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Peripartum fetal Doppler sonography and perinatal outcome: a systematic review and meta-analysis

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Abstract

Objective Systematically review and critically appraise the literature on the association between peripartum fetal Doppler sonography findings, i.e., acquired upon admission for spontaneous or induced labor, and perinatal outcome in term (37-42w) pregnancies.

Methods Medline, Embase, Web of Science, Cochrane Library, and clinicaltrials.gov databases were systematically searched from inception to 05/2024. Studies conducted in unselected populations of term (37-42w) pregnancies, admitted for spontaneous or induced labor, reporting the association between fetal Doppler findings and perinatal outcome, were eligible for inclusion. Study eligibility was assessed independently by two reviewers. Methodological quality was assessed using the Quality In Prognosis Studies (QUIPS)-tool. Effect estimates were pooled using random-effects meta-analyses. Summary Odds Ratios (ORs) and Mean Differences (MDs) are reported with 95% confidence intervals.

Results Thirty-seven studies, reporting on 11.505 women and neonates, were included. Fourteen studies reported on findings from the umbilical artery (UA), four on the middle cerebral artery (MCA), five on the umbilical vein (UV), and nine on the cerebroplacental ratio (CPR). An abnormal UA Doppler and CPR increased the odds of fetal distress (FD) during labor (UA: OR 3.67 [1.14, 11.78], $I^2 = 72\%$ – CPR: OR 3.19 [2.68, 3.80], $I^2 = 0\%$) and subsequent operative delivery (ODFD) (UA: OR 3.65 [1.66, 8.04], $I^2 = 81\%$ – CPR: OR 2.48 [1.66, 3.70], $I^2 = 57\%$). Likewise, the presence of UV pulsations was strongly associated with both outcomes (FD: OR 28.78 [11.21, 73.87], $I^2 = 0\%$ – ODFD: OR 303.36 [11.11, 8279.82], $I^2 = 0\%$). Regarding neonatal outcome, an Apgar-score < 7 at 5 min and NICU admission occurred more frequently if Doppler findings were abnormal in the UA (Apgar: OR 3.65 [1.82, 7.34], $I^2 = 0\%$ – NICU: OR 3.92 [2.36, 6.51], $I^2 = 0\%$), or in case of an abnormal CPR (Apgar: OR 3.64 [2.03, 6.54], $I^2 = 0\%$ – NICU: OR 2.71 [1.15, 6.38], $I^2 = 0\%$). Neonatal birthweight was also lower in the presence of an abnormal UA or CPR result, with a MD of -630.61g ([-1234.29, -26.93], $I^2 = 80\%$) and -146.52g ([-285.03, -8.01], $I^2 = 0\%$) respectively. Most studies (70.3%) were at high risk of bias on one or more domains; only 11 studies had an overall low risk of bias score.

Conclusion Doppler sonography in the peripartum period allows for the identification of fetuses at risk of adverse birth outcomes. Further research on optimal thresholds to define at-risk cases and subsequent management strategies is needed.

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Keywords Doppler ultrasonography, Parturition, Apgar score, Delivery, obstetric, Umbilical arteries, Umbilical veins, Middle Cerebral Artery, Fetal Distress, CTG, Pregnancy

Introduction

Assessing fetal well-being is a key responsibility of obstetric caregivers. The main goal is to avoid unnecessary (operative) intervention for the mother and hypoxic-ischemic injuries in the neonate [1]. An admission CTG is a commonly performed procedure to assess whether a fetus is 'fit for labor' [2]. When compared to intermittent auscultation in low-risk pregnancies at term, an admission CTG may increase the risk of having an intra-labor cesarean section, without overall improvement in perinatal outcome [3]. Moreover, despite being appropriately grown for gestational age (AGA), some fetuses may be exposed to various degrees of late-onset uteroplacental insufficiency, making them less able to cope with the stress of labor [4]. This is not necessarily identified by CTG carried out at admission on the labor ward [5].

Fetal oxygenation is highly dependent on uteroplacental blood flow. Doppler sonography of selected fetal blood vessels can detect and quantify uteroplacental (dys)function [6]. During labor, decreased placental perfusion during uterine contractions can induce transient hypoxemia in the fetal circulation. This triggers fetal chemoreceptors, leading up to a redistribution of blood flow to critical organs, such as the fetal brain [7], which can be identified by Doppler sonography [8–10]. As placental function may progressively deteriorate with advancing gestational age and the rate of decline in individual fetuses is difficult to predict [11], it has been hypothesized a screening test for placental dysfunction should best be introduced as close to labor as possible [12]. As such, this systematic review aimed to summarize and critically appraise the existing evidence on the association between Doppler findings from selected fetal blood vessels, acquired upon admission for or during spontaneous or induced labor, with delivery mode and perinatal outcome.

Methods

This systematic review was conducted following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [13]. The 2018 guideline for systematic reviews and meta-analyses of prognostic factor studies was also followed [14]. The protocol was registered in PROSPERO on 23/04/2023 (registration number CRD42023413264).

Research question

We transformed our research question into a PICOTS format (Population, Intervention, Comparator, Outcome, Timing, Setting) to guide the study selection process [14]. Studies focusing on unselected populations of term singleton pregnancies (37–42 weeks) were eligible for inclusion, without restrictions on geographical location, ethnicity, or age. Studies specifically targeting high-risk populations (e.g., pregnancies affected by pre-eclampsia, gestational diabetes, or fetuses known to be growth-restricted or small for gestational age), were not eligible. Studies that included a mix of low-risk pregnancies and women with certain antenatal complications, such as pre-existing or gestational diabetes, hypertensive disorders of pregnancy, etc., were however eligible for inclusion. The intervention consisted of Doppler sonography of selected fetal vessels in the peripartum period, i.e., carried out upon admission for or during labor, and regardless of the onset (spontaneous or induced). Vessels of interest included, but were not limited to, the fetal umbilical artery (UA) and vein (UV), the fetal middle cerebral (MCA), and vertebral artery (VA). Studies focusing on maternal blood vessels (e.g., uterine arteries) were not eligible for inclusion [15, 16]. Studies were eligible if they reported on one of the following outcomes, irrespective of the effect measure used to describe the strength of the association:

- Fetal distress (*FD*) on cardiotocography (CTG).
- Occurrence of meconium-stained amniotic fluid (*MSAF*).
- Spontaneous vaginal delivery rate (vs. operative delivery, i.e., cesarean section or assisted vaginal delivery for any indication).
- Operative delivery for suspected fetal distress (*ODFD*, i.e., assisted vaginal delivery or cesarean section because of suspected fetal distress).
- Perinatal outcome: Apgar-scores at one and five minutes, UA cord blood pH, neonatal birthweight and proportion of small for gestational age infants (*SGA*), need for neonatal assisted ventilation/resuscitation at birth or admission to the neonatal intensive care unit (NICU), and occurrence of serious neonatal morbidity or a composite adverse outcome (as defined by eligible studies).

Systematic search

A systematic search was conducted in the following databases: MEDLINE through PubMed, EMBASE, Web of Science Core Collection and Cochrane Central Register of Controlled Trials (CENTRAL). Search strings were developed around the concepts 'Doppler' and 'childbirth'. They consisted of medical subject headings (MESH) for MEDLINE, Emtree terms for EMBASE, and free text words for all databases. The strings were developed by one author (BP) and peer-reviewed by another reviewer author (ASP), following guidance provided by the 2015 Peer Review of Electronic Search Strategies (PRESS)-checklist [17]. Before running the final searches, the PubMed search was validated by combining the PubMed IDs of seven preidentified eligible studies with the concepts 'Doppler' and 'childbirth' (all combined with 'AND'), which resulted in the successful retrieval of the records from the MEDLINE database [5, 18–23]. The full search strings for every database are available in Appendix A. Records published from inception to the date the systematic searches were conducted (24 April 2023), were eligible for inclusion. The use of predefined search filters was avoided in every database. We also deployed snowball and citation searches, including cross-checking rfence lists from systematic reviews on related topics [24–31], to identify additional relevant records. The systematic search was updated on May 17 th, 2024, to ensure currency and identify eligible records past the previous search date [32]. The updated search strategy was consistent with the original one and pooled results are reported. Also, the trial registry Clinicaltrials.gov was consulted on May 27 th, 2024, to limit the risk of publication bias.

Study selection process

Results from the electronic searches were exported to Endnote reference manager (Clarivate, London, UK) to eliminate duplicates by one review author (BP). Two reviewers (BP and ASP) independently screened titles and abstracts for eligibility using Rayyan software (Qatar Computing Research Institute, Doha, Qatar). The study selection process was guided by the *PICOTS* format and additional selection criteria for study design, publication type, and language. Both observational retro- or prospective cohort and case–control studies, as well as interventional randomized or non-randomized trials were eligible for inclusion. Book chapters, commentaries, case reports, case series, and narrative or scoping reviews were excluded. Conference abstracts or letters to the editor were included if sufficient data could be derived from their content. Only records in English were eligible. A similar strategy was followed during the full-text review phase. In case of disagreement, a consensus was reached through discussion or if necessary, through arbitration from a third review author (JR).

Data extraction

A data extraction template was designed in Microsoft Excel based on the CHARMS-PF checklist (Checklist for data extraction and critical appraisal of prognostic factor studies) [14, 33]. First, data was extracted independently by two reviewers (BP and ASP), each addressing half of the eligible studies. Each half was subsequently checked for accuracy and completeness by the other reviewer, not involved in the first round of data extraction. Disagreements were resolved through discussion. When more than one record reported on the same study population, we used the most complete report for data extraction. In cases of incomplete data or suspicion of overlapping study populations [19, 20, 34–37], corresponding authors were contacted for additional information by e-mail. After having received no response within one month, only published data of the most complete reports were included. The data extraction sheets are available in Appendix B.

Risk of bias

Studies were judged on their methodological quality independently by both reviewers (BP and ASP) using the Quality In Prognosis Studies (QUIPS) tool [14, 38]. The QUIPS tool is a validated instrument for assessing risk of bias in prognostic factor studies, with reported moderate to substantial inter-rater reliability [38]. Risk of bias was assessed in six domains: study participation (selection bias, D1), bias due to attrition (D2), prognostic factor (D3) or outcome measurement (D4), adjustment for confounding variables (D5) and clarity of the statistical analysis and reporting (D6). Each domain was judged to be at high, moderate, or low risk of bias. For prognostic factor measurement (i.e., the Doppler findings), studies that provided a detailed ultrasound protocol were considered at low risk of bias, since this ensured the prognostic factor was measured similarly in all participants (e.g., the number of operators with relevant experience, timing of the examination in regards to the stage of labor/uterine contractions, insonation angles, number of measurements and waveforms used for the calculation of doppler indices, blinding of clinical staff for doppler data during intrapartum course, etc.). In case of dichotomization of Doppler findings as either normal or abnormal, a low-risk score was attributed when cut-off values with appropriate justification were provided (i.e., reference study quoted or derived from the statistical analysis). Studies reporting on suspected fetal distress on CTG were judged to be at low risk of bias when the following conditions were met:

(1) a detailed description of the criteria used to judge/classify FHR tracings, or reference given to international guidelines on this topic, and (2) independent review of FHR traces by a second investigator to limit inter-rater variability in judgment. Methodological comments, including quotes from the study publications, were made to support our judgments (Appendix C). An overall 'low risk of bias' score was attributed if every domain was rated as low to moderate risk of bias, and no domain was rated at high risk of bias [14]. A 'critical risk of bias' score was attributed when more than half of the domains (> = 3/6) were judged at high risk of bias. Descriptive statistics were used to report on critical disagreement between raters. This was defined as disagreement influencing the overall risk of bias score, i.e., a low to moderate vs. high-risk of bias score disagreement. All conflicts were resolved through discussion.

Data analysis

Data from studies sufficiently comparable in terms of design, fetal vessel studied, and outcomes/effect measures reported, were pooled. We assumed a priori statistical heterogeneity due to methodological and clinical diversity among the included studies (e.g., slight differences in eligibility criteria, sonographic techniques or devices, timing of the ultrasound examination, or outcome assessment methods). Therefore, we performed random-effects (RE) meta-analyses, first according to the *DerSimonian and Laird* (DL) Inverse Variance (IV) method [39], with subsequent conversion of summary effect estimates according to the *Hartung-Knapp-Sidik-Jonkman* (HKSJ) method [40]. The latter results in more adequate error rates compared to the DL method, especially when the number of studies in each meta-analysis is small and heterogeneity is high [40]. Summary effect estimates are reported as Odds Ratios (OR) or Mean Differences (MD) between groups of "normal" and "abnormal" Doppler findings, as defined in the study's methodology, together with corresponding 95% Confidence Intervals (CI). Sensitivity analyses were performed with the exclusion of studies at critical risk of bias. Heterogeneity was assessed using the I^2 statistic. Subgroup analyses according to Doppler thresholds were conducted to investigate the effect on statistical heterogeneity, providing at least 10 studies were included in a meta-analysis [39, 41]. Likewise, publication bias was assessed through visual inspection of funnel plots if at least 10 studies were included [14]. RevMan software (Cochrane Collaboration, version 5.4.1) was used for data analyses.

Results

Literature search

The systematic search generated 18.202 original records. The study selection process is displayed in the PRISMA flowchart in Fig. 1. From the 228 reports undergoing

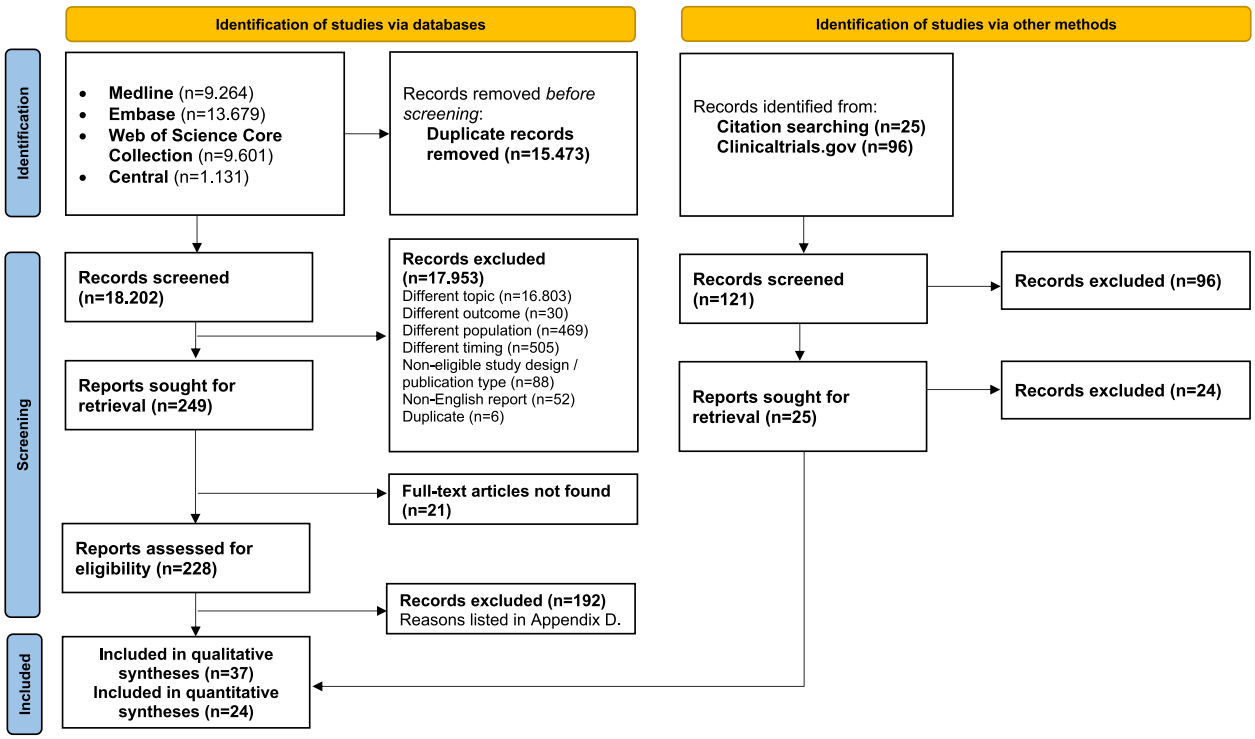

Fig. 1 PRISMA flowchart summarizing results of the systematic search and study selection process

full-text review, 36 were eligible for inclusion. One additional record was identified through citation searches [42], hence 37 records were included in our qualitative synthesis. No eligible records were identified by searching the trial registry Clinicaltrials.gov or cross-checking reference lists of related systematic reviews. Reasons for the exclusion of articles during the full-text review phase are provided in Appendix D.

Study characteristics

Of the 37 studies included, 36 were prospective and one was a retrospective cohort study [43]. Overall, these provided data on 11.505 pregnancies and neonates. Study characteristics are presented in Table 1. Two reports covered overlapping study populations but reported on Doppler findings from different fetal vessels (UV and the cerebroplacental ratio, CPR), hence both reports were included [19, 20], providing their data could not be pooled. Similarly, two reports from Dall'Asta et al. were identified reporting on the CPR, measured in early labor, and perinatal outcome, with partial overlap in recruitment periods and locations [5, 44]. Both reports were included for the risk of bias assessment, whereas only the 2019 report contained extractable data for our quantitative synthesis [5]. Also, during the updated search in 05/2024, the study report by Lam et al. [45] was replaced by the report from Moungmaithong et al. [46], reporting on the largest cohort derived from the same observational study [45, 46].

Risk of bias

Figure 2 shows the results of the bias assessment. Overall, 11 studies (29.7%) were judged at low risk of bias [5, 22, 34, 44, 46–52]. Conversely, 26 studies (70.3%) were at high risk of bias for one or more domains [18–21, 23, 42, 43, 53–71]. Bias related to the items 'participation' and 'confounding' was omnipresent, with only one [70] and six studies [5, 18, 34, 44, 52, 70] being at low risk of bias in these domains. Bias related to the domains of 'study attrition' [5, 18–20, 22, 34, 42–44, 46, 48, 49, 51–55, 59–62, 66, 67, 71] and 'statistical analysis and reporting' [5, 19, 20, 22, 34, 42–44, 46–49, 51, 53–56, 58, 59, 61, 62, 64, 65, 70] was judged more favorable, with 24/37 (64.9%) of studies being at low risk of bias on these domains respectively. The domain of 'prognostic factor measurement' and 'outcome measurement' were scored less favorable, with 43.2% (16/37) [5, 18–20, 22, 43, 44, 46–49, 58, 60–62, 65] and 29.7% (11/37) [5, 19, 20, 48, 49, 51, 55, 58, 64–66] of studies judged at low risk of bias. Five studies (13.5%) were assessed as being at critical risk of bias [21, 56, 63, 67, 68]. Results of the quality appraisal of individual studies are provided in Appendix E. An overview of critical disagreement rates for every domain is provided in Appendix C. Highest disagreement was encountered in the 'confounding' and 'outcome' domains (33.3% of studies), lowest disagreement in the 'attrition' domain (8.3% of studies).

Umbilical artery – UA

Fourteen studies reported on the association between UA Doppler findings, delivery mode, and perinatal outcome [23, 34, 47, 48, 54–56, 58, 59, 61, 64–66, 68]. As shown on the forest plots in Fig. 3 and 4, an abnormal UA Doppler was associated with FD during labor (OR 3.67, 95% CI 1.14–11.78) and need for ODFD (OR 3.65, 95% CI 1.66–8.04). For both outcomes, there was substantial heterogeneity in results (I^2 72% and 81%). Ten studies reported on the outcome 'ODFD'; the funnel plot showed asymmetry probably related to small study effect (Appendix F). No significant association was found between abnormal UA Doppler findings and the odds of spontaneous vaginal childbirth (OR 0.24, 95% CI 0–6638.87, $I^2 = 78\%$). Regarding neonatal outcome, an abnormal UA Doppler was associated with an Apgar = < 7 at five minutes (OR 3.65, 95% CI 1.82–7.34, $I^2 = 0\%$) but not at one minute (OR 2.73, 95% CI 0.64–11.69, $I^2 = 73\%$), need for assisted ventilation (OR 3.35, 95% CI 1.71–6.56), NICU admission (OR 3.92, 95% CI 2.36–6.51, $I^2 = 0\%$) and serious neonatal morbidity (OR 29.56, 95% CI 8.32–104.93). A significantly lower birthweight (MD − 630.61g, 95% CI − 1234.29, − 26.93, $I^2 = 80\%$) was also observed in infants with an abnormal UA Doppler and similarly, a larger proportion of these infants were reported to be SGA (OR 4.35, 95% CI 2.30–8.22, $I^2 = 0\%$). No significant association was found between UA Doppler findings and the occurrence of MSAF, need for neonatal resuscitation, perinatal mortality, low UA cord blood pH or a composite adverse perinatal outcome. Table 2 provides an overview of all outcomes, the summary effect estimates, 95% CIs, I^2 statistics, and number of studies/participants in every meta-analysis. Forest plots are provided in Appendix F.

Ten studies reported on the outcome 'ODFD'. In the subgroup of studies using a threshold of PI > = 1.2 to differentiate between cases [55, 56]; the OR for ODFD was 3.45 (95% CI 3.13–3.80) with low heterogeneity ($I^2 = 0\%$). Heterogeneity in the other subgroups (S/D ratio > = 3 [23, 65, 66] or other thresholds [34, 47, 48, 54, 61]) remained high ($I^2 > = 50\%$). The forest plot is provided in Appendix F. Sensitivity analyses with the exclusion of studies at critical risk of bias [56, 68] did not affect conclusions on the association between abnormal UA Doppler findings and occurrence of FD during labor (OR 3.60, 95% CI 1.07–12.09, $I^2 = 77\%$), ODFD (OR 3.73, 95% CI 1.49–9.35], $I^2 = 82\%$), low Apgar score at five minutes (OR 2.65, 95% CI 1.52–4.63,

Table 1 Key characteristics of studies included in this systematic review

Author Year	Study design[b]	Country	Uni- or Multi-centric	Labor onset	N	FV	Timing Doppler ultrasound (protocol)
Abdallah (2019) [47]	Prospective	Egypt	Uni	us	417	UA	Active stage (> = 6 cm)
Abitbol (1992) [53]	Prospective	USA	Uni	us	52	UA	Multiple timepoints: latent phase (= < 5 cm), active first stage (> 5 cm), 2nd stage of labor
Arduini (1992) [54]	Prospective	Italy	Uni	Spontaneous	534	UA	On admission, stage unspecified
Atabay (2017) [48]	Prospective	Turkey	Uni	us	311	UA, UV, MCA, CPR, VAI	Latent phase, < 4 cm of dilatation
Ayida (1994) [55]	Prospective	UK	Uni	Spontaneous	68	UA	On admission, stage unspecified
Chainarong (2018) [49]	Prospective	Thailand	Uni	us	384	UA, MCA, CPR	Latent phase, < 4 cm of dilatation
Chua (1996) [56]	Prospective	Singapore	Uni	us	1092	UA	On admission in early labor
Dall'Asta (2019) [5]	Prospective	Italy Spain	Multi	Spontaneous	562	UA, MCA, CPR	Latent phase, > 3 - 4 cm but < 5 cm of dilatation
Dall'Asta (2024) [44]	Prospective	Italy Spain UK	Multi	Spontaneous	804	UA, MCA, CPR	Latent phase, > 3 - 4 cm but < 5 cm of dilatation
de Campos Prado (2016) [50]	Prospective	Brazil	Multi	Induction	204	UA, MCA	On admission for induction, prior to administration of induction agents
Eslamian (2011) [21]	Prospective	Iran	Uni	Mixed	60	UA, UV, MCA	Active phase (> 3 cm dilatation)—prior to the 2nd stage
Fiolna (2019) [34]	Prospective	UK	Uni	Induction	1902	UA, MCA, CPR	Within 24 h from onset of induction
Fratelli (2018) [42]	Prospective	Italy	Uni	Induction	151	UA, UV, MCA, CPR	Within 3 h from onset of induction
Ghosh (2009) [22]	Prospective	Sweden	Uni	us	52	UV	Active first stage (> = 3 cm)—prior to the 2nd stage
Günay (2021) [57]	Prospective	Turkey	Uni	Induction	145	UA, MCA, CPR	Within 8 h from onset of induction
Howarth (1992) [58]	Prospective	South Africa	Uni	Spontaneous	100	UA	Early first stage (3 - 6 cm)
Kamal [59]	Prospective	Saudi Arabia	Uni	us	66	UA, UV	Active first stage (> 3 cm)—prior to the 2nd stage
Karcaaltincaba (2009) [51]	Prospective	Turkey	Uni	Induction	123	UA, MCA	On admission for induction, prior to and 4–6 h after dinoprostone administration
Krapp (2012) [52]	Prospective	Germany	Uni	us	90	DV	First stage, different stages of dilatation
Lam (2005) [60]	Prospective	Hong Kong	Uni	Induction	118	UA, MCA, CPR	On admission for induction
Lu (2021) [71]	Prospective	China	Uni	Induction	384	UA, MCA, CPR	On admission for induction
Malcus (1991) [61]	Prospective	Sweden Singapore	Multi	Spontaneous	562	UA	On admission, various stages of labor
Morales-Roselló (2022) [62]	Prospective	Spain	Uni	Mixed	182	UA, VA, CPR, VPR	Within 24 h from delivery
Morano (2018) [18]	Prospective	Italy	Uni	Mixed	250	VA	Onset of the 2nd stage

Table 1 (continued)

Author Year	Study design[b]	Country	Uni- or Multi-centric	Labor onset	N	FV	Timing Doppler ultrasound (protocol)
Moungmaithong (2024) [46]	Prospective	Hong Kong	Uni	Mixed	400	UA, MCA, CPR	On admission for IOL or spontaneous labor, < 3 cm of dilatation
Moussa (2023) [63]	Prospective	Egypt	Uni	us	200	UA, MCA, MCA-RI/UA-RI ratio	On admission to the maternity hospital
Ogunyemi (1992) [64]	Prospective	USA	Uni	us	102	UA	During labor, stage unspecified
Özden (1998) [23]	Prospective	Turkey	Uni	us	99	UA	During labor, stage unspecified
Prior (2014) [19]	Prospective	UK	Uni	us	589	UV	Latent phase, = < 4 cm dilatation
Prior (2015) [20]	Prospective	UK	Uni	Mixed	775	UA, MCA, CPR	Early spontaneous labor (= < 4 cm) or immediately prior to onset of induction
Sarno (1989) [65]	Prospective	USA	Uni	us	109	UA	Latent phase of labor, dilatation unspecified
Somerset (1993) [66]	Prospective	UK	Uni	Mixed	334	UA	As soon as possible after admission
Stumpfe (2019) [43]	Retrospective	Germany	Uni	Mixed	1008	UA, MCA, CPR	Latent phase, = < 4 cm dilatation
Szunyogh (2007) [67]	Prospective	Slovakia	Uni	us	81	DV	First stage
Tairy (2023)[a][68]	Prospective	Israel	Uni	Induction	133	UA, UV, MCA, CPR	Before onset of IOL
Yagel (1992) [69]	Prospective	Israel	Uni	us	60	UA, MCA	First stage, between 4 and 9 cm of dilatation
Zhou (2021) [70]	Prospective	China	Uni	us	392	UA, MCA, CPR	On admission in labor, = < 5 cm of dilatation

Only the first author for each study is presented

N number of participants with outcome data; *FV* fetal vessel; *US* ultrasound; *UA* umbilical artery; *us* unspecified, *UV* umbilical vein; *MCA* middle cerebral artery; *CPR* cerebroplacental ratio; *VA* vertebral artery; *VPR* vertebroplacental ratio; *VAI* venous-arterial index

[a] Conference proceeding, all other reports were journal articles

[b] All studies were cohort studies

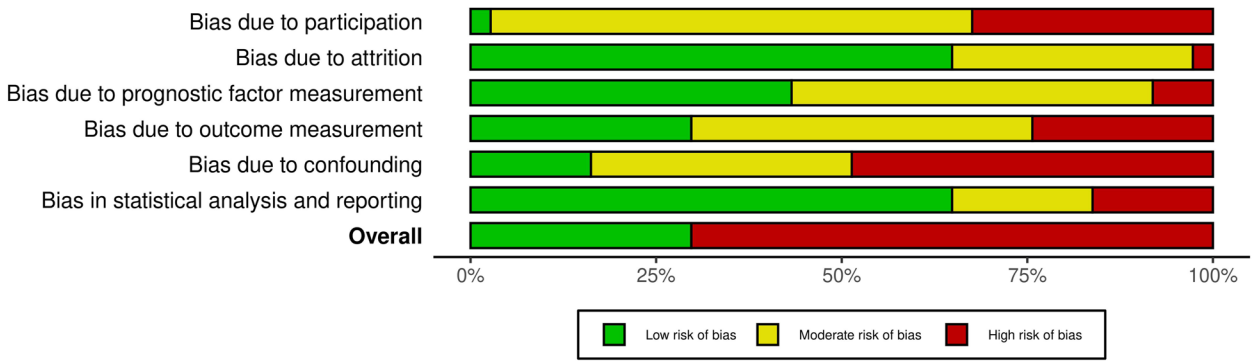

Fig. 2 Overall risk of bias assessment according to different domains of the QUIPS-tool

$I^2 = 0$) and need for NICU admission (OR 4.56, 95% CI 2.05–10.14], $I^2 = 0\%$). Forest plots are provided in Appendix F.

Middle Cerebral Artery – MCA

Data from four studies was used to assess the association between MCA Doppler findings, delivery mode and perinatal outcome [34, 48, 60, 68]. MCA Doppler findings were not associated with the occurrence of FD during

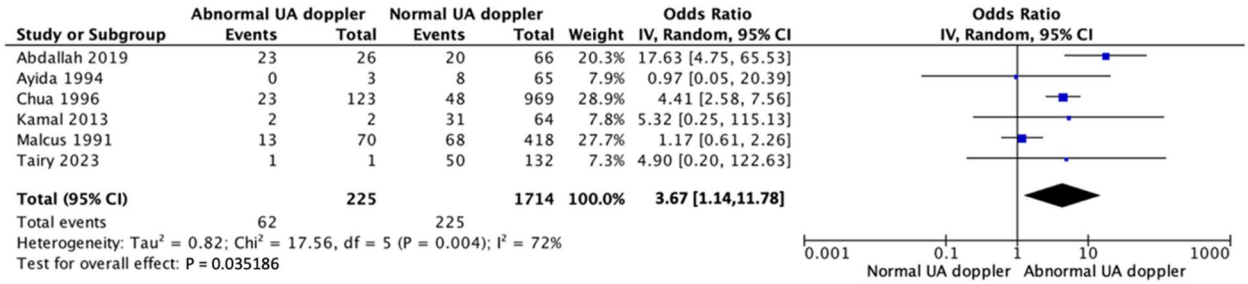

Fig. 3 Forest plot for the association between UA Doppler result and fetal distress (FD) during labor

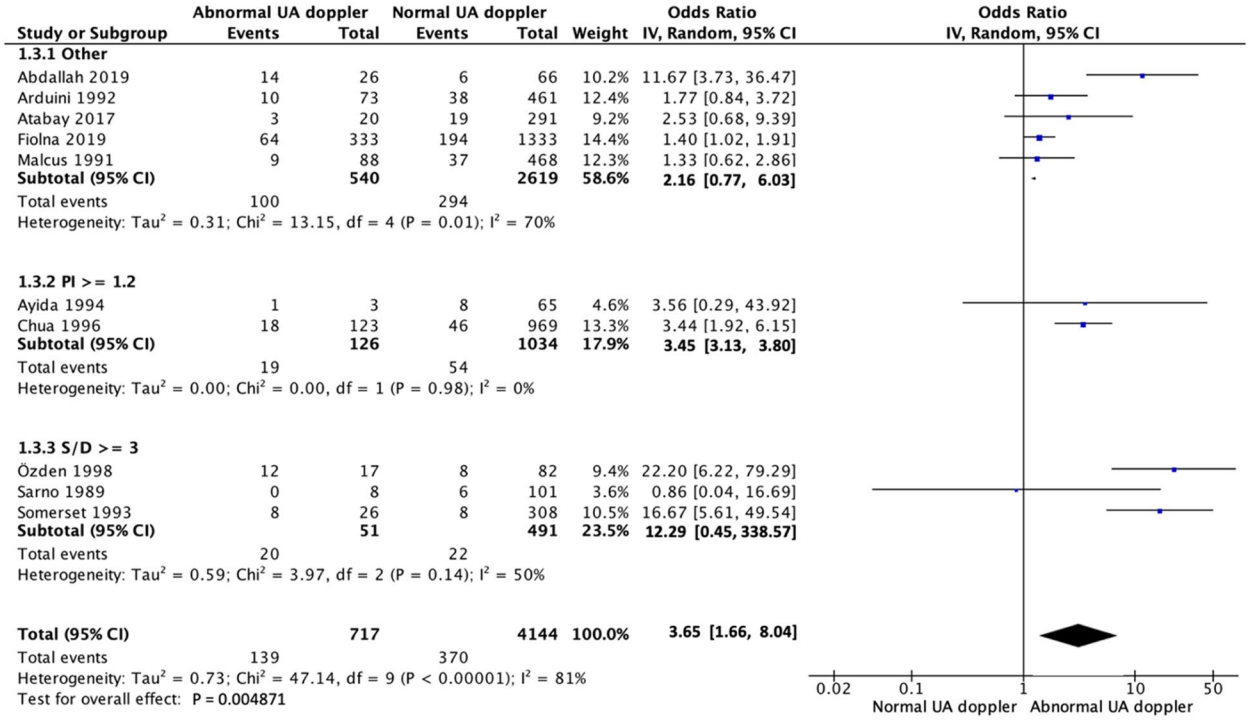

Fig. 4 Forest plot for the association between UA Doppler result and operative delivery for suspected fetal distress (ODFD)

labor, the need for ODFD, or the odds of spontaneous vaginal childbirth. They were however associated with the occurrence of MSAF (OR 7.59, 95% CI 2.39–24.12) and NICU admission (OR 15.54, 95% CI 3.17–76.19). The effect on both outcomes was assessed in only one study respectively. Table 3 provides an overview of all outcomes, effect estimates, 95% CIs, I^2 statistics and number of studies/participants in every meta-analysis. Forest plots are provided in Appendix F.

Cerebroplacental ratio – CPR

Nine studies report on the association between CPR (MCA-PI/UA-PI), delivery mode and perinatal outcome [5, 20, 34, 43, 48, 49, 57, 68, 71]. As demonstrated on the forest plot in Fig. 5, an abnormal CPR was associated with FD during labor (OR 3.19, 95% CI 2.68–3.80) and this was a consistent finding across studies ($I^2 = 0\%$). Likewise, it was associated with ODFD, with an OR of 2.48 (95% CI 1.66–3.70, $I^2 = 57\%$, Fig. 6). An abnormal CPR was significantly associated with adverse perinatal outcomes, such as an Apgar score < 7 at 5 min (OR 3.64, 95% CI 2.03–6.54, $I^2 = 0\%$), need for NICU admission (OR 2.71, 95% CI 1.15–6.38, $I^2 = 0\%$) and occurrence of serious neonatal morbidity (OR 19.33, 95% CI 2.07–180.69). Finally, lower birthweight was observed in fetuses with abnormal CPR, with a mean difference of − 146.52 g (95% CI − 285.03, − 8.01) and again, this was a consistent finding ($I^2 = 0\%$).

Table 2 Summary of findings on the association between UA Doppler result and delivery mode/perinatal outcome

Outcome	S	n/N	Statistic	Effect Estimate	I^2 (%)
FD during labor[a] [47, 55, 56, 59, 61, 68]	6	287/1939	OR (95% CI)	3.67 [1.14,11.78]	72
MSAF [61, 65]	2	121/669	OR (95% CI)	0.58 [0, 236,192.4]	55
ODFD [23, 34, 47, 48, 54–56, 61, 65, 66]	10	509/4861	OR (95% CI)	3.65 [1.66, 8.04]	81
SVD (vs. OD) [47, 48]	2	322/403	OR (95% CI)	0.24 [0, 6638.87]	78
Assisted ventilation[b] [56]	1	46/1092	OR (95% CI)	3.35 [1.71, 6.56]	NA
Neonatal resuscitation [54]	1	26/534	OR (95% CI)	2.47 [1.00, 6.10]	NA
Apgar (=) < 7/5 at 1 min [23, 55, 56, 61, 64, 65]	6	137/2015	OR (95% CI)	2.73 [0.64, 11.69]	73
Apgar (=) < 7 at 5 min [23, 54–56, 61, 64, 65]	7	48/2566	OR (95% CI)	3.65 [1.82, 7.34]	0
Low UA pH[a] [23, 61, 64]	3	65/572	OR (95% CI)	2.55 [0.12, 54.94]	68
NICU admission [47, 48, 54–56, 64]	6	106/2199	OR (95% CI)	3.92 [2.36, 6.51]	0
Neonatal birthweight (g) [23, 54, 64]	3	N = 735	MD (95% CI)	− 630.61 [− 1234.29, − 26.93]	80
SGA infant[a] [55, 61, 64, 65]	4	45/839	OR (95% CI)	4.35 [2.30, 8.22]	0
Serious neonatal morbidity[a][64]	1	20/102	OR (95% CI)	29.56 [8.32, 104.93]	NA
Perinatal mortality [23, 47, 65]	3	5/300	OR (95% CI)	4.90 [0.88, 27.42]	0
Composite adverse outcome[a] [34, 58, 64]	3	132/2092	OR (95% CI)	3.60 [0.02, 675.15]	90

S number of studies, *n* number of events, *N* total number of participants, *FD* fetal distress during labor on CTG/FHR monitoring, *MSAF* meconium-stained amniotic fluid, *NA* non-applicable, *ODFD* operative delivery (cesarean or instrumental vaginal) for suspected fetal distress, *SVD* spontaneous vaginal delivery, *OD* operative delivery (cesarean or instrumental vaginal, any indication), *UA pH* umbilical artery cord blood potential of hydrogen, *NICU* neonatal intensive care unit, *SGA* small for gestational age infant

[a] As defined by eligible studies (outcome definitions provided in Appendix B)

[b] Study at critical risk of bias, no sensitivity analysis performed

Table 3 Summary of findings on the association between MCA Doppler result and delivery mode/perinatal outcome

Outcome	S	n/N	Statistic	Effect Estimate	I^2 (%)
FD during labor[a,b] [68]	1	51/133	OR (95% CI)	1.07 [0.17, 6.66]	NA
MSAF [60]	1	26/118	OR (95% CI)	7.59 [2.39, 24.12]	NA
ODFD [34, 48]	2	280/1977	OR (95% CI)	2.76 [0, 66,554.93]	86%
SVD (vs. OD) [48]	1	261/311	OR (95% CI)	0.43 [0.15, 1.29]	NA
NICU admission [48]	1	7/311	OR (95% CI)	15.54 [3.17, 76.19]	NA
Composite adverse outcome[a] [34]	1	71/1890	OR (95% CI)	1.58 [0.93, 2.68]	NA

S number of studies; *n* number of events, *N* total number of participants, *FD* fetal distress during labor on CTG/FHR monitoring, *MSAF* meconium-stained amniotic fluid, *NA* non-applicable, *ODFD* operative delivery (cesarean or instrumental vaginal) for suspected fetal distress, *SVD* spontaneous vaginal delivery, *OD* operative delivery (cesarean or instrumental vaginal, any indication, *NICU* neonatal intensive care unit

[a] As defined by eligible studies (outcome definitions provided in Appendix B)

[b] Study at critical risk of bias, no sensitivity analysis performed

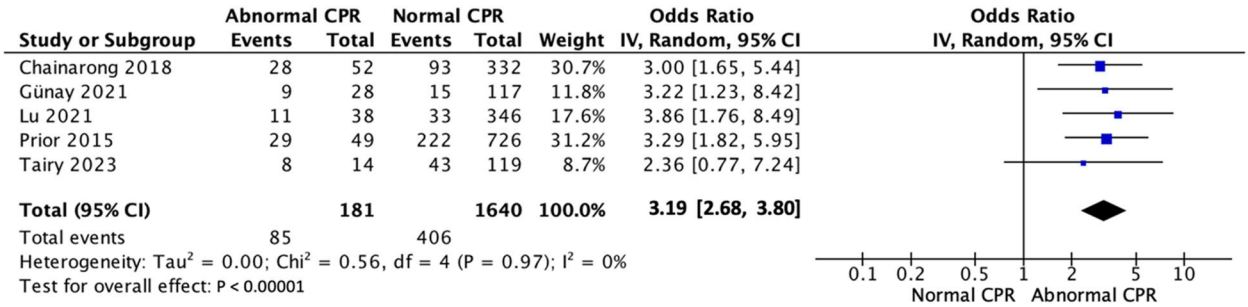

Fig. 5 Forest plot for the association between CPR result and fetal distress (FD) during labor

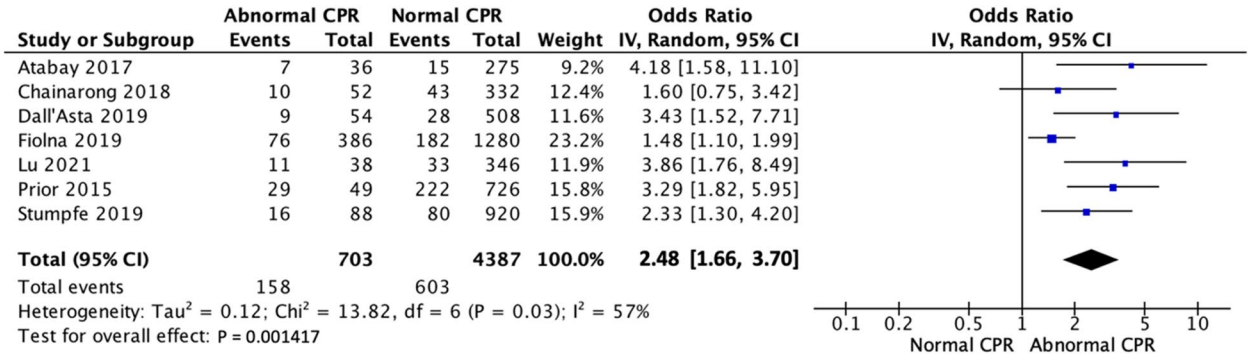

Fig. 6 Forest plot for the association between CPR result and operative delivery for suspected fetal distress (ODFD)

No significant association was found between the CPR result and spontaneous vaginal childbirth, the occurrence of MSAF, a low (< 7) Apgar score at one-minute, low UA cord blood pH, perinatal mortality, or a composite adverse perinatal outcome. An overview of the number of studies/participants in every meta-analysis is provided in Table 4, together with the summary effect estimates, 95% CIs, and I^2 statistics. The exclusion of the study by Tairy et al. [68] for being judged at critical risk of bias from the meta-analysis on FD during labor did not influence conclusions (OR 3.28, 95% CI 2.90–3.71, $I^2 = 0\%$). Forest plots are provided in Appendix F.

Umbilical Vein – UV

UV pulsations

Three studies reported on the association between UV pulsations, documented during the first stage of labor, with delivery mode and perinatal outcome [21, 22, 59]. The presence of UV pulsations was associated with FD during labor (OR 28.78, 95% CI 11.21–73.87, $I^2 = 0\%$) and ODFD (OR 303.36, 95% CI 11.11–8279.82, $I^2 = 0\%$). Regarding perinatal outcome, no significant association was found with low (< 7) Apgar score at 5 min, low UA cord blood pH or NICU admission. An overview of outcomes and summary effect estimates is provided in Table 5. Sensitivity analysis did not change conclusions on the occurrence of FD during labor (OR 32.91, 95% CI 13.33–81.28, $I^2 = 0\%$), low UA cord blood pH (OR 8.54,

Table 4 Summary of findings on the association between CPR result and delivery mode/perinatal outcome

Outcome	S	n/N	Statistic	Effect Estimate	I^2 (%)
FD during labor[b] [20, 49, 57, 68, 71]	5	491/1821	OR (95% CI)	3.19 [2.68, 3.80]	0
MSAF [20, 49]	2	157/1159	OR (95% CI)	1.23 [0, 3854.12]	79
ODFD [5, 20, 34, 43, 48, 49, 71]	7	761/5090	OR (95% CI)	2.48 [1.66, 3.70]	57
SVD (vs. OD) [5, 20, 43, 48, 57]	5	1851/2801	OR (95% CI)	0.56 [0.28, 1.12]	61
Apgar < 7 at 1 min [5, 20]	2	78/1337	OR (95% CI)	1.25 [0, 1410.51]	35
Apgar < 7 at 5 min [5, 20, 43, 49, 57]	5	38/2871	OR (95% CI)	3.64 [2.03, 6.54]	0
Low UA pH[b] [5, 20, 43, 48, 57]	5	412/2800	OR (95% CI)	1.50 [0.43, 5.22]	60
NICU admission [5, 20, 48, 49, 57]	5	37/2177	OR (95% CI)	2.71 [1.15, 6.38]	0
Neonatal birthweight (g) [5, 49]	2	N = 946	MD (95% CI)	− 146.52 [− 285.03, − 8.01]	0
SGA infant[b] [5, 49]	2	49/946	OR (95% CI)	1.41 [0.09, 21.93]	0
Serious neonatal morbidity[b] [20, 57]	2	5/920	OR (95% CI)	19.33 [2.07, 180.69]	NA[a]
Perinatal mortality [57]	1	1/145	OR (95% CI)	12.82 [0.51, 323.21]	NA
Composite adverse outcome[b] [5, 34]	2	96/2452	OR (95% CI)	2.06 [0.08, 56.16]	13

S number of studies, *n* number of events, *N* total number of participants, *FD* fetal distress during labor on CTG/FHR monitoring, *MSAF* meconium-stained amniotic fluid, *NA* non-applicable, *ODFD* operative delivery (cesarean or instrumental vaginal) for suspected fetal distress, *SVD* spontaneous vaginal delivery, *OD* operative delivery (cesarean or instrumental vaginal, any indication), *UA pH* umbilical artery cord blood potential of hydrogen, *NICU* neonatal intensive care unit, *SGA* small for gestational age infant

[a] No events reported in the study by Prior et al. [20]

[b] As defined by eligible studies (outcome definitions provided in Appendix B)

Table 5 Summary of findings on the association between UV pulsations and delivery mode/perinatal outcome

Outcome	S	n/N	Statistic	Effect Estimate	I^2 (%)
FD during labor[b] [21, 22, 59]	3	85/178	OR (95% CI)	28.78 [11.21, 73.87]	0
MSAF [21, 22, 59]	3	40/178	OR (95% CI)	11.45 [0.73, 180.83]	22
ODFD [22, 59]	2	22/118	OR (95% CI)	303.36 [11.11, 8279.82]	0
SVD (vs. OD) [22, 59]	2	82/118	OR (95% CI)	0.04 [0, 39.42]	0
Apgar < 7 at 5 min [22, 59]	2	6/117	OR (95% CI)	10.61 [0.04, 3126.03]	0
Low UA pH[b] [21, 22, 59]	3	13/145	OR (95% CI)	4.43 [0.2, 95.94]	0
NICU admission [21, 22, 59]	3	12/178	OR (95% CI)	4.04 [0.55, 29.49]	0
SGA infant[b] [22]	1	0/52	OR (95% CI)	Not estimable[a]	NA[a]

S number of studies, *n* number of events, *N* total number of participants, *FD* fetal distress during labor on CTG/FHR monitoring, *MSAF* meconium-stained amniotic fluid, *NA* non-applicable, *ODFD* operative delivery (cesarean or instrumental vaginal) for suspected fetal distress, *SVD* spontaneous vaginal delivery, *OD* operative delivery (cesarean or instrumental vaginal, any indication), *UA pH* umbilical artery cord blood potential of hydrogen, *NICU* neonatal intensive care unit, *SGA* small for gestational age infant

[a] No events reported in the study by Ghosh et al.[22]

[b] As defined by eligible studies (outcome definitions provided in Appendix B)

95% CI 0.84–87.00, $I^2 = 0\%$) or NICU admission (OR 2.91, 95% CI 0.34–24.93, $I^2 = 0\%$). A significant association however was observed with the occurrence of MSAF (OR 18.11, 95% CI 5.10–64.36, $I^2 = 0\%$). Forest plots are provided in Appendix F.

Corrected UV blood flow rate

Two studies investigated the association between UV blood flow rate, corrected for neonatal birthweight (ml/min/kg), with delivery mode and perinatal outcome [19, 48]. The results of the quantitative syntheses are summarized in Table 6. Low blood flow rates in the UV were associated with FD during labor (OR 1.64, 95% CI 1.01–2.66) and NICU admission (OR 3.61, 95% CI 2.83–4.60, $I^2 = 0\%$). No association was observed between low UV blood flow rates and the occurrence of MSAF, need for ODFD, spontaneous vaginal childbirth, low (< 7) Apgar score at 5 min, low UA cord blood pH, or the occurrence of serious neonatal morbidity. Forest plots are provided in Appendix F.

Other vessels – parameters

Moussa et al. investigated the association between the MCA/UA resistance index ratio (MCA-RI/UA-RI) and perinatal outcome in post-term pregnancies ($n = 200$) [63]. An MCA-RI/UA-RI ratio < 1 was associated with lower neonatal birthweight (MD − 1182.00 g, 95% CI − 1319.11, − 1044.89) and stillbirth (OR 8.61, 95% CI 1.06–70.17) [63]. It was also associated with cesarean section because of suspected fetal distress (OR 4.20, 95% CI 2.31–7.60) and NICU admission (RR 7.76, 95% CI 4.04–14.89) [63]. The study was judged at critical risk of bias (Appendix E). Morano et al. investigated the association between fetal VA Doppler findings at the onset of the 2nd stage and umbilical artery pH in a low-risk obstetric population laboring at term [18]. The VA PI

Table 6 Summary of findings on the association between corrected UV blood flow and delivery mode/perinatal outcome

Outcome	S	n/N	Summary	Effect Estimate	I^2 (%)
FD during labor[b] [19]	1	117/589	OR (95% CI)	1.64 [1.01, 2.66]	NA
MSAF [19]	1	72/589	OR (95% CI)	0.98 [0.52, 1.86]	NA
ODFD [19, 48]	2	197/900	OR (95% CI)	1.94 [0.33,11.29]	0
SVD (vs. OD) [19, 48]	2	494/900	OR (95% CI)	0.74 [0.12, 4.59]	0
Apgar < 7 at 5 min [19]	1	6/589	OR (95% CI)	0.89 [0.10, 7.69]	NA
Low UA pH[b] [19]	1	186/589	OR (95% CI)	0.99 [0.63, 1.56]	NA
NICU admission [19, 48]	2	16/900	OR (95% CI)	3.61 [2.83, 4.60]	0
Serious neonatal morbidity[b][19]	1	0/589	OR (95% CI)	Not estimable[a]	NA[a]

S number of studies, *n* number of events, *N* total number of participants, *FD* fetal distress during labor on CTG/FHR monitoring, *MSAF* meconium-stained amniotic fluid, *NA* non-applicable, *ODFD* operative delivery (cesarean or instrumental vaginal) for suspected fetal distress, *SVD* spontaneous vaginal delivery, *OD* operative delivery (cesarean or instrumental vaginal, any indication), *UA pH* umbilical artery cord blood potential of hydrogen, *NICU* neonatal intensive care unit

[a] No events reported in the study by Prior et al. [19]

[b] As defined by eligible studies (outcome definitions provided in Appendix B)

was independently associated with UA pH, with lower PI indices observed in cases with lower UA pH [18]. In a secondary analysis of a prospective cohort study, Morales-Roselló et al. aimed to investigate which parameter (UA PI, MCA PI, VA PI, CPR, VPR, and estimated fetal weight) best predicted adverse perinatal outcome in a cohort of fetuses delivered within 24 h of their last ultrasound assessment ($n = 182$) [62]. MCA PI MoM was found to be the best predictor, with an AUC of 0.76 (95% CI 0.66–0.85) [62]. Two studies investigated Doppler sonography of the fetal DV during the first stage of labor [52, 67]: Krapp et al. focused on the reproducibility of DV blood flow assessment during and between uterine contractions [52], whereas Szunyogh et al. investigated the effect of duration of membrane rupture, occurrence of MSAF and epidural analgesia on DV blood flow velocity waveforms [67]. Published data did not allow us to report on the association between Doppler findings and perinatal outcomes, and we were unable to retrieve additional data from the corresponding authors.

Discussion

Principal findings

Abnormal fetal Doppler findings, obtained on admission for or during spontaneous or induced labor at term, are associated with adverse maternal and neonatal outcomes. Most studies reported on findings from the UA or the CPR (MCA-PI/UA-PI). Fetal distress during labor and subsequent operative delivery, a low (= <7) Apgar score at 5 min, and NICU admission occurred more frequently in cases with an abnormal UA Doppler or CPR result. Lower neonatal birthweight was also observed in these cases, with a MD of − 630.61g (95% CI − 1234.29, − 26.93) and − 146.52g (95% CI − 285.03, − 8.01) for the UA and CPR respectively. Most studies (70.3%) were at high risk of bias on one or more domains of the QUIPS tool; only 11 studies (29.7%) had an overall low risk of bias score.

Comparison with existing literature

Doppler sonography of selected fetal blood vessels can quantify uteroplacental functional reserve [6, 72]. Its non-invasive nature makes it an interesting screening tool for identifying fetuses exposed to late-onset uteroplacental insufficiency, which may not lead to suboptimal fetal growth, but still increases the risk of adverse perinatal outcomes. Therefore, intrapartum management guided by fetal Doppler findings warrants further investigation [12, 73]. To our knowledge, this is the first systematic review on the association between fetal Doppler sonography, delivery mode and perinatal outcome in unselected term pregnant women admitted for spontaneous or induced labor. Our findings are complementary to previous systematic reviews focusing either on the UA [74, 75], the MCA [26, 74], or the CPR [24, 28–30, 74, 76] for predicting perinatal outcome in an antenatal setting. Like our systematic review, these were characterized by substantial heterogeneity [24, 26, 28–30, 75, 76] and inclusion of studies at risk of bias [26, 29, 75, 76]. Possible sources of heterogeneity are differences in study designs, populations under study, outcome definitions (e.g., CTG classification), and timing of the Doppler examination or thresholds used to guide clinical management. Besides standardization, the reproducibility and clinical impact of observational studies could be improved by ensuring blinding of managing clinicians, correction for confounders, and complete reporting.

In our systematic review, we also included three studies investigating the association between UV pulsations, documented during the first stage, with delivery mode and perinatal outcome [21, 22, 59]. In an antenatal setting, UV pulsations have been described in case of severe growth restriction [77, 78] or cardiac failure [79, 80]. Therefore, during labor, these might occur in fetuses at severe risk of decompensation and adverse outcomes. This was reflected by our results, as UV pulsations were most strongly associated with adverse perinatal outcome. Similarly, an abnormal UA Doppler was strongly associated with adverse outcomes, whereas an abnormal CPR, generally considered a milder sign of chronic uteroplacental hypoxia [81], was less strongly associated (albeit with overlapping confidence intervals).

Strengths and limitations

Our systematic search was conducted in multiple databases, including the grey literature, using sensitive search strings, hence resulting in the inclusion of a high number of studies. This allowed us to compare findings from different fetal vessels for many well-established indicators of perinatal outcome [82]. Studies were conducted in different countries and obstetric units, increasing the generalizability of our findings. However, we acknowledge most studies were conducted in university hospitals, where perinatal outcome was likely influenced by the availability of high-level care [83]. This does not necessarily reflect real-world conditions, particularly in low- and middle-income countries. We also acknowledge other limitations. Many study reports provided data that could not be pooled (i.e., no count data) and thus were not included in our quantitative synthesis. This could be resolved by conducting an individual patient data meta-analysis [84, 85]. During study selection, enquiries were made to obtain unpublished data from corresponding authors but proved unsuccessful. Several studies also reported on

"composite adverse outcomes". In small studies investigating rare outcomes, composite endpoints can increase statistical power [86]. A meta-analysis however generally overcomes this issue, and pooled analyses of composite endpoints are only indicated if their components have similar clinical relevance [87], which is not always the case [88]. As stated, we also encountered high heterogeneity in some meta-analyses. The small number of studies did not allow us to conduct subgroup analyses to detect genuine sources of heterogeneity [14, 41]. Random-effect meta-analyses were used to pool effect estimates, as this method incorporates the assumption of unexplained heterogeneity [14, 39]. Most studies also had small sample sizes and low rates of rare adverse outcomes, such as perinatal mortality. This raises specific statistical concerns, as meta-analyses of rare events often remain underpowered [89]. Conversely, the commonly used *DL* RE method [39] can result in a high probability of type 1 errors, especially when applied to small studies [40, 90]. Therefore, we converted summary effect estimates according to the *HKSJ* method, as this outperforms the DL method when the number of studies is small or heterogeneity is high [40]. Its use is recommended by The Cochrane Collaboration when available to authors, as it tends to widen CIs to reflect uncertainty in the estimation of between-study heterogeneity [39]. Despite resulting in substantive differences in the estimation of heterogeneity, these different methods generally do not majorly affect the significance of summary effect estimates [39, 91]. Nonetheless, in our systematic review, conversion did influence significance at a 5% level in 8/36 meta-analyses (Appendix F). As a final limitation, we acknowledge that the clinical implications of our systematic review are rather limited. First, several of the reported short-term outcomes are poorly predictive of individual neonatal mortality or long-term neurological outcomes [92, 93]. Second, methodological quality was concerning for most studies, especially the lack of correction for confounding variables. Third, substantial overlap in Doppler findings between cases with a 'normal' vs. 'adverse' outcome can result in high false positive rates at certain discriminatory thresholds, possibly resulting in unnecessary maternal and caregiver anxiety and obstetric intervention [24]. Fourth, no trials were identified investigating whether intrapartum management, guided by peripartum fetal Doppler sonography, can improve perinatal outcome, especially compared to already established techniques for fetal surveillance (e.g., CTG [2] or STAN monitoring [94]). Therefore, findings from our systematic review need to be interpreted with caution, and comparative, preferably randomized controlled trials are needed. Designing clinical trials for prognostic tests can be challenging, as outcomes are influenced by how adequately the test is performed and interpreted by managing clinicians, but also by the efficacy of subsequent interventions [95]. For several fetal vessels, discriminatory thresholds for clinical management range substantially between studies [96, 97], impeding the reproducibility of observational studies on Doppler sonography for predicting perinatal outcome, but also the design of a clinical trial. This is paramount, as in developed countries, 'hard' outcomes such as intrapartum stillbirth, early neonatal death, or hypoxic-ischemic encephalopathy are rare in term pregnancies [98–100]. Trials investigating the efficacy of certain interventions on these outcomes often require a multicentric and pragmatic design to recruit thousands of women over a long period of time to ultimately demonstrate a modest effect [101, 102].

Conclusion and implications

Abnormal fetal Doppler findings in the peripartum period are associated with adverse perinatal outcome. Most studies however were of suboptimal quality and had relatively small sample sizes, especially when investigating rare outcomes. Methodological and clinical diversity contributed to substantial statistical heterogeneity in some meta-analyses. Well-designed interventional, preferably randomized controlled trials are needed to assess the effectiveness of intrapartum fetal Doppler sonography to improve perinatal outcome.

Abbreviations

AGA	Appropriate for gestational age
CI	Confidence interval
CPR	Cerebroplacental ratio
CTG	Cardiotocography
DL	DerSimonian and Laird
FD	Fetal distress
HKSJ	Hartung-Knapp-Sidik-Jonkman
IV	Inverse variance
MASF	Meconium-stained amniotic fluid
MCA	Middle cerebral artery
MD	Mean difference
NICU	Neonatal intensive care unit
ODFD	Operative delivery for fetal distress
OR	Odds ratio
PI	Pulsatility index
PICOTS	Population, intervention, comparator, outcome, timing, and setting.
RE	Random-effects meta-analysis
SGA	Small for gestational age
UA	Umbilical artery
UV	Umbilical vein
QUIPS	Quality in prognosis studies

Supplementary Information

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Supplementary Material 1: Appendix A.

Supplementary Material 2: Appendix B.

Supplementary Material 3: Appendix C.

Supplementary Material 4: Appendix D.

Supplementary Material 5: Appendix E.

Supplementary Material 6: Appendix F.

Supplementary Material 7: PRISMA-S Checklist.

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Authors' contributions
B.P. : protocol development, protocol registration, systematic search, study selection, data extraction, methodological appraisal, data analysis, manuscript writing. A-S.P. : protocol revision, study selection, data extraction, methodological appraisal, manuscript editing. J.B. : protocol revision, manuscript editing. J.R. : protocol revision, manuscript editing.

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Data availability
The datasets supporting the conclusions of this article are included within the article and its additional files.

Declarations

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