following were applied:

Inclusion: Only peer-reviewed full-text articles published in English between January 2008 and December 2023 were considered. Studies had to include Doppler ultrasound data specifically related to SUA pregnancies with reported fetal or perinatal outcomes.

Exclusion: Conference abstracts, editorials, letters to the editor, case reports, review articles, and studies without original Doppler measurements or outcome data were excluded. Studies lacking clear diagnostic criteria for SUA or those involving postnatal-only SUA identification were also omitted.

Information sources To ensure a comprehensive and unbiased synthesis of the available evidence, multiple high-quality sources were used to identify studies relevant to the use of Doppler ultrasound in pregnancies complicated by Single Umbilical Artery (SUA). The information sources were chosen to reflect the scope and standards of systematic reviews conducted in clinical and obstetric research.

1. Electronic Databases

The following electronic databases were searched systematically:

PubMed (MEDLINE): A primary source of biomedical and clinical literature, PubMed was used to retrieve studies published in peer-reviewed journals, particularly those focused on maternalfetal medicine, ultrasound diagnostics, and obstetric outcomes.

Scopus: As one of the largest citation and abstract databases, Scopus provided access to multidisciplinary studies and allowed for citation tracking of key research articles not indexed in PubMed.

Web of Science (WoS): Web of Science was included to capture additional high-impact literature, particularly from international sources, and to supplement citation analysis and crossreferencing.

These three databases were selected for their extensive coverage, academic rigor, and compatibility with advanced Boolean and MeSHbased search strategies.

2. Manual Reference List Screening

The reference lists of all included studies and key review articles were manually screened to identify additional relevant publications that may not have been captured during the initial database search. This backward citation tracking method enhanced the sensitivity of the review and minimized the risk of missing pertinent studies.

3. Forward Citation Tracking

To capture more recent literature and studies citing foundational works, forward citation tracking was performed using Google Scholar and Scopus. This helped identify ongoing discussions and newly published studies on Doppler ultrasound in SUA pregnancies that may not yet be indexed in all databases.

4. Grey Literature and Trial Registers

Due to concerns about the methodological consistency and peer-review status, grey literature, including dissertations, conference proceedings, and unpublished manuscripts, was not included in this review. Similarly, clinical trial registries such as <u>ClinicalTrials.gov</u> and the WHO International Clinical Trials Registry Platform were consulted but did not yield eligible studies matching the inclusion criteria (i.e., completed trials with published results and relevant Doppler data).

5. Author Contact

In cases where essential information (e.g., specific Doppler indices or outcome data) was missing from published manuscripts, attempts were made to contact corresponding authors via email. However, no unpublished data were obtained through direct author correspondence for this review.

Main outcome(s) The primary outcomes of this systematic review focused on evaluating the clinical utility of Doppler ultrasound in pregnancies complicated by Single Umbilical Artery (SUA). The review specifically assessed how Doppler parameters correlate with adverse fetal and perinatal outcomes, and how they may guide obstetric management.

Primary Outcomes:

Intrauterine Growth Restriction (IUGR):

Identified based on biometric parameters below the 10th percentile for gestational age and associated with abnormal Doppler indices such as elevated Resistance Index (RI) or Pulsatility Index (PI).

Small for Gestational Age (SGA):

Defined as neonatal birth weight below the 10th percentile. The review evaluated the association of SGA with abnormal umbilical artery Doppler findings, particularly high S/D ratios.

Intrauterine Fetal Demise (IUFD):

Cases of fetal death in utero were reviewed in the context of preceding Doppler abnormalities, such as absent or reversed end-diastolic flow.

Preterm Delivery:

Assessed as delivery before 37 weeks' gestation, often prompted by Doppler findings indicating fetal compromise.

Neonatal Outcomes:

Including NICU admission, low Apgar scores, and cesarean section rates due to fetal distress identified via Doppler.

Effect Measures and Timing:

Effect measures included Odds Ratios (ORs), Confidence Intervals (CIs), and mean values for Doppler indices (RI, PI, S/D ratio).

Timing of Doppler assessments was stratified by trimester, with a focus on second and third trimester evaluations when fetal hemodynamic changes become more clinically relevant.

This review synthesizes the predictive value of Doppler findings and their impact on clinical decisions, including timing and mode of delivery in SUA pregnancies.

Additional outcome(s) In addition to primary fetal and perinatal outcomes, this review examined several secondary clinical outcomes relevant to the management of Single Umbilical Artery (SUA) pregnancies:

Mode of Delivery:

The frequency of cesarean section versus vaginal delivery was assessed, particularly in cases where Doppler abnormalities prompted early or emergency intervention.

Longitudinal Doppler Changes:

Serial Doppler measurements were evaluated to understand how Doppler indices evolve over time, helping to predict progression of placental insufficiency or fetal compromise.

Correlation with Structural or Chromosomal Anomalies:

The review investigated whether Doppler abnormalities were more frequent in non-isolated SUA cases, contributing to prenatal risk stratification.

Maternal Outcomes:

Although limited, some studies reported on maternal outcomes such as preeclampsia and gestational hypertension, which were analyzed for potential associations with abnormal Doppler readings.

Utility in Clinical Decision-Making:

The role of Doppler in guiding surveillance intensity, timing of steroid administration, hospitalization, and delivery planning was also reviewed as part of broader obstetric management strategies.

These additional outcomes contribute to a more comprehensive understanding of how Doppler ultrasound influences both fetal prognosis and maternal care decisions in SUA pregnancies. **Data management** A structured and systematic approach was employed to manage all records and data collected during the review process, ensuring transparency, consistency, and reproducibility.

Reference Management

All references identified through electronic database searches (PubMed, Scopus, Web of Science) were imported into EndNote reference management software. This tool was used to:

Automatically remove duplicate entries

Organize citations by database source

Assign preliminary labels for screening stages (title/ abstract/full text)

The deduplicated list was then exported into an Excel spreadsheet for further tracking and analysis.

Screening Process

Two independent reviewers conducted the title and abstract screening using the predefined inclusion and exclusion criteria. Discrepancies were resolved by discussion or by a third reviewer. Eligible studies were then retrieved in full-text format for detailed evaluation.

A PRISMA flow diagram was used to document the number of studies at each stage: identified, screened, assessed for eligibility, and included in the final synthesis.

Data Extraction

A standardized data extraction template was developed in Microsoft Excel. The following variables were extracted from each included study:

Study characteristics (authors, year, country, design)

Participant details (sample size, gestational age, SUA type)

Doppler parameters assessed (RI, PI, S/D ratio, vessels)

Fetal and perinatal outcomes (IUGR, SGA, IUFD, NICU admission, delivery mode)

Timing of Doppler assessments

Key findings and statistical measures (mean values, ORs, CIs)

To ensure accuracy, a second reviewer cross-validated all extracted data.

Data Synthesis and Storage

Extracted data were stored in secure, cloud-based folders with version control. For quantitative synthesis, data were imported into statistical software (SPSS and RevMan) for descriptive analysis and potential meta-analysis.

This structured process ensured rigorous data handling, minimized bias, and maintained auditability throughout the review.

Quality assessment / Risk of bias analysis To ensure the validity and reliability of the evidence included in this systematic review, a structured quality assessment was performed for all eligible primary studies.

Assessment Tool

The Newcastle-Ottawa Scale (NOS) was used for quality assessment of observational studies, including cohort and case-control designs. This tool evaluates methodological quality based on three main domains:

Selection of study groups

Comparability of groups

Outcome assessment or exposure measurement

Each study could receive a maximum of 9 stars, with higher scores indicating lower risk of bias. Studies scoring:

7-9 stars were considered high quality

5-6 stars moderate quality

Below 5 stars low quality

For any included cross-sectional studies, a modified version of the NOS or the AXIS tool was used, focusing on sample representativeness, reporting clarity, and risk of bias in measurement and analysis.

Reviewer Process

Two independent reviewers assessed each study's quality. Disagreements were resolved through discussion, and if needed, a third reviewer adjudicated. Quality scores were recorded in a shared Excel spreadsheet for transparency.

Use in Data Synthesis

The quality assessment results informed the interpretation of findings. Studies deemed low quality were not excluded outright but were analyzed with caution and discussed explicitly in the limitations section. Sensitivity analyses were planned to examine the influence of study quality on overall conclusions.

This systematic and reproducible approach ensured a rigorous evaluation of methodological integrity across all included studies.

Strategy of data synthesis The data analysis for this systematic review will include both qualitative synthesis and quantitative summary, depending on the type and consistency of the extracted data from eligible studies.

1. Descriptive (Qualitative) Analysis

A narrative synthesis will be conducted for all included studies. Key characteristics such as study design, population details (gestational age, SUA type), sample size, Doppler parameters used (RI, PI, S/D ratio), trimester of evaluation, and clinical outcomes (IUGR, SGA, IUFD, preterm delivery, NICU admission) will be summarized in tabular form.

Patterns and trends across studies will be highlighted, particularly in:

The predictive value of abnormal Doppler indices for adverse fetal outcomes

Differences across trimesters in Doppler findings

Variability in study design or methodology that may influence results

The quality of evidence will be considered when interpreting findings, with low-quality studies noted separately.

2. Quantitative (Statistical) Analysis

Where sufficient homogeneity exists across studies in terms of population, Doppler parameters, and reported outcomes, a meta-analysis will be performed using Review Manager (RevMan) and SPSS software.

Effect Measures:

Continuous variables (e.g., mean RI/PI values) will be reported as mean differences with 95% confidence intervals.

Dichotomous outcomes (e.g., IUGR, IUFD) will be summarized using odds ratios (OR) or risk ratios (RR) with 95% confidence intervals.

Heterogeneity:

Statistical heterogeneity will be assessed using the I² statistic. A value above 50% will be considered substantial heterogeneity. Depending on the level of heterogeneity, a random-effects model or fixed-effects model will be selected accordingly.

Subgroup Analysis:

Subgroup analyses may be performed based on trimester of Doppler assessment, presence of isolated versus non-isolated SUA, or geographical region, if sufficient data are available.

Sensitivity Analysis:

Sensitivity analyses will be conducted by excluding lower-quality studies (as assessed via NOS) to test the robustness of the main findings.

Publication Bias:

If at least 10 studies are included in the metaanalysis, a funnel plot will be generated to evaluate the presence of publication bias.

All analyses will be presented using clear tables, forest plots, and graphs, accompanied by interpretations relevant to clinical practice.

Subgroup analysis To better understand the variation in outcomes and the predictive value of Doppler ultrasound in Single Umbilical Artery (SUA) pregnancies, predefined subgroup analyses will be conducted where data permit. These analyses aim to identify specific populations or clinical scenarios in which Doppler assessment is particularly effective or where risks are significantly elevated.

1. Trimester of Doppler Assessment

Subgrouping by first, second, and third trimester Doppler evaluations will be performed to examine:

Differences in the sensitivity and specificity of Doppler indices (RI, PI, S/D ratio) across gestational age

The temporal relationship between abnormal Doppler findings and the development of adverse fetal outcomes such as IUGR, SGA, or IUFD

This analysis may help determine the optimal timing for Doppler surveillance in SUA pregnancies.

2. Isolated vs. Non-Isolated SUA

Studies will be categorized based on whether SUA is:

Isolated (i.e., without additional fetal anomalies)

Non-Isolated (i.e., associated with structural or chromosomal abnormalities)

This subgroup analysis will explore whether Doppler abnormalities are more prevalent or clinically meaningful in the presence of comorbid fetal conditions.

3. Geographic or Socioeconomic Region If possible, studies will be stratified by region (e.g., high-income vs. low- and middle-income countries) to evaluate:

Variability in clinical management practices

Differences in outcomes and Doppler usage across healthcare systems

This may reveal disparities in prenatal care quality or access to fetal surveillance.

4. Type of Study Design

Outcomes may also be stratified by study design (e.g., prospective vs. retrospective), as this may impact data quality, measurement bias, and followup completeness.

Purpose of Subgroup Analysis

These subgroup analyses will enhance the interpretability of results by identifying populationspecific trends and clarifying where Doppler ultrasound has the greatest predictive or diagnostic value in SUA pregnancies. They may also support recommendations for individualized monitoring strategies in clinical practice.

Sensitivity analysis To assess the robustness and reliability of the findings in this systematic review, a sensitivity analysis will be performed. This step is essential to determine whether the overall conclusions are influenced by specific study characteristics, methodological quality, or data outliers.

1. Study Quality

The primary sensitivity analysis will involve excluding studies rated as low quality based on the Newcastle-Ottawa Scale (NOS) or other applicable tools. By focusing on moderate- and high-quality studies, this analysis will reveal whether the inclusion of lower-quality evidence affects the direction or magnitude of associations between Doppler findings and adverse outcomes (e.g., IUGR, IUFD, SGA).

2. Sample Size

To reduce the potential bias introduced by small study effects, analyses will be repeated excluding studies with sample sizes below 100 participants. This will help determine if smaller studies disproportionately influence pooled estimates or heterogeneity.

3. Study Design

Sensitivity analysis may also involve comparing results from prospective studies only versus all included studies. Prospective studies generally provide higher-quality data with standardized follow-up and outcome reporting.

4. Trimester-Specific Doppler Assessment

If significant variability exists in outcomes across gestational age, separate sensitivity analyses may be conducted for second- and third-trimester Doppler assessments to confirm the consistency of findings related to timing.

By systematically removing or isolating certain subsets of studies, the sensitivity analysis will test the stability and validity of the main results, strengthen the credibility of the conclusions, and help guide clinical interpretation.

Language restriction Yes, only studies published in English will be included to ensure accurate interpretation of clinical terminology and methodological details.

Country(ies) involved Romania.

Other relevant information No ethical approval is required for this study, as it involves secondary analysis of published data without direct human participant involvement.

The review team includes clinicians and researchers with expertise in obstetrics, fetal medicine.

Keywords single umbilical artery; doppler; ultrasound.

Dissemination plans The findings of this systematic review will be disseminated through multiple academic and clinical channels to maximize its impact on research and practice in maternal-fetal medicine.

Primarily, the review will be submitted for publication in a peer-reviewed, open-access, Q1

medical journal specializing in obstetrics, gynecology, or diagnostic imaging (e.g., Diagnostics or Ultrasound in Obstetrics & Gynecology). This will ensure wide visibility among clinicians, researchers, and policy-makers.

In addition, the results will be presented at national and international conferences related to perinatology, obstetrics, and ultrasound, such as the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and European Congress of Perinatal Medicine.

Where appropriate, summaries and key recommendations will be shared through professional networks, institutional newsletters, and social media platforms (e.g., ResearchGate, LinkedIn) to engage a broader clinical audience.

Furthermore, the findings may be used to inform clinical protocols and educational materials in academic hospitals and training programs, with the goal of improving the antenatal management of Single Umbilical Artery (SUA) pregnancies.

No proprietary restrictions exist, and the authors are committed to transparent and accessible dissemination of all outcomes.

Contributions of each author

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