Prognostic Accuracy of Antenatal Doppler Ultrasound Measures in Predicting Adverse Perinatal Outcomes for Pregnancies Complicated by Diabetes: A Systematic Review

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OBJECTIVE: This study aimed to assess the prognostic accuracies of Doppler ultrasound measures in predicting adverse perinatal outcomes for pregnancies complicated with preexisting or gestational diabetes mellitus.

DATA SOURCES: An online database search of MEDLINE, Cochrane, Embase, CINAHL, Scopus, and Emcare from inception to April 2022 was conducted.

STUDY ELIGIBILITY CRITERIA: Studies reporting singleton, nonanomalous fetuses of women with either preexisting (type 1 or 2 diabetes mellitus) or gestational diabetes mellitus during pregnancy were included. In addition, the included studies assessed cerebroplacental ratio and middle cerebral artery and/or umbilical artery pulsatility index in the prediction of either: preterm birth, cesarean delivery for fetal distress, APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score <7 at 5 minutes, neonatal intensive care unit admission (>24 hours), acute respiratory distress syndrome, jaundice, hypoglycemia, hypocalcemia, or neonatal death.

METHODS: The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed and 610 articles were identified, of which 15 were included. Two authors independently extracted prognostic data from each article and assessed the study applicability and risk of bias using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) scoring criteria.

RESULTS: A total of 15 studies were included in the review and comprised prospective (n=10; 66%) and retrospective (n=5; 33%) cohorts. Sensitivity and positive predictive values varied widely across each Doppler measurement. Umbilical artery sensitivities were higher than those of cerebroplacental ratio and middle cerebral artery for hypoglycemia, jaundice, neonatal intensive care unit admission, respiratory distress, and preterm birth. Cerebroplacental ratio was the most reported index test; however, prognostic accuracy was worse than that of umbilical artery and middle cerebral artery Doppler across all adverse perinatal outcomes. Significant risk of bias was present in 14 (94%) studies, with substantial heterogeneity observed across studies in terms of study design and outcomes assessed.

CONCLUSION: Abnormal umbilical artery pulsatility index may be of more clinical value in predicting adverse perinatal outcomes compared with cerebroplacental ratio and middle cerebral artery pulsatility index in diabetic pregnancies. Further evaluation of umbilical artery Doppler measurements in diabetic pregnancies using standardized variables across studies is required for broader clinical application. The significant association between abnormal Doppler measurement and hypoglycemia may warrant further investigation.

Key words: cerebral artery, cerebroplacental ratio, composite adverse outcome, fetal distress, gestational diabetes mellitus, hypoglycemia, neonatal, pulsatility index, type 1 diabetes mellitus, type 2 diabetes mellitus, umbilical artery

Introduction

Pregnancies complicated by diabetes mellitus encompass both gestational diabetes mellitus and preexisting diabetes mellitus and carry significant risks of maternal and neonatal adverse outcomes.[1] This includes higher rates of fetal macrosomia, neonatal hypoglycemia, fetal acidosis, neonatal intensive care unit (NICU) admission, and cesarean delivery for fetal distress.[2,3] The pathogenesis surrounding these adverse outcomes is multifactorial and poorly understood.[4] One proposed mechanism is altered vascularization in the placenta.[5] Most placentas from pregnancies complicated by diabetes mellitus present histologically with villous immaturity, inflammation, and thickened blood vessel walls.[6] This is because of a number of pathogenic mechanisms, including tumor necrosis factor alpha production, hyperinsulinemia, and increased blood viscosity because of glycosylation of hemoglobin.[4,7] Furthermore, maternal hyperglycemia directly stimulates metabolic and hormonal changes in the fetus, subsequently increasing fetal oxygen demands.[7,8] The resulting combination of impaired placental perfusion and increased oxygen demands of the fetus leads to a state of chronic intrauterine

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AJOG MFM at a Glance

Why was this study conducted?

Adverse perinatal outcomes in high-risk pregnancies can be potentially mitigated through antenatal surveillance, particularly with fetal Doppler studies. However, the clinical applicability for neonates exposed to diabetes mellitus during pregnancy (a subgroup of "high-risk pregnancy") is poorly understood despite being routinely assessed.

Key findings

We systematically reviewed studies to assess the prognostic accuracy of Doppler measures in diabetic pregnancies. Umbilical artery pulsatility index had higher sensitivity for adverse perinatal outcomes compared with cerebroplacental ratio and middle cerebral artery Doppler, and thus may be of more clinical value in diabetic pregnancies. Substantial heterogeneity across studies did not allow for a meta-analysis.

What does this add to what is known?

Further evaluation of umbilical artery Doppler measurements in diabetic pregnancies using standardized variables across studies is required for broader clinical application.

Objective

This systematic review assessed the prognostic accuracy of CPR, MCA PI, and UA PI in predicting adverse perinatal outcomes for pregnancies complicated with preexisting or gestational diabetes mellitus. The clinical utility of the available evidence related to Doppler assessment and the manner in which this can influence clinical practice are also highlighted.

Methods

This systematic review was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement. The protocol for this systematic review was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42022353468).

hypoxia.[5,9] This phenomenon has been demonstrated in several studies, with evidence of extramedullary hematopoiesis and increased erythropoietin in amniotic fluid samples of neonates born to women with diabetes mellitus.[10,11]

Consequently, compensatory dynamic changes in fetal blood flow occur, which can be observed by measuring the fetal umbilical artery (UA) pulsatility index (PI) and middle cerebral artery (MCA) PI. The cerebroplacental ratio (CPR) is calculated as the ratio of the MCA PI to UA PI, and it is a marker of placental blood flow resistance.[5,12] A decreased CPR is thought to result from chronic hypoxia, in which 2 events occur. The first is an increase in vasoconstriction and placental blood volume within the UA, exacerbating vessel resistance and thus producing a high PI.[8,13,14] The second is termed the "brain-sparing effect," in which the MCA vasodilates in an attempt to redirect blood flow to the brain and other vital organs, resulting in reduced vascular resistance and a lower PI.[8,15,16]

The measurement of these Doppler indices is routinely implemented as part of the fetal well-being and placental function assessment in the third trimester of all high-risk pregnancies.[2,17] The third-trimester ultrasound is of particular clinical importance because it provides the last estimation of fetal parameters to assist in the decision-making around the mode and timing of delivery.[2,18] However, there is a paucity of high-quality published data to guide third-trimester fetal surveillance, particularly in regard to Doppler assessment.[2] Previous studies that have evaluated Doppler assessment in the third trimester primarily focus on the utility of Doppler assessment in a "high-risk pregnancy," with a specific focus on the maternal hypertensive disorder and the small-for-gestational-age fetus. These reviews demonstrated strong associations of an abnormal Doppler result with intrauterine growth restriction and fetal distress during delivery. However, the implications for defining placental insufficiency, frequency of ongoing Doppler measurements, and decision-making surrounding the timing of delivery remain inconclusive.[19–22] The clinical applicability in neonates born to mothers with diabetes mellitus (a subgroup of "high-risk pregnancy"), who suffer from placental insufficiency but are typically large for gestational age, is also poorly understood despite being routinely assessed. To the best of our knowledge, no reviews have compared the accuracy of the CPR and its component Dopplers in the prediction of adverse outcomes in pregnancies complicated by maternal diabetes mellitus.

Criteria, information sources, and search strategy

An online database search of MEDLINE, Cochrane, Embase, CINAHL, Scopus, and Emcare was performed for all relevant publications using variations of the search terms "ultrasound," "pregnancy," "cerebroplacental," "middle cerebral artery," "umbilical artery," and "diabetes." The search strategies (sample included in Appendix 1) used were developed with the support of a librarian at James Cook University. Reference lists from previous systematic reviews and included studies were also screened for relevant additional inclusions.

We included retrospective or prospective observational (cohort) studies. Eligible studies reported on at least 1 of the following: CPR, MCA PI, or UA PI in singleton, nonanomalous fetuses of women with either preexisting (type 1 or 2 diabetes mellitus) or gestational diabetes mellitus during pregnancy. Studies also had to compare Doppler findings with at least 1 adverse perinatal outcome including rate of preterm birth, cesarean delivery for fetal distress or nonreassuring fetal heart rate, APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score <7 at 5 minutes, NICU admission (>24 hours), acute respiratory distress syndrome,

jaundice, hypoglycemia, hypocalcemia, or neonatal death (regardless of blinding).

Studies assessing "high-risk pregnancy" that combined participants with diabetes mellitus, gestational hypertension, and intrauterine growth restriction were excluded, unless data solely on the population with diabetes mellitus could be extracted. Systematic and expert reviews, case reports, guidelines, and studies not written in English or involving animals were also excluded. No date limits were applied.

Study selection process

The titles and the abstracts of the articles identified from the databases were screened by 2 authors (B.M.R. and J.H.). Subsequently, the full texts of articles identified for inclusion were screened in a consensus meeting, and a third reviewer (B.S.M.A.) was sought in cases of disagreement. In cases of ambiguity, article authors were contacted to provide additional information. The literature search was conducted between January and April of 2022.

Data extraction

Data extraction was independently performed by 2 investigators (B.M.R. and B.S.M.A.). Data included authors, year of publication, country, the time frame of recruitment, sample size, and characteristics of patients (glycemic control, smoking status, ethnicity, and parity) where reported. Also extracted were data on the Doppler index tests and their respective thresholds and reference values in relation to targeted outcomes, as well as reported performance measures, including odds ratio (OR), correlations, the area under the curve (AUC), and detection rate at 10% false-positive rate.

Risk of bias of the included studies

The risk of bias and concerns about applicability were assessed by 2 authors (B.M.R. and J.H.) with the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool.[23] In cases of disagreement, a third reviewer (B.S.M.A.) was sought, and a consensus was reached through discussion. QUADAS-2 is designed to assess the quality of primary diagnostic accuracy studies. The tool consists of 4 key domains covering patient selection, index test, reference standard, and flow of patients through the study. Each domain is assessed in terms of risk of bias, and the first 3 are also assessed in terms of concerns regarding applicability. Signaling questions are included to help reach a judgment on the risk of bias (Appendix 2).[23] As recommended in the literature, the QUADAS-2 tool was not used in this review to generate a summary "quality score"; rather, the overall risk of bias and concerns regarding applicability were assessed.[24,25]

Data synthesis and analysis

We constructed a 2-by-2 table, which included true-positive, false-positive, true-negative, and false-negative values, for studies that provided sufficient information to run the analysis. Within each study, diagnostic test accuracy analysis was conducted in the R package epiR for each Doppler test (CPR, UA PI, and MCA PI), and performance measures such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value were calculated. Associations of Doppler measures with adverse outcomes were narratively summarized. The large heterogeneity in the type of diabetes mellitus, Doppler measurement thresholds, outcomes assessed, definitions of outcomes, and reported prognostic performance measures in the included studies did not allow for a meta-analysis.

Results

Study selection

A total of 610 studies were retrieved through electronic and manual searches. After the removal of duplicates and screening of titles and abstracts, 45 studies were retained for full-text assessment for eligibility. On full assessment, 15 studies met the inclusion criteria for this review, and 3 studies could not be retrieved. Figure 1 portrays a detailed PRISMA flow diagram of the study selection protocol.

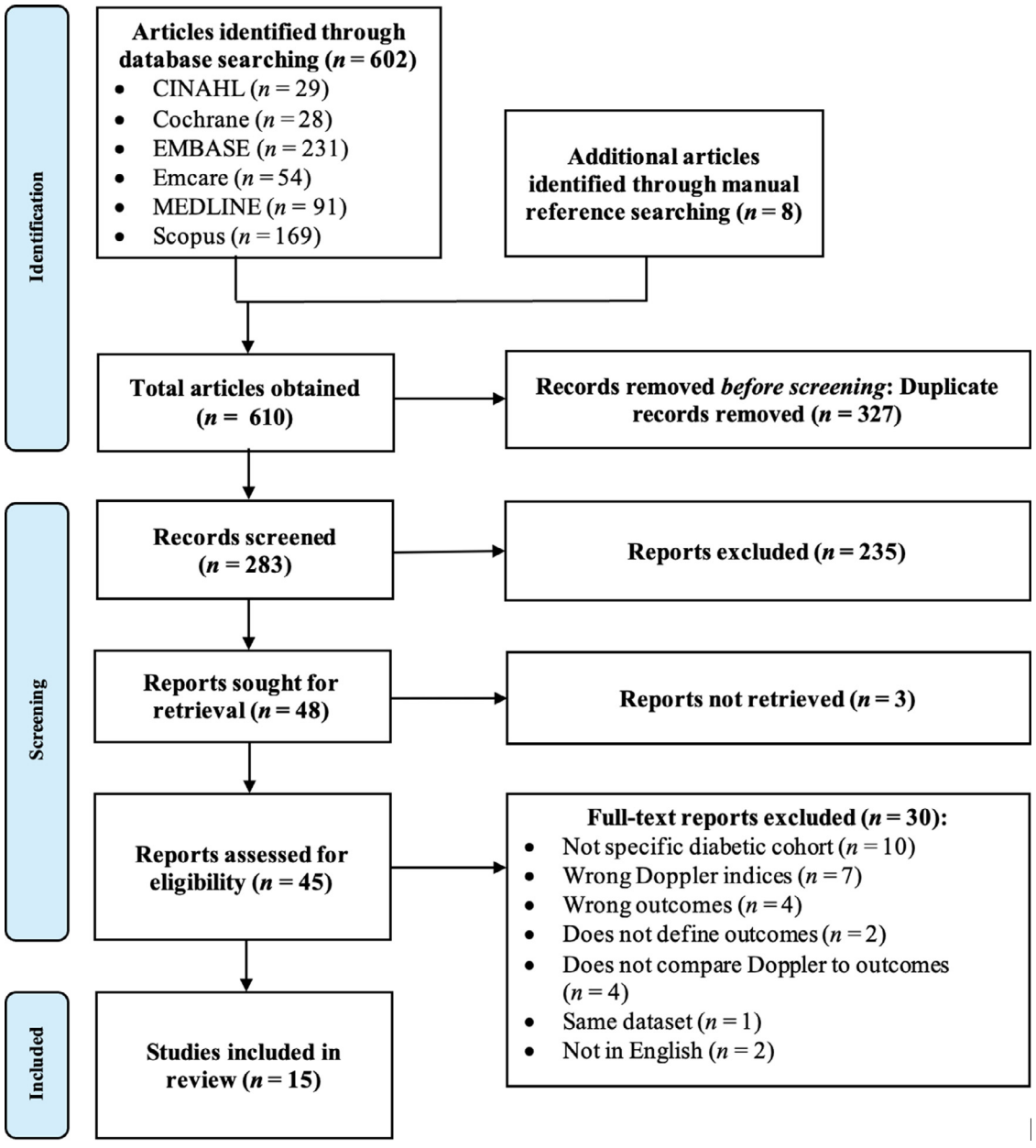
Characteristics of included studies

Detailed characteristics of the included studies are provided in Appendix 4. Of the 15 studies that met the inclusion criteria for this review, 10 were prospective observational[5,12,26–33] and 5 were retrospective studies.[4,34–37] The number of participants included in the different studies ranged from 40 to 1089, and maternal age ranged from 17 to 42 years. Five (33%) studies reported solely on gestational diabetes mellitus, 3 (20%) studies reported solely on preexisting diabetes mellitus (type 1 or 2 diabetes mellitus), and 7 (47%) studies reported on both. Three (20%) studies excluded small-for-gestational-age fetuses. Gestational age at examination ranged from 20 to 40 weeks, with only 6 (40%) studies using Doppler findings obtained solely within 4 weeks of birth. Most (60%) studies reported on maternal glycemic control, either in the form of intervention (diet, oral hypoglycemic agents, or insulin) or HbA1C measurements in the third trimester. Ethical approval was clearly stated in 12 (80%) studies.

Risk of bias of included studies

A summary of the QUADAS-2 assessment is provided in Appendix 3 and Figure 2. The risk of bias or suboptimal reporting was detected in 14 (93%) studies. Methods for participant selection had a high risk of bias in 6 (40%) studies. The interval between the index test and the outcome was >4 weeks in 5 studies (33%), and not stated in 1 study (7%). Most (80%) studies clearly outlined the Doppler technique. In 7 (47%) studies, it was unclear whether the obstetrician was blinded to the test results; in 6 (40%) studies, they were not blinded. Three of these studies stated that Doppler measurements had no influence on management of the mother or fetus, and 2 studies discussed how the results altered management and the respective outcomes. There were no studies of concern regarding applicability in the categories of patient selection or index test because studies that did not report on diabetes mellitus or MCA Doppler, UA Doppler, or CPR were excluded from the review.

FIGURE 1
PRISMA flowchart of the selection process



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Rane. Fetal Doppler studies as a predictor in pregnancies affected with diabetes mellitus. Am J Obstet Gynecol Glob Rep 2023.

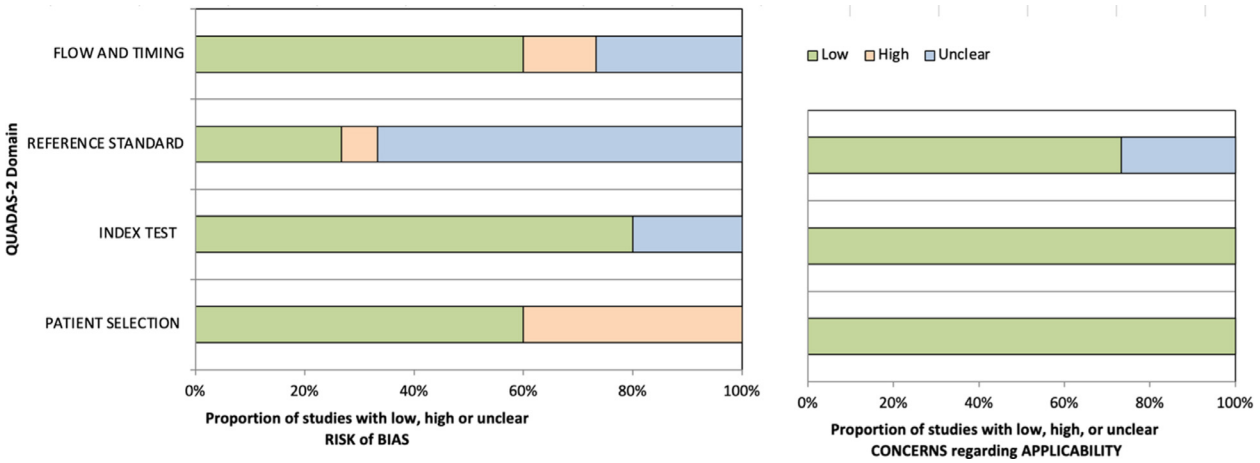
However, studies that met inclusion criteria that reported outcomes assessed to have a high risk of bias, or were not defined, were classified as "unclear" in the reference standard domain for applicability.

Synthesis of results

Cerebroplacental ratio. As shown in Figure 3 and Appendix 5, the prognostic accuracy of CPR in predicting adverse outcomes for pregnancies complicated by diabetes mellitus was evaluated in 7 studies.[4,5,28,29,32,36,37] The adverse outcomes assessed included composite adverse outcome, preterm birth, cesarean delivery for fetal distress, hypertensive disorder, 5-minute APGAR score <7, acidemia, NICU admission, respiratory distress, jaundice, hypoglycemia, neonatal death, and hypocalcemia. Sensitivity for all adverse outcomes was generally poor, with an average of 15%. However, in all cases, specificity was high, with an average of 92%.

Middle cerebral artery. Six[14,31,33–36] studies reported on MCA, with only 3 studies allowing for a 2×2 table construction.[30,33,35] As shown in Figure 4 and Appendix 5, assessed adverse outcomes were composite

FIGURE 2
Summary of quality assessment using the QUADAS-2 scoring system



QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies.

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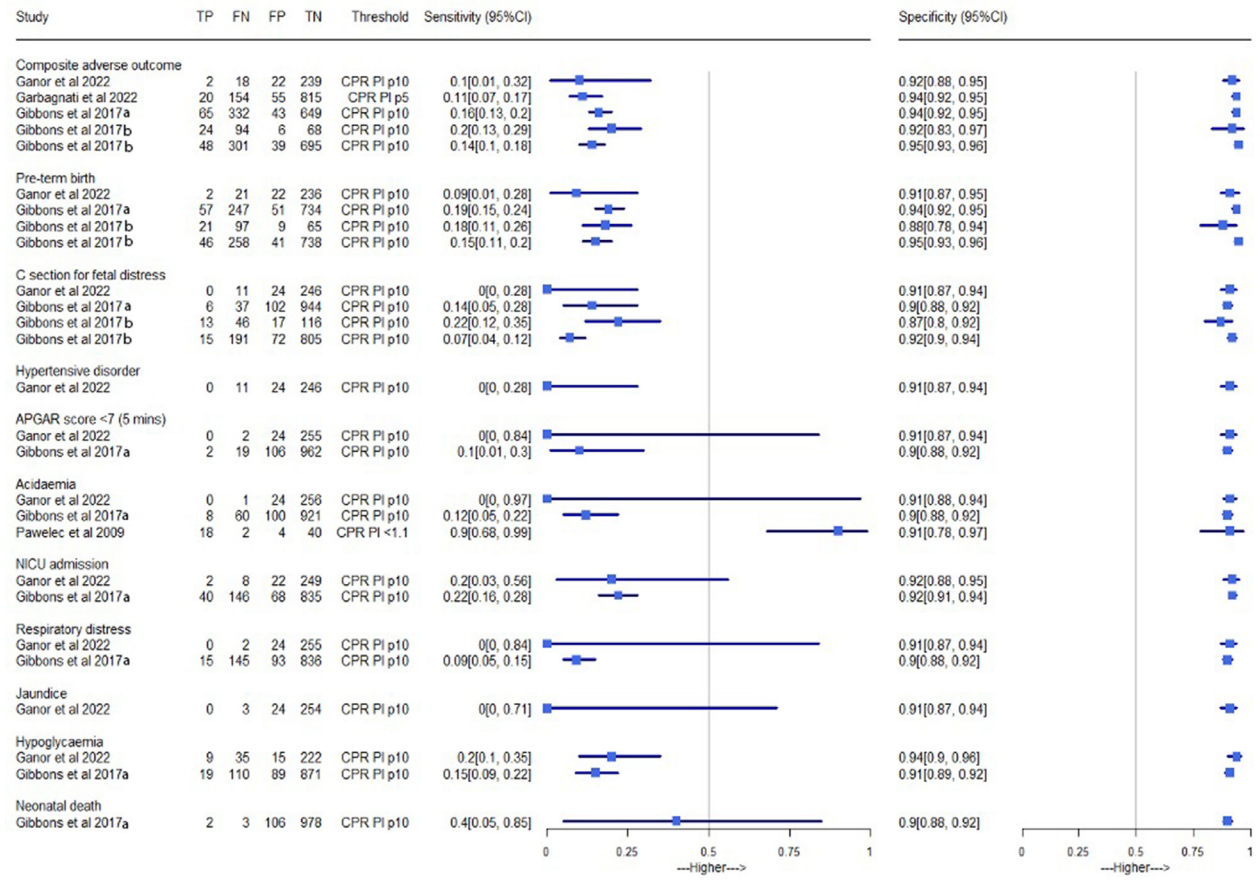
FIGURE 3
Sensitivity and specificity of CPR in predicting adverse perinatal outcomes



Sensitivity and specificity of CPR for composite adverse outcome, preterm birth, cesarean delivery for fetal distress, hypertensive disorder, 5-minute APGAR score <7, acidemia, NICU admission, respiratory distress, hyperbilirubinemia, hypoglycemia, neonatal death, and hypocalcemia.

CI, confidence interval; *CPR*, cerebroplacental ratio; *FN*, false negative; *FP*, false positive; *NICU*, neonatal intensive care unit; *p10*, <10th percentile; *p5*, <5th percentile; *PI*, pulsatility index; *TN*, true negative; *TP*, true positive.

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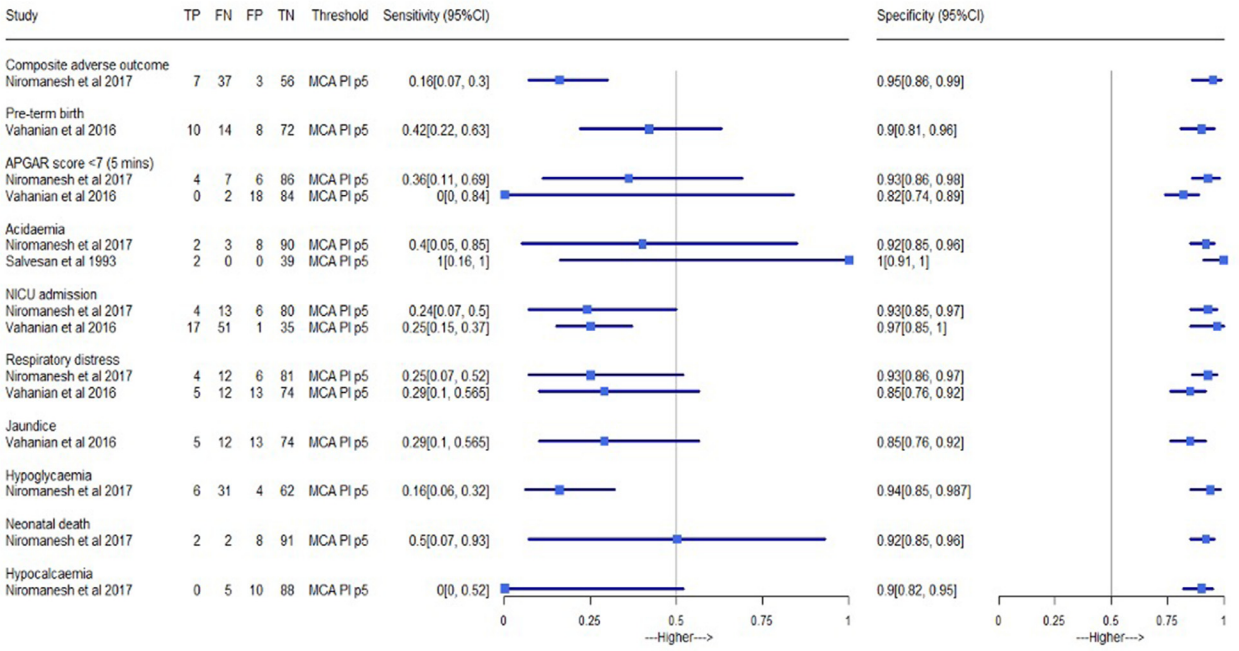
FIGURE 4
Sensitivity and specificity of MCA in predicting adverse perinatal outcomes



Sensitivity and specificity of MCA for composite adverse outcome, preterm birth, cesarean delivery for fetal distress, hypertensive disorder, 5-minute APGAR score <7, acidemia, NICU admission, respiratory distress, hyperbilirubinemia, hypoglycemia, and neonatal death.

CI, confidence interval; *FN*, false negative; *FP*, false positive; *MCA*, middle cerebral artery; *NICU*, neonatal intensive care unit; *p5*, <5th percentile; *PI*, pulsatility index; *TN*, true negative; *TP*, true positive.

Rane. Fetal Doppler studies as a predictor in pregnancies affected with diabetes mellitus. Am J Obstet Gynecol Glob Rep 2023.

adverse outcome, preterm birth, cesarean delivery for fetal distress, hypertensive disorder, 5-minute APGAR score <7, acidemia, NICU admission, respiratory distress, jaundice, hypoglycemia, and neonatal death. On average, MCA's sensitivity for predicting adverse outcomes was 31%. However, specificity was consistently high, with an average of 92%.

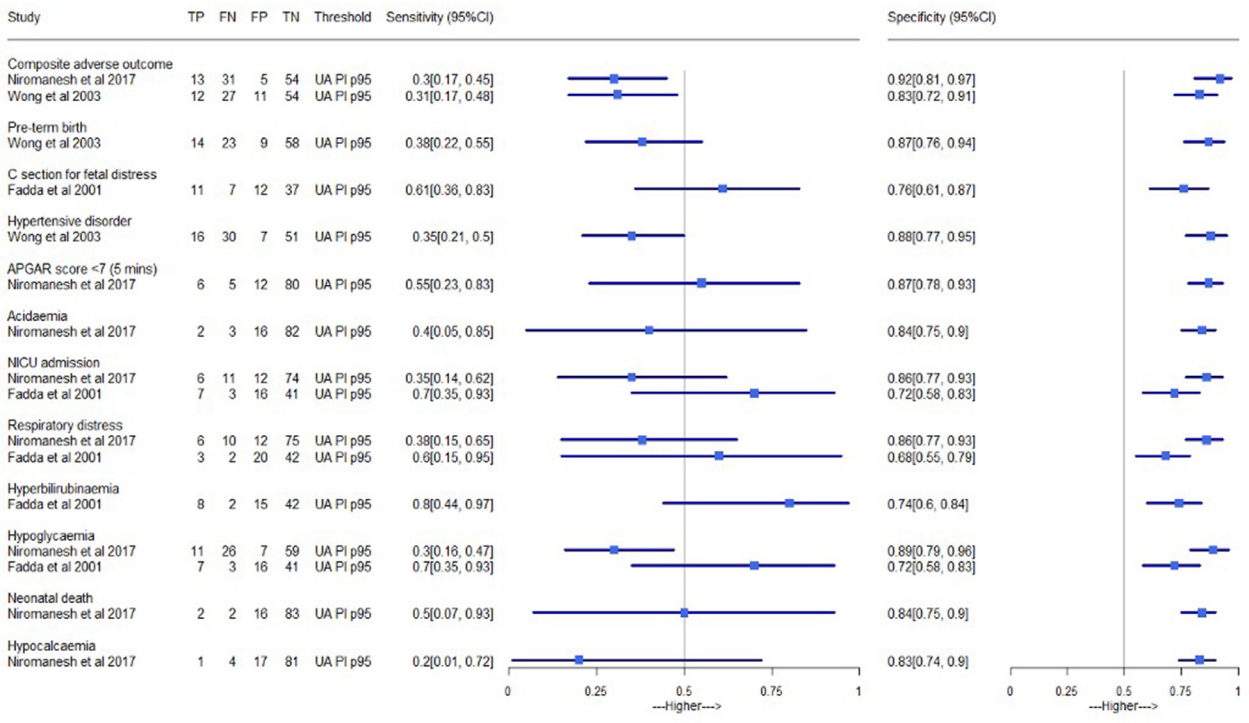
Umbilical artery. Six[26–31,34] studies reported the prognostic value of UA in pregnancies complicated by diabetes mellitus, with 3 studies allowing for a 2 × 2 table construction (Figure 5; Appendix 5).[27,30,34] Assessed adverse outcomes were composite adverse outcome, preterm birth, cesarean delivery for fetal distress, hypertensive disorder, 5-minute APGAR score <7, acidemia, NICU admission, respiratory distress, jaundice, hypoglycemia, neonatal death, and hypocalcemia. Higher sensitivity values were observed for UA across most of the adverse outcomes compared with CPR and MCA. On average, UA's sensitivity for predicting adverse outcomes was 46%. Specificity was lower when compared with its Doppler counterparts, with an average of 82% across all adverse outcomes.

Composite adverse outcome. Nine studies evaluated a composite adverse outcome,[4,5,12,26,28,30,34,36,37] and the definitions for a composite adverse outcome varied across studies (Appendix 3). However, all studies reported individual components. Abnormal CPR demonstrated a sensitivity that ranged from 10% to 20.3% and a PPV of 8.4% to 80% over 4 studies.[4,5,36,37] The OR was statistically significant (P<.003) in 3 studies and ranged from 1.91 to 2.93.[4,36,37] MCA was evaluated in 4 studies.[12,26,28,30] One study reported a sensitivity of 15.9% and a PPV of 70%,[30] with another reporting an AUC of 0.8.[28] Five studies reported on UA,[12,26,28,30,34] with 2 reporting higher sensitivity ranging from 30% to 31% and PPV of 52.2% to 72.2%.[30,34] Two studies reported no statistically significant association between abnormal UA Doppler and composite adverse outcome.[12,26]

Preterm birth. Five studies reported preterm birth as an individual outcome, with all defining preterm birth as <37 weeks' gestation.[4,5,34–36] An abnormal CPR demonstrated sensitivity ranging from 15.1% to 19% in pregnancies complicated by diabetes mellitus, and a PPV ranging from 8.3% to 70%.[4,5,36] OR was significant (P<.001) in 2 studies, demonstrating similar values of 3.24 and 3.32.[4,36] MCA was evaluated in 1 study that reported a sensitivity of 42%, PPV of 55.6%, and OR of 6.24 (P=.006). UA was assessed in 1 study that reported sensitivity and PPV of 37.8% and 60.9%, respectively, and an OR of 3.9 (95% confidence interval [CI], 1.5 −10.3; P=.004).

Cesarean delivery for fetal distress. Five studies reported on cesarean delivery for fetal distress,[4,5,27,31,36] with 3

FIGURE 5
Sensitivity and specificity of UA in predicting adverse perinatal outcomes



Sensitivity and specificity of UA for composite adverse outcome, preterm birth, cesarean delivery for fetal distress, hypertensive disorder, 5-minute APGAR score <7, acidemia, NICU admission, respiratory distress, hyperbilirubinemia, hypoglycemia, neonatal death, and hypocalcemia.

CI, confidence interval; *FN*, false negative; *FP*, false positive; *NICU*, neonatal intensive care unit; *p10*, <10th percentile; *p95*, >95th percentile; *PI*, pulsatility index; *TN*, true negative; *TP*, true positive; *UA*, umbilical artery.

Rane. Fetal Doppler studies as a predictor in pregnancies affected with diabetes mellitus. Am J Obstet Gynecol Glob Rep 2023.

providing definitions.[4,5,36] Abnormal CPR demonstrated sensitivity ranging from 0% to 22% and PPV ranging from 0% to 43.3% across 3 studies, with no significant OR reported.[4,5,36] No studies reported on MCA in relation to cesarean delivery for fetal distress. Two studies that evaluated UA reported a significant association,[27,31] with 1 study reporting an association of cesarean delivery for fetal distress in 16% of those with normal Doppler vs 48% of those with abnormal Doppler (P<.001), as well as sensitivity and PPV of 61.1% and 47.8%, respectively.[27]

Hypertensive disorder. Two studies reported on the development of hypertensive disorders, both defining this variable as pregnancy-induced hypertension or preeclampsia.[5,34] One study reported on CPR[5] and the other on UA,[34] producing a sensitivity of 0% and 34.8%, respectively. PPV was also reported as 0% and 69.6%, respectively, clearly demonstrating UA as a stronger predictor.

Five-minute APGAR score <7. Six studies evaluated the use of Doppler as a prognostic determinant of low APGAR score (<7) at 5 minutes.[4,5,28,30,34,35] Three studies reported on CPR producing a sensitivity and PPV ranging between 0% to 10% and 0% to 1.9%, respectively,[4,5] as well as an AUC of 0.61.[28] Three studies reported on MCA, with 2 studies demonstrating a sensitivity range of 0% to 36.4% and PPV range of 0 to 40%.[30,35] Three studies evaluated UA Doppler indices.[28,30,34] One study reported sensitivity and PPV of 54.5% and 33.3%, respectively. One study reported an AUC of 0.583.[28] Another study reported no association between abnormal UA and APGAR score.[34]

Acidemia. Eight studies evaluated the ability of Dopplers to predict acidemia and yielded conflicting results.[4,5,28,30–34] Most studies defined cutoffs for acidemia, with only 1 study not providing a definition.[28] The cutoffs varied between studies, 4 studies used UA pH <7.0 to 7.2,[5,30,32,34] 1 study used UA cord pH ≤7 or lactate ≥6 mmol,[4] and another study used umbilical venous pH below the fifth centile.[33] Three studies reported on CPR and allowed for a 2 × 2 table construction, providing a sensitivity range of 0% to 90% and a PPV ranging from 0% to 81.8%.[4,5,32] Two studies reporting on MCA allowed for 2 × 2 table construction, producing a sensitivity and PPV range of 40% to 100% and 20% to 100%, respectively.[30,33] One study reporting on UA allowed for 2 × 2 table construction, reporting a sensitivity and PPV of 40% and 11.1%, respectively.[30] Two

studies evaluated the association of acidemia with abnormal UA,[31,34] with only 1 reporting statistically significant results ($P<.01$).[31] One study reported AUCs of 0.71 and 0.625 for CPR and UA, respectively.[28]

Neonatal intensive care unit admission. Five studies reported on NICU admission,[4,5,27,30,35] with 2 studies reporting only on NICU admission requirements for >24 hours.[5,30] Two studies reported on CPR, and the sensitivity and PPV values ranged from 2% to 20% and 8.3 to 37%, respectively.[4,5] Two studies reported on MCA, with the sensitivity and PPV values ranging from 23.5% to 25% and 40% to 94.4%, respectively.[30,35] Two studies similarly reported on UA, with sensitivity and PPV of 35% to 70% and 30.4% to 33.3%, respectively.[27,30]

Respiratory distress. Six studies reported on respiratory distress.[4,5,27,29,30,35] Only 1 study provided a clear definition of what constituted respiratory distress syndrome, which were respiratory symptoms (eg, grunting, flaring, tachypnea, retractions), supplemental oxygen requirement, and NICU admission for further respiratory support, with the diagnosis verified by chest radiograph findings of reticulogranular patterns and air bronchograms.[5] Two studies evaluated CPR, reporting low sensitivities and PPV of 0% to 9.4% and 0% to 13.9%, respectively. MCA showed a comparably higher sensitivity range of 25% to 29.4% and a relatively higher PPV range of 27.8% to 40%.[30,35] UA demonstrated the highest sensitivities of the 3 Doppler measures, with a range of 37% to 60% and PPV ranging from 13% to 30.3% across 2 studies.[27,30] One study evaluated the association of MCA with respiratory distress, and reported a significant ($P=.003$) correlation (r=0.317).[29] Of the 2 studies that assessed the correlation between UA and respiratory distress,[27,29] only 1 reported significant ($P<.005$) correlation, reporting respiratory distress in 4.5% of those with normal Doppler and 13% of those with an abnormal Doppler.[27]

Jaundice. Four studies evaluated hyperbilirubinemia.[5,27,34,35] Two studies provided definitions, only including those who required phototherapy.[35,37] UA demonstrated the highest sensitivity and PPV of 80% and 34.8%, respectively, and an OR of 2.33 (95% CI, 0.97−8.93; $P<.05$) after accounting for maternal glycemic control.[27] MCA was reported in 1 study, with a sensitivity and PPV of 29.4% and 27.8%, respectively.[35] CPR was reported in 1 study, with both sensitivity and PPV having a value of 0%.[5]

Hypoglycemia. Six studies evaluated hypoglycemia as an adverse perinatal outcome.[4,5,27,30,34,35] Only 3 studies provided definitions, ranging from blood glucose levels (BGL) <2.6 mmol/L in the first 72 hours of life to[5] BGL <2.5 mmol/L,[30] or severe hypoglycemia requiring treatment.[4] Three studies reported the OR of an abnormal Doppler leading to hypoglycemia, all of which reported statistically significant values ($P<.05$) ranging from 1.72 (95% CI, 1.23−8.36) to 3.21 (95% CI, 1.01−2.94) for CPR[4,5] and 3.04 (1.37−5.53) for UA,[27] after accounting for maternal glycemic control. UA produced the highest sensitivity, with a range of 25.7% to 70% and a PPV range of 30.4% to 61.1% across 2 studies.[27,30] Two studies reported on MCA, producing a sensitivity and PPV range of 16.2% to 21.3% and 55.6% to 60%, respectively.[30,35] Abnormal CPR demonstrated a sensitivity that ranged from 20% to 15% and a PPV range of 17.6% to 37.5% across 2 studies.[4,5]

Neonatal death. Only 2 studies reported on neonatal death.[4,30] CPR was reported in 1 study, which demonstrated a sensitivity and PPV of 40% and 1.9%, respectively, but also an increased ($P=.048$) OR of 6.15 (95% CI, 1.02−37.23).[4] UA and MCA were reported in 1 study, with a sensitivity of 50% for both Dopplers, and MCA producing a slightly increased PPV value of 20% as opposed to 11.1% for UA.[30]

Hypocalcemia. Three studies reported on hypocalcemia,[27,30,34] with only 1 providing a threshold of blood calcium levels <8 mg/dL.[30] Both sensitivity and PPV for an abnormal MCA Doppler were reported at 0%.[35] Two studies reported a sensitivity and PPV range of 20% to 66.7% and 5.6% to 8.3%, respectively, for abnormal UA Doppler.[27,30] Two studies reported the correlation between abnormal UA and hypocalcemia as nonsignificant.[27,34]

Comment

Main findings

We systematically reviewed studies to assess the prognostic accuracy of Doppler ultrasound measures (CPR, MCA PI, and UA PI) in predicting adverse perinatal outcomes for pregnancies complicated by maternal diabetes mellitus. The purpose of this was to ascertain which Doppler measures have the highest predictive ability. A formal quality assessment of the included studies revealed few studies of high quality. We observed a large variation in thresholds used and the reported sensitivities. For all individual outcomes and composite adverse outcomes, sensitivity of UA seemed to be better than that of CPR and MCA Doppler. In the direct test comparisons, the prognostic accuracy and sensitivities of the UA outperformed that of MCA Doppler and CPR, particularly for hypoglycemia, jaundice, NICU admission, respiratory distress, and preterm birth, whereas for neonatal death, UA Doppler was similar to MCA Doppler. CPR was the most reported measurement, with the largest sample sizes; however, prognostic accuracy was worse than those of UA and MCA Doppler across all perinatal outcomes. Regarding overall Doppler performance, sensitivity and PPV values varied widely, but were generally low across all outcomes.

Strengths and limitations

The main strength of this review is that it provides data on a specific subgroup of "high-risk pregnancy," which has been the focus of previous reviews and often varies widely in terms of definitions and criteria across studies. The study was also performed according to a registered protocol, using well-established databases. Limitations of this review include the limited number of studies that met the inclusion criteria, and the small sample sizes of those that

did. Another limitation was the substantial heterogeneity of Doppler performance observed among studies, likely because of wide variations in interval timing between Doppler and birth, diabetes mellitus severity, definitions of adverse outcomes, and Doppler thresholds used for test positivity. This heterogeneity was also observed in the type of prognostic indicator described, which affected the ability to conduct a meta-analysis of the utility of Doppler performance across studies. Suboptimal reporting quality of studies was also observed, with no randomized control trials included.

Comparison with existing literature

Evidence from the literature suggests that high-risk pregnancies, with a specific focus on maternal hypertensive disorders and the small-for-gestational-age fetus, can be reduced through routine measurement of Doppler indices.[22] This has been implemented as part of the fetal well-being and placental function assessment in the third trimester of all high-risk pregnancies.[2,17] However, the clinical applicability in neonates born to mothers with diabetes mellitus (a subgroup of "high-risk pregnancy"), who suffer from placental insufficiency but are typically large for gestational age, is poorly understood despite being routinely assessed.[19−22] Currently, the implications of an abnormal UA or MCA Doppler in clinical practice are only used in infants with fetal growth restriction as an indication for consideration of the timing of birth.[22] The implications for neonates from pregnancies complicated by diabetes mellitus, who are typically large for gestational age, are less known. Thus, a proper understanding of existing literature on the prognostic accuracy of the Doppler ultrasound measures in predicting adverse perinatal outcomes for pregnancies complicated by maternal diabetes mellitus is important.

Our findings indicate that an abnormal UA PI may be of more clinical value in predicting an adverse perinatal outcome than CPR and MCA PI in a diabetic pregnancy, implying that abnormal UA could be more predictive of composite adverse outcome than MCA and CPR. This result is corroborated by previous studies that suggested that using UA Doppler in high-risk pregnancies had high predictive values and could reduce emergency obstetrical intervention and perinatal death by 30% (risk ratio, 0.71; 95% CI, 0.52 −0.98).[24,38] Another large retrospective cohort study found that UA PI was more commonly affected in diabetic pregnancies than MCA PI, and correlated significantly with diabetes mellitus severity ($P<.001$), suggesting that pathogenesis of diabetes mellitus may influence the UA more than MCA, and thus may be more linked to adverse outcomes.[36] Nonetheless, another review reported that CPR was significantly better than UA and MCA Doppler in predicting composite adverse outcomes.[22] Contrary to our study, the review reported that CPR performed better than UA in predicting emergency delivery for fetal distress ($P=.003$), but was comparable to UA Doppler in predicting perinatal death ($P=.686$), low APGAR score ($P=.595$), and NICU admission ($P=.107$). In this study, MCA was significantly worse than UA and CPR in predicting emergency delivery for fetal distress ($P=.034$; $P=.013$) and low APGAR score ($P=.017$), and significantly worse than CPR in predicting composite adverse outcome ($P<.001$). Recent data suggest that abnormal CPR measured up to 2 weeks remote from delivery yielded "fair" prediction for cesarean delivery for fetal distress (AUC, 0.71), but not for an adverse neonatal composite outcome (AUC, 0.56).[39]

Conclusions and implications

Pregnancies complicated by diabetes mellitus are at increased risk of adverse perinatal outcomes.[1] These risks can be mitigated by increased monitoring and informed decisions around the appropriate timing of birth.[2] The 36-week ultrasound is thus of particular clinical importance because it provides the last estimations to assist decision-making in late pregnancy.[2,18] Despite being a part of routine assessment, the clinical implications of an abnormal Doppler finding are poorly understood, particularly for pregnancies complicated by diabetes mellitus.[2] Clear threshold values and guidelines are needed to identify those at risk of an adverse perinatal outcome and offer early intervention as necessary. This is particularly relevant for rural and remote populations, who are located at long distances away from tertiary hospital care, and for whom the risks associated with adverse perinatal outcomes are thus significantly increased. The UA Doppler is the most universally measured and requires the lowest amount of skill. Conversely, the MCA Doppler is a highly technical and difficult measure to obtain accurately in later pregnancy. The MCA Doppler and CPR have been proposed as additional tests to UA Doppler,[22] but the proposition is not confirmed in this review given that our findings show that the prognostic accuracy of the UA Doppler outperformed that of MCA Doppler and CPR in pregnancies complicated by diabetes mellitus. The observed lower prognostic accuracy of CPR compared with UA and MCA Dopplers for all outcomes could have been because of the fact that most of the data available regarding the predictive ability of the CPR were related to cohorts of preterm pregnancies complicated by growth restriction.[40] Future studies, especially randomized control trials, on the prognostic accuracies of Doppler measures in pregnancies complicated by diabetes mellitus using standardized Doppler thresholds with consensus on adverse perinatal outcomes are needed. Interval timing between Doppler measurement and birth should also be standardized to increase reproducibility and interpretability of results across studies.

This review highlighted the disparity in studies specifically evaluating the prognostic performance of Doppler measurement in diabetic pregnancies. Within the scope of our review, abnormal UA PI provided higher sensitivities for adverse perinatal outcomes when compared with MCA PI and CPR, and thus may be of more clinical value for women with diabetes mellitus approaching their final stages of pregnancy. Regarding overall Doppler

performance, sensitivity and PPV values varied widely, but were generally low across all outcomes. Thus, the finding of an abnormal result must be interpreted with caution, and not used in isolation when making decisions surrounding timing and mode of delivery in a diabetic pregnancy. Further evaluation of the use of Doppler in pregnancies complicated by diabetes mellitus using standardized protocols is needed for broader clinical application. The significant association between abnormal Doppler measures and hypoglycemia in pregnancies complicated by diabetes mellitus may also warrant further evaluation. ■

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xagr.2023.100241.

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