Diagnostic performance of third-trimester ultrasound for the prediction of late-onset fetal growth restriction: a systematic review and meta-analysis

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OBJECTIVE: The objective of the study was to establish the diagnostic performance of ultrasound screening for predicting late smallness for gestational age and/or fetal growth restriction.

DATA SOURCES: A systematic search was performed to identify relevant studies published since 2007 in English, Spanish, French, Italian, or German, using the databases PubMed, ISI Web of Science, and SCOPUS.

STUDY ELIGIBILITY CRITERIA: We used rrospective and retrospective cohort studies in low-risk or nonselected singleton pregnancies with screening ultrasound performed at ≥32 weeks of gestation.

STUDY APPRAISAL AND SYNTHESIS METHODS: The estimated fetal weight and fetal abdominal circumference were assessed as index tests for the prediction of birthweight <10th (i.e. smallness for gestational age), less than the fifth, and less than the third centile and fetal growth restriction (estimated fetal weight less than the third or estimated fetal weight <10th plus Doppler signs). Quality of the included studies was independently assessed by 2 reviewers, using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. For the meta-analysis, hierarchical summary receiver-operating characteristic curves were constructed, and quantitative data synthesis was performed using random-effects models. The sensitivity of the abdominal circumference <10th centile and estimated fetal weight <10th centile for a fixed 10% false-positive rate was derived from the corresponding hierarchical summary receiver-operating characteristic curves. Heterogeneity between studies was visually assessed using Galbraith plots, and publication bias was assessed by funnel plots and quantified by Deeks' method.

RESULTS: A total of 21 studies were included. Observed pooled sensitivities of abdominal circumference and estimated fetal weight <10th centile for birthweight <10th centile were 35% (95% confidence interval, 20—52%) and 38% (95% confidence interval, 31—46%), respectively. Observed pooled specificities were 97% (95% confidence interval, 95—98%) and 95% (95% confidence interval, 93—97%), respectively. Modeled sensitivities of abdominal circumference and estimated fetal weight <10th centile for 10% false-positive rate were 78% (95% confidence interval, 61—95%) and 54% (95% confidence interval, 46—52%), respectively. The sensitivity of estimated fetal weight <10th centile was better when aimed to fetal growth restriction than to smallness for gestational age. Meta-regression analysis showed a significant increase in sensitivity when ultrasound evaluation was performed later in pregnancy ($P = .001$).

CONCLUSION: Third-trimester abdominal circumference and estimated fetal weight perform similar in predicting smallness for gestational age. However, for a fixed 10% false-positive rate extrapolated sensitivity is higher for abdominal circumference. There is evidence of better performance when the scan is performed near term and when fetal growth restriction is the targeted condition.

Key words: abdominal circumference, birthweight, cerebroplacental ratio, estimated fetal weight, fetal Doppler, late fetal growth restriction, late small for gestational age, meta-analysis, middle cerebral artery, systematic review, third trimester, ultrasound

Growth restriction 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 nondetection of this condition has been identified as a major cause of avoidable perinatal death,[4] and growth-restricted fetuses not identified during pregnancy have increased risks of fetal death[5] and perinatal complications.[6]

Growth restriction presents as 2 clinical phenotypes characterized by different evolutions and outcomes.

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AJOG at a Glance

Why was this study conducted?

To assess the performance of third-trimester ultrasound screening for the prediction of late-onset fetal growth restriction (smallness for gestational age/fetal growth restriction [FGR]).

Key findings

Pooled data on the prediction of birthweight <10th percentile showed observed sensitivities of abdominal circumference and estimated fetal weight <10th percentile of 35% and 38%, respectively. Pooled false-positive rates were 5% and 3%, respectively. Modeled sensitivities for 10% of false-positives results were 78% and 54%, respectively. Pooled sensitivity of estimated fetal weight <10th percentile for the prediction of late FGR was 83%. A meta-regression analysis showed a significant increase in sensitivity when ultrasound evaluation was performed later in pregnancy.

What does this add to what is known?

Performance of third-trimester ultrasound screening for late-onset growth restriction seems better when based on abdominal circumference, conducted near 37 weeks of gestational age and targets true FGR.

Early-onset growth restriction (usually defined as that detected <32 weeks)[7,8] presents a typical pattern of deterioration that progresses from escalating abnormalities in Doppler parameters to abnormal biophysical parameters.[9,10] In late-onset growth restriction, there is a common pattern of normal or minimally elevated umbilical Doppler indices with mildly abnormal cerebral Doppler but without obvious cardiovascular or biophysical changes.[11,12] Unlike the early-onset condition, the association between preeclampsia and late-onset growth restriction is weak.[13]

First- or second-trimester screening with uterine Doppler velocimetry, biochemical markers (angiogenic factors), and maternal characteristics may detect early-onset growth restriction in up to 90% of cases.[14,15] Furthermore, up to 60% of these cases may be flagged by preeclampsia.[16] In contrast, growth restriction in late pregnancy is still largely overlooked,[17,18] although it accounts for the largest proportion of adverse perinatal outcomes and stillbirths.[5,19]

To date, estimates on ultrasound (US) performance for the prediction of late-onset growth restriction have been based on systematic reviews on routine US performance[20,21] that show detection rates that are in the vicinity of 50%, which challenges the value of fetal size by US as an established part of antenatal care because it could give false reassurance of normal placental function.

However, a recent review in this Journal[8] stressed that no efforts have been made to differentiate the specific performance for late-onset clinical forms or control for potential significant covariates, such as baseline risk of the population, the gestational age at scan, or the parameter used for growth assessment (abdominal circumference [AC] alone vs estimated fetal weight [EFW]).

Another gap in the current knowledge is the differential performance for late-onset smallness for gestational age (SGA) vs late-onset growth restriction. Whereas growth restriction represents a pathological condition (mainly associated with placental insufficiency[22]), SGA represents the lowest end of the size spectrum, which accounts for many cases of constitutional smallness.

The objective of this study was to conduct a systematic review and meta-analysis to establish the diagnostic performance of US third-trimester screening for the prediction of late-onset SGA and/or fetal growth restriction (FGR).

Materials and Methods

Eligibility criteria, information sources, and search strategy

A systematic search was performed using databases PubMed, ISI Web of Science, and SCOPUS to identify relevant studies published in English, Spanish, French, Italian, or German. It was limited to those studies published since 2007. References of relevant publications were manually searched for additional potentially relevant published studies. The first search was run on Dec. 5, 2017. An update was extended until May 31, 2018.

This review was carried out adhering to the recommendation of the Synthesizing Evidence from Diagnostic Accuracy Test guidelines.[23] The study protocol was agreed on by the authors, and one of them (A.S.) who was external to the group acted as a reviewer. Before running the analysis, the protocol was registered at the international Prospective Register of Systematic Reviews (CDR42017080782).

All identified abstracts were assessed by 2 independent evaluators (J.C. and R.J.M.-P.) who were blinded to the authorship, authors' institutions, and study results. Studies meeting inclusion criteria were full text reviewed. A third investigator (F.F.) independently resolved any disagreement between evaluators. In cases of relevant studies with missing information, corresponding authors were reached by e-mail. Table 1 in the Supplemental Material details the search strategy and query syntaxes.

Study selection

Criteria for inclusion in this systematic review were observational cohort studies (retrospective and prospective) in low-risk or nonselected singleton pregnancies with screening US performed at ≥32 weeks.

Data extraction

The following data were extracted on a data sheet: mean maternal age at inclusion; mean maternal body mass index; mean gestational age at US; mean gestational age at delivery; number of pregnancies with US EFW or AC below 1 SD and below the third, fifth, and 10th centile; and number of pregnancies meeting criteria for SGA defined as birthweight (BW) below the 10th, fifth, and third centiles. Additionally, we extracted information on the number of pregnancies with FGR defined by smallness plus Doppler signs of placental insufficiency.[8]

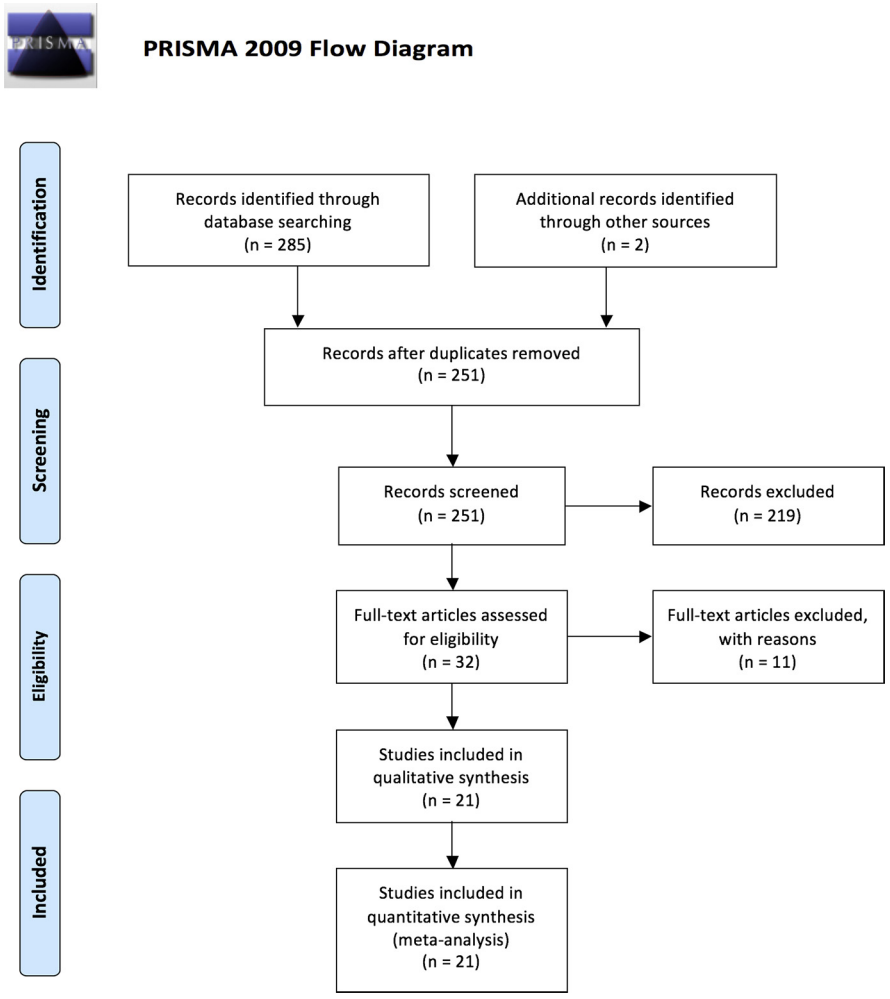
TABLE 1
Diagnostic performance of third-trimester US according to the reference and index test selected

Reference	Index test	Studies (patients)	AUC, %	Mean Se, %	Mean Sp, %	LR positive	LR negative	DOR	Se at a fixed 10% FPR, %
BW <10th centile	EFW <10th centile	13 (30,866)	79.4	38 (31–46)	95 (93–9%)	8.7 (6.2–11.8)	0.65 (0.58–0.71)	13.6 (9.2–19.0)	54
	EFW <5th centile	6 (19,841)	80.5	21 (17–26)	99 (98–99)	15.2 (10.3–21.3)	0.80 (0.76–0.84)	19.1 (12.5–27.6)	55
	EFW <3rd centile	3 (6265)	78.2	61 (47–73)	99 (98–99)	22.8 (6.1–54.2)	0.88 (0.80–0.93)	26.8 (6.6–66.4)	52
	EFW <1 SD	4 (43,556)	90.7	65 (52–77)	90 (89–93)	6.7 (5.8–7.6)	0.44 (0.32–0.56)	16.0 (10.8–22.5)	68
	AC <10th centile	6 (9592)	92.1	35 (20–52)	97 (95–98)	11.3 (7.0–16.7)	0.67 (0.53–0.80)	17.4 (9.2–29.1)	78
	AC <5th centile	2 (5865)	98.2	23 (4–67)	99 (98–100)	36.2 (18.0–55.8)	0.74 (0.40–0.95)	55.7 (19.1–119.0)	99
	AC <1 SD	3 (37,816)	87.1	49 (29–70)	93 (89–96)	6.7 (5.1–8.7)	0.55 (0.38–0.71)	12.6 (8.6–17.6)	60
BW <5th centile	EFW <10th centile	4 (7772)	79.0	39 (32–48)	95 (92–97)	7.5 (5.9–11.7)	0.63 (0.57–0.69)	13.5 (9.1–19.1)	79
	EFW <5th centile	2 (5215)	76.4	23 (19–27)	98 (98–99)	14.7 (9.7–21.1)	0.78 (0.74–0.82)	18.9 (11.8–28.3)	20
	EFW <3rd centile	2 (5215)	64.6	11 (5–22)	99 (96–100)	16.7 (2.1–51.6)	0.90 (0.81–0.97)	19.8 (2.1–63.9)	35
	EFW <1 SD	4 (43,715)	91.3	67 (52–80)	91 (89–92)	7.1 (6.0–8.2)	0.37 (0.25–0.50)	20.7 (12.0–32.6)	75
	AC <1 SD	2 (35,120)	92	59 (24–87)	93 (85–97)	8.3 (6.5–9.3)	0.45 (0.18–0.74)	21.6 (11.3–36.3)	76
BW <3rd centile	EFW <10th centile	7 (11,736)	91.4	54 (34–73)	94% (91–96%)	9.2 (5.5–13.9)	0.50 (0.32–0.67)	20.0 (8.9–37.2)	74
	EFW <5th centile	3 (6265)	91.5	33 (19–50)	98% (97–99%)	19.2 (8.8–34.6)	0.68 (0.54–0.81)	29.7 (11.2–60.5)	77
	EFW <3rd centile	3 (8018)	95.6	22 (8–48)	99% (98–100%)	30.9 (5.7–82.4)	0.78 (0.58–0.92)	46.3 (6.2–141.0)	91
	EFW <1 SD	3 (40,635)	90.8	76 (56–89)	90% (89–91%)	7.8 (6.5–8.8)	0.27 (0.14–0.44)	33.2 (14.6–62.2)	77
	AC <10th centile	3 (7084)	97.4	40 (24–59)	98% (97–99%)	21.1 (11.1–34.0)	0.61 (0.45–0.75)	37.5 (14.8–74.7)	99
	AC <1 SD	3 (37,816)	93.3	74 (45–91)	92% (89–95%)	9.0 (7.8–9.7)	0.30 (0.12–0.53)	36.0 (17.1–64.6)	85
FGR	EFW <10th centile	3 (8082)	93.0	70 (55–82)	95% (93–99%)	8.7 (6.2–11.8)	0.65 (0.58–0.71)	13.6 (9.2–19.0)	83

AC, abdominal circumference; *AUC*, area under the curve; *BW*, birthweight; *DOR*, diagnostic odds ratio; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *FPR*, false-positive rate; *LR*, likelihood ratio; *Se*, sensitivity; *Sp*, specificity; *US*, ultrasound.

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

FIGURE 1
Risk of bias summary of included studies



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Quality assessment

Two reviewers (J.C. and R.J.M.-P.) independently assessed the quality of the selected studies. Quality assessment was carried out using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool,[24] which assesses the quality of the included studies in terms of biases affecting their applicability in 4 domains: patient selection, index test, reference standard, and flow and timing.

Answers with regard to bias were categorized as low, high, or unclear risk according to the reviewer's judgment about each domain. Results from these questions were graphed and assessed using the Review Manager (RevMan) computer program (version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Statistical analysis

For each article, extracted information was used to produce a 2 × 2 table for calculation of sensitivity and specificity. Extracted results were pooled in a meta-analysis, and hierarchical summary receiver-operating characteristic (hSROC) curves were constructed. Models were fitted using a bivariate Reitsma model[25] equivalent to the hSROC proposed by Rutter and Gatsonis.[26,27] Quantitative data synthesis was performed using random effects modeling.

Outcomes (reference standards) were BW <10th, less than fifth, and less than third centiles and FGR (defined as EFW less than third centile or EFW <10th centile plus Doppler signs [cerebroplacental ratio less than fifth centile or middle cerebral artery pulsatility index less than fifth centile or mean uterine artery pulsatility index >95th centile]).

Each reference standard was assessed by EFW and AC as index tests, according the following groups: EFW <10th, less than fifth, less than third centile and <1 SD; AC <10th, less than fifth, less than third centile and <1 SD; FGR was evaluated only for EFW <10th as index test.

Results were presented as observed pooled sensitivity, specificity, and positive and negative likelihood ratios (LRs). Diagnostic odds ratios (DORs, positive LR/negative LR) were calculated to measure the global effectiveness of the diagnostic tests.

For groups with more than 10 studies,[28] publication bias was assessed using Deeks' funnel plot asymmetry tests (inverse of the square root of the effective sample size vs the diagnostic log odds ratio), in which $P < .05$ was considered as significant asymmetry.[29] Between-study heterogeneity was visually assessed using Galbraith plot (diagnostic log odds ratio against the inverse of the treatment effect) to visually identify outliers.[30]

Meta-regression (weighted linear regression) analyses was performed to assess the effect of mean gestational age at US on the performance of third trimester US (either EFW or AC <10th centile for BW <10th centile). Meta-regression was also used to compare the pooled effect sizes (sensitivity, specificity) of AC <10th vs EFW <10th centile and for SGA- vs FGR-aimed studies, using them as covariates[25,31] in separate models.

Finally, we calculated the sensitivity of the 2 indices (EFW or AC <10th centile) for a fixed 10% false-positive rate (FPR), according to the corresponding hSROCs of the 2 indices.

All statistical analyses were conducted using the Meta-Analysis of Diagnostic Accuracy[25–27] package [R project], MIDAS,[32] and METANDI[33] from STATA, version 13.2 (2013. Stata Statistical Software, release 13; StataCorp LP, College Station, TX).

Results

Study selection and study characteristics

A total of 285 studies were identified by database searching, with 2 additional studies included manually. Of them, 32 studies were eligible for full-text review. After review, 21 studies were retained.[34–54] Figure 1 depicts the review flow diagram.

The following authors were reached, and they provided aggregated data on their published studies: Skråstad et al,[55] Souka et al,[34] Sovio et al,[35] Hammad et al,[44] Sokol et al,[48] Simcox et al,[47] Caradeux et al,[49] Miranda et al,[41] Basuki et al,[51] Rial et al,[53] and Sotiriadis et al[54] (Table 2 in the Supplemental Material details the shared information). The characteristics of the included and excluded[55–66] articles are described in Supplemental Tables 1 and 2.

Risk of bias of the included studies

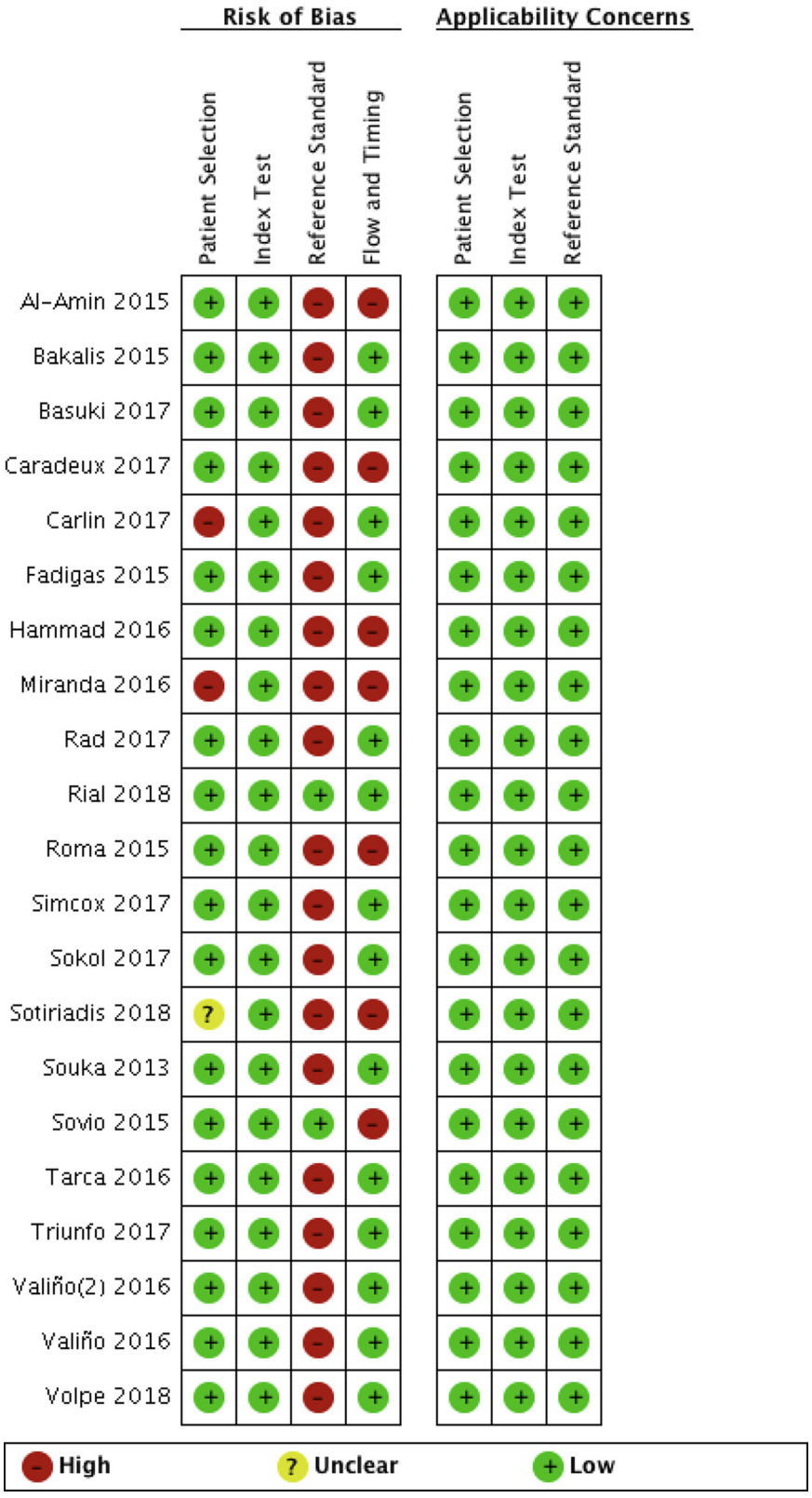
Among the 21 studies initially included, the authors considered high risk of bias in patient selection in 2 studies,[41,50] while 7 had high risk of bias in flow and timing.[35,38,39,41,44,49,54] Almost all studies showed high risk of bias in at least 1 item, except for Rial et al.[53] Figures 2 and 3 tabulate the risk of bias of the included studies according to the QUADAS-2 tool for diagnostic test accuracy reviews.

Synthesis of results

The 21 studies included a total of 80,663 fetuses. The total number of cases of SGA at birth was 6835 of 80,663 (disease prevalence of 8.5%). The mean maternal age was 31.2 years (SD of 3). Also, the maternal mean body mass index was 25.8 (SD of 3), while mean gestational age in the third-trimester US was 35.3 weeks (SD of 1.81) and mean gestational age at delivery was 39.6 weeks (SD of 0.6).

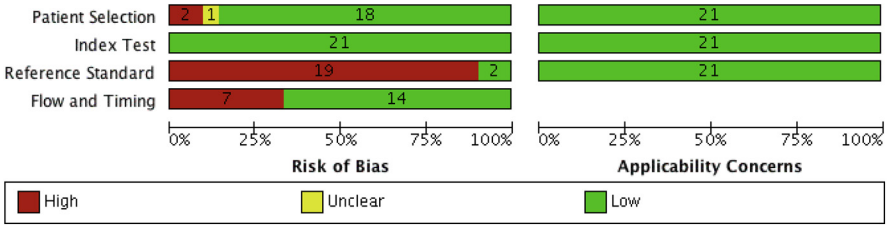
The Table summarizes the pooled diagnostic performance of US according to the reference standard and index test selected. Results on the diagnostic performance of EFW <10th centile and AC <10th centile as index tests for the prediction of a BW <10th centile as reference standard, and the performance of

FIGURE 2
Risk of bias graph of included studies



Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

FIGURE 3
PRISMA flow chart: summary of evidence search and selection



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

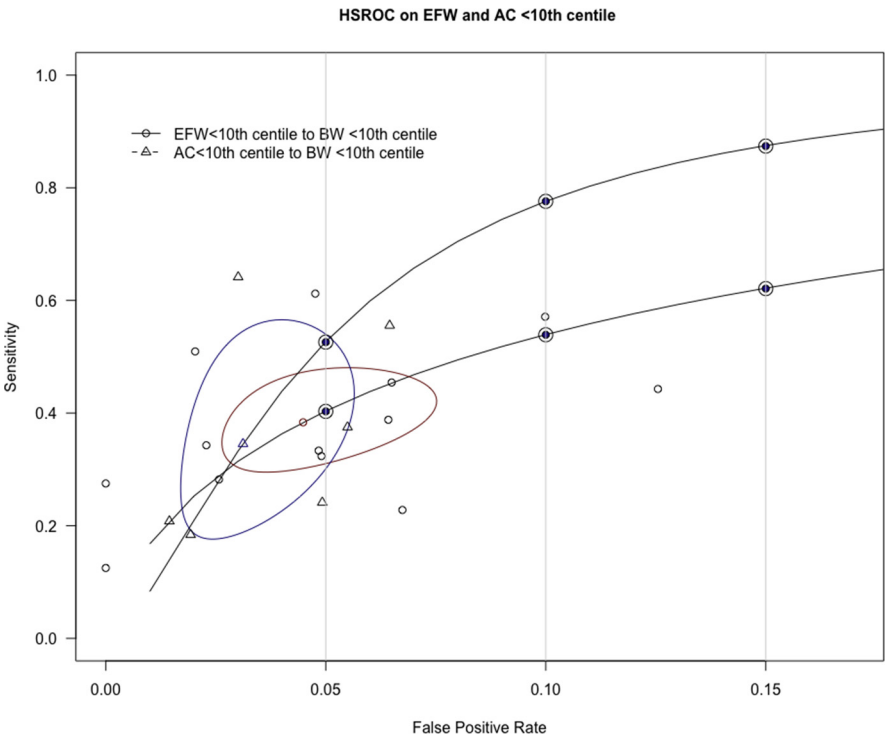
Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

EFW <10th centile for the prediction of late FGR are presented below as main text. The results for the other combinations of reference standards and index tests are presented in Annex 3 as Supplemental Material.

Birthweight below 10th centile as reference standard

EFW <10th centile as index test. A total of thirteen studies[35,38,52–54,39,41,42,44,46–48,50] had information on EFW <10th centile and BW <10th centile. The constructed hSROC curve (Figure 4) showed an area under the curve (AUC) of 79.4% with pooled sensitivity of 38% (95% confidence interval [CI], 31–46%) and a specificity of 95% (95% CI, 93–97%). The mean positive and negative LRs were 8.7 (95% CI, 6.2–11.8) and 0.65 (95% CI, 0.51–0.71), respectively, resulting in a DOR of 13.6 (95% CI, 9.2–19.0).

FIGURE 4
Diagnostic performance comparison between EFW <10th centile and AC <10th centile for the prediction of BW <10th centile



Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

Visual assessment of heterogeneity by Galbraith's plot depicted a low heterogeneity among studies, while Deeks' test found no significant publication bias (Supplemental Figure 1). Individual estimates of diagnostic performance for each study are shown in Supplemental Figure 2.

AC <10th centile as index test. Six studies[44,46,47,49,51,54] had information on AC <10th centile and BW <10th centile. The constructed hSROC curve (Figure 4) showed an AUC of 92.1%, with pooled sensitivity of 35% (95% CI, 20–52%) and specificity of 97% (95% CI, 95–98%). The mean positive and negative LRs were 11.3 (95% CI, 7.0–16.7) and 0.67 (95% CI, 0.53–0.80), respectively, resulting in a DOR of 17.4 (95% CI, 9.2–29.1).

Visual assessment of heterogeneity by Galbraith's plot depicted low heterogeneity among studies, while publication bias could not be assessed because of the small number of studies. Individual estimates of diagnostic performance for each study are shown in Supplemental Figure 3.

Late FGR as reference standard. Three studies[41,49,54] had information on EFW <10th centile as index test for the prediction of FGR. The constructed hSROC curve (Figure 5) showed an AUC of 93% with pooled sensitivity of 70% (95% CI, 55–82%) and specificity of 95% (95% CI, 93–99%). The mean positive and negative LRs were 8.7 (95% CI, 6.2–11.8) and 0.65 (95% CI, 0.58–0.71), respectively, resulting in a DOR of 13.6 (95% CI, 9.2–19.0).

Visual assessment of heterogeneity by Galbraith's plot depicted low heterogeneity among studies, while publication bias could not be assessed because of the small number of studies. Individual estimates of diagnostic performance for each study are shown in Supplemental Figure 4.

Comparison between EFW <10th centile and AC <10th centile for the prediction of BW <10th centile:

We compared AC <10th centile and EFW <10th centile for the prediction of BW <10th centile, using the index type as a covariate in a meta-regression model. No

significant effect of the index type was observed for either sensitivity (coefficient, −0.491 [95% CI, −1.22 to 0.237]; $P = .186$) or specificity (coefficient, 0.598 [95% CI, −0.226-1.423]; $P = .155$).

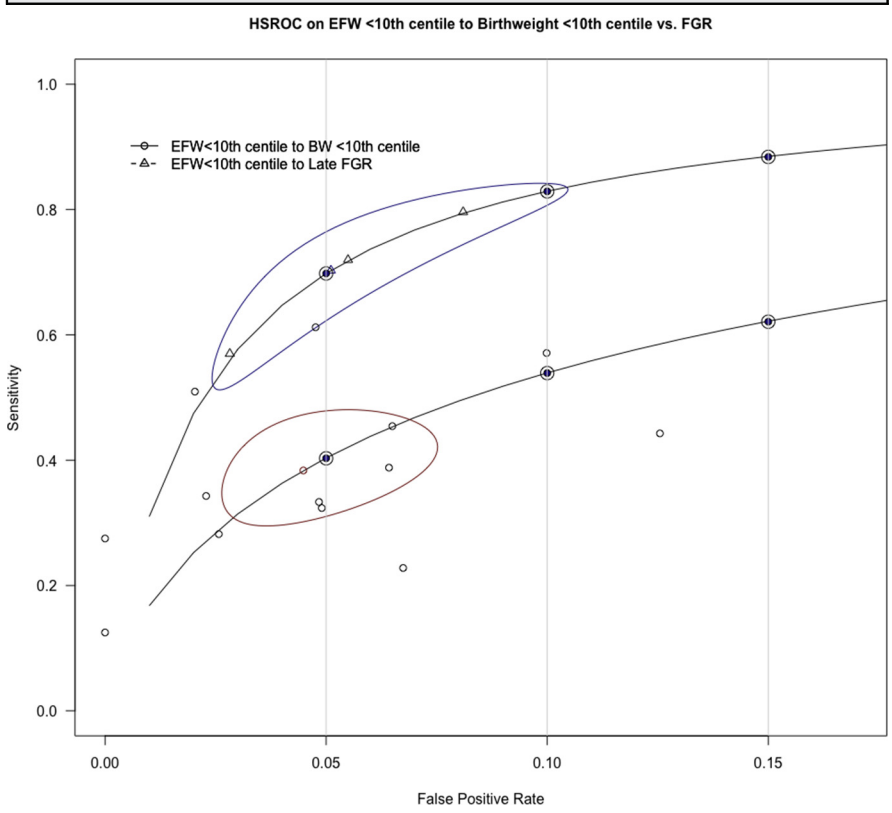
When modeling the performance of the 2 indices for 10% fixed FPR, the sensitivity of AC <10th centile was 78% (95% CI, 61−95%) against 54% (95% CI, 46−62%) of the EFW <10th centile. Figure 4 depicts both hsROC curves.

Diagnostic performance of EFW <10th centiles as index test for the prediction of BW <10th centile against FGR. Among those studies using EFW <10th as index test, we compared those aiming to FGR[41,49,54] against those aiming to SGA (BW <10th centile)[35,38,39,41,42,44,46−48,50,52−54] as standard tests in a meta-regression model. A significant effect toward better sensitivity for FGR was found (coefficient, −0.583 [95% CI, 0.168−0.998]; $P = .07$). There were no significant differences in specificity (coefficient, −0.086 [95% CI, −1.175-1.002]; $P = .867$).

For a fixed FPR of 10%, modeled sensitivity of EFW <10th for FGR (83% [95% CI, 71.3−94.5%]) was better than for SGA (BW <10th) (54% [95% CI, 46−62%]). Figure 5 displays both hSROCs of EFW <10th for the prediction of a BW <10th centile and FGR.

Influence of gestational age at scan. A meta-regression model was conducted to assess the influence of mean gestational age at US on the performance of third-trimester US (either EFW or AC <10th centile for the prediction of a BW <10th centile). Overall, we found a significant trend toward improved sensitivity when US was performed later in pregnancy (coefficient, 0.148 [95% CI, 0.066−0.229]; $P = .001$) (Figure 6), with no impact on specificity (coefficient, −0.0036 [95% CI, −0.0137 to 0.0066]; $P = .467$).

FIGURE 5
Performance of EFW for the prediction of FGR and SGA



Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

Comment

Fetal growth assessment is a cornerstone of routine prenatal care. In about 10% of pregnancies, fetal growth is lower than expected,[67] with most of these cases corresponding to constitutionally SGA, healthy fetuses. However, a fraction of these presents with a pathological growth pattern also known as FGR. This condition is associated with deficient placental function, worse perinatal outcome and higher rates of long-term cardiovascular and metabolic diseases.[68−70]

In terms of prediction, the fundamental difference is that while SGA is a neonatal outcome, FGR is a condition that could already be diagnosed prenatally, which makes it more amenable to prevention. Furthermore, as opposed to SGA, it comprises a disproportionally higher incidence of adverse outcomes. It is reassuring that our meta-analysis found a higher prediction capacity for FGR than SGA.

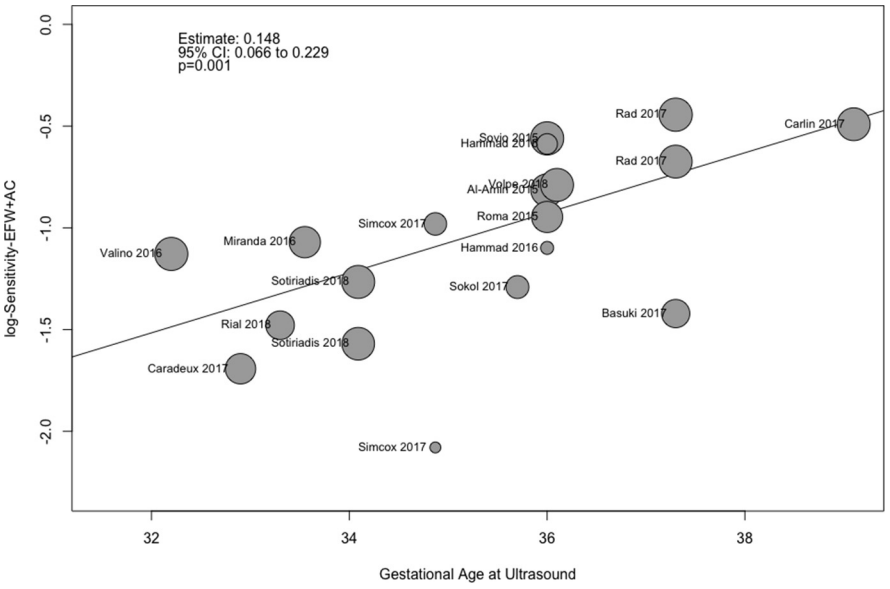
Currently there is good consensus that FGR presents as 2 clinical phenotypes (ie, early and late), characterized by different evolutions and outcomes.[7,71] In both conditions, detection failure confers increased risks of adverse perinatal outcome[6] and stillbirth.[5] This becomes especially relevant in late FGR, which is still largely overlooked.[17] Therefore, detecting late-onset FGR is central to prenatal care, and it mostly relies on cross-sectional evaluation of fetal size (usually AC or EFW).[8]

This systematic review and meta-analysis reliably depicts the overall performance of US during the third trimester for predicting late SGA and evaluates the influence of several factors that could account for the variability observed on individual studies.

EFW vs AC

To date, there is no consensus on which index test or threshold should be applied. This point was highlighted by a recent review[72] on differences across several international guidelines. As an example, the American College of Obstetricians and Gynecologists supports only the use of EFW the <10th centile, while the Royal College of Obstetricians and Gynaecologists supports the use of AC the <10th centile as an additional criterion.[73,74]

FIGURE 6
Sensitivity by gestational age at ultrasound



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A previous systematic review and meta-analysis concluded that AC has comparable diagnostic performance to EFW.[75] However, no attempt was made to differentiate the specific performance for late-onset clinical forms.

We tested for potential differences between AC <10th and EFW <10th centiles for SGA, using the 2 indices as a covariate in a meta-regression, and none of them appeared to be superior to the other. However, the wide confidence interval of the meta-regression coefficient suggests that this comparison is largely underpowered because of the small number of studies reporting on AC (n = 6).

Then we modeled the expected sensitivity for AC <10th and EFW <10th centiles for a fixed FPR of 10% based on the corresponding hSROCs and found that they would be significantly higher for AC than for EFW (78% vs 54%). However, these projections should be viewed with caution.

Both markers have theoretical advantages and disadvantages. Abdominal circumference is most strongly related to fetal nutritional status because it reflects liver size and abdominal subcutaneous fat storage and has the relatively stronger contribution to EFW calculation, so it may be the most susceptible to expected value bias. Moreover, its measurement can be technically challenging in the third trimester, especially in the presence of fetal flexion or oligohydramnios.

On the other side, EFW combines different biometric measurements (AC plus biparietal diameter, head circumference, and femur length) and may gather all the inherent measurement errors of each variable, thus resulting in an overall worse predictive performance.

On the other hand, it could be argued that EFW has some advantages over AC in most clinical settings. First, it is more consistent with the neonatal standards used to define SGA and, second, EFW accuracy can be retrospectively assessed against birthweight, whereas AC is not commonly measured by neonatologists.

Some guidelines (United Kingdom, Ireland, New Zealand, and France)[72] recommend using customized standards for growth evaluation, in which several fetal and maternal parameters are used to establish an optimal target. However, most of the widely used customized standards are based on weight rather than on individual biometrical parameters.[76] Finally, AC cannot compensate for the anatomical information provided by other planes included in the EFW, such as the head circumference, which are standard in third-trimester US.

Rather than considering EFW and AC as competing parameters, it has been proposed to combine them to better detect at-risk fetuses.[75,77] Accordingly, several international guidelines[72] define SGA on US as either an EFW <10th or an AC less than the fifth or 10th centile. However, a recent retrospective US study[78] carried out to compare this extended definition against EFW <10th centile found only a marginal improvement in the detection rate when combined (sensitivities of 78% vs 76%).

Gestational age at ultrasound

We found a significant improvement in the detection rate when ultrasound was performed later in gestation. This is consistent with the results of a previous randomized study[38] conducted in low-risk pregnancies, in which routine ultrasound examination performed at 36 weeks of gestation was more effective than at 32 weeks' gestation in detecting SGA/FGR.

A well-designed cohort study[35] in which clinicians were blinded to the ultrasound findings also reported better performance of 36 week vs 28 week scan for SGA (AUC of 88% vs 77%) and for severe SGA less than the centile, AUCs of 93% vs 82%). The same could be concluded from 2 prospective studies[36] carried out on the same population, which showed that universal screening (maternal characteristics plus EFW) performed at 30−34 weeks had a detection rate of 65%, while at 34-37 weeks, it was near 80% (10% false positives).

Overall, the results of this meta-analysis support the fact that third-trimester US screening should be conducted near 37 weeks to improve the detection of late-onset forms of SGA/FGR.

FGR vs SGA

The diagnosis of late FGR is key because a truly growth-restricted fetus and a constitutionally SGA differ fundamentally in their correlation with perinatal outcome, which also determines whether they benefit from interventions.

True FGR is a pathological condition, and it is associated with adverse sequelae, while constitutionally SGA infants tend to have significantly less severe outcomes.[71] Although conceptually FGR and SGA are clearly distinct conditions, their differentiation is rather challenging from a clinical point of view. Currently there is a published consensus that late FGR requires either severe smallness or smallness plus prenatal Doppler evidence of placental insufficiency.[7]

After an extensive literature search, we were able to identify only 3 studies[41,49,54] in which late FGR was specifically addressed. Overall, the observed pooled sensitivity of EFW <10th centile for the prediction of FGR was 70% for a 5% of false-positive results.

It is encouraging that the diagnostic performance of third-trimester screening is better when the outcome definition specifically targets true growth restriction rather than smallness as a surrogate. Complicating this scenario is the increasing recognition that a proportion of babies with BW >10th centile may in fact have had suboptimal fetal growth,[79] which could explain the low diagnostic performance shown by most of the index tests. In that sense, the next step would be to enrich the definition of FGR by incorporating other functional parameters such as placental histology or biochemical evidence of an biochemical angiogenic misbalance or other neonatal/infant measurements.[80]

References and standards

Regardless of these factors, the index test selected for antenatal screening of SGA, whether SGA at birth should be defined using customized, population-derived, or ethnic-specific standards is still a matter of discussion.[81−83] In this regard, major concerns have been raised on the risk of misdiagnosing SGA in local populations when externally derived universal standards are applied. This is beyond the scope of this systematic review and meta-analysis and constitutes an ongoing research area. Further prospective studies in different populations addressing this issue are required before a generalized recommendation can be done.

Strengths and limitations

Our analysis has several strengths. First, we carried out an extensive and systematic literature search. Second, the 21 studies collectively enrolled a notable number of SGA fetuses (n = 6835) among a large number of US evaluations (n = 80,663). Third, the study protocol was prospectively designed and registered at the international Prospective Register of Systematic Reviews to reduce the risk of reporting bias. Finally, by selecting only studies on low-risk or general populations carried out in the last 10 years, we could reliably estimate the performance in contemporary routine screening.

Nonetheless, we acknowledge some limitations. First, because of our design, our results are applicable only to late SGA (≥32 weeks). In that respect, we are unable to conclude whether the same finding on the differential performance shown by AC and EFW is also present in early SGA. Second, because of our definition of late FGR, some cases without prenatal Doppler evaluation may have been underdiagnosed. Third, most of the included studies were hampered by a lack of blinding of the index test. It could be argued that this could introduce bias because in most clinical scenarios, it is likely that clinical intervention (eg, delivery) will follow US in the limits of normality (eg, EFW or AC ∼10th centile) to prevent a BW <10th centile. We could not conduct a sensitivity analysis on studies with low risk of bias because of the fact that almost all of them reported at least 1 signaling question as high risk on the QUADAS-2 assessment.

Conclusion

In conclusion, this meta-analysis provides evidence that AC <10th centile and EFW <10th centile, as measured in clinical practice, have a similar performance for the prediction of late SGA. However, for a 10% fixed rate of false positives modeled sensitive may be better for AC than for EFW. The diagnostic performance of third-trimester screening may be better when the outcome definition specifically targets true FGR rather than SGA as a surrogate. Moreover, there is evidence of improvement of third-trimester US screening diagnostic performance when conducted near 37 weeks. ■

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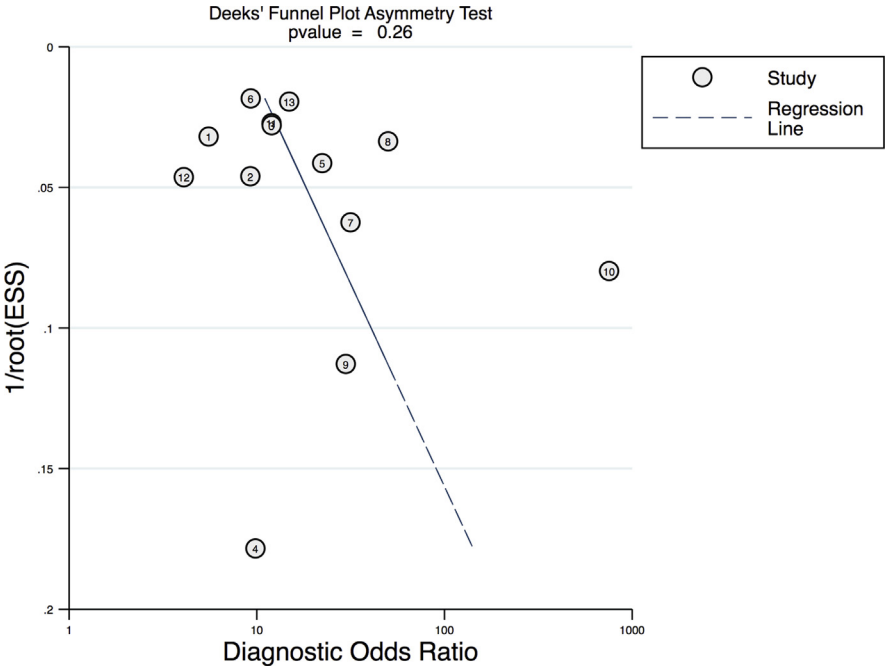
SUPPLEMENTATAL FIGURE 1

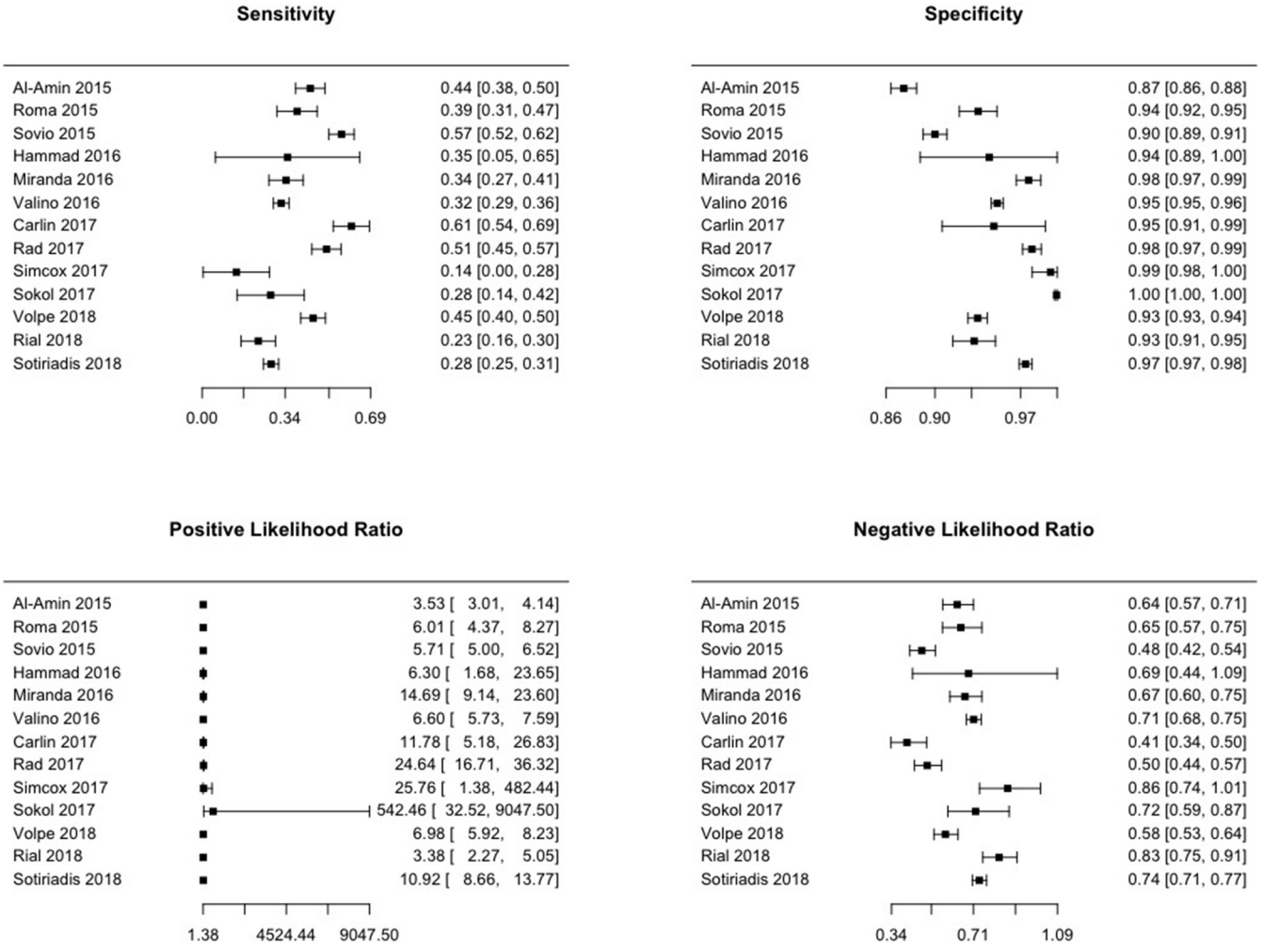
Deeks' funnel plot for publication bias for EFW <10th centile for the prediction of BW <10th centile



Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

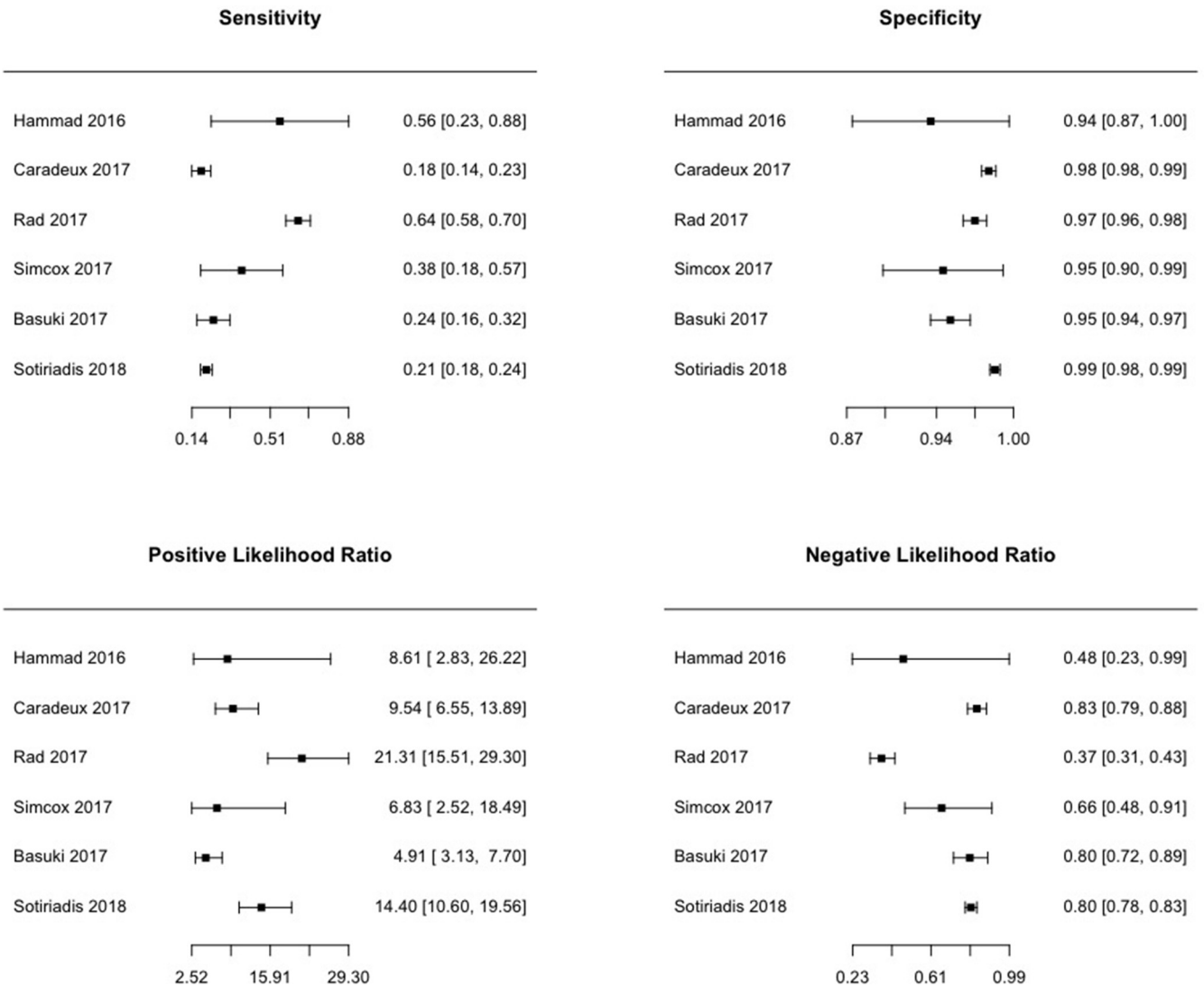
SUPPLEMENTATAL FIGURE 2

Individual estimates of each study reporting diagnostic performance of EFW <10th centile for the prediction of BW <10th centile



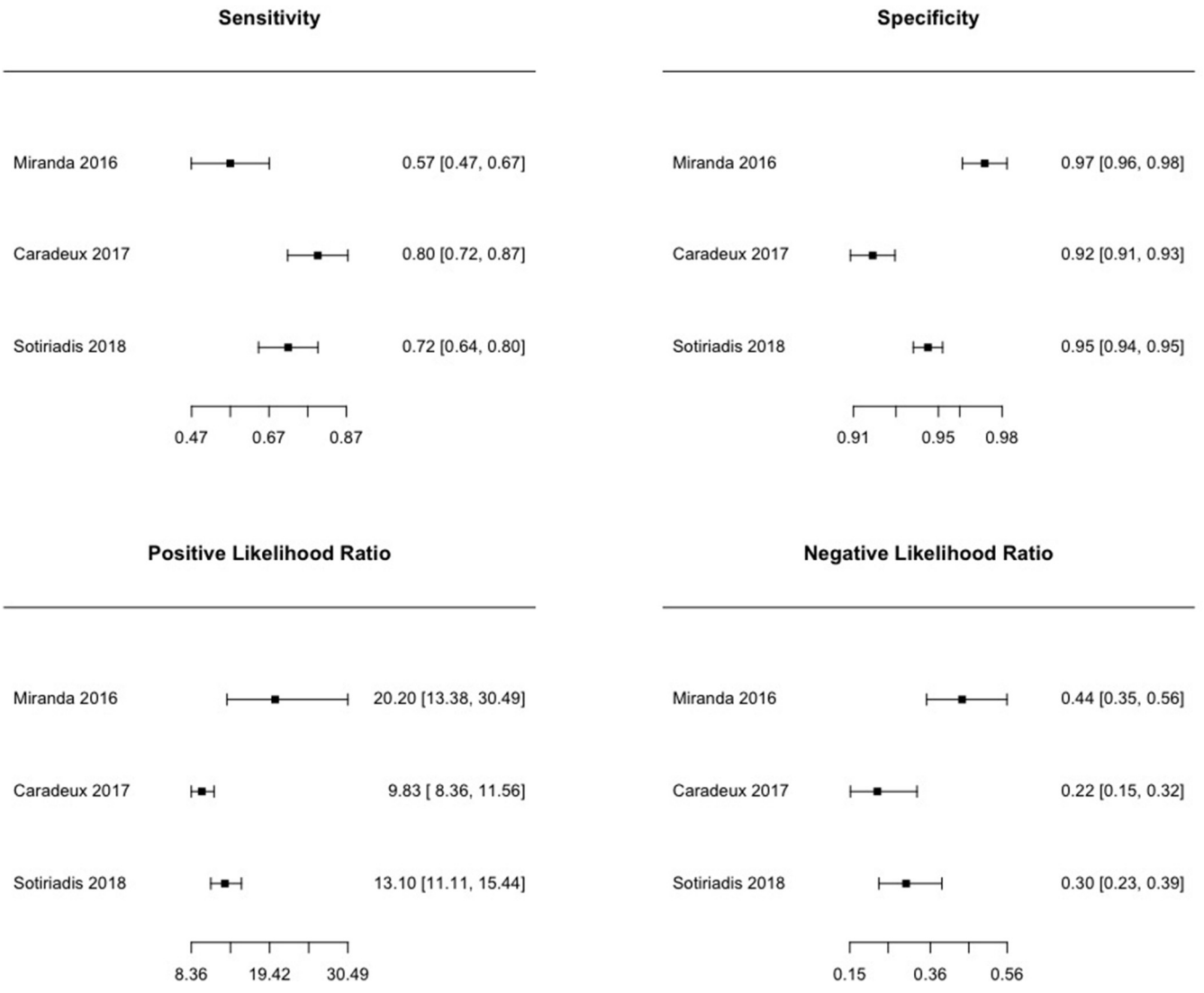
Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

SUPPLEMENTATAL FIGURE 3
Individual estimates of each study reporting diagnostic performance of AC <10th centile for the prediction of BW <10th centile



Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

SUPPLEMENTATAL FIGURE 4
Individual estimates of each study reporting diagnostic performance of EFW <10th centiles for the prediction of late FGR



Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Souka et al[34]	2013	Observational cross-sectional study	Athens, Greece	April 2006 to September 2011	Leto Maternity Hospital and from Attikon University Hospital	Uncomplicated singleton pregnancies that had a third-trimester ultrasound for fetal biometry	Hypertensive disorders of pregnancy or preeclampsia, preexisting or gestational diabetes mellitus, and a history of a previous pregnancy complicated by those conditions. Also, pregnancies with chromosomally and/or structurally abnormal fetuses, pregnancies resulting in intrauterine death and pregnancies diagnosed with severe early-onset growth restriction prior to the routine third-trimester scan.	31.7	23.1	EFW <10th centile	SGA: BW ≤5th centile	214	2288
Sovio et al[35]	2015	Prospective	Cambridge, United Kingdom	January 2008 to July 2012	Rosie Hospital	Primiparous women with a singleton pregnancy attending for their dating scan	Multiple pregnancy	30	25.1	EFW <10th centile	SGA was BW <10th percentile for sex and gestational age, calculated from a UK reference. Severe SGA (BW <3rd percentile) as a secondary outcome	352	3977

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Fadigas et al[36]	2015	Prospective	United Kingdom	February 2014 to September 2014	King's College Hospital, London, and Medway Maritime Hospital, Kent	Women attending to a screening study in singleton pregnancies at 35 −37 weeks' gestation. Resulting in live birth or the stillbirth of phenotypically normal babies	—	31.1	29.3	EFW z-score	SGA <10th: BW <10th centile SGA <5th: BW <5th centile SGA <3rd: BW <3rd centile	278	5515
Bakalis et al[37]	2015	Prospective	United Kingdom	May 2011 to April 2014	King's College Hospital, London, and Medway Maritime Hospital, Kent	Women attending for their routine hospital visit in the third trimester of pregnancy. Resulting live birth or the stillbirth of phenotypically normal babies	—	31.32	27.7	EFW z-score and AC z-score	SGA <5th: if the BW was <5th percentile after correction for gestational age at delivery	1727	30,849
Roma et al[38]	2015	Randomized controlled study	Barcelona, Spain	May 2011 to April 2014	San Joan de D'eu Hospital, Network Healthcare Manresa Foundation, Barcelona, Spain	(1) Viable singleton nonanomalous fetus; (2) pregnancy dating by ultrasound performed before 13 +6 weeks; (3) maternal age at recruitment ≥18 years; (4) absence of medical history of diabetes, autoimmune or renal diseases, hypertension or stillbirth	Women participating in another clinical trial within the previous 3 months, those unable to understand the study protocol, and those unwilling to give informed consent were excluded.	31.4	24.2	EFW <10th centile	FGR (customized BW <10th centile) and severe FGR (customized BW <3rd centile).	134	1115

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Al-Amin et al[39]	2015	Retrospective	Australia	January 2008 to January 2009 (RHH) and January 2009 to Jan 2010 (BH)	RHH and BH	Low-risk pregnancies with delivery information and antenatal fetal measurement at third trimester on medical records	All high-risk pregnancies were excluded from this research. The exclusion criteria included multiple pregnancies, type 1 diabetes mellitus, previous intrauterine growth restriction, renal failure and preeclampsia.	31.9	26.9	EFW <10th centile	SGA: below 10th percentile after weight adjustment per sex.	262	4079
Tarca et al[40]	2016	Retrospective	Detroit, Michigan	January 2009 to December 2014	Hutzel Women's Hospital (NICHD-NIH) (III)	(1) Singleton pregnancies. (2) delivery of a live neonate after 33 gestational weeks, and (3) 2 or more ultrasound examinations with fetal biometry parameters obtained at 36 weeks	Delivery prior to 33 gestational weeks, missing data about gestational age at delivery, fetal sex, and BW.	24.1	28.8	EFW z-score	SGA: BW <5th centile	144	3080

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Miranda et al[41]	2017	Prospective cohort (nested case control)	Barcelona, Spain	January 2012 to December 2014	Department of Maternal-Fetal Medicine in the Hospital Clinic of Barcelona	Singleton gestations attending between visits for their routine hospital visit in the third trimester of pregnancy	Premature rupture of membranes, chorioamnionitis, spontaneous preterm delivery, aneuploidies, or major structural abnormalities	31.1	22.8	EFW centile	SGA was defined by a BW <10th centile by local reference customized standards. Additionally, fetuses with a suspected EFWc and confirmed BW below the 10th centile and either abnormal CPR (<5th centile) or UtA-PI (>95th centile), and/or with a BW of <3rd centile according to local standards were classified as FGR	175	1050
Valiño et al[43]	2016	Prospective	United Kingdom	May 2011 to August 2014	King's College Hospital, London, and Medway Maritime Hospital, Kent	Singleton gestations attending between visits for their routine hospital visit in the third trimester (30−34 weeks) of pregnancy, with data available that resulted in the live birth or stillbirth of a phenotypically normal baby at ≥24 weeks' gestation	—	31	28.3	EFW <10th centile and EFW <5th centile	SGA: BW <10th centile	822	8268

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Valiño et al[43]	2016	Prospective	United Kingdom	February 2014 to December 2014	King's College Hospital, London, and Medway Maritime Hospital, Kent	Singleton gestations attending between visits for their routine hospital visit in the third trimester (35–37 weeks) of pregnancy, with data available that resulted in the live birth or stillbirth of a phenotypically normal baby at ≥24 weeks' gestation	—	37.7	29.4	EFW <5th centile	SGA: BW <10th centile	379	3953
Hammad et al[44]	2016	Randomized controlled study	United States	June 2012 to July 2014	Medical University of South Carolina, University of Arkansas Medical Center, and Eastern Virginia Medical School	Nonanomalous singleton, fetal anatomy ultrasound by 22weeks, and expected third-trimester care and delivery at one of the participating hospitals	High-risk pregnancies	25.6	25	EFW or AC <10th centile	FGR was defined as AC <10% for GA or EFW below 10% for GA	9	71

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Triunfo et al[45]	2017	Prospective	Barcelona, Spain	October 2014 to June 2015	Department of Maternal-Fetal Medicine in the Hospital Clinic of Barcelona	Low-risk consecutive singleton pregnancies, each referred to the Department of Maternal-Fetal Medicine in the Hospital Clinic of Barcelona for third-trimester scan at 37+1 weeks	Pregnancies with early-onset FGR (ruled out by 30–34 weeks' ultrasound EFW <10th centile, according to local standards), structural and or chromosomal anomalies, or evidence of fetal infection were excluded.	32.5	23.3	EFW centile	SGA was defined as a BW between 3rd and 10th centile, while FGR as BW <3rd centile, by customized local standards	129	946
Rad et al[46]	2017	Retrospective	Los Angeles, CA	December 2008 to May 2014	Cedars-Sinai Medical Center (III)	All singleton nonanomalous pregnancies undergoing ultrasound for fetal growth at >36 gestational weeks for any indication who delivered at our institution	Unknown or inaccurate GA dating, multiple gestations, major structural and/or chromosomal abnormalities, fetal demise, and delivery at a different institution	33.6	31	AC <10th centile	(1) SGA was defined as a BW <10th percentile for GA; (2) FGR was defined in 4 different ways: (1) AC percentile <10, (regardless of EFW); (2) EFW <10, (regardless of AC); (3) both AC and EFW <10; (4) either AC or EFW <10.	265	1594

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

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SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Simcox et al[47]	2017	Prospective (research)	Manchester, United Kingdom	November 2013 to July 2015	St Mary's Hospital (III)	Healthy uncomplicated singleton pregnancies	Fetuses subsequently shown to have a major congenital abnormality, multiple pregnancies, and maternal medical conditions known to affect fetal growth such as maternal diabetes, renal disease, and chronic hypertension	30.8	24.9	EFW centile	SGA was defined as final customized BW (IBR) <10th centile and FGR final customized BW (IBR) <3rd centile using GROW software	24	115
Sokol et al[48]	2017	Retrospective	Liverpool, United Kingdom (selective) and Zagreb, Croatia (universal)	May 2014 to February 2015	Liverpool Women's Hospital and University Hospital Centre (Petrova) Zagreb (III)	EFW <10th centile at the last third-trimester scan	Multiple pregnancy and significant chromosomal abnormalities	29.4	22.1	EFW <10th centile	SGA: BW <10th centile.	40	1006

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Caradeux et al[1]	2017	Prospective	Barcelona, Spain	January 2007 to December 2012	Department of Maternal-Fetal Medicine in the Hospital Clinic of Barcelona	Unselected consecutive singleton pregnancies	Exclusion criteria were chromosomal anomalies confirmed by genetic approaches (conventional karyotype or array-based comparative genomic hybridization); structural defects suspected at time of routine scans and confirmed postnatally; evidence of fetal infection confirmed by microbiological examination in maternal blood and/or amniotic fluid; and suspected early FGR (ultrasound EFW <10th centile, according to local standards[18]) or preeclampsia before 32 weeks	31.6	23.8	AC z-score	SGA was defined as a BW <10th centile, according to customized standards.[18] Late FGR was defined as BW <3rd centile; or <10th centile plus abnormal uterine artery Doppler (pulsatility index >95th centile[22]) or abnormal CPR (<5th centile[23]) within 1 week before delivery	210	2696

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

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SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Carlin et al[50]	2017	Prospective	Brussels, Belgium	March 2011 and May 2016	Department of Radiology and the Fetal Medicine Unit of the University Hospital Brugmann, Université Libre de Bruxelles	Women with singleton pregnancies scheduled for induction of labor or elective caesarean delivery and delivering a live born at ≥37 weeks of gestation and where both ultrasound and MR examinations were done within 48 hours before delivery	—	32	31	EFW <10th centile	BW <10th, BW <5th, and BW <3rd centiles	12	270
Basuki et al[51]	2018	Prospective	Spain	October 2014 to June 2015	BCNatal, Hospital Clinic of Barcelona	Low-risk consecutive singleton pregnancies, each referred to the Department of Maternal-Fetal Medicine in the Hospital Clinic of Barcelona for third-trimester scan at 37+1 weeks	Pregnancies with early-onset FGR (ruled out by 30−34 weeks' ultrasound EFW < 10th centile, according local standards), structural and or chromosomal anomalies, or evidence of fetal infection were excluded.	32.5	23.3	AC <10th centile	SGA was defined as a BW below the 10th centile, according to customized standards. FGR (late FGR) was defined as BW <3rd centile; or <10th centile plus abnormal abnormal UtA Doppler (PI >95th centile) or abnormal CPR (<5th centile)	116	868

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	Mean maternal age	Mean maternal BMI	Index test	SGA/FGR definition	n (SGA)	N
Volpe et al[52]	2018	Prospective	United Kingdom	September 2016 to June 2017	John Radcliffe Hospital, Oxford, United Kingdom	Unselected population of women undergoing universal third-trimester ultrasound. Singleton pregnancies	Chromosomal or major structural abnormalities. No further exclusions were made.	31.3	26.6	EFW <10th centile	Ultrasound SGA was defined as EFW <10th centile at 36 weeks; SGA at birth was defined as a BW below the sex-adjusted 10th centile.	372	4112
Rial et al[53]	2018	Prospective	Spain	January 2013 to December 2016	BCNatal, Hospital Clinic of Barcelona	Unselected population undergoing universal screening for cerebroplacental ratio and EFW at 33 weeks of gestation	Chromosomal or major structural abnormalities. No further exclusions were made.	34	23.5	EFW centile	Suspected SGA was defined as EFW below the 10th centile as BW below the 10th centile.	136	937
Sotiriadis et al[54]	2018	Retrospective	Greece	January 2014 to December 2016	Athens and Thessaloniki, Greece, and Third Department of Obstetrics and Gynecology, University of Athens, Greece	Pregnant women with singleton pregnancy, who attended first-second-, and third-trimester ultrasound scan as part of their routine antenatal care with pregnancy progressing after 32 weeks	Women with termination of pregnancy, intrauterine death and stillbirth before 32 weeks were excluded from the analysis.	31.4	24.9	EFW <10th centile	SGA: BW <10th centile	292	3228

AC, abdominal circumference; *BH*, Barwon Health; *BMI*, body mass index; *BW*, birthweight; *CPR*, cerebroplacental ratio; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *GA*, gestational age; *GROW*, Gestation-Related Optimal Weight; *IBR*, individual BW ratio; *MR*, magnetic resonance; *NICHD*, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; *NIH*, National Institutes of Health; *PI*, pulsatility index; *RHH*, Royal Hobart Hospital; *SGA*, smallness for gestational age; *UtA*, uterine artery.

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 2

Characteristics of the studies excluded with reasons

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	SGA/FGR definition	n	N	Reason for exclusion
Ben-Haroush et al[56]	2007	Retrospective	Petah Tiqva, Israel		Perinatal Division, Department of Obstetrics and Gynecology, Rabin Medical Centre, Beilinson Campus	Healthy, singleton pregnancy and ultrasound documentation of the fetal biparietal diameter, h circumference, abdominal circumference, and femur length performed at 28 and 34 weeks' gestation	None of the fetuses showed ananomaly on scanning at 14–16 or 20–22 weeks' gestation, and none of the mothers smoked or had medical or obstetric complications. Specifically, hypertensive or diabetic pregnancies were excluded.	SGA: BW <10th centile	19	259	GA at US range from 28 to 34 weeks
Souka et al[57]	2012	Observational cross-sectional study	Athens, Greece	January 2009 to July 2010	Leto Maternity Hospital and from Attikon University Hospital	Viable, singleton pregnancies with known outcomes that were delivered beyond 24 weeks	Hypertensive disorders of pregnancy, gestational diabetes mellitus and preeclampsia.Women with either a history of a previous pregnancy complicated by these conditions or a medical history of hypertension and diabetes mellitus (type 1 or type 2) were also excluded. Finally, pregnancies with chromosomal abnormalities and/or structural defects, pregnancies resulting in miscarriage or intrauterine death, and pregnancies diagnosed with severe early-onset growth restriction prior to the routine third-trimester scan were not considered in the analysis	SGA: BW at or below the 5th centile	121	2310	GA at US range from 30 to 34.8 weeks

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTAL TABLE 2

Characteristics of the studies excluded with reasons *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	SGA/FGR definition	n	N	Reason for exclusion
Skråstad et al[55]	2013	Randomized controled study	Norway	Between 1989 and 1992	National Center for Fetal Medicine in Norway	Nonselected population from a geo graphically well-defined area of 9 municipalities including and surrounding the city of Trondheim, Norway. The women were invited to participate in the study at their routine scan appointment. Inclusion was carried out before the ultrasound examination.	GA not confirmed by second-trimester ultrasound	EFW <5th centile	96	3156	SGA was defined as BW <2 SD.
DiLorenzo et al[58]	2013	Prospective	Trieste, Italy.	October 2007 to September 2009	Insitute for Maternal and Child Health—IRCCS "Burlo Garofolo" in	Women with singleton pregnancy who underwent the third-trimester ultrasound examination between 30 + 0 and 32 + 6 weeks of gestation and gave birth between 37 + 0 and 41 + 6 weeks	Major fetal abnormalities (such as aneuploidy and multiple congenital abnormality syndromes), miscarriage and termination of pregnancy. First-trimester	Moderate SGA: BW between 5th and 10th centile; severe SGA: BW <5th centile	87	1863	GA at US range from 30 to 33 weeks

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTAL TABLE 2

Characteristics of the studies excluded with reasons *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	SGA/FGR definition	n	N	Reason for exclusion
Revankar et al[59]	2014	Randomized controlled study	Belgaum, Karnataka, India	n/a (1 y)	KLES Dr Prabhakar Kore Hospital and Medical Research Center	Singleton pregnancy. Gestational age assigned by LMP and/or first trimester ultrasound and/or second-trimester anomaly scan. Normal midtrimester anomaly scan. Gestational age between 34 and 37 completed weeks.	High-risk antenatal women like gestational diabetes mellitus, cardiac disease, hypertensive disorders in pregnancy, severe anemia, intrauterine growth retardation, oligohydramnios, polyhydramnios, macrosomia, placenta previa, Rh isoimmunized pregnancy, known fetal abnormality, clinically suspected growth, liquor abnormalities, and malpresentations. Previous intrauterine fetal deaths/early neonatal death/ recurrent abortions.	EFW <10th centile	10	145	SGA: BW <2.5 kg
Stirnemann et al[60]	2014	Retrospective	French	2008–2011	Centre Europ'een de Diagnostic et d'Exploration de la Femme	Singletons delivered ≥37 weeks with known BW and gestational age at delivery	Fetal malformations, Doppler anomalies, and preterm delivery before 37 weeks were excluded.	SGA was defined by various percentile cutoffs of BW.	930	7755	GA at US range from 31 to 34 weeks
Callec et al[61]	2015	Prospective	France	2003–2006	Two universitary maternities (Nancy and Poitiers)	Women attending a prenatal visit at the Departments of Obstetrics and Gynecology of 2 French university hospitals before 24 weeks' gestation were invited to participate.	Exclusion criteria were multiple pregnancy, known diabetes mellitus, illiteracy, and intention to deliver outside the university hospital or to move outside the region within 3 years of examination	BW <10th centile	155	1897	GA at US range from 30 to 35 weeks

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTAL TABLE 2

Characteristics of the studies excluded with reasons *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	SGA/FGR definition	n	N	Reason for exclusion
Papastefanou et al[62]	2015	Retrospective	Athens, Greece	April 2006 to September 2011	"Attikon" University Hospital and Fetal Medicine Unit, Leto Maternity Hospital, Athens, Greece	Parous women with singleton pregnancies (index pregnancies) in which details of the previous delivery/ deliveries were recorded	We excluded pregnancies with chromosomally and/or structurally abnormal fetuses, pregnancies resulting in intrauterine death or pregnancies diagnosed with severe early-onset growth restriction prior to 30 weeks of gestation, and pregnancies with diabetes and hypertensive disorders.	SGA was defined as BW ≤5th centile	73	1298	GA at US range from 31.2 to 35.8 weeks
Triunfo et al[63]	2016	Prospective	Barcelona, Spain	January 2010 to December 2012	Department of Maternal—Fetal Medicine in the Hospital Clinic of Barcelona	Consecutive singleton pregnancies were recruited from those attending for routine first-trimester aneuploidy screening.	Any pregnancy with aneuploidy or major fetal abnormality and those involving termination, miscarriage or fetal death, suspected FGR (EFW)[17] <10th percentile according to local standards[18]) or preeclampsia before 32 weeks	Late FGR was defined as birth weight <3rd percentile according to local standards,[18] or 3rd—10th percentiles with prenatal abnormalities of cerebroplacental ratio (<5th percentile)[20] or UtA Doppler PI (>95th percentile),[21] with delivery from 34 weeks onward.	82	1303	GA at US range from 31.8 to 33.56 weeks

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTAL TABLE 2

Characteristics of the studies excluded with reasons *(continued)*

Author	Year	Type	Place of enrollment	Time of enrollment	Institution	Inclusion criteria	Exclusion criteria	SGA/FGR definition	n	N	Reason for exclusion
Peyronnet et al[64]	2016	Retrospective	France	January 2011 to December 2012	Louis-Mourier de Colombes	Singleton pregnancies with BW <3rd centile delivered after 32 weeks	Multiple pregnancies were excluded, as well as fetuses with antenatal-diagnosed birth defects, in utero transfers from another maternity unit, births before 32 weeks of age, fetuses that were suspected SGA before the third-trimester ultrasound, and patients who did not have an ultrasound in the third trimester.	BW <3rd centile based on Salomon et al (Salomon LJ, Bernard JP, de Stavola B, Kenward M, Ville Y. Poids et taille de naissance: courbes e' quations. J Gynecol Obstet Biol Reprod 2007;36:50–6.)	142	5451	GA at US range from 30 to 34 weeks
Sekar et al[65]	2016	Prospective	Australia	February to December 2013	The Royal Brisbane and Women's Hospital	Pregnant women with singleton pregnancies who were either booked for induction of labor or elective cesarean delivery were invited to participate in the study so that the ultrasound scan was performed within 1 week of planned delivery.	Women with multiple pregnancies and known fetal abnormalities were excluded.	EFW <10th percentile of BW for gestational age were classified as SGA	15	150	GA at US range from 38.5 to 41 weeks.
Reboul et al[66]	2017	Prospective	Quebec, Canada	May 2010 to August 2012	IRNPQEO (Integrated ResearchNetwork in Perinatology of Quebec and Eastern Ontario)	Women, recruited in the first trimester, who had complete outcome data and had undergone third-trimester ultrasound examination	Women with fetal malformation, chromosomal anomaly, or multiple pregnancy were excluded.	SGA was defined as BW <10th percentile according to Kramer BW curves	158	1805	GA at US range from 31 to 33 weeks

BMI, body mass index; *BW*, birthweight; *EFW*, estimated fetal weight; *EFWc*, Estimated fetal weight centile; *FGR*, fetal growth restriction; *GA*, gestational age; *LMP*, last menstrual period; *PI*, pulsatility index; *SGA*, smallness for gestational age; *US*, ultrasound; *UtA*, uterine artery.

Caradeux. Ultrasound performance for late-onset fetal growth restriction. Am J Obstet Gynecol 2019.