BMJ Open

A protocol for a systematic review of systematic reviews of late pregnancy ultrasound parameters that identify fetuses at risk of adverse perinatal outcomes.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058293
Article Type:	Protocol
Date Submitted by the Author:	12-Oct-2021
Complete List of Authors:	Aderoba, Adeniyi; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, ; HealthMATE 360, Department of Maternal and Perinatal Health Nasir, Naima; Univerity of Oxford Nuffield Department of Medicine, Centre for Tropical Medicine and Global Health Quigley, Maria; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, Impey, Lawrence; Oxford University Hospitals NHS Trust, Department of Fetal Medicine Rivero-Arias, Oliver; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, Kurinczuk, Jennifer; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health,
Keywords:	Ultrasonography < OBSTETRICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Fetal medicine < OBSTETRICS, Prenatal diagnosis < OBSTETRICS, Maternal medicine < OBSTETRICS, PERINATOLOGY

TITLE

A protocol for a systematic review of systematic reviews of late pregnancy ultrasound parameters that identify fetuses at risk of adverse perinatal outcomes.

Authors

Adeniyi Kolade Aderoba, MBBS, MSc - National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. adeniyi.aderoba@gmail.com

Naima Nasir, BPharm, MSc - Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford. naima.nasir@keble.ox.ac.uk

Maria A Quigley, MSc, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. maria.quigley@npeu.ox.ac.uk

Lawrence Impey, MD, Department of Fetal Medicine, John Radcliffe Hospital, Oxford University Hospitals NHS Trust. lawrence.impey@ouh.nhs.uk

Oliver Rivero-Arias, DPhil, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. oliver.rivero@npeu.ox.ac.uk

Jennifer J Kurinczuk, MD, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. jenny.kurinczuk@npeu.ox.ac.uk

Corresponding Author

Dr Adeniyi K. Aderoba

National Perinatal Epidemiology Unit (NPEU)

Nuffield Department of Population Health

University of Oxford

Old Road Campus, Oxford, OX3 7LF

Email: adeniyi.aderoba@dph.ox.ac.uk, adeniyi.aderoba@gmail.com

Keywords

Ultrasound, late-pregnancy, universal scan, routine scan, stillbirth, adverse perinatal outcome(s), umbrella review, systematic review of systematic reviews,

Word count - 2901

ABSTRACT

Introduction

Stillbirths and neonatal deaths are leading contributors to the global burden of disease and pregnancy ultrasound has the potential to help decrease this burden. In the absence of a universal protocol for ultrasound parameters that can be used either individually or in combination with other ultrasound parameters to identify pregnancies at risk of adverse perinatal outcomes, many treatment pathways involving ultrasound exist in clinical practice. Systematic reviews have rapidly increased over the past decade owing to the diverse nature of ultrasound parameters and the wide range of possible adverse perinatal outcomes. This systematic review will summarize the evidence on key ultrasound parameters in the published literature to help develop a late pregnancy ultrasound protocol that identifies pregnancies at risk of adverse perinatal outcomes.

Methods

This study will follow the recent Cochrane guidelines for a systematic review of systematic reviews. A comprehensive literature search will be conducted using EMBASE (OvidSP), MEDLINE (OvidSP), CDSR, CINAHL (EBSCOhost) and Scopus. Systematic reviews evaluating at least one ultrasound parameter in late pregnancy to detect pregnancies at risk of adverse perinatal outcomes will be included. Two independent reviewers will screen, assess the quality including the risk of bias using the ROBIS tool, and extract data from eligible systematic reviews that meet the study inclusion criteria. Overlapping data will be assessed and managed with decision rules, and study evidence including the GRADE assessment of certainty of results will be presented as a narrative synthesis as described in the Cochrane guidelines for an overview of reviews.

Ethics and dissemination

This research utilizes publicly available published data; thus, an Ethics Committee review is not required. The findings will be published in a peer-reviewed journal.

Prospero registration number: CRD42021266108

Strengths and limitations of this study

- To the best of our knowledge, this will be the first systematic review of systematic reviews of late pregnancy ultrasound parameters that identify fetuses at risk of adverse prenatal outcomes.
- The review will use a rigorous methodology based on current guidelines and will provide a high-quality summary for clinicians, guideline developers, and policymakers. In addition, the detailed methods allow for an easy update in the future and applicability to similar conditions.
- Double counting duplicate data might give undue weight to some studies and a potential limitation of this review might be the tendency to lose data by dropping systematic reviews with overlapping primary studies.

BACKGROUND

Stillbirths and neonatal deaths remain leading contributors to the global burden of disease in high- and low-income countries.[1] Annually, over two million stillbirths occur, and additional babies die during the neonatal period.[1] In addition, many babies who survive severe pregnancy and childbirth complications live with permanent brain damage and have special education needs.[2] Evidence exists that when at-risk fetuses are identified before birth, the risk of these adverse perinatal outcomes is mitigated.[3,4]

Many systematic reviews show that late pregnancy ultrasound can help to detect pregnancy complications in women with suspected high-risk conditions such as fetal growth restriction (FGR) and small for gestational age (SGA).[5] However, in low-risk pregnancies, routine late pregnancy ultrasound is not recommended because current evidence, primarily from a Cochrane review, shows that it is not beneficial for a woman or her baby.[6] Routine late pregnancy ultrasound is also not used in many countries,[7,8] perhaps due to the methodological weaknesses identified in the Cochrane review.[9] These weaknesses include using different definitions for a positive test, varied test performance, and not combining a positive ultrasound test with interventions known to improve perinatal outcomes,[10] such as induction of labour[11] or elective caesarean section.

In the absence of a universal protocol that articulates ultrasound parameters that can be used either individually or in combination to identify pregnancies at risk of adverse perinatal outcomes, many different treatment pathways exist in clinical practice. Similarly, due to the diverse nature of ultrasound parameters and the wide range of possible adverse perinatal outcomes,[12] the last decade has witnessed a rapid proliferation of systematic reviews in this area.[13–18] Therefore, clinicians and policymakers are overwhelmed by the current pace of evidence.[19] It has also been challenging to have an overarching assessment of the cost-effectiveness of late pregnancy ultrasound, given that multiple combinations of ultrasound parameters are possible. As a consequence, current estimates of the cost-effectiveness of late pregnancy ultrasound have focused on individual parameters.[20–22] A systematic review of systematic reviews, also referred to as an umbrella review or overview of reviews, may help with evidence synthesis to support the development of an ultrasound protocol by identifying effective late pregnancy ultrasound parameters for the identification of pregnancies at risk of adverse perinatal outcomes despite being apparently low risk.[23] It will also provide guidance as to the effective parameters for use in women who are suspected to be at high risk of adverse outcomes. Thus, it will pave the way for more relevant and up-to-date clinical guidelines and estimates of cost-effectiveness.

Objective

This study aims to systematically review existing systematic reviews to identify effective ultrasound parameters, for a late pregnancy ultrasound and management protocol that detects pregnancies at risk of adverse perinatal outcomes.

METHODS

This systematic review of systematic reviews protocol was developed using the guidelines by Aromataris et al.[24,] and Pollock et al. [25] Further guidance comes from adapting guidelines for systematic review protocols,[26] searches,[27] quality and certainty of evidence,[28,29] synthesis,[30,31] and reporting[32]. This study was registered in the PROSPERO registry (Registration number: CRD42021266108)

Inclusion criteria

Type of studies

The study will include qualitative systematic reviews with numerical outcome data that fulfil the criteria defined by Labarca et al., [33] which are "systematic reviews that reported at least one inclusion criterion, searched at least one database, reported a pooled measure of effect for at least one outcome, and evaluated the risk of bias of the primary studies". This review will also include systematic reviews of randomized and non-randomized studies because it aims to determine the ultrasound parameter(s) that effectively identify adverse perinatal outcomes.

Although Cochrane reviews tend to have superior methodological quality,[34] this protocol presumes that data overlap would likely exist between Cochrane and non-Cochrane systematic reviews, and an overview of only Cochrane reviews might not sufficiently answer this study's research question. Further, avoiding bias from double counting overlapping data (i.e. duplicate primary studies) in the systematic reviews in an overview of reviews is methodologically challenging, time-intensive and prone to non-systematic and non-transparent conduct.[35] This study will note systematic reviews with overlapping primary studies. However, using the evidence-based decision tool by Pollock et al.,[35] recommended for Cochrane overview of reviews,[25] non-overlapping systematic reviews will hopefully be analyzed for each outcome. To balance this methodological complexity with the potential bias from overlapping data, a systematic review from a group of overlapping reviews will be prioritized for inclusion based on the following decision rule - if it has the best presentation of results in terms of recency, quality and completeness of numerical outcome data.

Type of participants

Singleton pregnancies from 34 weeks corresponding to the gestational age at which the fetal lungs are thought to be sufficiently mature to support independent neonatal life. This study will not be limited to any context or language.

Type of intervention

A systematic review will be included if ultrasound parameters are assessed alone in late pregnancy (i.e., from 34 weeks) or when combined with one or more ultrasound parameters to predict stillbirth or adverse perinatal outcomes. In the context of this study, an ultrasound parameter refers to any

of the following: a characteristic sign or test that is observable while examining the contents of a pregnant uterus (i.e., fetus, umbilical cord, placenta, or amniotic fluid) during an ultrasound scan.

Comparator and outcomes

This umbrella review will focus on systematic reviews that identified at least one of this study's primary or secondary outcomes by comparing a positive test in which one or more late pregnancy ultrasound parameters are assessed, with a negative test with the same parameters. The primary outcomes of this study are stillbirth or any other adverse perinatal outcome(s). In this study, late pregnancy is defined as gestational age from 34 weeks. Adverse perinatal outcome refers to any outcome that is similar to any of the core outcome sets for neonatal research by Webbe et al.[12] These core outcomes include: (1) survival – stillbirth, perinatal or neonatal death, (2) sepsis, (3) necrotizing enterocolitis, (4) brain injury on imaging, (5) general gross motor ability, (6) general cognitive ability, (7) quality of life, 8) adverse events, (9) visual impairment or blindness, (10) retinopathy of prematurity, (11) chronic lung disease/bronchopulmonary dysplasia and (12) hearing impairment or deafness. The secondary outcomes are small or large for gestational age babies, fetal growth restriction, breech presentation, oligo or polyhydramnios, low-lying or invasive placenta, or other high-risk fetal conditions known to be associated with stillbirth or adverse perinatal outcomes.

Exclusion criteria

Systematic reviews to be excluded are:

- Systematic reviews assessing ultrasound in twins or higher-order pregnancies
- Scoping reviews with a systematic search
- Animal studies
- Reviews without a meta-analysis or with non-numerical outcome data
- Systematic reviews that compared a positive test with an ultrasound parameter(s) against a positive test with another ultrasound parameter(s), rather than with a negative test with the same ultrasound parameter(s). This study is not designed to rank or make direct or indirect comparisons between ultrasound parameters but to identify clinically effective parameters for a late pregnancy ultrasound protocol.
- Systematic reviews with extensive overlapping primary studies that do not meet the criteria of recency, quality and completeness of data for each outcome
- Studies with ultrasound performed solely in labour
- Previous systematic reviews on ultrasound with more recent published versions
- Studies with ultrasound parameters that cannot be assessed at the 36-week scan or in which predicted adverse perinatal outcomes were evaluated before 36-weeks' gestation or both
- Studies in which ultrasound was performed earlier in pregnancy (before 34 weeks)
- Studies that only assessed the cost-effectiveness of ultrasound
- Systematic reviews in which ultrasound assessment focused entirely on congenital anomalies. Congenital anomalies may range widely in their types, severity of symptoms

and interventions that can alleviate them. Therefore, existing systematic reviews are likely to be heterogeneous in their populations, interventions, and comparators. As advised by the Cochrane guidelines, answering an umbrella review question is likely not feasible in this scenario.[25]

- Withdrawn systematic reviews
- Conference abstracts

Information sources and search strategy

The following databases will be searched from inception: EMBASE (OvidSP), MEDLINE (OvidSP), Cochrane Database of Systematic Reviews (www.cochranelibrary.com), Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCOhost), and Scopus (www.scopus.com). Relevant thesaurus headings for ultrasonography, prenatal, fetus echography, and fetal Doppler will be used, along with free-text search strings constructed for the title or abstract fields to search for pregnancy, prenatal, (or pre-natal, etc.) ultrasonography (or ultrasound, etc.), using the proximity indicator to narrow the search appropriately. Two systematic review search filters will be used for Ovid Embase[36] and Ovid Medline,[37] respectively. These filters will be adapted for the CINAHL (EBSCOhost) and Scopus searches. Additional relevant references will be retrieved from searches constructed for the World Health Organization (WHO) Global Index Medicus library (www.globalindexmedicus.net).

In addition, the reference lists of eligible studies will be manually searched for further relevant systematic reviews. The searches will be re-run just before the final analyses, and systematic reviews which meet the inclusion criteria will be added. The search strategy will be peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) guideline statement,[38] by an information specialist (EH). The complete search strategy is available in supplementary materials. Search results from the different databases will be merged in the Mendeley reference management application to facilitate deduplication. The results will then be exported to the Covidence systematic review management software for review.

Data collection

Selection of studies

Systematic review screening and selection will be conducted independently by two reviewers using Covidence, a web-based software review platform. After removing duplicates, the search results will first be screened by their titles and abstracts for eligible systematic reviews using the inclusion and exclusion criteria. The full-text publications selected will then undergo full eligibility screening for the systematic reviews. The reasons for exclusion at each screening stage will be documented. Disagreements will be resolved by consensus between the two independent reviewers or by a discussion with the co-investigator team if agreement cannot be reached. Search results and the studies included or excluded will be summarized in a PRISMA flow diagram.

Data extraction

Data will be extracted from each systematic review but not from their underlying studies using a structured form based on the 13-item standardized data extraction tool suggested by Aromataris et al.[24] (Figure 1)

Figure 1: Items suggested in the standard data extraction tool by Aromataris et al.[24]

1. Citation details
2. Objectives of the included review
3. Type of review
4. Participant details
5. Setting and context
6. The number and names of databases sourced and searched
7. Date range of database searching
8. Publication date range of studies included in the review that inform each outcome of interest
9. Number of studies, types of studies and country of origin of studies included in each review
10. Instrument used to appraise the primary studies and the rating of their quality
11. Outcomes reported that are relevant to the umbrella review question e.g., stillbirth or any of the core outcome sets for neonatal research by Webbe et al.
12. Method of synthesis/analysis employed to synthesize the evidence
13. Comments or notes the umbrella review authors may have regarding any included study

Two independent reviewers will extract data from each systematic review using structured data extraction forms. To ensure consistency, the reviewers will conduct calibration exercises with three randomly selected systematic reviews before commencing data extraction. If discrepancies exceed 10%, an additional training exercise with the structured data extraction form will be conducted. Discordance noted during data extraction will be resolved by consensus between the two independent reviewers or by discussing with the co-investigator team if agreement cannot be reached.

Quality assessment of systematic reviews

The risk of bias for each included systematic review will be evaluated independently by two reviewers using the ROBIS tool.[28] Each question in the ROBIS tool checklist can be scored as 'met', 'not met', 'unclear' or 'not applicable'. Discordant assessments between the reviewers will be resolved by consensus or discussion with the co-investigator team if agreement cannot be reached.

Data analysis and synthesis

A meta-analysis is not planned because of the likely different types, definitions, and thresholds of the ultrasound parameters and the wide range of adverse perinatal outcomes. Therefore, a narrative approach will be employed using reporting guidelines for systematic review of systematic

reviews,[25] and further guidance in synthesizing and reporting outcomes will involve adapting guidelines for conducting systematic reviews without meta-analysis.[30,31]

Data will be mapped for each adverse perinatal outcome with tables and narrative summaries of each systematic review contributing to an outcome. The date range of the studies used to map ultrasound parameters for each adverse perinatal outcome will be reported to show the recency of evidence. If applicable, the absence of data for an outcome and systematic reviews with overlapping primary studies will also be noted. The data from systematic reviews of randomized studies will be presented separately because current guidelines do not favour combining randomized and non-randomized studies in systematic reviews.[39] In addition, separate results will be presented for systematic reviews involving universal ultrasound (i.e., routine ultrasound for all pregnant women) and reviews in which participants with a positive test are treated with an intervention known to improve perinatal outcomes such as induction of labour or caesarean section.

Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria,[29] the certainty of the evidence for each outcome from the included systematic reviews will be extracted from each study when available or assessed with data from the reviews by two independent reviewers. Disagreements will be resolved by consensus between the reviewers or by discussion with the co-investigator team. The GRADE criteria rate the certainty of results as "high", "moderate", "low", or "very low" based on five domains. These domains include 1) risk of bias, 2) imprecision, 3) inconsistency, 4) indirectness, and 5) publication bias.[29] Ratings will be downgraded by one level for flaws in each domain up to a maximum of three levels for all domains. All randomized controlled trials are rated as high certainty but may be downgraded by one or two grades for serious or very serious flaws in any of these domains. Observational studies start from the low grade and are upgraded when assessed to have any of the following: a large magnitude of effect, a dose-response effect gradient, and all residual confounding decrease effect size in cases where an effect exists. In the case of reviews that access observation studies with the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[40] all studies are rated high certainty and downgraded afterwards for flaws detected because the ROBIN-I tool accounts for the risk of bias resulting from non-randomization.[41]

This study will also assess the imprecision of systematic reviews by examining its "optimal information size" and 95% confidence interval.[42] Optimal information size refers to the number of patients required for a systematic review to power its results adequately.[42] A precise, systematic review should meet this criterion, and its 95% confidence interval if it includes the line of no effect should exclude both appreciable benefit and no benefit. Guyatt et al. suggested that systematic reviews should be rated down if the confidence interval of risk ratios crosses the line of no effect and is less than 0.75 or above 1.25.[42] Therefore, effect sizes crossing the line of no effect with risk ratio thresholds less than 0.75 or above 1.25 will be interpreted as having wide confidence intervals. The confidence interval of risk ratios will also be considered wide if it does not cross the line of no effect (1.0), but it is less than or equal to 1.25, when the direction of effect is beneficial, or it is more than or equal to 0.75, when the direction of effect is not beneficial.

Ultrasound parameters will be classified as: 1) beneficial, 2) probably beneficial, 3) no effect, 4) probably not beneficial, 5) not beneficial, and 6) inconclusive based on a framework employed in

two recent umbrella reviews.[43,44] To accommodate the definitions of narrow and wide confidence intervals described above, we adapted the framework as shown in Figure 2. Similar to these reviews,[43,44] tables with graphic icons developed by the World Health Organization,[45] will be used to illustrate the class of each ultrasound parameter and the certainty of the evidence.

Figure 2 – Adapted framework for synthesizing study recommendations

Direction of effect	Confidence Interval	GRADE	Study Recommendation	Recommendation Graphic signs*
Beneficial	Narrow CI not crossing the line of no effect	Moderate or high	Beneficial	
Not beneficial	Narrow CI not crossing the line of no effect	Moderate or high	Not beneficial	
No effect	Narrow CI crossing the line of no effect	Moderate or high	No effect	
Beneficial	CI not crossing the line of no effect	Low	Probably beneficial	
Beneficial	Narrow CI crossing the line of no effect	Moderate or high	Probably beneficial	
Beneficial	Wide CI not crossing the line of no effect	Moderate or high	Probably beneficial	
Not beneficial	CI not crossing the line of no effect	Low	Probably not beneficial	
Not beneficial	Narrow CI crossing the line of no effect	Moderate or high	Probably not beneficial	
Not beneficial	Wide CI not crossing the line of no effect	Moderate or high	Probably not beneficial	
Beneficial, not beneficial or no effect	Narrow CI crossing the line of no effect	Low	Inconclusive	
Beneficial, not beneficial or no effect	Wide CI crossing the line of no effect	Low, moderate or high	Inconclusive	
Beneficial or not beneficial	CI not crossing the line of no effect	Very low	Inconclusive	
Beneficial, not beneficial or no effect	CI crossing the line of no effect	Very low	Inconclusive	

* All icons provided by Freepik at www.flaticon.com.

If the data are available, separate results will be presented for systematic reviews involving randomised controlled trials, those with universal ultrasound (i.e., routine ultrasound for all study participants) and reviews in which participants with a positive test are treated with an intervention known to improve perinatal outcomes such as induction of labour or caesarean section. A limited scope for a meta-analysis is anticipated. However, where feasible, results will be pooled using a random-effects meta-analysis, with standardised mean differences for continuous outcomes and risk ratios for binary outcomes. In particular, a nested meta-analysis may be conducted for pregnancies with universal ultrasound and those in which late pregnancy ultrasound is coupled

with induction of labour or a caesarean section. Heterogeneity will be assessed using both the chi-squared test and the I-squared statistic. I-squared statistic greater than 50% will be considered as identifying substantial heterogeneity.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

CONCLUSION

This paper presents a protocol for a systematic review of systematic reviews of key late pregnancy ultrasound parameters to identify pregnancies at risk of adverse perinatal outcomes. It will use rigorous methodology based on current guidelines[16–19,21,23–25,] and to the best of our knowledge, this is the first systematic overview of systematic reviews in this area. Adverse perinatal outcomes remain a critical contributor to under-five-year mortality and lifelong neurodevelopmental complications.[1,2] Despite anticipated heterogeneity due to the diverse nature of ultrasound parameters and the wide range of possible adverse perinatal outcomes, this research has the potential to provide a high-quality summary for clinicians, guideline developers, and policymakers and highlight existing knowledge gaps.

Data availability statement
No datasets generated and/or analyzed for this protocol.

Ethics and dissemination
This research utilizes publicly available published data thus, Ethics Committee review is not required. The findings will be published in a peer-reviewed journal.

Funding
A Nuffield Department of Population Health/Keble College tuition-free studentship funds the first author for his DPhil, the umbrella project for this study.

Authors' contributions

AKA conceptualized and designed the study and drafted the protocol. AKA, MAQ, LI, ORA and JJK provided inputs on methodological issues. The search strategy was developed by AKA and peer reviewed by EH. AKA and NN will screen and select articles, assess the quality of studies and extra data. All authors reviewed the final protocol and approved the manuscript. AKA is the guarantor of the article.

Competing interest statement
None declared

Patient consent for publication
Not required.

Acknowledgement
We acknowledge Elinor Harriss (ER) for helping to peer review and refine the search strategy.

REFERENCE

1. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet. 2016 Feb 6;387(10018):587–603.
2. Draper E, Gallimore I, Smith L, Fenton A, Kurinczuk L, Smith P, et al. MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2018. Leicester; 2020.
3. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol. 2005 Mar;25(3):258–64.
4. Gardosi J, Giddings S, Buller S, Southam M, Williams M. Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public Health. 2014;128(8):698–702.
5. Lees CC, Stampalija T, Baschat AA, Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020 Aug 1;56(2):298–312.
6. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev. 2015 Jun 29;2015(6).
7. National Collaborating Centre for Women's and Children's Health, National Institute for Health and Clinical Excellence. Antenatal care : routine care for the healthy pregnant woman. Welsh A, editor. London: RCOG Press; 2008. 428 p.
8. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 204 Summary: Fetal Growth Restriction. Obstet Gynecol. 2019 Feb 1;133(2):390–2.
9. Smith G. A critical review of the Cochrane meta-analysis of routine late-pregnancy ultrasound. BJOG An Int J Obstet Gynaecol. 2021 Jan 28;128(2):207–13.
10. Smith G. A critical review of the Cochrane meta-analysis of routine late-pregnancy ultrasound. BJOG An Int J Obstet Gynaecol. 2021 Jan 28;128(2):207–13.
11. Middleton P, Shepherd E, Morris J, Crowther CA, Gomersall JC. Induction of labour at or beyond 37 weeks' gestation. Cochrane Database Syst Rev. 2020 Jul 15;2020(7).
12. Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: Development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020 Jul 1;105(4):425–31.
13. Al-Hafez L, Chauhan SP, Riegel M, Balogun OA, Hammad IA, Berghella V. Routine third-trimester ultrasound in low-risk pregnancies and perinatal death: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020 Nov;2(4):100242.
14. Heazell AEP, Hayes DJL, Whitworth M, Takwoingi Y, Bayliss SE, Davenport C. Biochemical tests of placental function versus ultrasound assessment of fetal size for stillbirth and small-for-gestational-age infants. Cochrane Database Syst Rev. 2019 May 14;2019(5).
15. Martinez-Portilla RJ, Caradeux J, Meler E, Lip-Sosa DL, Sotiriadis A, Figueras F. Third-trimester uterine artery Doppler for prediction of adverse outcome in late small-for-

gestational-age fetuses: systematic review and meta-analysis. Vol. 55, Ultrasound in Obstetrics and Gynecology. John Wiley and Sons Ltd; 2020. p. 575–85.
16. Goto E. Usefulness of ultrasound fetal anthropometry in primary and secondary screening to identify small for gestational age: A meta-analysis. J Clin Ultrasound. 2019 May 11;47(4):212–8.
17. Moraitis AA, Shreeve N, Sovio U, Brocklehurst P, Heazell AEP, Thornton JG, et al. Universal third-trimester ultrasonic screening using fetal macrosomia in the prediction of adverse perinatal outcome: A systematic review and meta-analysis of diagnostic test accuracy. Vol. 17, PLoS Medicine. Public Library of Science; 2020.
18. Vogel JP, Vannevel V, Robbers G, Gwako G, Lavin T, Adanikin A, et al. Prevalence of abnormal umbilical arterial flow on Doppler ultrasound in low-risk and unselected pregnant women: a systematic review. Reprod Health. 2021 Dec;18(1).
19. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: How will we ever keep up? PLoS Med. 2010 Sep;7(9):e1000326.
20. Wastlund D, Moraitis AA, Thornton JG, Sanders J, White IR, Brocklehurst P, et al. The cost-effectiveness of universal late-pregnancy screening for macrosomia in nulliparous women: a decision analysis. BJOG An Int J Obstet Gynaecol. 2019;126(10):1243–50.
21. Wilson ECF, Wastlund D, Moraitis AA, Smith GCS. Late Pregnancy Ultrasound to Screen for and Manage Potential Birth Complications in Nulliparous Women: A Cost-Effectiveness and Value of Information Analysis. Value Heal. 2021 Apr 1;24(4):513–21.
22. Wastlund D, Moraitis AA, Dacey A, Sovio U, Wilson ECF, Smith GCS. Screening for breech presentation using universal late-pregnancy ultrasonography: A prospective cohort study and cost effectiveness analysis. PLoS Med. 2019;16(4).
23. Thomson D, Russell K, Becker L, Klassen T, Hartling L. The evolution of a new publication type: Steps and challenges of producing overviews of reviews. Res Synth Methods. 2010 Jul;1(3–4):198–211.
24. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015 Sep 1;13(3):132–40.
25. Pollock M, Fernandes R, Becker L, Pieper D, Hartling L. Overviews of Reviews. In: Higgins J, Thomas J, Chander J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. version 6. Cochrane; 2021.
26. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Rev Esp Nutr Humana y Diet. 2016 Jan 1;20(2):148–60.
27. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev. 2021 Dec 26;10(1):39.
28. Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan 1;69:225–34.
29. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated 2013. GRADE Working Group; 2013.
30. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline.

BMJ. 2020 Jan 16;368.

31. McKenzie JE, Brennan SE. Synthesizing and presenting findings using other methods. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. version 6. Cochrane; 2021. p. 321–47.
32. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372(1):n71.
33. Labarca G, Ortega F, Arenas A, Reyes T, Rada G, Jorquera J. Extrapulmonary effects of continuous airway pressure on patients with obstructive sleep apnoea: Protocol for an overview of systematic reviews. Vol. 7, BMJ Open. BMJ Publishing Group; 2017. p. e015315.
34. Pollock M, Fernandes RM, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions. BMC Med Res Methodol. 2017 Dec 23;17(1):48.
35. Pollock M, Fernandes RM, Newton AS, Scott SD, Hartling L. A decision tool to help researchers make decisions about including systematic reviews in overviews of reviews of healthcare interventions. Vol. 8, Systematic Reviews. BioMed Central Ltd.; 2019.
36. Canadian Agency for Drugs and Technologies in Health (CADTH). Strings Attached: CADTH Database Search Filters [Internet]. 2016 [cited 2021 Jun 14]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst
37. The University of Texas. Ovid Medline - Search Filters for Various Databases [Internet]. LibGuides at University of Texas School of Public Health. 2014 [cited 2021 Jun 14]. Available from: https://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters
38. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016 Jul 1;75:40–6.
39. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:4008.
40. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355.
41. Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol. 2019 Jul 1;111:105–14.
42. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - Imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.
43. Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: An overview of Cochrane systematic reviews. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018.
44. Ota E, da Silva Lopes K, Middleton P, Flenady V, Wariki WMV, Rahman MO, et al. Antenatal interventions for preventing stillbirth, fetal loss and perinatal death: an overview of Cochrane systematic reviews. Vol. 2020, Cochrane Database of Systematic Reviews.

John Wiley and Sons Ltd; 2020.
45. World Health Organization. WHO recommendations: Optimizing health worker roles for maternal and newborn health through task shifting - WHO OptimizeMNH [Internet]. [cited 2021 Jun 15]. Available from: https://optimizemnh.org/optimizing-health-worker-roles-maternal-newborn-health/

BMJ Open

A protocol for a systematic review of systematic reviews of late pregnancy ultrasound parameters that identify fetuses at risk of adverse perinatal outcomes.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058293.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Jan-2022
Complete List of Authors:	Aderoba, Adeniyi; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, ; HealthMATE 360, Department of Maternal and Perinatal Health Nasir, Naima; Univerity of Oxford Nuffield Department of Medicine, Centre for Tropical Medicine and Global Health Quigley, Maria; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, Impey, Lawrence; Oxford University Hospitals NHS Trust, Department of Fetal Medicine Rivero-Arias, Oliver; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, Kurinczuk, Jennifer; University of Oxford, National Perinatal Epidemiology Unit, Nuffield Department of Population Health,
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Global health, Patient-centred medicine, Research methods, Health services research
Keywords:	Ultrasonography < OBSTETRICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Fetal medicine < OBSTETRICS, Prenatal diagnosis < OBSTETRICS, Maternal medicine < OBSTETRICS, PERINATOLOGY

TITLE

A protocol for a systematic review of systematic reviews of late pregnancy ultrasound parameters that identify fetuses at risk of adverse perinatal outcomes.

Authors

Adeniyi Kolade Aderoba, MBBS, MSc - National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. adeniyi.aderoba@gmail.com

Naima Nasir, BPharm, MSc - Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford. naima.nasir@keble.ox.ac.uk

Maria A Quigley, MSc, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. maria.quigley@npeu.ox.ac.uk

Lawrence Impey, MD, Department of Fetal Medicine, John Radcliffe Hospital, Oxford University Hospitals NHS Trust. lawrence.impey@ouh.nhs.uk

Oliver Rivero-Arias, DPhil, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. oliver.rivero@npeu.ox.ac.uk

Jennifer J Kurinczuk, MD, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. jenny.kurinczuk@npeu.ox.ac.uk

Corresponding Author

Dr Adeniyi K. Aderoba

National Perinatal Epidemiology Unit (NPEU)

Nuffield Department of Population Health

University of Oxford

Old Road Campus, Oxford, OX3 7LF

Email: adeniyi.aderoba@dph.ox.ac.uk, adeniyi.aderoba@gmail.com

Keywords

Ultrasound, late-pregnancy, universal scan, routine scan, stillbirth, adverse perinatal outcome(s), umbrella review, systematic review of systematic reviews,

Word count - 2901

ABSTRACT

Introduction

Stillbirths and neonatal deaths are leading contributors to the global burden of disease and pregnancy ultrasound has the potential to help decrease this burden. In the absence of high-GRADE evidence on universal obstetric ultrasound screening at or close to term, many different screening strategies have been proposed. Systematic reviews have rapidly increased over the past decade owing to the diverse nature of ultrasound parameters and the wide range of possible adverse perinatal outcomes. This systematic review will summarize the evidence on key ultrasound parameters in the published literature to help develop an obstetric ultrasound protocol that identifies pregnancies at risk of adverse perinatal outcomes at or close to term.

Methods

This study will follow the recent Cochrane guidelines for a systematic review of systematic reviews. A comprehensive literature search will be conducted using EMBASE (OvidSP), MEDLINE (OvidSP), CDSR, CINAHL (EBSCOhost), and Scopus. Systematic reviews evaluating at least one ultrasound parameter in late pregnancy to detect pregnancies at risk of adverse perinatal outcomes will be included. Two independent reviewers will screen, assess the quality including the risk of bias using the ROBIS tool, and extract data from eligible systematic reviews that meet the study inclusion criteria. Overlapping data will be assessed and managed with decision rules, and study evidence including the GRADE assessment of the certainty of results will be presented as a narrative synthesis as described in the Cochrane guidelines for an overview of reviews.

Ethics and dissemination

This research utilizes publicly available published data; thus, an Ethics Committee review is not required. The findings will be published in a peer-reviewed journal.

Prospero registration number: CRD42021266108

Strengths and limitations of this study

- To the best of our knowledge, this will be the first systematic review of systematic reviews of obstetric ultrasound parameters that identify fetuses at risk of adverse prenatal outcomes at or close to term.
- The review will use a rigorous methodology based on current guidelines and will provide a high-quality summary for clinicians, guideline developers, and policymakers. In addition, the detailed methods allow for an easy update in the future and applicability to similar conditions.
- Double counting duplicate data might give undue weight to some studies and a potential limitation of this review might be the tendency to lose data by dropping systematic reviews with overlapping primary studies.

BACKGROUND

Stillbirths and neonatal deaths remain leading contributors to the global burden of disease in high- and low-income countries.[1] Annually, over two million stillbirths occur, and additional babies die during the neonatal period.[1] In addition, many babies who survive severe pregnancy and childbirth complications live with permanent brain damage and have special education needs.[2] Evidence exists that when at-risk fetuses are identified before birth, the risk of these adverse perinatal outcomes is mitigated.[3,4]

Many systematic reviews show that late pregnancy ultrasound can help to detect pregnancy complications in women with suspected high-risk conditions such as fetal growth restriction (FGR) and small for gestational age (SGA).[5] However, in low-risk pregnancies, routine late pregnancy ultrasound is not recommended because current evidence, primarily from a Cochrane review, shows that it is not beneficial for a woman or her baby.[6] Routine late pregnancy ultrasound is also not used in many countries,[7,8] perhaps due to the methodological weaknesses identified in the Cochrane review.[9] These weaknesses include using different definitions for a positive test, varied test performance, and not combining a positive ultrasound test with interventions known to improve perinatal outcomes,[9] such as induction of labour[10] or elective caesarean section.

In the absence of high-GRADE (Grading of Recommendations Assessment, Development and Evaluation criteria[11]) evidence on universal obstetric ultrasound screening at or close to term to prevent adverse outcomes, many different screening strategies have been proposed. Similarly, due to the diverse nature of ultrasound parameters and the wide range of possible adverse perinatal outcomes,[12] the last decade has witnessed a rapid proliferation of systematic reviews in this area.[13–18] Therefore, clinicians and policymakers are overwhelmed by the current pace of evidence.[19] It has also been challenging to have an overarching assessment of the cost-effectiveness of late pregnancy ultrasound, given that multiple combinations of ultrasound parameters are possible. As a consequence, current estimates of the cost-effectiveness of late pregnancy ultrasound have focused on individual parameters.[20–22] A systematic review of systematic reviews, also referred to as an umbrella review or overview of reviews, may help with evidence synthesis to support the development of an obstetric ultrasound protocol by identifying effective ultrasound parameters for the identification of pregnancies at risk of adverse perinatal outcomes despite being apparently low risk at or close to term.[23] It will also provide guidance as to the effective parameters for use in women who are suspected to be at high risk of adverse outcomes. Thus, it will pave the way for more relevant and up-to-date clinical guidelines for routine screening and estimation of cost-effectiveness.

Objective

This study aims to systematically review existing systematic reviews to identify effective ultrasound parameters, for an obstetric ultrasound and management protocol that detects pregnancies at risk of adverse perinatal outcomes at or close to term.

METHODS

This systematic review of systematic reviews protocol was developed using the guidelines by Aromataris et al.[24,] and Pollock et al. [25] Further guidance comes from adapting guidelines for systematic review protocols,[26] searches,[27] quality and certainty of evidence,[11,28] synthesis,[29,30] and reporting[31]. This study was registered in the PROSPERO registry (Registration number: CRD42021266108)

Inclusion criteria

Type of studies

The study will include qualitative systematic reviews with numerical outcome data that fulfil the criteria defined by Labarca et al., [32] which are "systematic reviews that reported at least one inclusion criterion, searched at least one database, reported a pooled measure of effect for at least one outcome, and evaluated the risk of bias of the primary studies". This review will also include systematic reviews of randomized and non-randomized studies because it aims to determine the ultrasound parameter(s) that effectively identify adverse perinatal outcomes.

Although Cochrane reviews tend to have superior methodological quality,[33] this protocol presumes that data overlap would likely exist between Cochrane and non-Cochrane systematic reviews, and an overview of only Cochrane reviews might not sufficiently answer this study's research question. Further, avoiding bias from double counting overlapping data (i.e. duplicate primary studies) in the systematic reviews in an overview of reviews is methodologically challenging, time-intensive and prone to non-systematic and non-transparent conduct.[34] This study will note systematic reviews with overlapping primary studies. However, using the evidence-based decision tool by Pollock et al.,[34] recommended for Cochrane overview of reviews,[25] non-overlapping systematic reviews will hopefully be analyzed for each outcome. To balance the methodological complexity associated with analysing overlapping data with the potential bias from dropping them, a systematic review from a group of overlapping reviews will be prioritized for inclusion based on the following decision rule - if it has the best presentation of results in terms of recency, quality and completeness of numerical outcome data.

Type of participants

Singleton pregnancies at the 36-week scan will be included because this study aims to provide evidence for a late pregnancy ultrasound screening strategy to prevent stillbirths, perinatal mortality, and adverse neurodevelopmental outcomes. Although the gestational age widow constituting the 36-week scan varies,[35–40] this study will include systematic reviews with obstetric scans from 35+0 weeks gestation. This study will not be limited to any context or language.

Type of intervention

A systematic review will be included if ultrasound parameters are assessed alone in late pregnancy (i.e., from 35+0 weeks) or when combined with one or more ultrasound parameters to predict stillbirth or adverse perinatal outcomes. In the context of this study, an ultrasound parameter refers to any of the following: a characteristic sign or test that is observable while examining the contents of a pregnant uterus (i.e., fetus, umbilical cord, placenta, or amniotic fluid) during an ultrasound scan.

Comparator and outcomes

This umbrella review will focus on systematic reviews that identified at least one of this study's primary or secondary outcomes by comparing a positive test in which one or more late pregnancy ultrasound parameters are assessed, with a negative test with the same parameters. The primary outcomes of this study are stillbirth or any other adverse perinatal outcome(s). In this study, late pregnancy is defined as gestational age from 35+0 weeks. Adverse perinatal outcome refers to any outcome that is similar to any of the core outcome sets for neonatal research by Webbe et al.[12] These core outcomes include: (1) survival – stillbirth, perinatal or neonatal death, (2) sepsis, (3) necrotizing enterocolitis, (4) brain injury on imaging, (5) general gross motor ability, (6) general cognitive ability, (7) quality of life, 8) adverse events, (9) visual impairment or blindness, (10) retinopathy of prematurity, (11) chronic lung disease/bronchopulmonary dysplasia and (12) hearing impairment or deafness. Outcomes associated with prematurity, items 3, 10, and 11 will be excluded because this study aims to provide evidence for an obstetric ultrasound screening strategy at or close to term to avert stillbirths, perinatal mortality, and adverse neurodevelopmental outcomes. The secondary outcomes are small or large for gestational age babies, fetal growth restriction, breech presentation, oligo or polyhydramnios, low-lying or invasive placenta, or other high-risk fetal conditions known to be associated with stillbirth or adverse perinatal outcomes.

Exclusion criteria

Systematic reviews to be excluded are:

- Systematic reviews assessing ultrasound in twins or higher-order pregnancies
- Scoping reviews with a systematic search
- Animal studies
- Reviews without a meta-analysis or with non-numerical outcome data
- Systematic reviews that compared a positive test with an ultrasound parameter(s) against a positive test with another ultrasound parameter(s), rather than with a negative test with the same ultrasound parameter(s). This study is not designed to rank or make direct or indirect comparisons between ultrasound parameters but to identify clinically effective parameters for a late pregnancy ultrasound protocol.
- Systematic reviews with extensive overlapping primary studies that do not meet the criteria of recency, quality and completeness of data for each outcome
- Studies with ultrasound performed solely in labour
- Previous systematic reviews on ultrasound with more recent published versions
- Studies with ultrasound parameters that cannot be assessed at the 36-week scan or in which adverse perinatal outcomes were evaluated before 35+0 weeks' gestation or both
- Studies that only assessed the cost-effectiveness of ultrasound

- Systematic reviews in which ultrasound assessment focused entirely on congenital anomalies. Congenital anomalies may range widely in their types, severity of symptoms and interventions that can alleviate them. Therefore, existing systematic reviews are likely to be heterogeneous in their populations, interventions, and comparators. As advised by the Cochrane guidelines, answering an umbrella review question is likely not feasible in this scenario.[25]
- Withdrawn systematic reviews
- Conference abstracts

Information sources and search strategy

The following databases will be searched from inception: EMBASE (OvidSP), MEDLINE (OvidSP), Cochrane Database of Systematic Reviews (www.cochranelibrary.com), Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCOhost), and Scopus (www.scopus.com). Relevant thesaurus headings for ultrasonography, prenatal, fetus echography, and fetal Doppler will be used, along with free-text search strings constructed for the title or abstract fields to search for pregnancy, prenatal, (or pre-natal, etc.) ultrasonography (or ultrasound, etc.), using the proximity indicator to narrow the search appropriately. Two systematic review search filters will be used for Ovid Embase[41] and Ovid Medline,[42] respectively. These filters will be adapted for the CINAHL (EBSCOhost) and Scopus searches. Additional relevant references will be retrieved from searches constructed for the World Health Organization (WHO) Global Index Medicus library (www.globalindexmedicus.net).

In addition, the reference lists of eligible studies will be manually searched for further relevant systematic reviews. The searches will be re-run just before the final analyses, and systematic reviews which meet the inclusion criteria will be added. The search strategy will be peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) guideline statement,[43] by an information specialist (EH). The complete search strategy is available in supplementary materials. Search results from the different databases will be merged in the Covidence systematic review management software to facilitate deduplication and selection of studies. The results will then be exported to Microsoft Excel for review.

Data collection

Selection of studies

Systematic review screening and selection will be conducted independently by two reviewers using Covidence, a web-based software review platform. After removing duplicates, the search results will first be screened by their titles and abstracts for eligible systematic reviews using the inclusion and exclusion criteria. The full-text publications selected will then undergo full eligibility screening for the systematic reviews. The reasons for exclusion at each screening stage will be documented. Disagreements will be resolved by consensus between the two independent reviewers or by a discussion with the co-investigator team if an agreement cannot be reached. Search results and the studies included or excluded will be summarized in a PRISMA flow diagram.

Data extraction

Data will be extracted from each systematic review but not from their underlying studies using a structured form based on the 13-item standardized data extraction tool suggested by Aromataris et al.[24] (Figure 1). Two independent reviewers will extract data from each systematic review using structured data extraction forms. To ensure consistency, the reviewers will conduct calibration exercises with three randomly selected systematic reviews before commencing data extraction. If discrepancies exceed 10%, an additional training exercise with the structured data extraction form will be conducted. Discordance noted during data extraction will be resolved by consensus between the two independent reviewers or by discussing with the co-investigator team if an agreement cannot be reached.

Quality assessment of systematic reviews

The risk of bias for each included systematic review will be evaluated independently by two reviewers using the ROBIS tool.[28] Each question in the ROBIS tool checklist can be scored as 'met', 'not met', 'unclear' or 'not applicable'. Discordant assessments between the reviewers will be resolved by consensus or discussion with the co-investigator team if agreement cannot be reached.

Data analysis and synthesis

A meta-analysis is not planned because of the likely different types, definitions, and thresholds of the ultrasound parameters and the wide range of adverse perinatal outcomes. Therefore, a narrative approach will be employed using reporting guidelines for systematic review of systematic reviews,[25] and further guidance in synthesizing and reporting outcomes will involve adapting guidelines for conducting systematic reviews without meta-analysis.[29,30]

Data will be mapped for each adverse perinatal outcome with tables and narrative summaries of each systematic review contributing to an outcome. The date range of the studies used to map ultrasound parameters for each adverse perinatal outcome will be reported to show the recency of evidence. If applicable, the absence of data for an outcome and systematic reviews with overlapping primary studies will also be noted. The data from systematic reviews of randomized studies will be presented separately because current guidelines do not favour combining randomized and non-randomized studies in systematic reviews.[44] In addition, separate results will be presented for systematic reviews involving universal ultrasound (i.e., routine ultrasound for all pregnant women) and reviews in which participants with a positive test are treated with an intervention known to improve perinatal outcomes such as induction of labour or caesarean section.

Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria,[11] the certainty of the evidence for each outcome from the included systematic reviews will be extracted from each study when available or assessed with data from the reviews by two independent reviewers. Disagreements will be resolved by consensus between the reviewers or by discussion with the co-investigator team. The GRADE criteria rate the certainty of results as "high", "moderate", "low", or "very low" based on five domains. These domains include 1) risk of bias, 2) imprecision, 3) inconsistency, 4) indirectness, and 5) publication bias.[11] Ratings will be

downgraded by one level for flaws in each domain up to a maximum of three levels for all domains. All randomized controlled trials are rated as high certainty but may be downgraded by one or two grades for serious or very serious flaws in any of these domains. Observational studies start from the low grade and are upgraded when assessed to have any of the following: a large magnitude of effect, a dose-response effect gradient, and all residual confounding decrease effect size in cases where an effect exists. In the case of reviews that access observation studies with the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[45] all studies are rated high certainty and downgraded afterwards for flaws detected because the ROBIN-I tool accounts for the risk of bias resulting from non-randomization.[46]

This study will also assess the imprecision of systematic reviews by examining its "optimal information size" and 95% confidence interval.[47] Optimal information size refers to the number of patients required for a systematic review to power its results adequately.[47] A precise, systematic review should meet this criterion, and its 95% confidence interval if it includes the line of no effect should exclude both appreciable benefit and no benefit. Guyatt et al. suggested that systematic reviews should be rated down if the confidence interval of risk ratios crosses the line of no effect and is less than 0.75 or above 1.25.[47] Therefore, effect sizes crossing the line of no effect with risk ratio thresholds less than 0.75 or above 1.25 will be interpreted as having wide confidence intervals. The confidence interval of risk ratios will also be considered wide if it does not cross the line of no effect (1.0), but it is less than or equal to 1.25, when the direction of effect is beneficial, or it is more than or equal to 0.75, when the direction of effect is not beneficial.

Ultrasound parameters will be classified as: 1) beneficial, 2) probably beneficial, 3) no effect, 4) probably not beneficial, 5) not beneficial, and 6) inconclusive based on a framework employed in two recent umbrella reviews.[48,49] To accommodate the definitions of narrow and wide confidence intervals described above, we adapted the framework as shown in Figure 2. Similar to these reviews,[48,49] tables with graphic icons developed by the World Health Organization,[50] will be used to illustrate the class of each ultrasound parameter and the certainty of the evidence.

If the data are available, separate results will be presented for systematic reviews involving randomised controlled trials, those with universal ultrasound (i.e., routine ultrasound for all study participants) and reviews in which participants with a positive test are treated with an intervention known to improve perinatal outcomes such as induction of labour or caesarean section. A limited scope for a meta-analysis is anticipated. However, where feasible, results will be pooled using a random-effects meta-analysis, with standardised mean differences for continuous outcomes and risk ratios for binary outcomes. In particular, a nested meta-analysis may be conducted for pregnancies with universal ultrasound and those in which late pregnancy ultrasound is coupled with induction of labour or a caesarean section. Heterogeneity will be assessed using both the chi-squared test and the I-squared statistic. I-squared statistic greater than 50% will be considered as identifying substantial heterogeneity.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

CONCLUSION

This paper presents a protocol for a systematic review of systematic reviews of key obstetric ultrasound parameters to identify pregnancies at risk of adverse perinatal outcomes at or close to term. It will use rigorous methodology based on current guidelines[16–19,21,23–25,] and to the best of our knowledge, this is the first systematic overview of systematic reviews in this area. Adverse perinatal outcomes remain a critical contributor to under-five-year mortality and lifelong neurodevelopmental complications.[1,2] Despite anticipated heterogeneity due to the diverse nature of ultrasound parameters and the wide range of possible adverse perinatal outcomes, this research has the potential to provide a high-quality summary for clinicians, guideline developers, and policymakers and highlight existing knowledge gaps.

Data availability statement
No datasets generated and/or analyzed for this protocol.

Ethics and dissemination
This research utilizes publicly available published data thus, Ethics Committee review is not required. The findings will be published in a peer-reviewed journal.

Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

AKA conceptualized and designed the study and drafted the protocol. AKA, MAQ, LI, ORA and JJK provided inputs on methodological issues. The search strategy was developed by AKA and peer reviewed by EH. AKA and NN will screen and select articles, assess the quality of studies and extra data. All authors reviewed the final protocol and approved the manuscript. AKA is the guarantor of the article.

Competing interest statement
None declared

Patient consent for publication
Not required.

Acknowledgement
We acknowledge Elinor Harriss (ER) for helping to peer review and refine the search strategy.

Figure 1: Items suggested in the standard data extraction tool by Aromataris et al.[24]
Figure 2 – Adapted framework for synthesizing study recommendations

REFERENCE

1. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet [Internet]. 2016 Feb 6 [cited 2021 Jan 21];387(10018):587–603. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673615008375
2. Draper E, Gallimore I, Smith L, Fenton A, Kurinczuk L, Smith P, et al. MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2019. [Internet]. Leicester; 2021 [cited 2022 Jan 19]. Available from: https://www.npeu.ox.ac.uk/mbrrace-uk/reports
3. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol [Internet]. 2005 Mar [cited 2020 Feb 22];25(3):258–64. Available from: https://pubmed.ncbi.nlm.nih.gov/15717289/
4. Gardosi J, Giddings S, Buller S, Southam M, Williams M. Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public Health [Internet]. 2014 [cited 2021 Apr 14];128(8):698–702. Available from: https://pubmed.ncbi.nlm.nih.gov/25151298/
5. Lees CC, Stampalija T, Baschat AA, Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol [Internet]. 2020 Aug 1 [cited 2021 Mar 4];56(2):298–312. Available from: https://pubmed.ncbi.nlm.nih.gov/32738107/
6. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev [Internet]. 2015 Jun 29 [cited 2020 Jan 28];2015(6):CD001451. Available from: https://pubmed.ncbi.nlm.nih.gov/26121659/
7. National Collaborating Centre for Women's and Children's Health, National Institute for Health and Clinical Excellence. Antenatal care : routine care for the healthy pregnant woman. Welsh A, editor. London: RCOG Press; 2008. 428 p.
8. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 204 Summary: Fetal Growth Restriction. Obstet Gynecol [Internet]. 2019 Feb 1 [cited 2021 Jan 9];133(2):390–2. Available from: http://journals.lww.com/00006250-201902000-00032
9. Smith G. A critical review of the Cochrane meta-analysis of routine late-pregnancy ultrasound. BJOG An Int J Obstet Gynaecol [Internet]. 2021 Jan 28 [cited 2020 Oct 11];128(2):207–13. Available from: https://pubmed.ncbi.nlm.nih.gov/32598533/
10. Middleton P, Shepherd E, Morris J, Crowther CA, Gomersall JC. Induction of labour at or beyond 37 weeks' gestation. Cochrane Database Syst Rev [Internet]. 2020 Jul 15 [cited 2021 Jan 21];2020(7). Available from: https://pubmed.ncbi.nlm.nih.gov/32666584/
11. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. [Internet]. Updated 2013. GRADE Working Group; 2013 [cited 2021 Jun 15]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html
12. Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: Development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed [Internet]. 2020 Jul 1 [cited 2021 Feb 28];105(4):425–31. Available from: http://dx.doi.org/10.1136/archdischild-2019-317501

13. Al-Hafez L, Chauhan SP, Riegel M, Balogun OA, Hammad IA, Berghella V. Routine third-trimester ultrasound in low-risk pregnancies and perinatal death: a systematic review and meta-analysis. Am J Obstet Gynecol MFM [Internet]. 2020 Nov [cited 2021 Feb 21];2(4):100242. Available from: https://pubmed.ncbi.nlm.nih.gov/33345941/
14. Heazell AEP, Hayes DJL, Whitworth M, Takwoingi Y, Bayliss SE, Davenport C. Biochemical tests of placental function versus ultrasound assessment of fetal size for stillbirth and small-for-gestational-age infants. Cochrane Database Syst Rev [Internet]. 2019 May 14 [cited 2020 Feb 11];2019(5). Available from: http://doi.wiley.com/10.1002/14651858.CD012245.pub2
15. Martinez-Portilla RJ, Caradeux J, Meler E, Lip-Sosa DL, Sotiriadis A, Figueras F. Third-trimester uterine artery Doppler for prediction of adverse outcome in late small-for-gestational-age fetuses: systematic review and meta-analysis. Vol. 55, Ultrasound in Obstetrics and Gynecology. John Wiley and Sons Ltd; 2020. p. 575–85.
16. Goto E. Usefulness of ultrasound fetal anthropometry in primary and secondary screening to identify small for gestational age: A meta-analysis. J Clin Ultrasound [Internet]. 2019 May 11 [cited 2021 Mar 10];47(4):212–8. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jcu.22688
17. Moraitis AA, Shreeve N, Sovio U, Brocklehurst P, Heazell AEP, Thornton JG, et al. Universal third-trimester ultrasonic screening using fetal macrosomia in the prediction of adverse perinatal outcome: A systematic review and meta-analysis of diagnostic test accuracy. Pajkrt E, editor. PLOS Med [Internet]. 2020 Oct 13 [cited 2021 Feb 1];17(10):e1003190. Available from: https://dx.plos.org/10.1371/journal.pmed.1003190
18. Vogel JP, Vannevel V, Robbers G, Gwako G, Lavin T, Adanikin A, et al. Prevalence of abnormal umbilical arterial flow on Doppler ultrasound in low-risk and unselected pregnant women: a systematic review. Reprod Health [Internet]. 2021 Dec [cited 2021 Mar 9];18(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33579315/
19. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: How will we ever keep up? PLoS Med [Internet]. 2010 Sep [cited 2021 Jun 7];7(9):e1000326. Available from: www.plosmedicine.org
20. Wastlund D, Moraitis AA, Thornton JG, Sanders J, White IR, Brocklehurst P, et al. The cost-effectiveness of universal late-pregnancy screening for macrosomia in nulliparous women: a decision analysis. BJOG An Int J Obstet Gynaecol [Internet]. 2019 [cited 2020 Dec 5];126(10):1243–50. Available from: https://pubmed.ncbi.nlm.nih.gov/31066982/
21. Wilson ECF, Wastlund D, Moraitis AA, Smith GCS. Late Pregnancy Ultrasound to Screen for and Manage Potential Birth Complications in Nulliparous Women: A Cost-Effectiveness and Value of Information Analysis. Value Heal [Internet]. 2021 Apr 1 [cited 2021 Jun 9];24(4):513–21. Available from: https://pubmed.ncbi.nlm.nih.gov/33840429/
22. Wastlund D, Moraitis AA, Dacey A, Sovio U, Wilson ECF, Smith GCS. Screening for breech presentation using universal late-pregnancy ultrasonography: A prospective cohort study and cost effectiveness analysis. PLoS Med. 2019;16(4).
23. Thomson D, Russell K, Becker L, Klassen T, Hartling L. The evolution of a new publication type: Steps and challenges of producing overviews of reviews. Res Synth Methods [Internet]. 2010 Jul [cited 2021 May 17];1(3–4):198–211. Available from: https://pubmed.ncbi.nlm.nih.gov/26061466/
24. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: Methodological development, conduct and reporting of

an umbrella review approach. Int J Evid Based Healthc [Internet]. 2015 Sep 1 [cited 2021 May 4];13(3):132–40. Available from: https://journals.lww.com/01787381-201509000-00004

25. Pollock M, Fernandes R, Becker L, Pieper D, Hartling L. Overviews of Reviews. In: Higgins J, Thomas J, Chander J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. version 6. Cochrane; 2021.
26. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Rev Esp Nutr Humana y Diet [Internet]. 2016 Jan 1 [cited 2021 May 17];20(2):148–60. Available from: http://www.crd.york.ac.uk/prospero
27. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev [Internet]. 2021 Dec 26 [cited 2021 May 17];10(1):39. Available from: https://doi.org/10.1186/s13643-020-01542-z
28. Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol [Internet]. 2016 Jan 1 [cited 2021 May 4];69:225–34. Available from: https://pubmed.ncbi.nlm.nih.gov/26092286/
29. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. BMJ. 2020 Jan 16;368.
30. McKenzie JE, Brennan SE. Synthesizing and presenting findings using other methods. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. version 6. Cochrane; 2021 [cited 2021 Jun 7]. p. 321–47. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/9781119536604.ch12
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021 Mar 29 [cited 2021 May 6];372(1):n71. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.n71
32. Labarca G, Ortega F, Arenas A, Reyes T, Rada G, Jorquera J. Extrapulmonary effects of continuous airway pressure on patients with obstructive sleep apnoea: Protocol for an overview of systematic reviews [Internet]. Vol. 7, BMJ Open. BMJ Publishing Group; 2017 [cited 2021 May 13]. p. e015315. Available from: http://bmjopen.bmj.com/
33. Pollock M, Fernandes RM, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions. BMC Med Res Methodol [Internet]. 2017 Dec 23 [cited 2021 Jun 12];17(1):48. Available from: http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0325-5
34. Pollock M, Fernandes RM, Newton AS, Scott SD, Hartling L. A decision tool to help researchers make decisions about including systematic reviews in overviews of reviews of healthcare interventions [Internet]. Vol. 8, Systematic Reviews. BioMed Central Ltd.; 2019 [cited 2021 Jun 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/30670086/
35. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCSS, S Smith GC, et al. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study.

Lancet [Internet]. 2015 Nov 21 [cited 2018 Dec 23];386(10008):2089–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26360240

36. Vannuccini S, Ioannou C, Cavallaro A, Volpe G, Ruiz-Martinez S, Impey L. A reference range of fetal abdominal circumference growth velocity between 20 and 36 weeks' gestation. Prenat Diagn. 2017 Nov 1;37(11):1084–92.
37. Henrichs J, Verfaille V, Jellema P, Viester L, Pajkrt E, Wilschut J, et al. Effectiveness of routine third trimester ultrasonography to reduce adverse perinatal outcomes in low risk pregnancy (the IRIS study): nationwide, pragmatic, multicentre, stepped wedge cluster randomised trial. BMJ [Internet]. 2019 Oct 15 [cited 2020 Feb 3];367:l5517. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.l5517
38. Akolekar R, Ciobanu A, Zingler E, Syngelaki A, Nicolaides KH. Routine assessment of cerebroplacental ratio at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. Am J Obstet Gynecol [Internet]. 2019 Jul 1 [cited 2022 Jan 19];221(1):65.e1-65.e18. Available from: https://pubmed.ncbi.nlm.nih.gov/30878322/
39. Ciobanu A, Rouvali A, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates: screening by maternal factors, fetal biometry, and biomarkers at 35-37 weeks' gestation. Am J Obstet Gynecol [Internet]. 2019 May 1 [cited 2022 Jan 19];220(5):486.e1-486.e11. Available from: https://pubmed.ncbi.nlm.nih.gov/30707967/
40. MacDonald TM, Robinson AJ, Hiscock RJ, Hui L, Dane KM, Middleton AL, et al. Accelerated fetal growth velocity across the third trimester is associated with increased shoulder dystocia risk among fetuses who are not large-for-gestational-age: A prospective observational cohort study. PLoS One [Internet]. 2021 Oct 1 [cited 2022 Jan 19];16(10). Available from: /pmc/articles/PMC8528331/
41. Canadian Agency for Drugs and Technologies in Health (CADTH). Strings Attached: CADTH Database Search Filters [Internet]. 2016 [cited 2021 Jun 14]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst
42. The University of Texas. Ovid Medline - Search Filters for Various Databases [Internet]. LibGuides at University of Texas School of Public Health. 2014 [cited 2021 Jun 14]. Available from: https://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters
43. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol [Internet]. 2016 Jul 1 [cited 2021 May 17];75:40–6. Available from: https://pubmed.ncbi.nlm.nih.gov/27005575/
44. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ [Internet]. 2017 Sep 21 [cited 2021 Jun 12];358:4008. Available from: http://dx.doi.org/10.1136/bmj.j4008http://www.bmj.com/
45. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ [Internet]. 2016 [cited 2021 Jun 15];355. Available from: https://pubmed.ncbi.nlm.nih.gov/27733354/
46. Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol [Internet]. 2019 Jul 1 [cited 2021 Jun 15];111:105–14. Available from:

https://pubmed.ncbi.nlm.nih.gov/29432858/
47. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - Imprecision. J Clin Epidemiol [Internet]. 2011 Dec [cited 2021 Jun 15];64(12):1283–93. Available from: https://pubmed.ncbi.nlm.nih.gov/21839614/
48. Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: An overview of Cochrane systematic reviews. Cochrane Database Syst Rev [Internet]. 2018 Nov 14 [cited 2021 Jun 8];2018(11):CD012505. Available from: https://pubmed.ncbi.nlm.nih.gov/30480756/
49. Ota E, da Silva Lopes K, Middleton P, Flenady V, Wariki WM, Rahman MO, et al. Antenatal interventions for preventing stillbirth, fetal loss and perinatal death: an overview of Cochrane systematic reviews [Internet]. Vol. 12, The Cochrane database of systematic reviews. John Wiley and Sons Ltd; 2020 [cited 2021 Jan 21]. p. CD009599. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009599.pub2/full
50. World Health Organization. WHO recommendations: Optimizing health worker roles for maternal and newborn health through task shifting - WHO OptimizeMNH [Internet]. [cited 2021 Jun 15]. Available from: https://optimizemnh.org/optimizing-health-worker-roles-maternal-newborn-health/

Figure 1: Items suggested in the standard data extraction tool by Aromataris et al.[24]

1. Citation details
2. Objectives of the included review
3. Type of review
4. Participant details
5. Setting and context
6. The number and names of databases sourced and searched
7. Date range of database searching
8. Publication date range of studies included in the review that inform each outcome of interest
9. Number of studies, types of studies and country of origin of studies included in each review
10. Instrument used to appraise the primary studies and the rating of their quality
11. Outcomes reported that are relevant to the umbrella review question e.g., stillbirth or adverse neurodevelopmental outcomes
12. Method of synthesis/analysis employed to synthesize the evidence
13. Comments or notes the umbrella review authors may have regarding any included study

Figure 2 – Adapted framework for synthesizing study recommendations

Direction of effect	Confidence Interval	GRADE	Study Recommendation	Recommendation Graphic signs*
Beneficial	Narrow CI not crossing the line of no effect	Moderate or high	Beneficial	
Not beneficial	Narrow CI not crossing the line of no effect	Moderate or high	Not beneficial	
No effect	Narrow CI crossing the line of no effect	Moderate or high	No effect	
Beneficial	CI not crossing the line of no effect	Low	Probably beneficial	
Beneficial	Narrow CI crossing the line of no effect	Moderate or high	Probably beneficial	
Beneficial	Wide CI not crossing the line of no effect	Moderate or high	Probably beneficial	
Not beneficial	CI not crossing the line of no effect	Low	Probably not beneficial	
Not beneficial	Narrow CI crossing the line of no effect	Moderate or high	Probably not beneficial	
Not beneficial	Wide CI not crossing the line of no effect	Moderate or high	Probably not beneficial	
Beneficial, not beneficial or no effect	Narrow CI crossing the line of no effect	Low	Inconclusive	
Beneficial, not beneficial or no effect	Wide CI crossing the line of no effect	Low, moderate or high	Inconclusive	
Beneficial or not beneficial	CI not crossing the line of no effect	Very low	Inconclusive	
Beneficial, not beneficial or no effect	CI crossing the line of no effect	Very low	Inconclusive	

* All icons provided by Freepik at www.flaticon.com.