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Third-trimester uterine artery Doppler for prediction of adverse outcome in late small-for-gestational-age fetuses: systematic review and meta-analysis

R. J. MARTINEZ-PORTILLA[1,2], J. CARADEUX[3], E. MELER[1], D. L. LIP-SOSA[1], A. SOTIRIADIS[4] and F. FIGUERAS[1]

[1]*Fetal Medicine Research Center, BCNatal Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital Sant Joan de Déu), Institut Clínic de Ginecologia, Obstetricia i Neonatologia, Universitat de Barcelona, Barcelona, Catalonia, Spain;* [2]*Centre for Evidence-Based Medicine, Nuffield Department of Primary Health Sciences, University of Oxford, Oxford, UK;* [3]*Fetal Medicine Unit, Clínica Dávila, Santiago, Chile;* [4]*Second Department of Obstetrics and Gynecology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece*

KEYWORDS: adverse perinatal outcome; fetal growth restriction; perinatal death; SGA; uterine artery Doppler

CONTRIBUTION

What are the novel findings of this work?
This study provides evidence of a higher risk of adverse outcome in suspected third-trimester small-for-gestational-age (SGA) fetuses with abnormal uterine artery Doppler, which is comparable to that in late SGA fetuses with abnormal cerebroplacental ratio.

What are the clinical implications of this work?
The findings from this study should enable clinicians to assess the risk of adverse perinatal outcome in SGA fetuses, using the likelihood ratios of abnormal third-trimester uterine artery Doppler to calculate the posterior probability, using an evidence-based approach.

ABSTRACT

Objective *To investigate the predictive ability for adverse perinatal outcome of abnormal third-trimester uterine artery Doppler in late small-for-gestational-age (SGA) fetuses.*

Methods *A systematic search was performed to identify relevant observational studies and randomized controlled trials evaluating the performance of abnormal third-trimester uterine artery Doppler for the prediction of adverse perinatal outcome in suspected SGA fetuses and SGA neonates. Abnormal uterine artery Doppler was defined as uterine artery pulsatility index $> 95^{th}$ percentile or ≥ 2 SD above the mean, or bilateral uterine artery notching. Hierarchical summary receiver-operating-characteristics (ROC) curves were constructed using random-effects modeling. Bayesian analysis was used to calculate the posterior probability of adverse perinatal outcome following an abnormal or normal uterine artery Doppler assessment.*

Results *Seventeen observational studies (including 7552 fetuses either diagnosed with suspected SGA (*n = *3461) or later diagnosed as a SGA neonate (*n = *4091)) met the inclusion criteria; no randomized-controlled trials met the inclusion criteria. Summary ROC curves showed that, among suspected SGA fetuses, the best predictive accuracy of abnormal third-trimester uterine artery Doppler was for perinatal mortality and the worst was for composite adverse perinatal outcome, with areas under the summary ROC curves of 0.90 and 0.66, respectively. The corresponding positive and negative likelihood ratios were 16.5 and 0.6 for perinatal mortality and 2.82 and 0.65 for composite adverse perinatal outcome, respectively. Following an abnormal* vs *normal uterine artery Doppler assessment, the posterior risks for composite adverse perinatal outcome, admission to the neonatal intensive care unit, Cesarean section for intrapartum fetal compromise, 5-min Apgar score < 7, neonatal acidosis and perinatal death were: 52.3%* vs *20.2%, 48.6%* vs *18.7%, 23.1%* vs *15.2%, 3.59%* vs *1.32%, 9.15%* vs *5.12% and 31.4%* vs *1.64%, respectively.*

Conclusion *Abnormal uterine artery Doppler in the third trimester appears to be moderately useful in predicting perinatal death in pregnancies with suspected SGA.*

Correspondence to: Dr F. Figueras, Fetal Medicine Department, Hospital Clinic of Barcelona, University of Barcelona, Sabino de Arana 1, 08028 Barcelona, Catalonia, Spain (e-mail: ffiguera@clinic.cat)

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INTRODUCTION

Fetal growth restriction (FGR) is associated with an increased risk of adverse pregnancy outcomes such as fetal death, perinatal morbidity, neonatal mortality, suboptimal neurodevelopment and delayed adverse effects into adolescence and adulthood[1–3]. Prenatal non-detection of this condition has been identified as a major cause of avoidable perinatal death[4,5], and growth-restricted fetuses not identified during pregnancy have increased risks of fetal death[4,6] and perinatal complications[7].

FGR presents as two clinical phenotypes characterized by different evolutions and outcomes. Early-onset FGR (usually defined as that detected < 32 weeks)[8,9] presents a typical pattern of deterioration that progresses from escalating abnormalities in Doppler parameters to abnormal biophysical parameters[10,11]. In late-onset FGR, there is a common pattern of normal or minimally elevated umbilical artery Doppler indices with mildly abnormal cerebral Doppler but without obvious cardiovascular or biophysical changes[12,13]. Unlike the early-onset condition, the association between pre-eclampsia and late-onset FGR is weak[14].

When early-onset FGR is suspected, the inclusion of uterine artery Doppler in the assessment has the advantage that it reflects placental insufficiency from the maternal side and captures the placental insufficiency secondary to pathophysiological mechanisms other than early defective trophoblastic invasion[15]. There is expert consensus that abnormal uterine artery Doppler is a diagnostic criterion for early-onset FGR, while, for late-onset FGR, there was agreement between only 55% of experts and it was therefore not included as a diagnostic criterion[9,16]. While it could be speculated that uterine artery Doppler has the potential confounding characteristic of being useful both for prediction of outcome and for diagnosis, it may be argued that its prediction capacity overshadows its diagnostic performance.

Late-onset FGR has been found to be associated with a higher frequency of placental signs of maternal underperfusion[15,17], higher risk of abnormal fetal-brain Doppler indices[18] and an increased risk of adverse perinatal outcome regardless of fetal size and brain Doppler[19–22]. Therefore, in suspected late-onset small-for-gestational-age (SGA) fetuses, uterine artery Doppler has been proposed as a tool, along with cerebroplacental ratio (CPR), umbilical artery Doppler and estimated fetal weight, for the selection of cases with a higher risk of adverse perinatal outcome due to placental impairment[23,24]. Nonetheless, uterine artery Doppler has not achieved expert consensus for inclusion as a diagnostic criterion of late-onset FGR[9].

The objective of this systematic review and meta-analysis was to investigate the ability of abnormal third-trimester uterine artery Doppler to predict adverse perinatal outcome in fetuses with suspected late SGA.

METHODS

Protocol and registration

Before formal searching for articles, the study protocol was registered in the prospective international register of systematic reviews (PROSPERO: CRD42018116489). This systematic review was carried out adhering to the recommendations of the Synthesizing Evidence from Diagnostic Accuracy Test (SEDATE) guidelines[25]. The study protocol was agreed on by all authors, one of whom (A.S.) acted as an external reviewer.

Information sources and search strategy

A systematic search was performed in PubMed, ISI Web of Science and SCOPUS databases to identify relevant studies published in English, French, Spanish, Italian or German. There was no time limitation for the search. Relevant publications were searched manually for additional information. The first search was run on 3 December 2018. An update was extended until 20 July 2019. In cases of a relevant study with missing information, the corresponding author was contacted by e-mail.

In the search strategy (Appendix S1), the following terms were included: ((‘fetal growth retardation’ [MeSH Terms] OR (‘fetal’ [All Fields] AND ‘growth’ [All Fields] AND ‘retardation’ [All Fields]) OR ‘fetal growth restriction’ [All Fields]) AND small-for-gestational [All Fields]) AND ‘humans’ [MeSH Terms].

Eligibility criteria

Criteria for inclusion were according to a PIRS (Population, index test, reference standard and type of study) format for diagnostic test accuracy for meta-analyses. Population criteria were: (1) suspected SGA fetus in the third trimester, defined as estimated fetal weight below the 10th, 5th or 3rd percentile or > 2 standard deviations (SD) below the mean, or a decline of more than 1 SD between two ultrasound examinations at least 2 weeks apart, diagnosed at or after 32 weeks’ gestation; or (2) SGA neonate, defined as birth weight below the 10th percentile, diagnosed after 37 weeks’ gestation. The index test was third-trimester abnormal uterine artery Doppler measurement, defined as pulsatility index (PI) > 95th percentile or ≥ 2 SD above the mean, resistance index > 0.50, bilateral uterine artery notching or the presence of any abnormal uterine artery Doppler waveform. Reference standards (outcomes) were: (1) composite adverse perinatal outcome, according to the definition of each individual study, which commonly included any type of adverse outcome occurring in the studied population; (2) Cesarean section due to intrapartum fetal compromise (CS-IFC), according to the definition of each study; (3) need for admission to the neonatal unit; (4) 5-min Apgar score < 7; (5) neonatal acidosis, defined as umbilical artery pH < 7.1 or ≤ 7.15; and (6) perinatal death, including stillbirth and neonatal death within the first 48 h after delivery.

Observational studies (prospective or retrospective) and randomized-controlled trials were eligible for inclusion.

Exclusion criteria were: (1) cross-sectional study or case series; (2) Doppler assessment outside the third trimester of pregnancy; (3) fewer than 10 fetuses evaluated; (4) accuracy test estimates not reported or insufficient information to create 2 × 2 tables; (5) no response from corresponding author when further information was requested, or no useful information gathered from their response.

Study selection

All identified abstracts were assessed by two independent evaluators (J.C. and E.M.) who were blinded to the authorship, authors' institutions and study results. The full text of studies meeting the inclusion criteria were reviewed. A third investigator (R.M.-P.) resolved independently any disagreement between evaluators.

Data collection process and data items

The following data were extracted from included studies into a datasheet: study characteristics (author, setting, year of publication, study period, study design, prospective or retrospective data collection), patient characteristics (definition of the included population, total number of women initially included in the study, mean maternal body mass index (BMI), number of nulliparous women), how the test was carried out (gestational age at diagnosis, definition of abnormal uterine artery Doppler) and characteristics of the outcome or reference standard (among suspected SGA fetuses or SGA neonates, definition of the reference standard, gestational age at birth).

Assessment of risk of bias

Two reviewers (D.L.-S. and R.M.-P.) evaluated independently the quality of the selected studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool[26], which assesses biases affecting applicability in four domains: patient selection, index test, reference standard, and flow and timing. Risk of bias in each of these domains was categorized as low, high or unclear. The results were plotted and assessed using Review Manager (RevMan)[27].

Diagnostic accuracy measures and synthesis of results

For each study, extracted information was used to produce a 2 × 2 table for calculation of sensitivity and specificity. Obtained results were pooled in a meta-analysis and hierarchical summary receiver-operating-characteristics (hSROC) curves were constructed. Models were fitted using a bivariate Reitsma model[28] equivalent to the hSROC proposed by Rutter and Gatsonis[29,30]. Quantitative data synthesis was performed using a random-effects model, assessing the reference standards (outcomes) in suspected SGA fetuses and in SGA neonates. Results were presented using pooled sensitivity, specificity, positive (LR+) and negative (LR−) likelihood ratios and hSROC curves. Publication bias was assessed using Deeks's funnel plot asymmetry test for publication bias (inverse of the square root of the effective sample size *vs* the diagnostic log odds ratio) in case of 10 or more studies; $P < 0.05$ was considered to indicate significant asymmetry[31]. Between-study heterogeneity was assessed visually to identify outliers using Galbraith's plot (diagnostic log odds ratio against the inverse of the treatment effect)[32]. Bayesian analysis was used to calculate the posterior probability of adverse outcome given an abnormal or normal third-trimester uterine artery Doppler result in suspected SGA fetuses, based on the baseline prevalence of the outcome, converted to odds using the formula odds = risk/(1 − risk) and multiplied by the pooled LR+ and LR−, respectively. Results were then converted back to prevalence and presented using Fagan's plots.

Additional analyses were conducted to establish the association between abnormal third-trimester uterine artery Doppler and adverse outcome, using bivariate analysis in which the exposed group consisted of those cases with abnormal uterine artery Doppler and the non-exposed group consisted of those with normal uterine artery Doppler, while cases were the number of fetuses with adverse outcome in each group. The analysis was conducted using the Mantel–Haenszel method by random-effects modeling and presented as odds ratio (OR) for each outcome. Heterogeneity was assessed by I^2 and Cochran's Q. Statistical analyses were conducted using the Meta-Analysis of Diagnostic Accuracy (MADA)[33] and binary outcome meta-analysis (META) packages in R[34].

RESULTS

Study selection and study characteristics

A total of 4820 articles were identified by database searching and four additional studies through manual searching, of which 93 were eligible for full-text review. No randomized-controlled trials met the inclusion criteria. After full-text review, 17 observational studies were finally included (Figure 1). The authors provided the full database in nine studies[24,35–42]. The characteristics of the included and excluded articles are described in Tables S1 and S2, respectively.

Risk of bias in included studies

Of the 17 included studies, six[18,21,40,41,43,44] presented a high risk of bias in the reference standard because the diagnosis and management of suspected SGA and SGA were made with knowledge of a previous abnormal uterine artery Doppler result. Three more had unclear risk of bias in the same category[20,36,38] and one had unclear risk of bias in patient selection[42]. The rest of the studies had low risk of bias in all categories[22,24,37,39,45–47]. Figures S1 and S2 show risk of bias in the included studies, according to the QUADAS-2 tool for diagnostic test accuracy reviews.

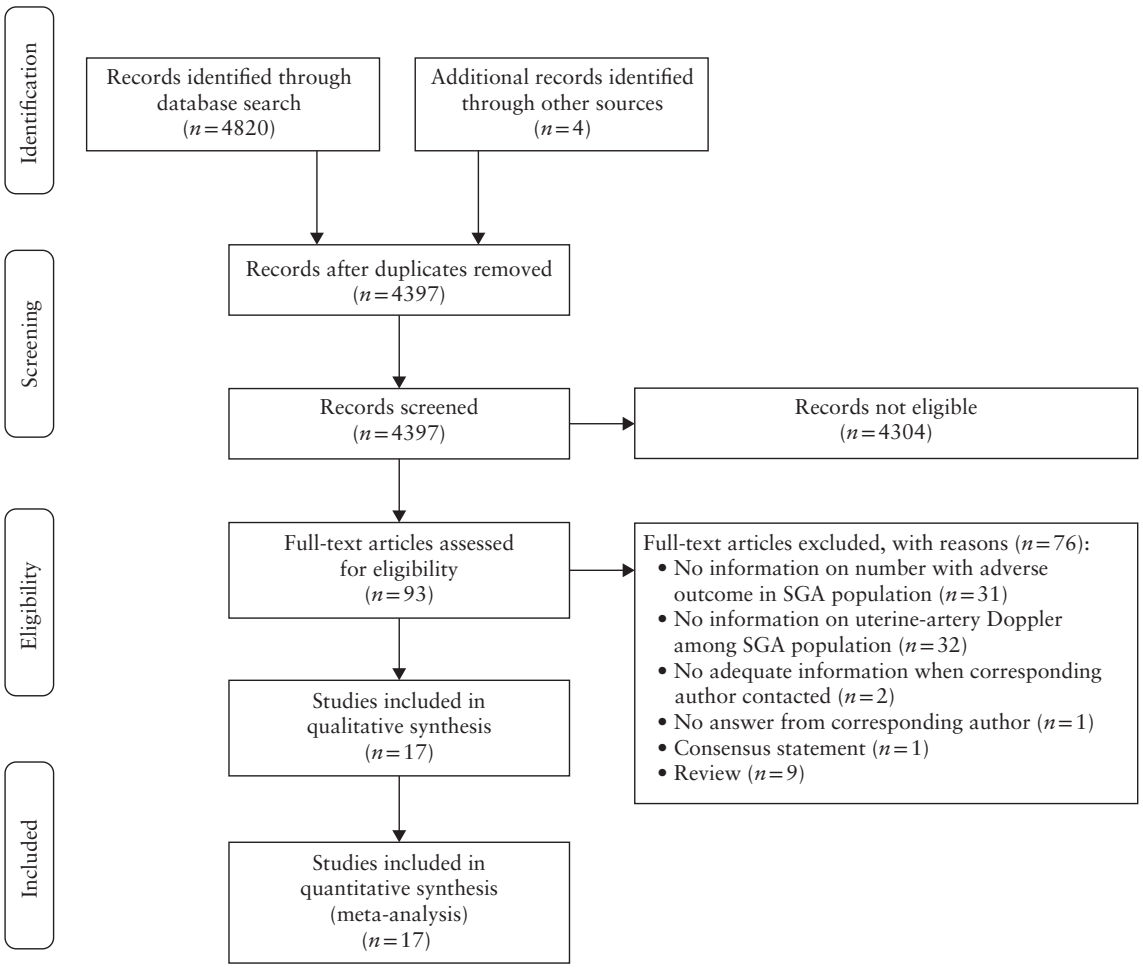

Figure 1 Flowchart summarizing inclusion of studies evaluating performance of abnormal third-trimester uterine artery Doppler for prediction of adverse perinatal outcome in late small-for-gestational-age (SGA) fetuses and neonates.

Synthesis of results

The 17 included studies comprised 41 492 women, including 7552 fetuses that either were diagnosed with suspected SGA ($n = 3461$) or were later classified as a SGA neonate ($n = 4091$). Mean gestational age at ultrasound assessment was 34.3 (range 32.3–38.6) weeks of gestation. There were 1302 instances of abnormal uterine artery Doppler, of which 777 (21.7%) were in suspected SGA fetuses and 525 (11.2%) were in fetuses that were later classified as a SGA neonate. Mean maternal age at evaluation was 32.2 (SD 1.3) years and mean maternal BMI was 23.4 (SD 1.7) kg/m^2. Among studies evaluating suspected SGA[18,21,22,24,36–42,44–47] (numbers are not mutually exclusive), 28% (460/1641) of cases had composite adverse perinatal outcome, 25.9% (555/2147) required admission to the neonatal unit, 17% (187/1102) had CS-IFC, 1.7% (12/725) had 5-min Apgar score < 7, 6.1% (78/1279) had neonatal acidosis and 2.7% (5/185) had perinatal death. Among studies evaluating SGA neonates[20,36,38,39,41–43] (numbers are not mutually exclusive), 29.7% (265/891) of cases had composite adverse perinatal outcome, 18.6% (165/888) required admission to the neonatal unit, 12.5% (465/3727) had CS-IFC, 1.8% (65/3540) had 5-min Apgar score < 7, 3.5% (83/2372) had neonatal acidosis and 0.7% (26/3562) had perinatal death.

Uterine artery Doppler for prediction of adverse perinatal outcome in suspected small-for-gestational-age fetuses

Information on the prediction of any composite of adverse perinatal outcome by abnormal uterine artery Doppler was available in eight studies[24,36,37,39–42,47]; pooled sensitivity and specificity were 46% (95% CI, 37.4–54.9%) and 83.2% (95% CI, 75.4–88.9%), respectively. Among eight studies[18,21,22,36,38,39,41,46], pooled sensitivity and specificity for neonatal unit admission were 44.9% (95% CI, 34.2–56.1%) and 83.4% (95% CI, 76.4–88.6%), respectively. Among five studies[18,39,41,42,44], pooled sensitivity and specificity for CS-IFC were 34.6% (95% CI, 23.7–47.4%) and 79.8% (95% CI, 74.3–84.4%), respectively. Among three studies[36,41,42], pooled sensitivity and specificity for 5-min

Apgar score < 7 were 54.0% (95% CI, 26.1–79.6%) and 74.2% (95% CI, 63.0–82.9%), respectively. Among six studies[18,36,39,41,42,44], pooled sensitivity and specificity for neonatal acidosis were 35% (95% CI, 19.3–54.7%) and 77.3% (95% CI, 72.7–81.3%), respectively. Only one study[45] had information on perinatal mortality among suspected SGA fetuses; pooled sensitivity and specificity were 40.0% (95% CI, 10.0–80.0%) and 97.2% (95% CI, 93.5–98.8%), respectively. The hSROC for each adverse perinatal outcome in suspected SGA fetuses is shown in Figure 2a. Table 1 shows the predictive performance parameters for each adverse perinatal outcome in suspected SGA fetuses.

Uterine artery Doppler for prediction of adverse perinatal outcome in small-for-gestational-age neonates

Seven studies[20,36,38,39,41–43] had information on the prediction of adverse perinatal outcome by abnormal uterine artery Doppler in fetuses that were later classified as a SGA neonate. From these, four studies had information on the prediction of composite adverse perinatal outcome[36,39,41,42]. Pooled area under the SROC curve, sensitivity, specificity, +LR and −LR for this outcome were 80.6, 33.8% (95% CI, 24.7–47.2%), 84.1% (95% CI, 80.7–87%), 2.14 (95% CI, 1.64–2.70) and 0.79 (95% CI, 0.69–0.88), respectively. Detection rates

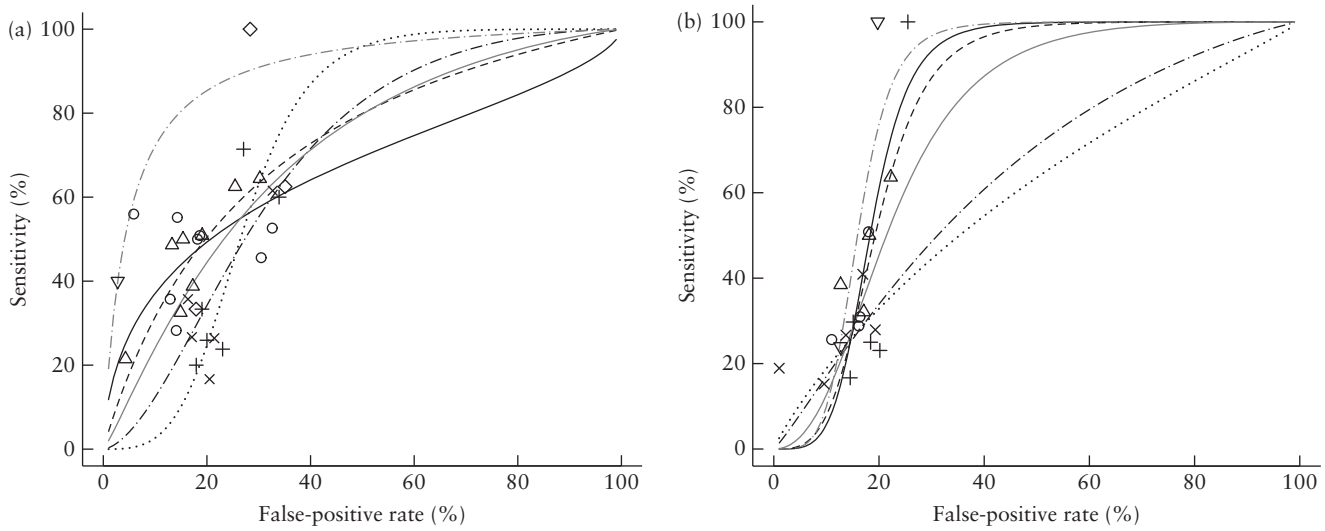

Figure 2 Hierarchical summary receiver-operating-characteristics curves for abnormal third-trimester uterine artery Doppler in prediction of composite adverse perinatal outcome (——, ○), neonatal unit admission (– – –, △), neonatal acidosis (·····, +), Cesarean section for intrapartum fetal compromise (–·–, ×), 5-min Apgar score < 7 (——, ◇) and perinatal mortality (–·–, ▽) in suspected late small-for-gestational-age (SGA) fetuses (a) and SGA neonates (b).

Table 1 Performance of abnormal third-trimester uterine artery Doppler for prediction of adverse perinatal outcome in suspected late small-for-gestational-age (SGA) fetuses and SGA neonates

Outcome	*Studies* (n)	*Cases* (n)	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR−*	*DR (%) at:* *25% FPR*	*50% FPR*
Suspected SGA fetus									
Composite adverse perinatal outcome	8	1641	0.658	46.0 (37.4–54.9)	83.2 (75.4–88.9)	2.82 (1.87–4.1)	0.65 (0.55–0.76)	54	69
NU admission	8	2147	0.715	44.9 (34.2–56.1)	83.4 (76.4–88.6)	2.71 (2.26–3.23)	0.66 (0.58–0.74)	57	80
CS-IFC	5	1102	0.686	34.6 (23.7–47.4)	79.8 (74.3–84.4)	1.48 (1.04–1.98)	0.88 (0.75–0.99)	45	83
5-min Apgar score < 7	3	725	0.698	54.0 (26.1–79.6)	74.2 (63.0–82.9)	1.92 (1.15–2.75)	0.69 (0.43–0.95)	53	80
Neonatal acidosis	6	1279	0.719	35.0 (19.3–54.7)	77.3 (72.7–81.3)	1.55 (1.02–2.11)	0.83 (0.65–0.99)	44	96
Perinatal mortality	1	185	0.895	40.0 (10.0–80.0)	97.2 (93.5–98.8)	16.50 (3.80–38.10)	0.60 (0.26–0.90)	89	96
SGA neonate									
Composite adverse perinatal outcome	4	891	0.806	33.8 (24.7–47.2)	84.1 (80.7–87.0)	2.14 (1.64–2.70)	0.79 (0.69–0.88)	83	100
NU admission	4	888	0.792	43.1 (31.5–55.4)	82.1 (78.6–85.1)	2.41 (1.88–2.98)	0.69 (0.57–0.81)	75	99
CS-IFC	5	3727	0.633	22.5 (15.5–31.5)	86.9 (81.9–90.6)	1.72 (1.43–2.04)	0.89 (0.83–0.94)	42	71
5-min Apgar score < 7	4	3540	0.756	41.6 (22.8–63.2)	81.1 (75.4–85.7)	2.19 (1.54–2.84)	0.71 (0.52–0.89)	61	94
Neonatal acidosis	5	2372	0.591	30.9 (21.1–42.9)	81.5 (77.6–85.1)	1.69 (1.23–2.21)	0.85 (0.73–0.95)	39	64
Perinatal mortality	2	3562	0.831	44.5 (13.2–80.8)	84.8 (79.6–88.9)	2.86 (1.34–4.22)	0.64 (0.29–0.95)	91	100

Values in parentheses are 95% CI. AUC, area under the receiver-operating-characteristics curve; CS-IFC, Cesarean section for intrapartum fetal compromise; DR, detection rate; FPR, false-positive rate; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NU, neonatal unit.

at false-positive rate of 25% and 50% were 83% and 100%, respectively. The hSROC for each adverse perinatal outcome among SGA neonates is shown in Figure 2b. Table 1 shows the predictive performance parameters for each adverse perinatal outcome in SGA neonates.

Posterior risks of adverse perinatal outcome in suspected small-for-gestational-age fetuses

The posterior probability of each adverse perinatal outcome following a normal or abnormal uterine artery Doppler result was calculated based on the prior prevalence of each adverse outcome multiplied by the positive and negative likelihood ratios of an abnormal uterine artery Doppler result, respectively, in the suspected SGA population. Fetuses classified as suspected SGA had a prior risk of any composite of adverse perinatal outcome, neonatal unit admission, CS-IFC, 5-min Apgar score < 7, neonatal acidosis and perinatal death of 28%, 25.9%, 16.9%, 1.9%, 6.1% and 2.7%, respectively. An abnormal uterine artery Doppler finding increased the corresponding risks to 52.3%, 48.6%, 23.1%, 3.59%, 9.15% and 31.4%, respectively, while normal uterine artery Doppler assessment reduced the corresponding risks to 20.2%, 18.7%, 15.2%, 1.32%, 5.12% and 1.64%, respectively. Fagan's plots with all Bayesian calculations are shown in Figure 3.

Association between abnormal uterine artery Doppler and adverse perinatal outcome

Among the suspected SGA population, the pooled OR by random-effects modeling for any composite of adverse perinatal outcome, neonatal unit admission, CS-IFC, 5-min Apgar score < 7, neonatal acidosis and perinatal death was 4.38 (95% CI, 2.15–8.93), 4.21 (95% CI, 3.30–5.37), 2.03 (95% CI, 1.41–2.92), 3.18 (95% CI, 1.05–9.60), 1.60 (95% CI, 0.93–2.72) and 23.3 (95% CI, 3.16–172.04), respectively (Figure 4). Heterogeneity was due to true-effect and I^2 demonstrated it to be high (85%) for composite adverse outcome only, while the other outcomes showed 0% heterogeneity. No publication bias was found among studies (bias: -0.2455; $P = 0.625$).

Among SGA neonates, the pooled OR by random-effects modeling for any composite of adverse perinatal outcome, neonatal unit admission, CS-IFC, 5-min Apgar score < 7, neonatal acidosis and perinatal death was 2.77 (95% CI, 1.87–4.11), 3.45 (95% CI, 2.22–5.36), 2.61 (95% CI, 1.41–4.86), 2.32 (95% CI, 1.32–4.07), 2.02 (95% CI, 1.13–3.62) and 2.58 (95% CI, 1.09–6.11), respectively (Figure 5). Heterogeneity was due to random-sampling and I^2 ranged from 0% to 64%. No publication bias was found among studies (bias: 0.9375; $P = 0126$).

DISCUSSION

This study shows that late SGA babies with abnormal uterine artery Doppler in the third trimester have a 2- to 3-fold increased risk of adverse outcome, and that the predictive performance is only moderate and similar to that reported for other parameters used to differentiate constitutional smallness from FGR.

Pathophysiological issues

About a third of pregnancies with abnormal third-trimester uterine artery Doppler have lower values at the beginning of pregnancy, and this group still has an exceedingly high incidence of placenta-related diseases[15,48]. This suggests that uterine artery Doppler has the potential advantage of capturing placental insufficiency with differing pathways: that resulting from defective trophoblastic invasion early in pregnancy, as well as that emerging late in pregnancy and most likely related to other pathological mechanisms[15]. Interestingly, women who demonstrated a *de novo* rise in third-trimester uterine artery PI are more likely to deliver a SGA neonate and to present with significantly higher umbilical artery PI, lower middle cerebral artery PI and lower CPR[48]. As CPR reflects the hemodynamic changes in the fetal side and uterine artery Doppler those in the maternal side, it could be assumed that they are biologically independent. Indeed, in late-onset FGR, specific placental lesions (mainly related to vascular placental malperfusion) have been found to be associated more frequently with abnormal uterine artery Doppler than with abnormal brain Doppler[17].

Another alternative hypothesis is that new-onset abnormal uterine artery Doppler is the result of maternal cardiovascular maladaptation, which has been suggested to be a pathophysiological pathway involved in late-onset placental insufficiency[49].

Clinical implications

While FGR and SGA are clearly distinct conditions conceptually, from a clinical point of view, their differentiation is challenging; not all small babies are growth restricted and, vice versa, not all growth restricted babies are small. There has been an effort by the academic and scientific community to reach consensus on the qualifying criteria for FGR[9]. Among these criteria is uterine artery Doppler, which reflects placental insufficiency from the maternal side and has good agreement among experts in early- but not in late-onset SGA. Overall, the results of this meta-analysis show that abnormal uterine artery Doppler in suspected late-onset SGA fetuses yields a positive and negative likelihood ratio of 2.82 and 0.65, respectively, for composite adverse perinatal outcome. This translates into an increase in the risk of adverse perinatal outcome from 28% to 53.3%, while a negative (normal) result would decrease the risk to 20.2%. Similar results were reported in a recent meta-analysis[50] in which CPR yielded a positive and negative likelihood ratio for the prediction of any composite of adverse perinatal outcome of 2.5 and 0.6, respectively. This, in turn, would mean that, in a suspected late SGA population, in which the risk of adverse outcome

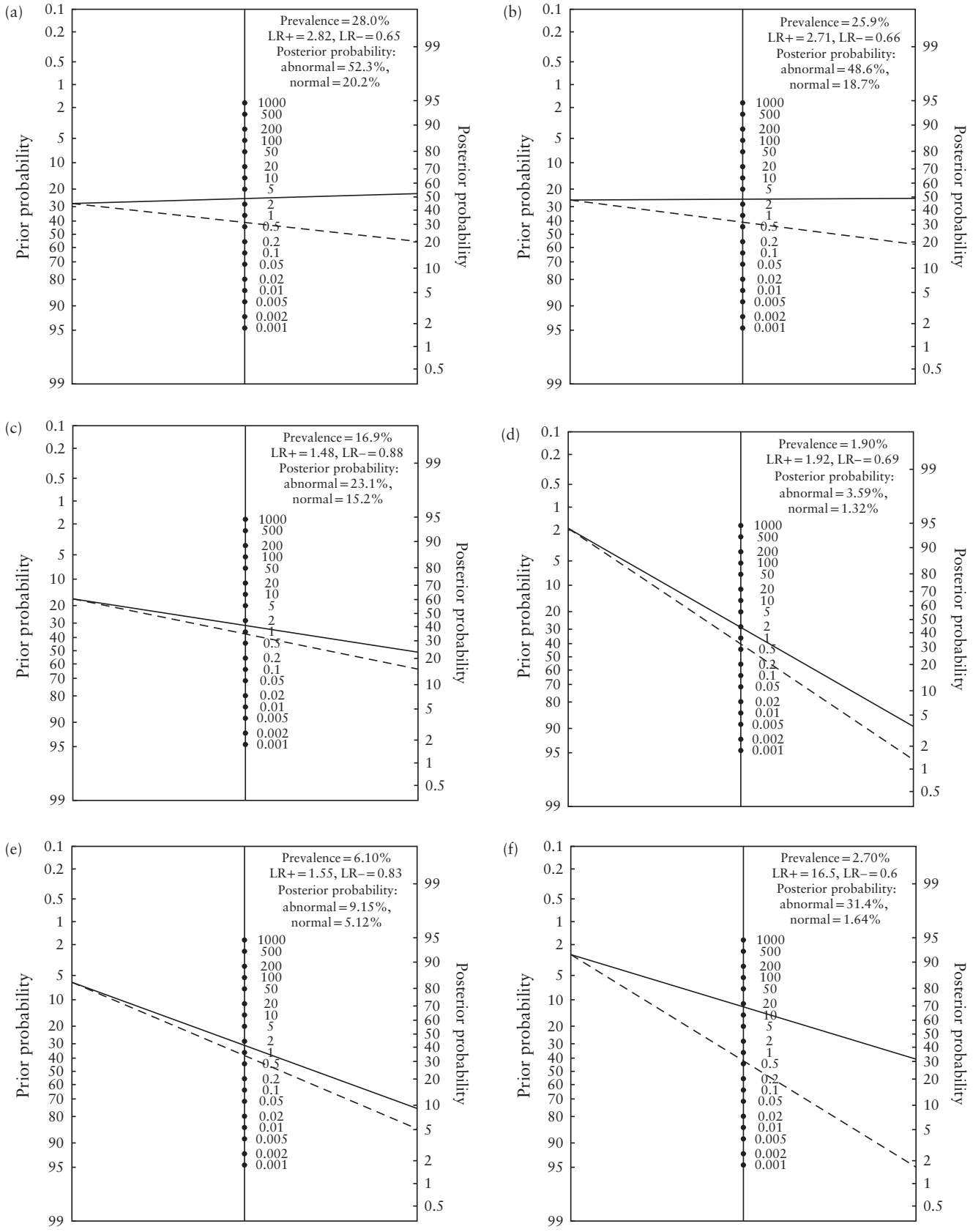

Figure 3 Fagan's plots showing posterior risk of composite adverse perinatal outcome (a), neonatal unit admission (b), Cesarean section for intrapartum fetal compromise (c), 5-min Apgar score < 7 (d), neonatal acidosis (e) and perinatal mortality (f) in suspected late small-for-gestational-age fetuses following abnormal (——) and normal (- - -) third-trimester uterine artery Doppler result. Posterior risk calculated based on prevalence of each outcome multiplied by positive (LR+) or negative (LR−) likelihood ratio of abnormal uterine artery Doppler result.

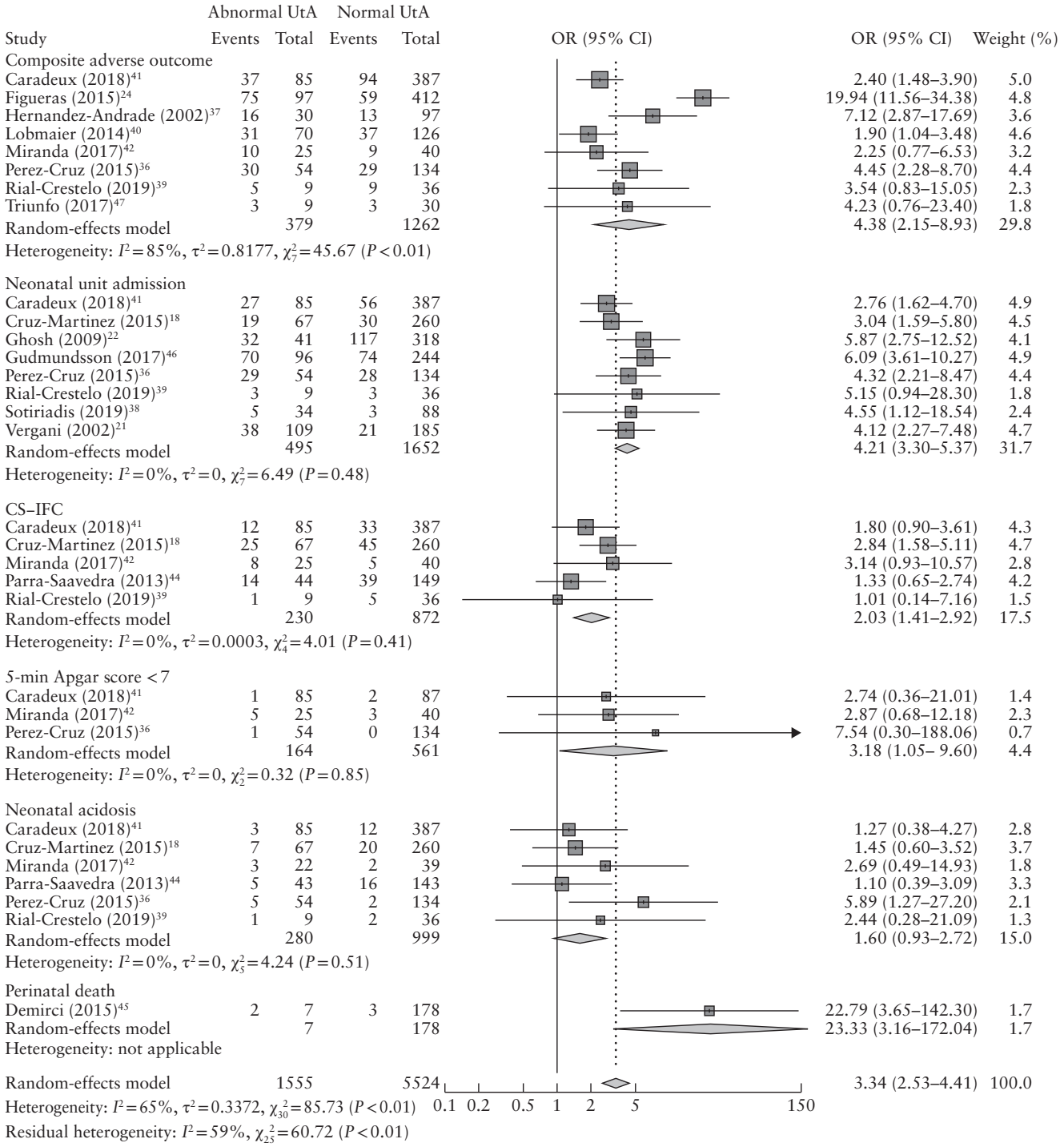

Figure 4 Forest plots showing odds ratios (OR) for association between abnormal third-trimester uterine artery (UtA) Doppler and adverse perinatal outcome in suspected late small-for-gestational-age fetuses. First author only is shown for references.

is 28%, abnormal CPR would increase the risk of adverse outcome to 49%, while normal CPR would decrease it to 18.2%.

The DIGITAT trial compared neonatal and pregnancy outcomes in suspected late-onset SGA pregnancies undergoing systematic labor induction at ≥ 37 weeks with those managed expectantly[51]. Although the study found no differences between the strategies, the findings have been translated into most guidelines as a recommendation to induce labor at term, under the rationale that labor induction has the potential to prevent some instances of adverse outcome[52]. Thus, given that labor induction has been set as the default management strategy, the clinical challenge now is to identify those pregnancies in which expectant management would be safe. In this context, a test (or combination of tests) with good ruling-out capacity would be more meaningful. An observational study[23] compared systematic *vs* selective induction in late SGA based on Doppler parameters (including uterine artery Doppler), smallness severity (< 3rd centile),

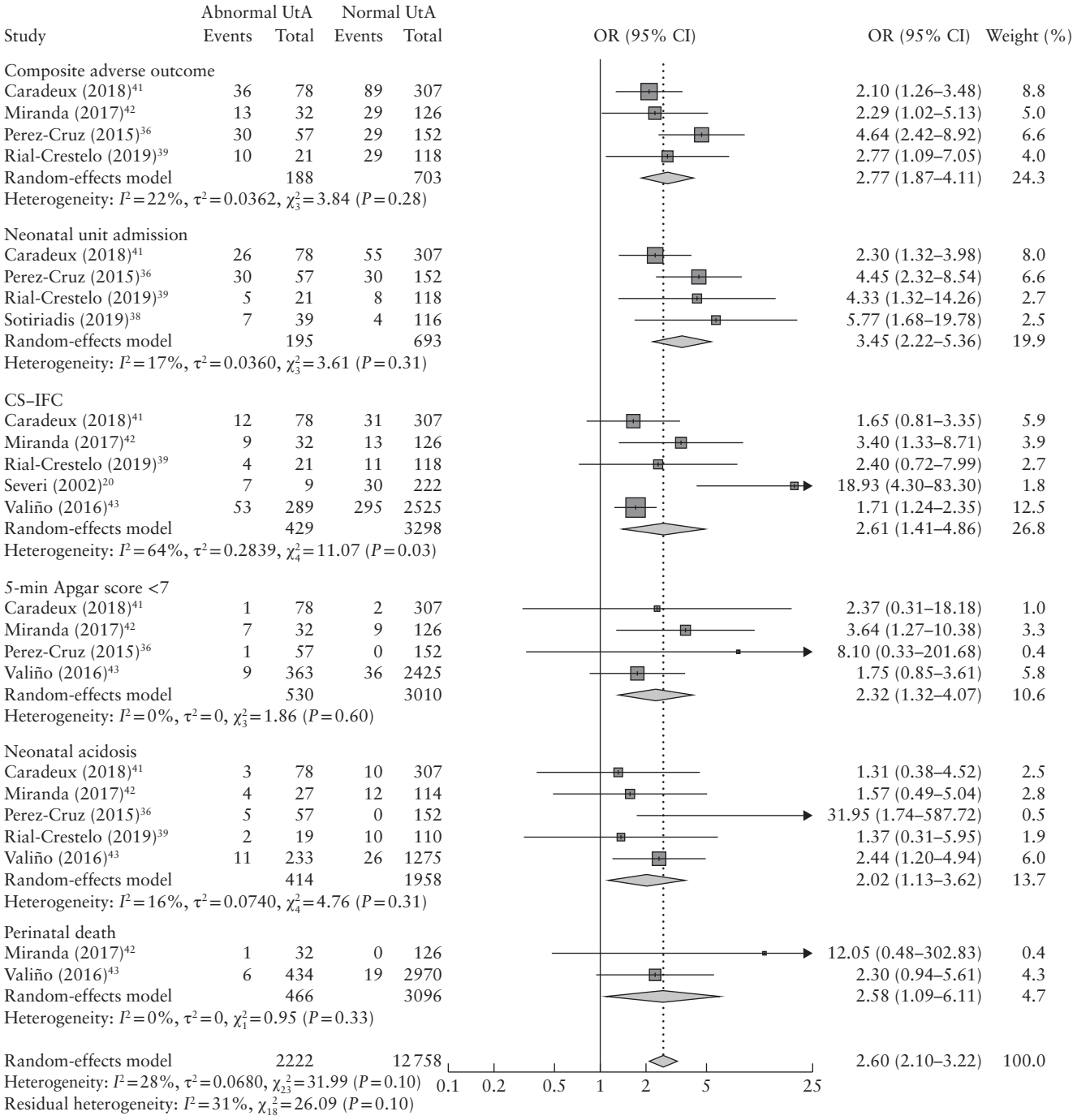

Figure 5 Forest plots showing odds ratios (OR) for association between abnormal third-trimester uterine artery (UtA) Doppler and adverse perinatal outcome in small-for-gestational-age neonates. First author only is shown for references.

hypertension and first-trimester biochemical markers of placental dysfunction. It was found that selective induction was associated with an improvement in a number of neonatal outcomes (admission to the neonatal unit, need for assisted ventilation and any composite of adverse perinatal outcome). Although one-third of the babies had abnormal uterine artery Doppler, the results were not stratified according to criteria for FGR. These results suggest that, at least when all clinical criteria are normal, expectant management beyond 37 weeks would be safe. Thus, a combination of normal uterine artery Doppler and other normal criteria would be reassuring. Assuming independence, the negative likelihood ratios (i.e. the capacity to rule out disease) of several tests could be combined to calculate the risk of adverse outcome given normal test results. For example, using our findings, if the baseline risk of adverse outcome in suspected SGA is 28%, normal uterine artery Doppler assessment would decrease the risk of adverse outcome to 19.4%, which is similarly the case for normal CPR (18.2%). Assuming independence of these biomarkers, whenever both are normal in the same patient, the risk would be multiplied

by both negative likelihood ratios, decreasing it from 28% to 13%.

Strengths and limitations

Our analysis has several strengths. First, we carried out an extensive and systematic literature search. Second, the 17 included studies collectively enrolled a notable number of suspected SGA fetuses ($n = 3461$) among a large number of ultrasound evaluations ($n = 41\,492$). Third, the study protocol was prospectively designed and registered with PROSPERO to reduce the risk of reporting bias. Finally, the Bayesian approach used in the analysis allowed us to translate the effect sizes into clinically meaningful risks of adverse events. Nonetheless, we acknowledge some limitations. First, due to the study design, our results are applicable only to late SGA (≥ 32 weeks). Second, most of the included studies were hampered by lack of blinding of the uterine artery Doppler measurements. Third, it could be argued that the use of multiple likelihood ratios would be an inadequate approach, as they may not be totally independent from each other; for example, CPR values may also depend on uterine perfusion reflected by uterine artery Doppler. The clinical finding of Severi *et al.*[20] and others[18,35,53–55] that the association of uterine artery Doppler with adverse outcome is independent of brain Doppler makes a strong correlation between these parameters unlikely.

Conclusion

In late-onset SGA babies, abnormal uterine artery Doppler increases the risk of adverse perinatal outcome to an extent similar to that of other accepted criteria for late FGR. However, because of its limited predictive ability as a standalone test, uterine artery Doppler should be used in combination with other tests to guide clinical decisions.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Search strategy

Table S1 Characteristics of included studies

Table S2 Excluded articles and reasons for exclusion

Figure S1 Risk of bias and applicability concerns in each included study.

Figure S2 Summary of risk of bias and applicability concerns among included studies.

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Doppler uterino en el tercer trimestre para la predicción de resultados adversos en fetos pequeños para la edad gestacional: revisión sistemática y metaanálisis

RESUMEN

Objetivo Investigar la capacidad de predicción de resultados perinatales adversos del Doppler uterino anómalo en el tercer trimestre en fetos pequeños para la edad gestacional (PEG).

Métodos Se realizó una búsqueda sistemática para identificar estudios observacionales pertinentes y ensayos controlados aleatorizados que hubieran evaluado el comportamiento del Doppler uterino anómalo en el tercer trimestre para la predicción de resultados perinatales adversos en fetos con sospecha de ser PEG y en neonatos PEG. El Doppler uterino anómalo se definió como el índice de pulsatilidad de la arteria uterina >95 percentil o DE ≥2 por encima de la media, o escotadura bilateral de la arteria uterina. Se elaboraron modelos de efectos aleatorizados para la elaboración de una curva jerárquica resumen de las características operativas del receptor (ROC, por sus siglas en inglés). Se utilizó el análisis bayesiano para calcular la probabilidad a posteriori de un resultado perinatal adverso después de una evaluación de Doppler uterino anómalo o normal.

Resultados Diecisiete estudios observacionales (incluidos 7552 fetos diagnosticados como sospechosos de ser PEG (n=3461) o diagnosticados posteriormente como neonatos PEG (n=4091)) cumplieron los criterios de inclusión; ningún ensayo controlado aleatorizado cumplió los criterios de inclusión. Las curvas resumen ROC mostraron que, entre los fetos sospechosos de ser PEG, la mayor precisión predictiva del Doppler uterino anómalo en el tercer trimestre fue para la muerte perinatal y la peor fue para el resultado perinatal adverso compuesto, con áreas por debajo de las curvas resumen ROC de 0,90 y 0,66, respectivamente. Los cocientes de verosimilitud correspondientes, positivo y negativo, fueron de 16,5 y 0,6 para la mortalidad perinatal y de 2,82 y 0,65 para el resultado perinatal adverso compuesto, respectivamente. Los riesgos posteriores a una evaluación de Doppler uterino anómalo vs normal, para el resultado perinatal adverso compuesto, la admisión en la unidad de cuidados intensivos para neonatos, la cesárea por deterioro fetal durante el parto, el test de Apgar a los 5 minutos <7, la acidosis neonatal y la muerte perinatal, fueron: 52,3% vs 20,2%, 48,6% vs 18,7%, 23,1% vs 15,2%, 3,59% vs 1,32%, 9,15% vs 5,12% y 31,4% vs 1,64%, respectivamente.

Conclusión El Doppler uterino anómalo en el tercer trimestre parece ser moderadamente útil para predecir la muerte perinatal en embarazos con sospecha de ser PEG.

孕晚期子宫动脉多普勒预测晚期小胎龄胎儿不良结局：系统评价及元分析

摘要

目标：研究晚期小胎龄（SGA）胎儿的妊娠晚期子宫动脉多普勒异常对围产期不良结局的预测能力。

方法：系统检索确定相关的观察研究和随机对照试验，评估妊娠晚期子宫动脉多普勒异常表现，以预测疑似SGA胎儿和SGA新生儿围产期不良结局。子宫动脉多普勒异常定义为子宫动脉搏动指数>95%或高于平均值≥2 SD，或双侧子宫动脉切迹。通过随机效应建模方法，描绘出分层汇总受试者工作特征（ROC）曲线。根据贝叶斯分析法，计算了异常或正常子宫动脉多普勒评估后的围产期不良结局后验概率。

结果：17项观察研究（包括7552名被诊断为疑似SGA（n=3461）或后来被诊断为SGA新生儿（n=4091）的胎儿）符合纳入标准，并无随机对照试验符合纳入标准。汇总ROC曲线表明：在疑似SGA胎儿中，妊娠晚期子宫动脉多普勒异常的最佳预测准确率为围产期死亡率，最差为综合不良围产期预后，汇总ROC曲线下方面积分别为0.90和0.66。相应的围产期死亡率正负似然比分别为16.5和0.6，综合不良围产期预后分别为2.82和0.65。在子宫动脉多普勒异常与正常对比评估后，综合不良围产期预后、新生儿重症监护病房入院、剖宫产术治疗胎儿宫内窘迫、5分钟Apgar评分<7、新生儿酸中毒和围产期死亡的后发风险分别为52.3%对20.2%、48.6%对18.7%、23.1%对15.2%、3.59%对1.32%、9.15%对5.12%和31.4%对1.64%。

结论：妊娠晚期子宫动脉多普勒异常在预测疑似SGA妊娠围产期死亡方面似乎有一定的作用。