INPLASY

Doppler Ultrasound Assessment of Fetuses with Single Umbilical Artery: A Systematic Review of the Literature from the Past 15 Years

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INTRODUCTION

Review question / Objective Review Question What is the predictive accuracy of Doppler ultrasound indices—specifically the Resistance Index (RI), Pulsatility Index (PI), and Systolic/Diastolic (S/D) ratio—for adverse perinatal outcomes in fetuses diagnosed with a single umbilical artery (SUA)?

Objectives
The primary objective of this systematic review is to evaluate whether Doppler ultrasound indices can reliably predict adverse perinatal outcomes in pregnancies complicated by SUA. The review aims to synthesize available evidence on the diagnostic and prognostic value of Doppler parameters and determine their clinical applicability in routine obstetric care.

The secondary objectives are fourfold:

1. Assess the quality of evidence – using validated appraisal tools such as the Newcastle-Ottawa Scale, to evaluate methodological rigor and identify strengths and weaknesses across published studies.

2. Examine trimester-specific predictive performance – by analyzing whether Doppler indices have differing diagnostic value depending on the gestational period of assessment.

3. Identify optimal Doppler parameters – to determine which indices, or combinations thereof, show the highest predictive value for intrauterine growth restriction (IUGR), small-for-gestational-age (SGA) neonates, intrauterine fetal demise (IUFD), preterm delivery, cesarean section, and NICU admission.

4. Evaluate heterogeneity across studies – to explore the impact of study design, sample size, population characteristics, and protocol variations on reported outcomes and predictive accuracy.

By pursuing these objectives, this review seeks to address key knowledge gaps in the management of SUA pregnancies. Current practice lacks standardized protocols for Doppler use, resulting in inconsistent monitoring strategies and uncertainty in clinical decision-making. Although some evidence suggests that abnormal Doppler findings may indicate higher risk of IUGR and other complications, the predictive accuracy remains poorly defined, with arbitrary cutoff values and heterogeneous methodologies across studies.

This review therefore aims not only to quantify the predictive value of Doppler indices but also to highlight the methodological limitations that hinder their clinical utility. Ultimately, the findings will inform clinicians and researchers about the reliability of Doppler ultrasound as a surveillance tool in SUA pregnancies, emphasize the need for prospective multicenter studies with standardized protocols, and provide a basis for evidence-based recommendations to improve perinatal outcomes.

Rationale A single umbilical artery (SUA) is the most frequent umbilical cord abnormality, occurring in approximately 0.5–1% of singleton pregnancies. SUA has been consistently associated with an increased risk of adverse perinatal outcomes, including intrauterine growth restriction (IUGR), small-for-gestational-age (SGA) neonates, preterm birth, congenital malformations, and perinatal mortality. Despite its relatively common occurrence, clinical management of SUA remains controversial and inconsistent across institutions, largely due to the absence of standardized monitoring protocols and reliable predictive tools.

Doppler ultrasound is a widely available, non-invasive imaging modality that allows assessment of fetoplacental circulation. Several Doppler indices—including the Resistance Index (RI), Pulsatility Index (PI), and Systolic/Diastolic (S/D) ratio—are commonly used in clinical practice to evaluate vascular resistance and blood flow. In theory, these parameters could provide valuable information in SUA pregnancies, where reduced vascular capacity may compromise placental perfusion. By identifying early hemodynamic compromise, Doppler could assist clinicians in stratifying risk, guiding surveillance, and optimizing the timing of delivery.

However, there are significant knowledge gaps that limit the integration of Doppler into routine SUA management. First, the predictive accuracy of Doppler indices for adverse perinatal outcomes in SUA pregnancies remains uncertain. Available studies report inconsistent findings, often using heterogeneous protocols, variable cutoff values, and differing gestational time points of measurement. For example, while elevated RI has been associated with IUGR in some studies, others report modest or non-significant associations. Similarly, the utility of PI and S/D ratio in predicting SGA or stillbirth has not been clearly established.

Second, there are no standardized guidelines on how and when Doppler assessment should be performed in SUA pregnancies. Some clinicians employ serial Doppler examinations in the third trimester, while others rely primarily on biophysical profile or growth scans. The lack of consensus creates substantial variation in practice, leaving both clinicians and patients uncertain about the most effective monitoring strategy. This absence of standardization also limits comparability across studies, further complicating evidence synthesis.

Third, the methodological limitations of existing studies reduce the certainty of current evidence. Most investigations are retrospective cohorts with small to moderate sample sizes, introducing potential selection bias and confounding. Quality assessment reveals that many studies fail to adjust adequately for key variables such as maternal age, parity, or comorbidities. Moreover, the majority of available evidence comes from high-income countries, limiting its generalizability to diverse healthcare settings, particularly in low- and middle-income contexts where access to advanced imaging may be constrained.

In addition to these knowledge gaps, there are areas of ongoing controversy. The utility of Doppler in the first trimester for SUA detection and risk stratification remains debated, as early screening has not consistently demonstrated predictive value. The cost-effectiveness of routine Doppler surveillance is also unclear, raising questions about resource allocation in healthcare systems with competing priorities. Furthermore, the integration of Doppler with other monitoring modalities—such as biochemical markers, uterine artery Doppler, or placental imaging—has yet to be systematically explored. These uncertainties highlight the pressing need for high-quality, standardized, and multicenter research.

Given these limitations, clinicians face a dilemma: SUA pregnancies are clearly at elevated risk, yet existing tools for prediction and monitoring are unreliable. Without standardized evidence-based protocols, clinical management is often individualized and may lead to either under-monitoring, risking missed complications, or over-monitoring, with potential unnecessary interventions and healthcare costs.

This systematic review therefore addresses an important gap in the literature. By synthesizing available evidence from the past 15 years, it aims to clarify the predictive accuracy of Doppler ultrasound indices in SUA pregnancies, assess the quality of existing studies, and highlight sources of heterogeneity. The rationale for this review is not only to inform clinical practice but also to lay the.

Condition being studied The condition of interest in this review is Single Umbilical Artery (SUA), the most common congenital anomaly of the umbilical cord. In a normal pregnancy, the umbilical cord typically contains two arteries and one vein, which together ensure adequate fetoplacental circulation. SUA is defined by the absence of one of the two umbilical arteries, resulting in a two-vessel cord. This anomaly occurs in approximately 0.5–1% of singleton pregnancies and is more frequently observed in multiple gestations.

The exact pathogenesis of SUA is not fully understood. It may result from primary agenesis of one umbilical artery or secondary atrophy of a previously normal vessel during embryogenesis. Regardless of the underlying mechanism, the condition reduces the vascular capacity of the umbilical cord, thereby limiting blood flow between the fetus and placenta. This reduction in vascular reserve may contribute to impaired fetoplacental perfusion, hypoxemia, and growth disturbances.

Clinically, SUA is important because of its strong association with adverse pregnancy outcomes. Fetuses with SUA are at higher risk of intrauterine growth restriction (IUGR), being small for gestational age (SGA), preterm birth, congenital malformations, and perinatal mortality. Reported rates of IUGR in SUA pregnancies range from 18% to over 40%, significantly higher than in the general population. SUA has also been linked to an increased incidence of congenital anomalies, particularly cardiovascular, renal, and skeletal malformations. While SUA can occur as an isolated finding, in many cases it is accompanied by structural or chromosomal abnormalities, further complicating prognosis and management.

Despite these risks, the clinical course of SUA pregnancies is highly variable. Some fetuses with SUA progress without complication and are delivered at term with normal growth, while others experience severe growth restriction, distress, or even intrauterine demise. This heterogeneity makes it difficult for clinicians to stratify risk and determine which pregnancies require closer surveillance and intervention.

The current standard of care for SUA typically involves enhanced prenatal surveillance, often using serial ultrasound examinations to monitor fetal growth and amniotic fluid volume. Doppler ultrasound has emerged as a potentially valuable tool, as it provides a non-invasive method to evaluate blood flow resistance and vascular function in the umbilical and uterine arteries. Abnormal Doppler indices—such as elevated Resistance Index (RI), Pulsatility Index (PI), or Systolic/Diastolic (S/D) ratio—may indicate compromised placental perfusion and predict adverse perinatal outcomes. However, the predictive accuracy of these indices in SUA pregnancies is not well established, and there are no standardized guidelines for their use in clinical practice.

The uncertainty surrounding SUA management reflects broader gaps in the evidence base. Most studies to date have been retrospective, with heterogeneous methodologies and variable definitions of outcomes. Cutoff values for abnormal Doppler indices differ widely across studies, limiting their comparability and clinical utility. Moreover, few investigations have explored trimester-specific performance or integrated Doppler findings with other monitoring strategies, such as biophysical profiles or biochemical markers.
The burden of SUA is not limited to adverse short-term outcomes. Preterm birth, intrauterine growth restriction, and congenital anomalies contribute to long-term morbidity, including impaired neurodevelopment and increased healthcare utilization. Consequently, improving the predictive tools available for SUA management has significant implications not only for perinatal survival but also for long-term child health and healthcare resource allocation.

In summary, SUA is a congenital umbilical cord anomaly that substantially increases the risk of adverse perinatal outcomes. Its unpredictable clinical course poses major challenges for obstetric management. Current surveillance practices rely heavily on ultrasound, but there is no consensus on the role of Doppler indices in risk

stratification. Clarifying the utility of Doppler ultrasound in this context is therefore of major clinical and public health importance, with potential to improve outcomes for.

METHODS

Search strategy A comprehensive and systematic search strategy was developed to identify all relevant studies assessing the predictive value of Doppler ultrasound indices in pregnancies complicated by single umbilical artery (SUA). The search was guided by the PRISMA 2020 statement for systematic reviews and was prospectively registered in PROSPERO. A medical librarian was consulted to optimize the strategy and ensure the inclusion of appropriate subject headings, Boolean operators, and search limits. Pilot testing of the search terms was undertaken before the final search to confirm sensitivity and specificity.

Databases Searched

Three major electronic databases were selected because of their wide coverage of biomedical and clinical literature:

PubMed/MEDLINE

Scopus

Web of Science Core Collection

These databases were chosen to maximize retrieval of both clinical and epidemiological studies, encompassing diverse geographic regions and study designs.

Search Period and Language

The search covered a 15-year period, from January 1, 2008 to December 31, 2023, to capture the most relevant and up-to-date evidence reflecting advances in Doppler ultrasound technology and obstetric practice. Only studies published in English were included, to ensure accurate interpretation of methodological details and clinical outcomes.

Search Terms and Strategy

The search strategy was constructed using combinations of controlled vocabulary (e.g., MeSH terms in PubMed) and free-text keywords. Boolean operators (AND/OR) were applied to combine terms related to the population, intervention, and outcomes of interest.

PubMed (executed January 15, 2024):

1. “single umbilical artery”[MeSH Terms] OR “single umbilical artery”[Title/Abstract] OR “SUA” [Title/Abstract]

2. “ultrasonography, doppler”[MeSH Terms] OR “doppler ultrasound”[Title/Abstract] OR “doppler” [Title/Abstract]

3. “pregnancy outcome”[MeSH Terms] OR “fetal outcome”[Title/Abstract] OR “perinatal outcome” [Title/Abstract] OR “IUGR”[Title/Abstract] OR “intrauterine growth restriction”[Title/Abstract]

4. #1 AND #2 AND #3
Filters: Publication date 2008–2023; English language; Humans
Results: 623 records

Scopus (executed January 15, 2024):

TITLE-ABS-KEY(“single umbilical artery” OR “SUA”) AND

TITLE-ABS-KEY(“doppler ultrasound” OR “doppler”) AND

TITLE-ABS-KEY(“pregnancy outcome” OR “fetal outcome” OR “IUGR”)
Filters: 2008–2023; English language; Article type: Journal
Results: 734 records

Web of Science Core Collection (executed January 15, 2024):

TS=(“single umbilical artery” OR “SUA”) AND

TS=(“doppler ultrasound” OR “doppler”) AND

TS=(“pregnancy outcome” OR “fetal outcome” OR “IUGR”)
Filters: 2008–2023; English language; Document type: Article
Results: 489 records

Additional Sources

Reference lists of relevant studies and systematic reviews were hand-searched to identify additional

eligible articles. This yielded 604 extra records, increasing the comprehensiveness of the review.

Results of Search

PubMed: 623 records

Scopus: 734 records

Web of Science: 489 records

Hand-searched references: 604 records
Total retrieved: 2,450 records

After removal of duplicates (n=550), 1,800 records remained for title and abstract screening. Of these, 900 were excluded for irrelevance. Full-text review was conducted for 200 studies, and 185 were excluded for reasons such as lack of Doppler indices, inappropriate study design, or insufficient data. Ultimately, 15 studies met all eligibility criteria and were included in the final review, of which 12 provided sufficient data for meta-analysis.
Validation of Search Strategy

To ensure methodological rigor, the search was validated through:

Consultation with a medical librarian to refine Boolean logic and index terms.

Pilot testing of key terms against known relevant studies.

Cross-checking retrieved articles against reference lists of included studies and recent reviews to ensure no key evidence was missed.

Strengths of the Search Strategy

Broad coverage across three leading biomedical databases.

Use of both MeSH terms and free-text search words to maximize sensitivity.

Inclusion of reference list screening to minimize risk of missing eligible studies.

Time frame chosen to reflect contemporary practice and advances in Doppler technology.

Limitations of the Search Strategy

Restriction to English-language studies may have excluded relevant evidence published in other languages, particularly from low- and middle-income countries.

Exclusion of grey literature, such as conference abstracts without full text, may introduce publication bias.

Despite a comprehensive approach, funnel plot analysis suggested the possibility of unpublished negative findings, which could have led to overestimation of effect sizes.

Summary

This systematic and reproducible search strategy enabled the identification of all relevant studies examining the role of Doppler ultrasound in SUA pregnancies published between 2008 and 2023. By combining database searches with manual reference screening and rigorous validation procedures, the approach ensured a high level of sensitivity while maintaining methodological transparency. The final set of 15 included studies represents the best available evidence for evaluating the predictive accuracy of Doppler indices in SUA pregnancies.

Participant or population This review will address studies involving pregnant women diagnosed with a single umbilical artery (SUA), irrespective of maternal age, parity, or geographic location. SUA is defined as the congenital absence of one of the two umbilical arteries, confirmed through prenatal ultrasound or postnatal examination of the umbilical cord.

Inclusion of Participants

Eligible participants are:

Pregnant women with SUA diagnosis confirmed via prenatal ultrasonography (second or third trimester) or postnatal pathological examination.

Both isolated SUA (no other structural or chromosomal abnormalities detected) and non-isolated SUA (associated with congenital anomalies or chromosomal conditions).

All gestational ages at the time of SUA diagnosis will be considered, including first-trimester detection where reported.

Participants from studies conducted in any healthcare setting (tertiary hospitals, community

clinics, or academic centers) and from diverse geographic regions.

Exclusion of Participants

The following will not be considered within the scope of the review:

Pregnancies with umbilical cord anomalies other than SUA (e.g., velamentous cord insertion, true knots, or vasa previa).

Studies focusing exclusively on chromosomal abnormalities or structural malformations without assessment of Doppler indices.

Case reports or case series with fewer than 10 participants, given limited generalizability.

Animal studies or experimental models.

Relevance of Participants to the Review Question

This participant group is highly relevant because SUA pregnancies are clinically heterogeneous, with outcomes ranging from uncomplicated deliveries to severe complications such as intrauterine growth restriction (IUGR), preterm birth, and intrauterine fetal demise (IUFD). The uncertainty in predicting which fetuses are at highest risk underscores the need for reliable surveillance tools. By focusing specifically on pregnancies complicated by SUA, this review seeks to evaluate the diagnostic accuracy of Doppler ultrasound indices in this high-risk group and determine whether they can be used to guide evidence-based monitoring and management.

In summary, the review will exclusively address pregnant women with SUA, across different populations and healthcare systems, with or without associated anomalies, to provide a comprehensive synthesis of evidence on the predictive role of Doppler ultrasound in this condition.

Intervention The intervention of interest in this review is the use of Doppler ultrasound assessment to evaluate fetoplacental circulation in pregnancies complicated by a single umbilical artery (SUA). Doppler ultrasound is a non-invasive imaging technique that measures blood flow velocity and vascular resistance, providing insights into the adequacy of fetal and placental perfusion.

Specific Doppler Parameters

The review will focus on studies that utilize standardized Doppler indices as markers of fetoplacental function, including:

Resistance Index (RI): an indicator of downstream vascular resistance, commonly measured in the umbilical artery.

Pulsatility Index (PI): reflecting the variability of blood flow velocity during the cardiac cycle, useful in assessing placental and fetal circulation.

Systolic/Diastolic (S/D) Ratio: a measure of relative systolic to diastolic flow, with elevated values suggesting increased resistance.

These indices are widely used in obstetric practice and represent the most commonly reported Doppler measures in the context of SUA.

Application of the Intervention

In included studies, Doppler assessments may be performed at varying gestational ages (first, second, or third trimester) and with different protocols (number of measurements, angle of insonation, equipment used). Both single-time assessments and serial Doppler examinations across pregnancy are considered within the scope of this review.

Comparator(s)

The comparator groups in eligible studies may include:

Normal pregnancies without SUA, used as external or historical controls.

Internal comparisons within SUA cohorts (e.g., normal versus abnormal Doppler findings).

Clinical Purpose of the Intervention

The goal of Doppler assessment in SUA pregnancies is to determine its predictive accuracy for adverse perinatal outcomes, such as intrauterine growth restriction (IUGR), small-for-gestational-age (SGA) neonates, preterm birth, intrauterine fetal demise (IUFD), cesarean delivery, and neonatal intensive care unit (NICU) admission. By detecting early signs of hemodynamic compromise, Doppler could help clinicians stratify risk, optimize surveillance, and guide delivery decisions.

Relevance to Review

Although Doppler ultrasound is widely applied in the monitoring of high-risk pregnancies, its role in SUA management remains uncertain. Evidence is fragmented, methodologies vary significantly across studies, and cutoff values for abnormal indices lack standardization. By systematically evaluating Doppler as an intervention in SUA pregnancies, this review aims to clarify its clinical utility, identify the most informative parameters, and highlight the need for standardized protocols to improve obstetric outcomes.

Comparator Where applicable, the comparators in this review will include populations or subgroups used to evaluate the relative predictive value of Doppler ultrasound in pregnancies with a single umbilical artery (SUA).

Types of Comparators

1. Normal pregnancies (without SUA):

Many studies compare SUA pregnancies with pregnancies featuring a three-vessel umbilical cord.

These comparisons allow for assessment of whether adverse outcomes (e.g., intrauterine growth restriction, preterm birth, neonatal morbidity) are significantly more frequent in SUA pregnancies and whether Doppler indices differ between groups.

2. Internal comparisons within SUA cohorts:

Some studies stratify SUA pregnancies into groups with normal Doppler indices versus abnormal Doppler indices.

This design allows for direct evaluation of the prognostic role of Doppler in identifying high-risk cases within the SUA population.

3. Historical or institutional controls:

In certain retrospective studies, control groups are derived from historical datasets of uncomplicated pregnancies.

These provide baseline outcome rates against which SUA pregnancies can be compared.

Justification for Comparators

The inclusion of comparator groups is essential for:

Determining whether Doppler findings in SUA pregnancies differ significantly from those in normal pregnancies.

Establishing the incremental value of Doppler indices in predicting adverse outcomes beyond baseline SUA risk.

Evaluating whether Doppler abnormalities within SUA populations correlate with worse clinical outcomes compared to SUA cases with normal Doppler findings.

Relevance

Comparative analyses will help clarify the role of Doppler ultrasound as a surveillance tool. By contrasting SUA pregnancies with both normal pregnancies and internal SUA subgroups, the review will assess whether Doppler indices provide clinically meaningful discrimination between low- and high-risk cases. This will support evidence-based recommendations for integrating Doppler into routine SUA monitoring.

Study designs to be included This review will include observational study designs that provide original data on Doppler assessment in single umbilical artery (SUA) pregnancies: prospective and retrospective cohort studies, case-control studies, and cross-sectional studies. Case reports, case series with fewer than 10 participants, conference abstracts without full text, animal studies, and studies not reporting Doppler indices will be excluded.

Eligibility criteria In addition to the population, intervention, comparator, and outcomes already defined, the following inclusion and exclusion criteria will be applied to ensure methodological rigor and clinical relevance:

Inclusion Criteria

Population: Pregnant women with a prenatal or postnatal diagnosis of single umbilical artery (SUA).

Intervention: Doppler ultrasound assessment including at least one of the following indices: Resistance Index (RI), Pulsatility Index (PI), or Systolic/Diastolic (S/D) ratio.

Comparator: Normal pregnancies, historical controls, or internal comparisons within SUA cohorts.

Outcomes: Studies reporting adverse perinatal outcomes such as intrauterine growth restriction (IUGR), small-for-gestational-age (SGA), intrauterine fetal demise (IUFD), preterm delivery, cesarean section, or neonatal intensive care unit (NICU) admission.

Study Design: Cohort (prospective or retrospective), case-control, or cross-sectional studies.

Language: English-language publications only.

Publication Type: Full-text peer-reviewed journal articles.

Exclusion Criteria

Case reports or small case series with fewer than 10 participants.

Conference abstracts or unpublished studies without full-text availability.

Studies without Doppler indices data, or where Doppler findings are not reported separately for SUA pregnancies.

Animal studies or experimental models.

Studies focusing exclusively on chromosomal abnormalities or congenital malformations without reference to Doppler assessment or perinatal outcomes.

Duplicate publications or overlapping datasets (the most complete or recent version will be retained).

Justification

These criteria ensure that only methodologically robust studies with clinically relevant populations and outcomes are included, while excluding evidence of low quality or insufficient detail. The focus on peer-reviewed, English-language studies enhances reliability and interpretability, though it may limit inclusion of potentially relevant data from other languages or grey literature.

Information sources A comprehensive search strategy was developed to ensure the inclusion of all relevant literature examining Doppler ultrasound in pregnancies complicated by single umbilical artery (SUA). Multiple information sources were consulted to capture both published and referenced studies.

Electronic Databases

Three major biomedical databases were searched:

PubMed/MEDLINE: selected for its comprehensive coverage of biomedical and clinical literature, including indexed MeSH terms.

Scopus: chosen for its broad interdisciplinary scope, capturing studies not always indexed in PubMed.

Web of Science Core Collection: included to identify additional peer-reviewed articles and facilitate citation tracking.

These databases were searched from January 1, 2008 to December 31, 2023, ensuring coverage of the last 15 years, a period during which Doppler ultrasound technology and obstetric practices have evolved significantly.

Additional Sources

To maximize completeness, the following supplementary strategies were used:

Reference list screening: Bibliographies of all included articles and relevant systematic reviews were manually checked to identify additional eligible studies. This yielded an extra 604 records beyond the database searches.

Citation tracking: Forward and backward citation searches were conducted in Web of Science to capture more recent or related work.

Language and Publication Restrictions

Only studies published in English were included, in order to ensure accurate evaluation of methodology and outcomes. Eligible publications were restricted to peer-reviewed journal articles with full-text availability. Conference abstracts, dissertations, and other grey literature were excluded due to limited methodological detail and lack of peer review.

Validation of Sources

The search strategy was designed in consultation with a medical librarian to improve precision and sensitivity. Pilot searches were conducted to ensure that the terms identified key known studies. The strategy was then adapted for each database using appropriate controlled vocabulary and free-text keywords.

Summary of Sources

PubMed/MEDLINE: 623 records

Scopus: 734 records

Web of Science: 489 records

Hand-searched references: 604 records

After deduplication, 1,800 unique records were screened, leading to the inclusion of 15 studies in the final review.

Rationale for Source Selection

These sources were selected to ensure comprehensive coverage of high-quality peer-reviewed studies in obstetrics and fetal medicine. By combining large biomedical databases with manual reference screening, the strategy reduced the risk of omitting relevant evidence. Although the exclusion of grey literature and non-English studies may introduce some publication bias, this approach ensures that only studies with sufficient methodological transparency and peer review are included.

Main outcome(s) The primary outcome of this review is the predictive accuracy of Doppler ultrasound indices—specifically the Resistance Index (RI), Pulsatility Index (PI), and Systolic/Diastolic (S/D) ratio—for detecting adverse perinatal outcomes in pregnancies complicated by single umbilical artery (SUA).

The principal adverse outcome of interest is intrauterine growth restriction (IUGR), given its strong association with impaired fetoplacental perfusion in SUA pregnancies. Doppler findings will be evaluated for their diagnostic performance in predicting IUGR, with effect measures including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and odds ratios (OR).

Timing of outcome assessment will vary according to gestational age at Doppler measurement (first, second, or third trimester), and analyses will account for potential differences in predictive accuracy across these time points.

Secondary outcomes include:

Small-for-gestational-age (SGA) neonates

Preterm delivery (<37 weeks of gestation)

Intrauterine fetal demise (IUFD)

Mode of delivery (cesarean section due to fetal distress)

Neonatal intensive care unit (NICU) admission

For all outcomes, pooled effect measures such as odds ratios or risk ratios will be calculated where data allow. Heterogeneity across studies will be assessed, and subgroup analyses will explore the impact of study design, Doppler protocol, and gestational timing on predictive performance.

By focusing on these outcomes, the review aims to determine whether Doppler ultrasound can reliably identify SUA pregnancies at greatest risk of adverse outcomes, thereby informing clinical surveillance strategies and delivery planning.

Additional outcome(s) In addition to the primary outcome of intrauterine growth restriction (IUGR), this review will consider a set of additional outcomes that provide a broader perspective on perinatal health in single umbilical artery (SUA) pregnancies. These outcomes reflect both short-term neonatal morbidity and maternal-fetal management implications.

The additional outcomes include:

Small-for-gestational-age (SGA): Birthweight below the 10th percentile for gestational age, reflecting impaired fetal growth not meeting IUGR diagnostic thresholds.

Preterm delivery: Birth occurring before 37 weeks of gestation, either spontaneous or iatrogenic, with timing documented to assess associations with abnormal Doppler indices.

Cesarean delivery: Particularly cesarean section performed for fetal distress, used as a proxy for intrapartum compromise.

Neonatal intensive care unit (NICU) admission: Indicator of early neonatal morbidity requiring

specialized care, often due to growth restriction, prematurity, or intrapartum complications.

Intrauterine fetal demise (IUFD): Documented stillbirth, particularly associated with absent or reversed end-diastolic flow on Doppler assessment.

Effect measures for these outcomes will include odds ratios (OR), relative risks (RR), and diagnostic accuracy metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), where available. Timing of assessment will consider trimester-specific Doppler evaluation to determine whether predictive accuracy differs across gestational stages.

Evaluating these additional outcomes will provide a comprehensive understanding of how Doppler indices perform not only in predicting IUGR but also in anticipating other clinically relevant complications of SUA pregnancies. This broader outcome framework will help determine whether Doppler can serve as an integrated surveillance tool, guiding risk stratification, obstetric decision-making, and perinatal care planning.

Data management All records identified through electronic databases and manual reference searches were managed using a structured and transparent process to ensure accuracy, reproducibility, and minimization of bias.

Record Management

Search results from PubMed, Scopus, and Web of Science were exported into a citation management software (e.g., EndNote or Zotero). Duplicate records were automatically identified and removed, followed by a manual verification to ensure completeness. After de-duplication, 1,800 unique records were retained for screening. Titles and abstracts were imported into a screening platform (such as Covidence or Rayyan), which allowed two reviewers to independently evaluate eligibility according to predefined criteria.

Screening and Selection

Title/abstract screening: Two reviewers independently screened all records for relevance.

Full-text screening: Potentially eligible articles were retrieved in full and assessed against inclusion/exclusion criteria. Discrepancies were resolved through discussion, with arbitration by a third reviewer when necessary.

PRISMA flow diagram: The entire process of identification, screening, eligibility, and inclusion was documented in accordance with PRISMA guidelines.

Data Extraction

Data from included studies were extracted using a standardized, pilot-tested data extraction form. Extracted information included:

Study characteristics (author, year, region, design, sample size)

Population demographics (maternal age, parity, gestational age at diagnosis)

Intervention details (type of Doppler indices assessed, timing of assessment, protocol)

Comparator groups (normal pregnancies or internal controls)

Outcomes (IUGR, SGA, IUFD, preterm delivery, cesarean section, NICU admission)

Effect measures (sensitivity, specificity, odds ratios, predictive values)

Two reviewers performed extraction independently to minimize errors, with discrepancies resolved by consensus.

Data Storage and Security

All records and extracted data were stored in a secure, password-protected electronic database accessible only to the review team. Version control was maintained to track changes, and backup copies were kept to prevent data loss.

Quality Assurance

Study quality was assessed using the Newcastle-Ottawa Scale for observational studies. Extracted data and quality assessments were cross-checked by reviewers to ensure consistency. Agreement between reviewers was documented, and inter-rater reliability was calculated.

This systematic and transparent approach to data management ensured that the review process remained reproducible, unbiased, and compliant with international standards.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of included studies were assessed systematically to ensure reliability of findings. Given that the majority of eligible studies were observational in design, the Newcastle–Ottawa Scale (NOS) was applied. This validated tool evaluates studies across three domains:

1. Selection of study groups (representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start).

2. Comparability of cohorts (control for potential confounders such as maternal age, parity, or comorbidities).

3. Outcome assessment (method of outcome determination, adequacy of follow-up, statistical robustness).

Each study was awarded a maximum of nine stars, with ≥7 indicating high quality, 4–6 moderate quality, and <4 low quality. Two reviewers independently applied the NOS to all included studies. Initial agreement between reviewers was high (Cohen's $\kappa = 0.78$), and discrepancies were resolved by consensus or arbitration by a third reviewer.

Common Sources of Bias

Across the 15 included studies, several recurrent risks of bias were identified:

Study design limitations: Seven studies were retrospective, increasing susceptibility to selection bias and incomplete follow-up.

Heterogeneity of Doppler protocols: Differences in measurement techniques, cutoff thresholds, and timing of assessment introduced inconsistency.

Outcome reporting: Some studies provided limited detail on outcome definitions (e.g., IUGR vs. SGA) or failed to report long-term neonatal outcomes.

Confounder adjustment: Not all studies adequately controlled for potential maternal or obstetric confounders.

Certainty of Evidence

The overall certainty of evidence was further evaluated using the GRADE framework. Evidence for IUGR prediction was judged as moderate certainty, downgraded for risk of bias and inconsistency. For SGA prediction, certainty was low, downgraded for bias, inconsistency, and imprecision. For IUFD prediction, certainty was very low due to small sample sizes and methodological limitations.

Summary

The structured application of NOS and GRADE ensured transparent assessment of study quality and facilitated interpretation of findings. Although several studies achieved high-quality ratings, the predominance of retrospective designs, heterogeneity in protocols, and incomplete adjustment for confounding collectively lowered the overall certainty of the evidence base.

Strategy of data synthesis Data synthesis will be performed in accordance with the PRISMA 2020 guidelines. The goal is to summarize and, where possible, quantitatively pool the evidence regarding the predictive accuracy of Doppler ultrasound indices in pregnancies complicated by single umbilical artery (SUA).

Narrative Synthesis

Initially, a narrative synthesis will describe the characteristics of included studies, including study design, population demographics, sample size, gestational timing of Doppler assessment, and indices measured (Resistance Index, Pulsatility Index, Systolic/Diastolic ratio). Descriptive tables will summarize methodological features, quality assessment scores, and reported outcomes.

Quantitative Synthesis (Meta-analysis)

Where studies report comparable data, a meta-analysis will be conducted using random-effects models, given the expected heterogeneity across populations and methodologies. Effect measures will include:

Diagnostic accuracy metrics (sensitivity, specificity, positive predictive value, negative predictive value).

Effect estimates (odds ratios or risk ratios with 95% confidence intervals) for associations between abnormal Doppler indices and adverse outcomes (e.g., intrauterine growth restriction, small-for-gestational-age neonates, preterm birth,

intrauterine fetal demise, cesarean delivery, and NICU admission).

Pooled sensitivity and specificity will be presented in forest plots. Heterogeneity will be quantified using the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Sources of heterogeneity will be further explored through subgroup analyses.

Subgroup and Sensitivity Analyses

By study design: prospective versus retrospective studies.

By sample size: small (<200 participants) versus large studies (≥200 participants).

By gestational timing: Doppler performed in first, second, or third trimester.

By Doppler parameter: RI, PI, S/D ratio analyzed separately.
Sensitivity analyses will be performed by excluding studies at high risk of bias to assess robustness of findings.

Publication Bias

Potential publication bias will be assessed visually through funnel plots and statistically using the Egger test, when at least 10 studies are available for a given outcome.

Certainty of Evidence

The overall strength of evidence for each outcome will be graded using the GRADE framework, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Data Management and Software

Meta-analyses will be conducted using statistical software such as RevMan or Stata, ensuring reproducibility of analyses.

Summary

This synthesis strategy combines both narrative and quantitative approaches, enabling a structured assessment of Doppler indices in SUA pregnancies. By pooling results while accounting for heterogeneity, the review will provide clinically meaningful estimates of predictive accuracy and identify gaps for future high-quality research.

Subgroup analysis This review will focus on pregnant women diagnosed with a single umbilical artery (SUA), identified either during prenatal ultrasound assessment or confirmed postnatally at delivery. The SUA condition is the most common congenital anomaly of the umbilical cord, characterized by the absence of one of the two umbilical arteries. Given the clinical heterogeneity of SUA pregnancies, the review will consider several subgroups of participants to allow for meaningful synthesis of findings.

Group 1: Isolated SUA Pregnancies

These are cases in which SUA is detected in the absence of any additional structural malformations or chromosomal abnormalities. Isolated SUA is relatively frequent and presents a unique challenge in obstetric management, as some fetuses progress normally while others experience significant complications such as intrauterine growth restriction (IUGR) or preterm delivery. Including this group allows for evaluation of whether Doppler indices alone can stratify risk in otherwise uncomplicated SUA pregnancies.

Group 2: Non-Isolated SUA Pregnancies

This group includes SUA cases associated with congenital anomalies (especially cardiovascular or renal) or chromosomal abnormalities. Non-isolated SUA pregnancies generally carry a higher baseline risk of adverse outcomes. By including these cases, the review can examine whether Doppler ultrasound adds predictive value beyond the known risks associated with malformations.

Group 3: Comparator Groups

Comparisons may be drawn from two categories:

Normal pregnancies with a three-vessel cord: These serve as external controls, allowing assessment of whether SUA pregnancies have higher rates of adverse outcomes and whether Doppler parameters differ significantly from those in the general population.

Internal comparisons within SUA cohorts: Some studies classify participants based on Doppler findings (normal vs. abnormal indices), which allows evaluation of prognostic accuracy within the SUA population itself.

Diversity Across Settings

The review will include participants regardless of maternal age, parity, socioeconomic status, or geographic origin. Studies from North America, Europe, Asia, South America, and Africa are expected, ensuring diversity of clinical practices and population characteristics. This breadth enhances generalizability but also introduces heterogeneity, which will be carefully assessed in subgroup analyses.

Relevance to Outcomes

Focusing on these groups allows the review to address its central question: whether Doppler indices (Resistance Index, Pulsatility Index, Systolic/Diastolic ratio) can predict adverse outcomes such as IUGR, small-for-gestational-age neonates, preterm birth, intrauterine fetal demise, cesarean delivery, and neonatal intensive care unit admission. Stratifying by isolated vs. non-isolated SUA, as well as by comparator groups, will help determine the utility of Doppler both as a diagnostic and prognostic tool.

Sensitivity analysis Sensitivity analysis will be performed to evaluate the robustness of the findings and to determine whether the overall conclusions are influenced by specific methodological or clinical factors. Because included studies vary considerably in design, quality, and reporting, sensitivity analyses are essential for identifying potential sources of bias and for assessing the stability of pooled estimates.

Exclusion of Low-Quality Studies

Studies judged to have a high risk of bias or rated as low quality on the Newcastle–Ottawa Scale will be excluded in sensitivity analyses. By repeating the meta-analysis with only high- and moderate-quality studies, we can evaluate whether the observed associations are consistent across more reliable evidence.

Impact of Study Design

Given that retrospective studies are more prone to selection and reporting bias, results will be compared between prospective and retrospective designs. Excluding retrospective studies in sensitivity testing will show whether prospective data alone support the predictive role of Doppler indices in SUA pregnancies.

Sample Size Considerations

Small studies (<200 participants) often contribute to heterogeneity and publication bias. Sensitivity analyses will be performed by excluding small-sample studies to assess whether larger cohorts yield more consistent and precise effect estimates.

Doppler Parameters and Timing

Sensitivity analyses will explore the impact of restricting analysis to specific Doppler indices (e.g., only Resistance Index or only Pulsatility Index) or to specific gestational periods (second vs. third trimester). This will allow determination of whether findings are driven by particular indices or time points of measurement.

Statistical Models

Both random-effects and fixed-effects models will be applied to pooled data. Comparing these results will help determine whether heterogeneity significantly influences effect estimates and whether conclusions remain stable across different statistical assumptions.

Outcome-Specific Sensitivity

For each outcome (IUGR, SGA, preterm delivery, IUFD, NICU admission, cesarean delivery), sensitivity analyses will be applied to evaluate whether associations remain robust when excluding outlier studies or those with incomplete reporting.

Publication Bias

Because publication bias may inflate positive findings, sensitivity analysis will also consider the exclusion of studies from high-income countries only, to test whether results change when restricting to more diverse healthcare settings.

Language restriction This review applied a language restriction to English-language publications only. The decision was based on practical considerations, including the need for accurate interpretation of study methodologies, Doppler indices, and outcome.

Country(ies) involved Romania.

Other relevant information This review addresses an important and clinically relevant question in obstetrics: whether Doppler ultrasound indices can serve as reliable predictive tools in pregnancies complicated by single umbilical artery (SUA). Beyond the methodological details already

presented, several additional aspects highlight the significance of this work.

First, SUA represents the most common umbilical cord anomaly, affecting approximately 0.5–1% of singleton pregnancies. Although often detected incidentally during routine ultrasound, SUA is associated with increased risks of intrauterine growth restriction, preterm delivery, congenital anomalies, and perinatal mortality. Clinicians frequently face uncertainty about how best to monitor these pregnancies, as current management strategies vary widely and lack standardized guidelines.

Second, Doppler ultrasound is a non-invasive, widely accessible, and cost-effective tool. If its predictive accuracy in SUA pregnancies can be clearly established, it could be integrated into standard protocols globally, including in low- and middle-income settings where advanced diagnostic resources may be limited.

Third, this review will also shed light on the limitations of current evidence. Many existing studies are retrospective, with heterogeneous methodologies, inconsistent outcome definitions, and variable cutoff values for Doppler indices. By systematically assessing study quality and risk of bias, the review will provide a transparent evaluation of the strength of current evidence and identify areas where further research is most urgently needed.

Finally, the findings have the potential to influence future research priorities and clinical guidelines. By highlighting knowledge gaps, such as the absence of standardized Doppler thresholds and the need for large multicenter prospective studies, this review can contribute to shaping evidence-based surveillance strategies for SUA pregnancies.

In summary, this systematic review is not only relevant for academic purposes but also for clinical practice and public health, as it addresses a frequent obstetric condition with important implications for perinatal outcomes and healthcare resource utilization.

Keywords single umbilical artery; doppler; ultrasound.

Dissemination plans The findings of this systematic review will be disseminated through multiple academic and professional channels to ensure broad visibility and impact. Results will be prepared as a full manuscript for submission to a peer-reviewed scientific journal in the field of obstetrics, gynecology, and perinatal medicine. The manuscript will follow international reporting standards, including the PRISMA 2020 guidelines, to ensure transparency and reproducibility.

In addition to journal publication, results will be presented at national and international conferences, including meetings dedicated to maternal–fetal medicine, obstetrics, and ultrasound research. Conference presentations will enable timely communication of findings to clinicians, researchers, and policymakers, fostering dialogue on the integration of Doppler ultrasound into the management of single umbilical artery pregnancies.

Summaries of the review will also be shared through institutional platforms and academic networks, ensuring that practitioners and trainees in obstetrics and gynecology can access the results in a practical and clinically relevant format. Where feasible, findings will be adapted into educational materials for use in training programs at medical schools and residency curricula, enhancing knowledge translation.

Finally, the review team will explore opportunities for collaboration with guideline-developing bodies and professional societies, contributing evidence to support the development of standardized protocols for monitoring pregnancies complicated by SUA. By making the results accessible to a wide audience, the review aims to promote evidence-based clinical practice and stimulate further high-quality research in this important area of perinatal care.

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