Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis

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OBJECTIVE: The objective of the study was to establish the risk of fetal death in early-onset growth-restricted fetuses with absent or reversed end-diastolic velocities in the umbilical artery or ductus venosus.

DATA SOURCES: A systematic search was performed to identify relevant studies published in English, Spanish, French, Italian, or German using the databases PubMed, ISI Web of Science, and SCOPUS, without publication time restrictions.

STUDY ELIGIBILITY CRITERIA: The study criteria included observational cohort studies and randomized controlled trials of early-onset growth-restricted fetuses (diagnosed before 34 weeks of gestation), with information on the rate of fetal death occurring before 34 weeks of gestation and absent or reversed end-diastolic velocities in the umbilical artery and/or ductus venosus.

STUDY APPRAISAL AND SYNTHESIS METHODS: For quality assessment, 2 reviewers independently assessed the risk of bias using the Newcastle-Ottawa Scale for observational studies and the Cochrane Collaboration's tool for randomized trials. For the meta-analysis, odds ratio for both fixed and random-effects models (weighting by inverse of variance) were used. Heterogeneity between studies was assessed using tau^2, $\chi 2$ (Cochrane Q), and I^2 statistics. Publication bias was assessed by a funnel plot for meta-analyses and quantified by the Egger method.

RESULTS: A total of 31 studies were included in this meta-analysis. The odds ratios for fetal death (random-effects models) were 3.59 (95% confidence interval, 2.3—5.6), 7.27 (95% confidence interval, 4.6—11.4), and 11.6 (95% confidence interval, 6.3—19.7) for growth-restricted fetuses with umbilical artery absent end-diastolic velocities, umbilical artery reversed end-diastolic velocities, and ductus venosus absent or reversed end-diastolic velocities, respectively. There was no substantial heterogeneity among studies for any of the analyses.

CONCLUSION: Early-onset growth-restricted fetuses with either umbilical artery or ductus venosus absent or reserved end-diastolic velocities are at a substantially increased risk for fetal death.

Key words: Doppler, ductus venosus, fetal death, fetal growth restriction, perinatal mortality, umbilical artery

Growth restriction is associated with an increased risk of adverse pregnancy outcomes, such as fetal death, perinatal morbidity, neonatal mortality, suboptimal neurodevelopment,[1-4] and adverse effects into adolescence and adulthood.[5] Suboptimal antenatal care for growth-restricted fetuses has been identified as a major cause of avoidable perinatal death,[6] and accordingly, growth-restricted fetuses not identified prenatally show an increased risk of fetal death,[7] and perinatal complications.[8]

In cases of early-onset growth restriction, placental insufficiency is commonly reflected in the umbilical artery waveform.[9] A smaller cross-section of the vasculature caused by such mechanisms as chronic reactive vasoconstriction of the tertiary stem villi[10] are assumed to result in upstream modifications in the flow velocity of the umbilical artery. The result is an augmented pulsatile wave-form signifying an increased impedance.

In extreme cases, this is manifested as absent or reversed end-diastolic velocity associated with critically low umbilical flow before 34 weeks of gestation.[11] These cases represent end stages of placental histological and functional damage and are associated with an increased risk of perinatal death[12] and long-term abnormal neurodevelopment.[4]

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Redistribution of the umbilical venous blood toward the ductus venosus is associated with less fetal growth,[13] and frank growth restriction is an important compensatory mechanism.[14,15] However, the pulsatile waveform of the ductus venosus blood velocity has become an important clinical indicator of hypoxic challenge in severe growth restriction.[16] An augmented atrial contraction wave that is linked to an absent or reversed end-diastolic velocity in the ductus venosus has been associated with an increased risk of perinatal mortality and neonatal morbidity.[17]

However, the single most important prognostic factor in preterm growth restriction is gestational age at delivery.[3,18] The main challenge in management of these pregnancies is timely delivery, in which the risk of fetal death has to be weighed against the risk of neonatal mortality and morbidity. Thus, fetuses are not delivered until the risk of dying in utero surpasses the risk of adverse perinatal outcome because of prematurity.[19] While the risk of neonatal mortality and severe morbidity is well documented in contemporary series on growth-restricted neonates,[3,18,20] the risk of fetal death when Doppler changes are present is still controversial.[18,20]

The objective of this study was to conduct a systematic review and meta-analysis to establish the risks of fetal death in early-onset growth-restricted fetuses with absent or reversed velocity waveforms in the umbilical artery or ductus venosus.

Materials and Methods

Eligibility criteria, information sources, 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, without publication date restriction. References of relevant publications were manually searched for additional potentially relevant published studies. The first search was run on Feb. 17, 2017. Afterward an update was extended until June 20, 2017.

This review was carried out adhering to the Meta-analysis Of Observational Studies in Epidemiology guidelines,[21] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic review and meta-analysis in randomized control trials.[22] The study protocol was agreed between the authors before running the analysis, and one author (T.K.) being external to the group, acted as a reviewer of it.

All abstracts identified were assessed by 2 independent evaluators (J.C. and R.M.), both blinded to 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. Annex 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) and randomized control trials of early-onset growth-restricted fetuses (diagnosed before 34 weeks of gestation), with information on the rate of fetal death occurring before 34 weeks of gestation and on the presence of absent or reversed end-diastolic velocity waveforms in the umbilical artery or the ductus venosus.

Data extraction

The following data were extracted on a data sheet based on Cochrane Consumers and Communication Review Group's data extraction template: countries in which the study was carried out, study period, inclusion and exclusion criteria, sample size, information on Doppler end-diastolic waveforms in the umbilical artery and ductus venosus, and the frequency of fetal death with each waveform pattern.

The risk of fetal death was analyzed for the following groups: (1) umbilical artery absent end-diastolic velocity; (2) umbilical artery reversed end-diastolic velocity; (3) umbilical artery absent or reversed end-diastolic velocity; and (4) ductus venosus absent or reversed end-diastolic velocity. Studies that for a given comparison reported no fetal death were excluded. Furthermore, instances of interruption of pregnancy cases were excluded for analysis.

Quality assessment

Two reviewers (J.C. and R.M.) independently assessed the quality of the selected studies. Quality assessment of observational studies was carried out using the Newcastle-Ottawa Scale.[23] Each study was judged on 3 dimensions: the selection of the study groups; the comparability of the groups; and the ascertainment of the exposure. The quality of randomized studies was assessed with the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials,[24] which consists of 6 questions that addresses sequence generation, allocation concealment, blinding, incomplete data, reporting bias, and other biases.

Answers with regard to bias were categorized to low risk, high risk, and unclear risk. Results from these questions were graphed and assessed using Review Manager (computer program; version 5.3, 2014, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Statistical analysis

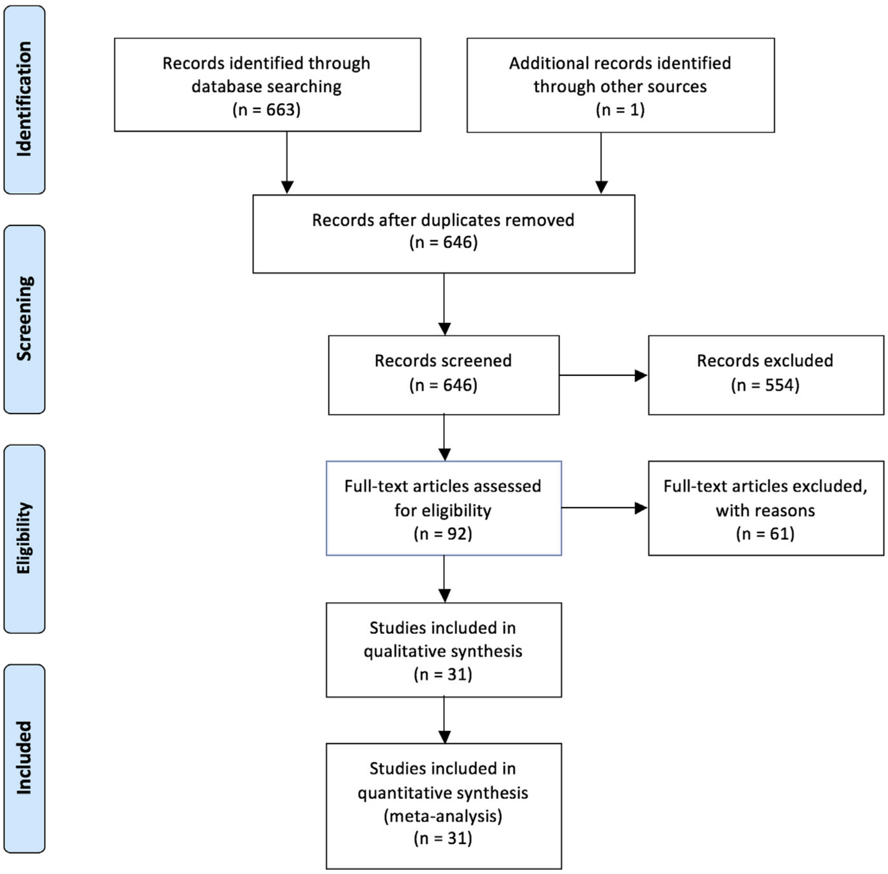
Extracted results were pooled in a meta-analysis. The meta-analysis was performed by computing odds ratios (ORs) using both fixed and random-effects models (weighting by inverse of variance). Between-study heterogeneity was assessed using tau^2, $\chi 2$ (Cochrane Q), and I^2 statistics.

According to the Cochrane handbook, the heterogeneity measured by I^2 was interpreted as nonimportant (<30%), moderate (30–60%), or substantial (>60%).[25] Results were presented using forest plots.

An influence analysis was performed to ascertain the results of the meta-analysis by excluding each of the individual studies. Publication bias was assessed by a funnel plot for meta-analysis and quantified by the Egger method.[26,27]

A meta-regression procedure of the log-OR was performed to evaluate the

FIGURE 1
PRISMA flow chart: Summary of evidence search and selection



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

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contribution of mean gestational age at delivery and mean birthweight on the association between ductus venosus absent or reversed end-diastolic velocity and fetal death.

Statistical analysis was conducted using STATA software for Mac (version 15, Stata Corp, College Station, TX) (module meta[28]) and R (version 3.1.2, The R Foundation for Statistical Computing) (package meta, version 4.2[29]).

Results

Study selection

A total of 663 studies were identified by database searching, with 1 additional study included manually. Of these, 92 studies were eligible for full-text review. After the review, 31 studies were retained for analysis (28 cohort studies[12,30-56] and 3 randomized control trials[20,57,58]). Figure 1 depicts the review flow diagram.

The following authors were reached and they provided aggregated data on their published studies: Monier et al, 2017[56]; Cruz-Lemini et al, 2012[52]; Cosmi et al. 2005[12]; Turan et al, 2011[51]; the Growth Restriction Intervention Trial (GRIT) Study Group[20] (Annex 2 in the supplemental material details the shared information). The characteristics of the included articles are described in Supplemental Table 1.

Risk of bias of the included studies

Among the cohort studies, 4 were considered as having a low risk of bias, while 8 had medium risk because they either had no study controls for each Doppler pattern or the analyzed exposure (abnormal Doppler pattern) was present at the start of the study. Finally, 16 had a high risk of bias, and all of them shared a combination of lack of representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, exposure present at the start of the study, or the lack of study controls for each Doppler pattern.

Table 1 tabulates the risk of bias of the observational studies included in the meta-analysis, according to the Newcastle-Ottawa Scale.[23] On the other hand, the risk of bias for randomized control trials was assessed according to Cochrane's tool designed for this purpose and it is depicted in the Supplemental Figures 1 and 2.

Synthesis of results

A total of 5909 Doppler assessments (and 336 fetal deaths) were included in the analysis.

Umbilical artery absent end-diastolic velocity and fetal death

The weighted OR of umbilical artery absent end-diastolic velocity for fetal death was 3.59 (2.29−5.62), with no differences between the fixed and the random-effects models. Figure 2 shows the forest plot for the individual and overall OR for fetal death in cases with umbilical artery absent end-diastolic velocity. No significant heterogeneity was found among studies.

Influence analysis showed that the exclusion of 1 study[56] resulted in a 26% increased weighted OR (Supplemental Table 2). The funnel plot (Supplemental Figure 3) did not suggest the existence of publication bias. Likewise, the Egger k-coefficient was not significant (1.30, 95% confidence interval [CI], −1.12 to 2.73; $P = .069$), further making unlikely a publication bias. Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 4 and 5).

Umbilical artery reversed end-diastolic velocity and fetal death

Under the random-effects models, the weighed OR of umbilical artery reversed end-diastolic velocity for fetal death was 7.27 (4.61−11.44; $P < .001$). Figure 3 shows the forest plot for the individual and overall ORs for fetal death in cases with umbilical artery reversed end-diastolic velocity. The tau^2 (0.291;

TABLE 1
Newcastle-Ottawa scale for risk of bias assessment for observational studies

Study		Selection				Comparability		Outcome			
Author	Year	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Study controls for umbilical artery/ductus venosus absent end diastolic velocity	Study controls for umbilical artery/ductus venosus reverse end diastolic velocity	Assessment of outcome	Long-enough follow-up	<10% lost to follow-up	Stars
Battaglia et al[30]	1993	*	*	*		*		*	*	*	7
Valcamonico et al[31]	1994	*	*			*	*	*	*	*	7
Ozcan et al[32]	1998	*	*	*	*	*		*	*	*	8
Madazli et al[33]	2001	*	*	*	*	*		*	*	*	8
Hofstaetter et al[34]	2002	*	*	*	*	*		*	*	*	8
Soregaroli et al[35]	2002	*	*	*	*	*	*	*	*	*	9
Baschat et al[36]	2003	*	*	*		*		*	*	*	7
Ertan et al[37]	2003		*	*		*		*	*	*	6
Bilardo et al[38]	2004	*	*	*		*		*	*	*	7
Figueras et al[39]	2004	*	*	*	*	*		*	*	*	8
Cosmi et al[12]	2005	*	*	*		*		*	*	*	7
Schwarze et al[40]	2005	*	*	*		*		*	*	*	7
Mari et al[41]	2007		*	*		*		*	*	*	6
Crispi et al[42]	2008	*	*	*		*		*	*	*	7
Hernandez-Andrade et al[43]	2008	*	*	*		*	*	*	*	*	8
Picconi et al[44]	2008	*	*	*		*		*	*	*	7
Rizzo et al[45]	2008	*	*	*		*	*	*	*	*	8
Brodszki et al[46]	2009	*	*	*		*		*	*	*	7
Robertson et al[47]	2009	*	*	*		*		*	*	*	7
Shand et al[48]	2009	*	*	*	*	*	*	*	*	*	9
Spinillo et al[49]	2009	*	*	*	*	*	*	*	*	*	9
Benavides-Serralde et al[50]	2011	*	*	*		*	*	*	*	*	8

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(continued)

TABLE 1
Newcastle-Ottawa scale for risk of bias assessment for observational studies *(continued)*

Study		Selection				Comparability		Outcome			
Author	Year	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Study controls for umbilical artery/ductus venosus absent end diastolic velocity	Study controls for umbilical artery/ductus venosus reverse end diastolic velocity	Assessment of outcome	Long-enough follow-up	<10% lost to follow-up	Stars
Turan et al[51]	2011	*	*	*		*		*	*	*	7
Cruz-Lemini et al[52]	2012	*	*	*		*		*	*	*	7
Abdelhalim et al[53]	2014	*	*	*	*	*	*	*	*	*	9
Crimmins et al[54]	2014	*	*	*	*	*		*	*	*	8
Frauenschuh et al[55]	2015			*		*		*	*	*	5
Monier et al[56]	2017	*	*	*		*	*	*	*		7

Star indicates that cells with a star indicate that the corresponding item is addressed satisfactorily in the publication in question.

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$P = .06$) and Q-value (28.8) suggested heterogeneity and the I^2 (36%) quantified it as moderate.

Influence analysis showed that the exclusion of 1 study[56] resulted in a 13.4% increased weighted OR (Supplemental Table 3). The funnel plot (Supplemental Figure 6) did not suggest the existence of publication bias. Likewise, the Egger k-coefficient was not significant (0.1, 95% CI, −1.16 to 1.36; $P = .868$). Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 7 and 8).

Umbilical artery absent or reversed end-diastolic velocity and fetal death

Under the random-effects models, the weighed OR of umbilical artery absent or reversed end-diastolic velocity for fetal death was 6.80 (4.52−10.24; $P < .001$). Figure 4 shows the forest plot for the individual and overall ORs for fetal death in cases with umbilical artery absent or reversed end-diastolic velocity. Tau^2 (0.22; $P = .14$), and the Q-value (31.49) suggests an absence of important heterogeneity, also implied by the I^2 value of 24%.

Influence analysis showed that the exclusion of any of 2 studies[35,56] resulted in a 12.3% and 11.3% increased weighted OR, respectively (Supplemental Table 4). The funnel plot for publication bias assessment is shown in Supplemental Figure 9. The Egger k-coefficient method for publication bias was not significant (0.678; −0.25 to 1.61; $P = .147$). Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 10 and 11).

Ductus venosus absent or reversed end-diastolic velocity and fetal death

Under the random-effects models, the weighed OR of ductus venosus absent or reversed end-diastolic velocity for fetal death was 11.16 (6.31−19.73; $P < .001$). Figure 5 shows the forest plot for the individual and overall ORs for fetal death in cases with ductus venosus absent or reversed end-diastolic velocity. The tau^2 (0.521; $P = .019$), Q-value (25.52), and the I^2 (49%) showed a moderate heterogeneity between studies.

Influence analysis showed that the exclusion of 1 study[54] results in a 12.6% increased OR (Supplemental Table 5). The Egger k-coefficient was −1.01 (95% CI, −3.25 to 1.22; $P=.341$), suggesting a lack of publication bias. The funnel plot for visually assessing publication bias is depicted in Supplemental Figure 12. Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 13 and 14).

The meta-regression procedure showed that neither mean gestational age at delivery (estimate, −0.14; $P=.58$) nor mean birthweight (estimate, −0.001; $P = .54$) significantly explained the variability of the effect of ductus venosus absent or reversed end-diastolic velocity on fetal death. Supplemental Figures 15 and 16 show the bubble graphs with the fitted meta-regression line of the mean gestational age at delivery and mean birthweight.

Comment

In the management of early-onset growth-restricted fetuses with severe Doppler abnormalities, the fine balance of the risk of fetal death (if left in utero) and the risk of prematurity (if delivered) guides the decision on the gestational age to deliver, aiming at maximizing survival without major sequelae.

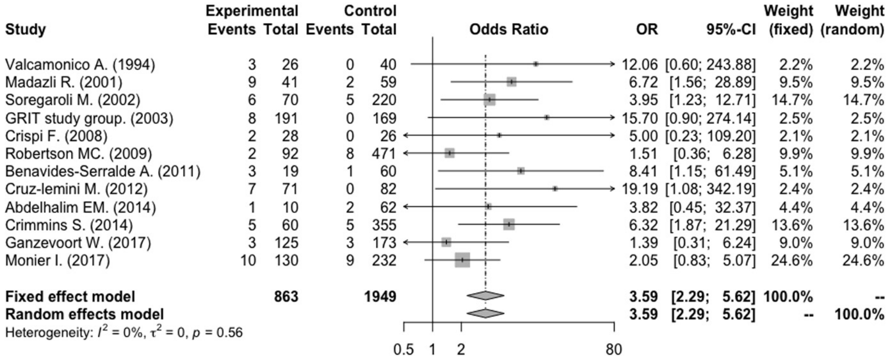
While there are contemporary series reporting the risks of prematurity (infant mortality and severe morbidity) among fetal growth-restricted babies with severe Doppler abnormalities,[3,18,20] the risk of fetal death for different Doppler patterns has not been well described. This risk has often been stated within individual studies, which may not necessarily reflect the risk of the broad spectrum of fetuses exhibiting Doppler abnormalities. With 5909 Doppler evaluations analyzed, this meta-analysis depicts the association between umbilical artery and ductus venosus with absent or reverse end-diastolic velocity waveforms and the risk of fetal death among fetuses with early-onset growth restriction.

Only a few well-designed prospective studies have been conducted that allow establishing the risk of perinatal death for individual Doppler abnormalities. Good evidence comes from 2 randomized studies. The first, the GRIT study,[20] compared immediate vs delayed delivery in growth-restricted fetuses below 36 weeks of gestation and demonstrated that early delivery to avoid fetal death was counterbalanced by neonatal death and neurological sequelae. However, antenatal surveillance was not standardized; and, therefore, reported rates of perinatal death have been found higher than expected.

More recently, the Trial of Randomized Umbilical and Fetal Flow in Europe study[3] aimed to describe perinatal morbidity and mortality in early-onset fetal growth restriction based on time of antenatal diagnosis and delivery. They found better-than-expected perinatal outcomes in this high-risk group of

FIGURE 2

OR of umbilical artery absent end diastolic velocity for fetal death



Forest plot of the odds ratio of umbilical artery absent end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random effects model).

CI, confidence interval; *OR* odds ratio.

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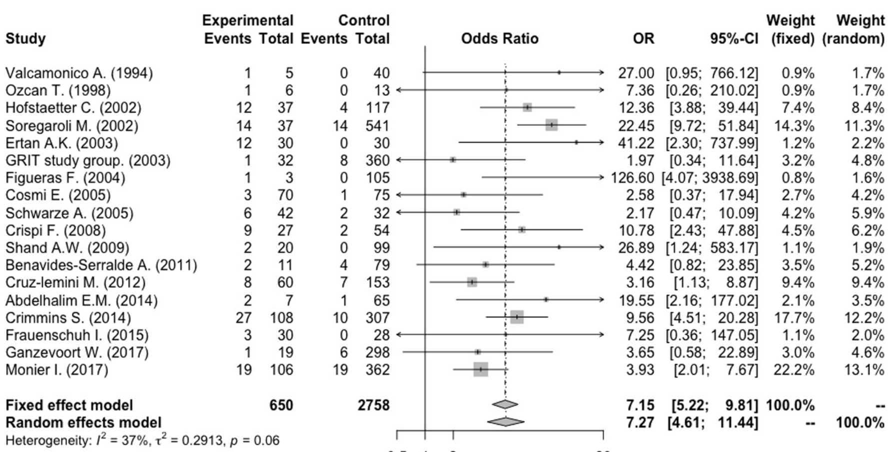
FIGURE 3

OR of umbilical artery reverse end diastolic velocity for fetal death Forest plot of the odds ratio of umbilical artery reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random effects model)



CI, confidence interval; *OR* odds ratio.

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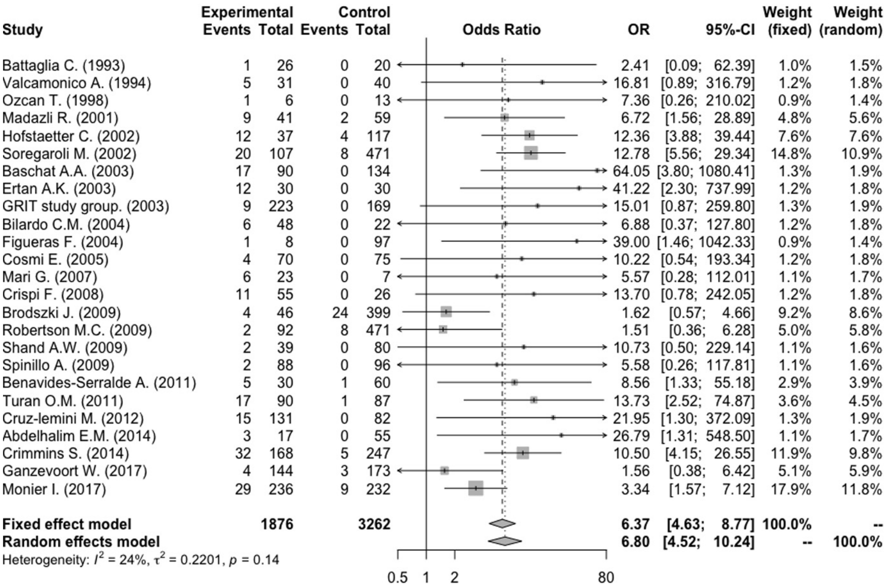
FIGURE 4
OR of umbilical artery absent or reverse end diastolic velocity



Forest plot of the odds ratio of umbilical artery absent or reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model).

CI, confidence interval; *OR* odds ratio.

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fetuses (an overall probability of survival without major morbidity of approximately 70%), which could be attributed to good adherence to a management protocol. This underscores the importance of standardizing the prenatal care of these pregnancies, in particular in defining the optimal gestational age for delivery.

The results of this meta-analysis can be used to guide the decision on the gestational age to delivery to maximize intact survival. Our pooled data on the fetal death rate in fetuses with umbilical artery absent end-diastolic velocity yields a risk of fetal death of 6.8% (59 of 863). This risk is outweighed by the risks of infant mortality or severe morbidity, as reported in the Trial of Randomized Umbilical and Fetal Flow in Europe study, at 33−34 weeks.

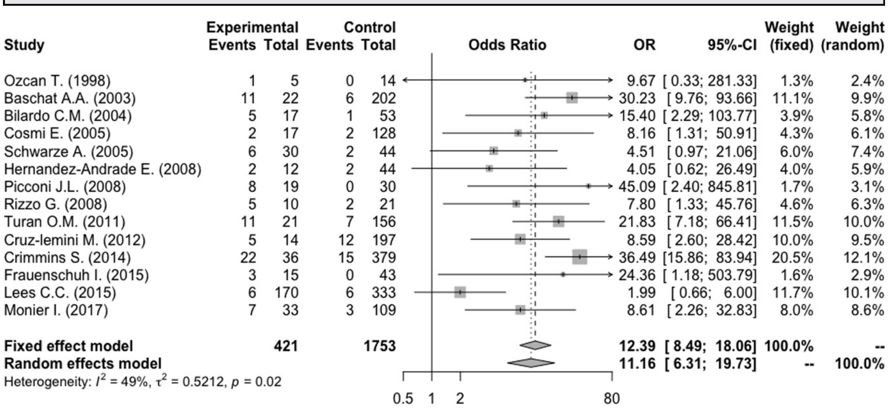
For cases with umbilical artery reversed end-diastolic velocity or ductus venosus absent or reversed end-diastolic velocity, the pooled risks of fetal death (19% [72 of 376] and 20% [77 of 377], respectively) are higher than the risk of neonatal mortality or severe morbidity from 30 weeks onward. Only 5 studies[12,32,45,52,56] separately reported risks for absent and reversed end-diastolic velocities in the ductus venosus; thus, a meta-analysis was not attempted with these groups separated. Among them, the risk of fetal death of cases with ductus venosus reversed end-diastolic velocity was 46% (21 of 46). This risk is outweighed by the risks of prematurity at ≤28 weeks.

Our analysis has several strengths. First, we carried out an extensive and systematic literature search without time restrictions. Second, the 31 studies collectively enrolled a notable number of fetal deaths ($n = 336$) among a large number with Doppler evaluations ($n = 5909$). Third, for the umbilical artery, we were able to separately estimate the risks of fetal death for cases with absent and with reversed end-diastolic velocities.

Nonetheless, we also acknowledge some limitations. First, because we included only studies of early-onset growth-restricted fetuses requiring delivery before 34 weeks, the applicability is restricted to this period of pregnancy, the reason being that umbilical artery Doppler does not reliably reflect placental insufficiency beyond this gestational age.[59]

Second, the small number of studies separately reporting risks for absent and reversed end-diastolic velocities in the ductus venosus prevented us from carrying out separate meta-analyses, and we had to combine both patterns into 1 single category. The argument can also be made that with better equipment and

FIGURE 5
OR of ductus venosus absent or reverse end diastolic velocity



Forest plot of the odds ratio of ductus venosus absent or reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random effects model).

CI, confidence interval; *OR* odds ratio.

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skills, zero velocity would be reported less, and, consequently, a technical issue (skills and equipment) decides how many cases with absent end-diastolic velocity are identified.

Third, the included studies were hampered by clinical heterogeneity because case definition, types of antenatal testing, and frequency of these tests varied widely among studies. However, it could be argued that this is an area of ongoing research and that just recently a consensus definition has been reached.[60] Nonetheless, the selection criteria of our study could be reasonably assumed to capture reasonably this recent definition.

Fourth, timely delivery and fetal death are competing factors. Thus, differences in management could also account for the heterogeneity we found in the studies reporting risks in fetuses with ductus venosus absent or reversed end-diastolic velocities. The meta-regression performed on these studies does not seem to indicate such risk of work-up bias.

Fifth, only series in which the Doppler status has been concealed to the clinicians should have been included; however, there were few studies with concealed Doppler assessment,[12,30-32,34,35,38,44,45] none of which were recent. For ethical reasons, newer studies with such a design are unlikely to be carried out.

Finally, among cases with umbilical artery absent or reversed end-diastolic velocities, one quarter concomitantly have ductus venosus absent or reversed end-diastolic velocities.[36] The resolution of information reported in the included studies does not allow ascertaining the risk for fetal death of umbilical artery reversed end-diastolic velocity with and without ductus venosus absent or reversed end-diastolic velocity. Conversely, the proportion of cases with ductus venosus absent or reversed end-diastolic velocities and positive diastolic flow in the umbilical artery is negligible.[36]

In conclusion, early-onset growth-restricted fetuses with either umbilical artery/ductus venosus absent or reversed end-diastolic velocities are at a substantially increased risk for fetal death. The risks reported in this meta-analysis may be useful for counseling pregnancies with early-onset growth restriction on the optimal gestational age for delivery. ■

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REFERENCES

1. von Beckerath A-K, Kollmann M, Rotky-Fast C, Karpf E, Lang U, Klaritsch P. Perinatal complications and long-term neurodevelopmental outcome of infants with intrauterine growth restriction. Am J Obstet Gynecol 2013;208:130.e1-6.

2. McCowan LME, George-Haddad M, Stacey T, Thompson JMD. Fetal growth restriction and other risk factors for stillbirth in a New Zealand setting. Aust N Z J Obstet Gynaecol 2007;47:450-6.

3. Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42:400-8.

4. Doyle LW. Long-term neurologic outcome for the very preterm growth-restricted fetus. Pediatrics 2011;127:e1048-9.

5. Løhaugen GCC, Østgård HF, Andreassen S, et al. Small for gestational age and intrauterine growth restriction decreases cognitive function in young adults. J Pediatr 2013;163:447-53.

6. Richardus JH, Graafmans WC, Verloove-Vanhorick SP, Mackenbach JP. EuroNatal International Audit Panel, EuroNatal Working Group. Differences in perinatal mortality and suboptimal care between 10 European regions: results of an international audit. BJOG 2003;110:97-105.

7. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108.

8. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol 2005;25:258-64.

9. Savchev S, Figueras F, Sanz-Cortes M, et al. Evaluation of an optimal gestational age cut-off for the definition of early- and late-onset fetal growth restriction. Fetal Diagn Ther 2014;36:99-105.

10. Sebire NJ. Umbilical artery Doppler revisited: pathophysiology of changes in intrauterine growth restriction revealed. Ultrasound Obstet Gynecol 2003;21:419-22.

11. Kiserud T, Ebbing C, Kessler J, Rasmussen S. Fetal cardiac output, distribution to the placenta and impact of placental compromise. Ultrasound Obstet Gynecol 2006;28:126-36.

12. Cosmi E, Ambrosini G, D'Antona D, Saccardi C, Mari G. Doppler, cardiotocography, and biophysical profile changes in growth-restricted fetuses. Obstet Gynecol 2005;106:1240-5.

13. Kiserud T, Rasmussen S, Skulstad S. Blood flow and the degree of shunting through the ductus venosus in the human fetus. Am J Obstet Gynecol 2000;182(1 Pt 1):147-53.

14. Bellotti M, Pennati G, De Gasperi C, Battaglia FC, Ferrazzi E. Role of ductus venosus in distribution of umbilical blood flow in human fetuses during second half of pregnancy. Am J Physiol Heart Circ Physiol 2000;279:H1256-63.

15. Kiserud T, Kessler J, Ebbing C, Rasmussen S. Ductus venosus shunting in growth-restricted fetuses and the effect of umbilical circulatory compromise. Ultrasound Obstet Gynecol 2006;28:143-9.

16. Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR, Simensen B. Ductus venosus blood velocity and the umbilical circulation in the seriously growth-retarded fetus. Ultrasound Obstet Gynecol 1994;4:109-14.

17. Morris RK, Selman TJ, Verma M, Robson SC, Kleijnen J, Khan KS. Systematic review and meta-analysis of the test accuracy of ductus venosus Doppler to predict compromise of fetal/neonatal wellbeing in high risk pregnancies with placental insufficiency. Eur J Obstet Gynecol Reprod Biol 2010;152:3-12.

18. Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007;109(2 Part 1):253-61.

19. Mari G, Hanif F. Intrauterine growth restriction: how to manage and when to deliver. Clin Obstet Gynecol 2007;50:497-509.

20. GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. BJOG 2003;110:27-32.

21. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. JAMA 2000;283:2008-12.

22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6.

23. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.

24. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011;343:889-93.

25. Cochrane Handbook for Systematic Reviews of Interventions. Identifying and measuring

heterogeneity. The Cochrane Collaboration. Available at: http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm. 2011. Accessed May 21, 2017.

26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

27. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533-7.

28. Doménech JM. Meta-Analysis OR, RR, RD, IR, ID, B, MD & R Combined: User-written command mar for Stata [computer program]. V1.3.4. Barcelona: Graunt 21; 2016.

29. Schwarse G. Meta: An R package for meta-analysis. R News 2007;7(3):40-5. Available at: http://cran.r-project.org/doc/Rnews/Rnews_2007-3.pdf. Accessed December 8, 2017.

30. Battaglia C, Artini PG, Galli PA, D'Ambrogio G, Droghini F, Genazzani AR. Absent or reversed end-diastolic flow in umbilical artery and severe intrauterine growth retardation. An ominous association. Acta Obstet Gynecol Scand 1993;72:167-71.

31. Valcamonico A, Danti L, Frusca T, et al. Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. Am J Obstet Gynecol 1994;170:796-801.

32. Ozcan T, Sbracia M, D'Ancona RL, Copel JA, Mari G. Arterial and venous Doppler velocimetry in the severely growth-restricted fetus and associations with adverse perinatal outcome. Ultrasound Obstet Gynecol 1998;12:39-44.

33. Madazli R, Uludağ S, Ocak V. Doppler assessment of umbilical artery, thoracic aorta and middle cerebral artery in the management of pregnancies with growth restriction. Acta Obstet Gynecol Scand 2001;80:702-7.

34. Hofstaetter C, Gudmundsson S, Hansmann M. Venous Doppler velocimetry in the surveillance of severely compromised fetuses. Ultrasound Obstet Gynecol 2002;20:233-9.

35. Soregaroli M, Bonera R, Danti L, et al. Prognostic role of umbilical artery Doppler velocimetry in growth-restricted fetuses. J Matern Fetal Neonatal Med 2002;11:199-203.

36. Baschat AA, Gembruch U, Weiner CP, Harman CR. Qualitative venous Doppler waveform analysis improves prediction of critical perinatal outcomes in premature growth-restricted fetuses. Ultrasound Obstet Gynecol 2003;22:240-5.

37. Ertan AK, He JP, Tanriverdi HA, Hendrik J, Limbach HG, Schmidt W. Comparison of perinatal outcome in fetuses with reverse or absent enddiastolic flow in the umbilical artery and/or fetal descending aorta. J Perinat Med 2003;31:307-12.

38. Bilardo CM, Wolf H, Stigter RH, et al. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet Gynecol 2004;23:119-25.

39. Figueras Retuerta F, Bennasar M, Eixarch E, et al. Arterial, venous and intracardiac parameters in growth-restricted fetuses: associations with adverse perinatal outcome. Ultrasound Rev Obstet Gynecol 2004;4:179-85.

40. Schwarze A, Gembruch U, Krapp M, Katalinic A, Germer U, Axt-Fliedner R. Qualitative venous Doppler flow waveform analysis in preterm intrauterine growth-restricted fetuses with ARED flow in the umbilical artery—correlation with short-term outcome. Ultrasound Obstet Gynecol 2005;25:573-9.

41. Mari G, Hanif F, Kruger M, Cosmi E, Santolaya-Forgas J, Treadwell MC. Middle cerebral artery peak systolic velocity: a new Doppler parameter in the assessment of growth-restricted fetuses. Ultrasound Obstet Gynecol 2007;29:310-6.

42. Crispi F, Hernandez-Andrade E, Pelsers MMAL, et al. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. Am J Obstet Gynecol 2008;199:254.e1-8.

43. Hernandez-Andrade E, Figueroa-Diesel H, Jansson T, Rangel-Nava H, Gratacos E. Changes in regional fetal cerebral blood flow perfusion in relation to hemodynamic deterioration in severely growth-restricted fetuses. Ultrasound Obstet Gynecol 2008;32:71-6.

44. Picconi JL, Kruger M, Mari G. Ductus venosus S-wave/isovolumetric A-wave (SIA) index and A-wave reversed flow in severely premature growth-restricted fetuses. J Ultrasound Med 2008;27:1283-9.

45. Rizzo G, Capponi A, Vendola M, Pietrolucci ME, Arduini D. Relationship between aortic isthmus and ductus venosus velocity waveforms in severe growth restricted fetuses. Prenat Diagn 2008;28:1042-7.

46. Brodszki J, Morsing E, Malcus P, Thuring A, Ley D, Maršál K. Early intervention in management of very preterm growth-restricted fetuses: 2-year outcome of infants delivered on fetal indication before 30 gestational weeks. Ultrasound Obstet Gynecol 2009;34:288-96.

47. Robertson MC, Murila F, Tong S, Baker LS, Yu VY, Wallace EM. Predicting perinatal outcome through changes in umbilical artery Doppler studies after antenatal corticosteroids in the growth-restricted fetus. Obstet Gynecol 2009;113:636-40.

48. Shand AW, Hornbuckle J, Nathan E, Dickinson JE, French NP. Small for gestational age preterm infants and relationship of abnormal umbilical artery Doppler blood flow to perinatal mortality and neurodevelopmental outcomes. Aust New Zeal J Obstet Gynaecol 2009;49:52-8.

49. Spinillo A, Montanari L, Roccio M, Zanchi S, Tzialla C, Stronati M. Prognostic significance of the interaction between abnormal umbilical and middle cerebral artery Doppler velocimetry in pregnancies complicated by fetal growth restriction. Acta Obstet Gynecol 2009;88:159-66.

50. Benavides-Serralde A, Scheier M, Cruz-Martinez R, et al. Changes in central and peripheral circulation in intrauterine growth-restricted fetuses at different stages of umbilical artery flow deterioration: new fetal cardiac and brain parameters. Gynecol Obstet Invest 2011;71:274-80.

51. Turan OM, Turan S, Berg C, et al. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 2011;38:295-302.

52. Cruz-Lemini M, Crispi F, Van Mieghem T, et al. Risk of perinatal death in early-onset intrauterine growth restriction according to gestational age and cardiovascular Doppler indices: a multicenter study. Fetal Diagn Ther 2012;32:116-22.

53. Abdelhalim EM, Kishk EAF, Atwa KA, Metawea MAH. Validity of umbilical artery Doppler waveform versus umbilical vein Doppler waveform in the prediction of neonatal outcome in intrauterine growth restriction cases. Middle East Fertil Soc J 2014;19:281-6.

54. Crimmins S, Desai A, Block-Abraham D, Berg C, Gembruch U, Baschat AA. A comparison of Doppler and biophysical findings between liveborn and stillborn growth-restricted fetuses. Am J Obstet Gynecol 2014;211:669.e1-10.

55. Frauenschuh I, Wirbelauer J, Karl S, et al. [Prognostic factors of perinatal short-term outcome in severe placental insufficiency using Doppler sonography to assess end-diastolic absent and reverse blood flow in umbilical arteries]. Z Geburtshilfe Neonatol 2015;219:28-36.

56. Monier I, Ancel P-Y, Ego A, et al. Fetal and neonatal outcomes of preterm infants born before 32 weeks of gestation according to antenatal versus postnatal assessments of restricted growth. Am J Obstet Gynecol 2017;216:516.e1-10.

57. Lees CC, Marlow N, van Wassenaer-Leemhuis A, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet (London, England) 2015;385:2162-72.

58. Ganzevoort W, Mensing van Charante N, Thilaganathan B, et al. How to monitor pregnancies complicated by fetal growth restriction and delivery below 32 weeks: a post-hoc sensitivity analysis of the TRUFFLE study. Ultrasound Obstet Gynecol 2017;49:769-77.

59. Parra-Saavedra M, Crovetto F, Triunfo S, et al. Placental findings in late-onset SGA births without Doppler signs of placental insufficiency. Placenta 2013;34:1136-41.

60. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016;48:333-9.

Annex 1: Supplemental material: search strategy

Selected keywords

death, Doppler, ductus venosus, fetal Doppler, fetal growth restriction, growth retardation, growth restriction, intrauterine growth restriction, mortality, small for gestational age, stillbirth, umbilical artery

PUBMED query

(mortality OR stillbirth OR death) AND Doppler AND fetal AND (ductus venosus OR umbilical artery) AND (growth retardation OR growth restriction OR IUGR OR FGR OR SGA OR small for gestational age OR small-for-gestational age OR small-for-gestational-age) AND (English [la] OR French [la] OR Spanish [la] OR Italian [la] OR German [la]) NOT review [pt] NOT review [ti] NOT meta-analysis [ti]

Total yield: 320 articles

SCOPUS query

(mortality OR stillbirth OR death) AND doppler AND fetal AND (ductus venosus OR umbilical artery) AND (growth retardation OR growth restriction OR iugr OR fgr OR sga OR small for gestational age OR small-for-gestational age OR small-for-gestational-age) AND NOT review [title] AND NOT metanalysis [title] AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "cp") AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "HEAL") AND (LIMIT-TO (LANGUAGE, "English") OR LIMIT-TO (LANGUAGE, "German") OR LIMIT-TO (LANGUAGE, "Spanish") OR LIMIT-TO (LANGUAGE, "Italian").

Total yield: 268 articles

ISI web of Science query

TS = ([mortality OR stillbirth OR death] AND Doppler AND fetal AND [ductus venosus OR umbilical artery] AND [growth retardation OR growth restriction OR IUGR OR FGR OR SGA OR small for gestational age OR small-for-gestational age OR small-for-gestational-age]).

Refined by languages: (English OR German OR French OR Spanish OR unspecified) AND [excluding] databases: (MEDLINE) AND [excluding] document types: (Review OR Editorial).

Time span: all years.

Search language = Auto

Total yield: 75 articles

Search time frame

The first search was run on Feb. 17, 2017. Afterward, an update was extended until June 20, 2017.

Annex 2: Supplementary material Aggregated data were provided by the authors of the following studies included in the meta-analysis

- Monier I, Ancel P-Y, Ego A, et al. Fetal and neonatal outcomes of preterm infants born before 32 weeks of gestation according to antenatal versus postnatal assessments of restricted growth. Am J Obstet Gynecol 2017;216:516.e1-10.[56]

Study population: 2919 singleton nonanomalous infants 24—31 weeks of gestational age from the EPIPAGE 2 study.

Umbilical artery and Ductus venosus for fetal death among suspected fetal growth restriction/small-for-gestational-age infants

	Suspected fetal growth restriction/small-for-gestational-age infants	
Variable	**Fetal death n (%[a])**	**Livebirths n (%[a])**
Total	82 (11.8)	502 (81.2)
Umbilical artery		
Normal	7 (9.1)	153 (30.5)
Elevated Doppler index	2 (2.5)	70 (13.8)
Absent end-diastolic velocity	10 (11.9)	120 (23.8)
Reversed end-diastolic velocity	19 (22.4)	87 (17.4)
Missing	44 (54.0)	72 (14.5)
Ductus venosus		
Normal	2 (2.5)	98 (19.6)
Elevated Doppler index	1 (1.4)	8 (1.6)
Absent a-wave	3 (3.5)	8 (1.6)
Reversed a-wave	4 (4.5)	18 (3.6)
Missing	72 (88.1)	370 (73.6)

[a] Weighted percentage.

- Cruz-Lemini M, Crispi F, Van Mieghem T, et al. Risk of perinatal death in early-onset intrauterine growth restriction according to gestational age and cardiovascular Doppler indices: a multicenter study. Fetal Diagn Ther 2012;32:116-22.[52]

Study population: 222 singletons nonanomalous early-onset (<34 weeks) suspected fetal growth restriction.
* There are more cases than reported in the original paper because some were excluded from the initial analysis because of incomplete data on other variables different from umbilical artery and ductus venosus).

Umbilical artery and ductus venosus for fetal death among suspected fetal growth restriction

Variable	Suspected fetal growth restriction: Fetal death n (%[a])	Suspected fetal growth restriction: Live births n (%[a])
Total	18 (8.1)	204 (91.9)
Umbilical artery		
Present end-diastolic velocity	0 (0)	82 (40.2)
Absent end-diastolic velocity	7 (38.8)	64 (31.4)
Reversed end-diastolic velocity	8 (44.4)	52 (25.5)
Missing	3 (16.6)	6 (2.9)
Ductus venosus		
Present a-wave	10 (55.6)	188 (92.2)
Absent a-wave	2 (11.1)	3 (1.5)
Reversed a-wave	5 (27.8)	9 (4.4)
Missing	1 (5.6)	4 (2.0)

[a] Weighted percentage.

- GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. BJOG 2003;110:27-32.[20]

Study population: 392 singleton pregnancies randomized before 34 weeks.

Umbilical artery and Ductus venosus for fetal death

Variable	Fetal death n (%[a])	Live births n (%[a])
Total	9 (2.2)	383 (97.7)
Umbilical artery		
Present end-diastolic velocity	0 (0.0)	169 (44.1)
Absent end-diastolic velocity	8 (88.8)	183 (47.7)
Reversed end-diastolic velocity	1 (1.1)	31 (8.1)

[a] Weighted percentage.

- Cosmi E, Ambrosini G, D'Antona D, Saccardi C, Mari G. Doppler, cardiotocography, and biophysical profile changes in growth-restricted fetuses. Obstet Gynecol 2005;106:1240-5.[12]

Study population: 145 fetuses with an estimated weight below the 10th percentile and abnormal umbilical artery pulsatility index.

Umbilical artery and ductus venosus for fetal death

Variable	Suspected fetal growth restriction: Fetal death n (%[a])	Live births n (%[a])
Total	4 (2.8)	141 (97.2)
Umbilical artery		
Positive end-diastolic velocity	0 (0.0)	74 (52.4)
Absent end-diastolic velocity	1 (0.2)	0 (0.0)
Reversed end-diastolic velocity	3 (0.8)	67 (47.5)
Ductus venosus		
Present a-wave	2 (0.5)	126 (89.3)
Absent or reversed a-wave	2 (0.5)	15 (10.3)

[a] Weighted percentage.

- Turan OM, Turan S, Berg C, et al. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 2011;38:295-302.[52]

Gestational age at diagnosis of the whole cohort of growth restricted babies:

- Mean: 31.7 weeks
- Range: 24.6 - 38.4 weeks

Gestational age at delivery of those fetal deaths with Umbilical artery absent or reversed end-diastolic velocity:

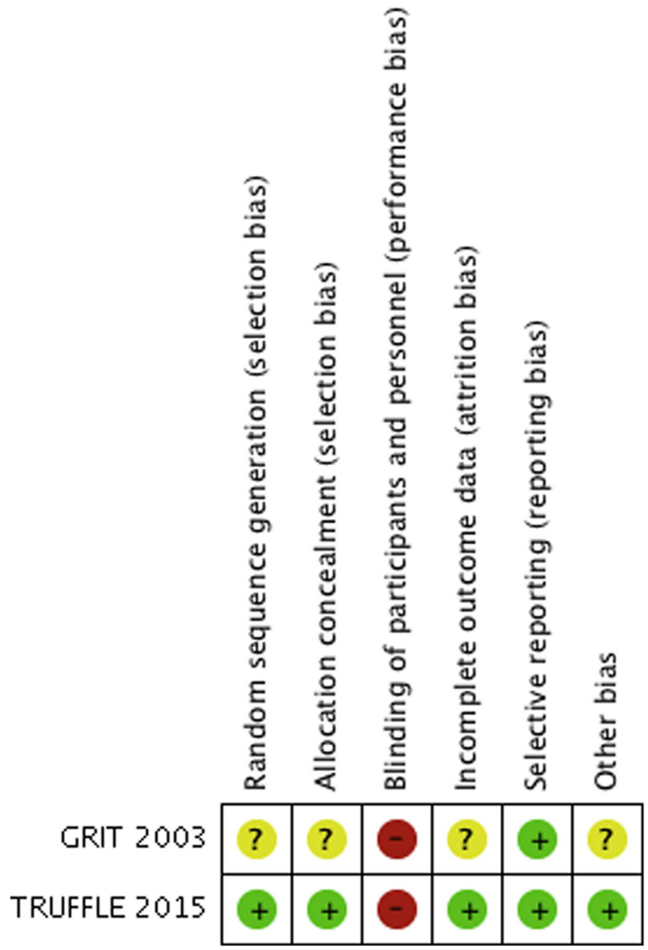
- Mean: 27.6 weeks
- Range: 24.6 - 30.6 weeks

Gestational age at delivery of those fetal deaths with Ductus venosus absent or reversed end-diastolic velocity:

- Mean: 28 weeks
- Range: 24.6 - 30.6 weeks

All ductus venosus with absent or reversed end-diastolic velocity had umbilical artery absent or reversed end-diastolic velocity.

SUPPLEMENTAL FIGURE 1
Risk of bias summary of included randomized studies

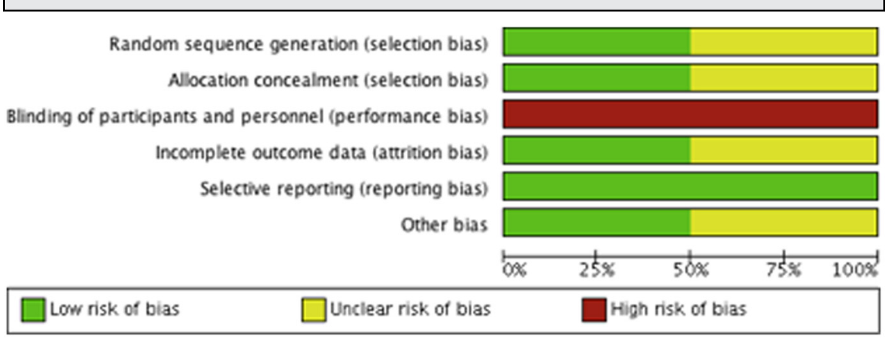


This is a review of authors' judgments about each risk of bias item for each included study.

GRIT, Growth Restriction Intervention Trial Study Group; *TRUFFLE*, Trial of Randomized Umbilical and Fetal Flow in Europe.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 2
Risk of bias graph of included randomized studies

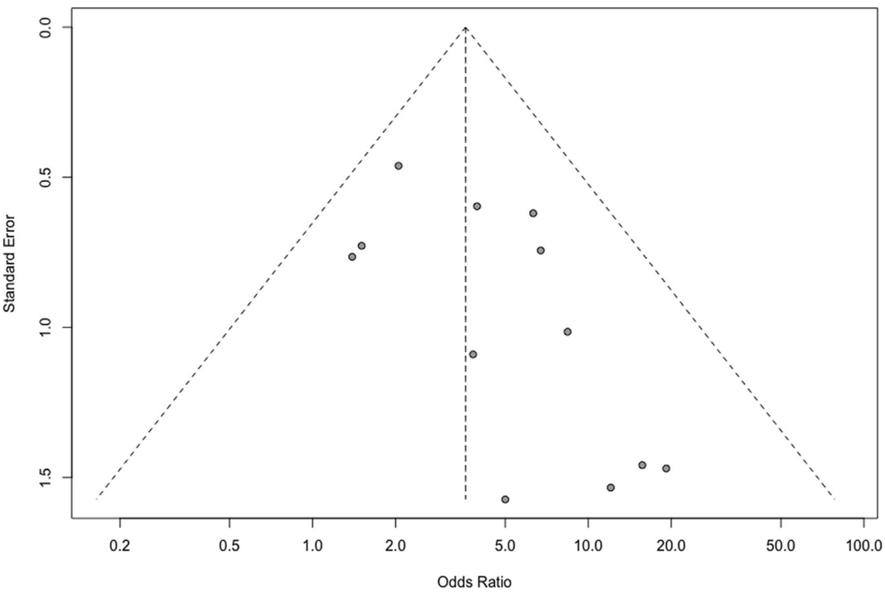


This is a review of review authors' judgments about each risk of bias item presented as percentages across all included studies.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 3

Funnel plot for umbilical artery absent end-diastolic velocity



This is a funnel plot with pseudo 95% confidence limits for umbilical artery absent end diastolic velocity.

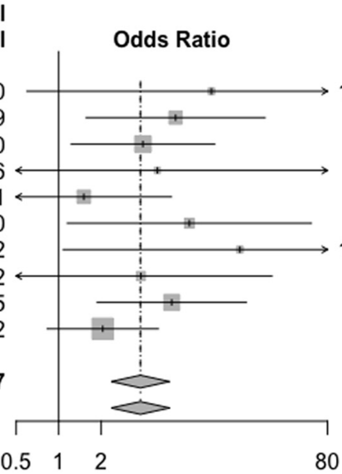
Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 4

Forest plot of of umbilical artery absent end-diastolic velocity

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight (fixed)	Weight (random)
Valcamonico A. (1994)	3	26	0	40	12.06	[0.60; 243.88]	2.5%	2.5%
Madazli R. (2001)	9	41	2	59	6.72	[1.56; 28.89]	10.7%	10.7%
Soregaroli M. (2002)	6	70	5	220	3.95	[1.23; 12.71]	16.6%	16.6%
Crispi F. (2008)	2	28	0	26	5.00	[0.23; 109.20]	2.4%	2.4%
Robertson MC. (2009)	2	92	8	471	1.51	[0.36; 6.28]	11.1%	11.1%
Benavides-Serralde A. (2011)	3	19	1	60	8.41	[1.15; 61.49]	5.7%	5.7%
Cruz-lemini M. (2012)	7	71	0	82	19.19	[1.08; 342.19]	2.7%	2.7%
Abdelhalim EM. (2014)	1	10	2	62	3.82	[0.45; 32.37]	5.0%	5.0%
Crimmins S. (2014)	5	60	5	355	6.32	[1.87; 21.29]	15.4%	15.4%
Monier I. (2017)	10	130	9	232	2.05	[0.83; 5.07]	27.8%	27.8%
Fixed effect model		**547**		**1607**	**3.79**	**[2.35; 6.10]**	**100.0%**	**--**
Random effects model					**3.79**	**[2.35; 6.10]**	**--**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.63$



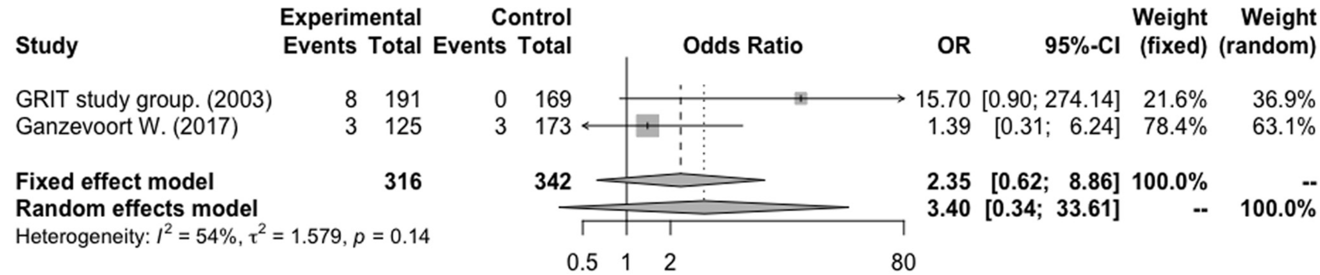
Forest plot of the odds ratio of umbilical artery absent end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; *OR*, odds ratio.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 5

Forest plot of of umbilical artery absent end-diastolic velocity



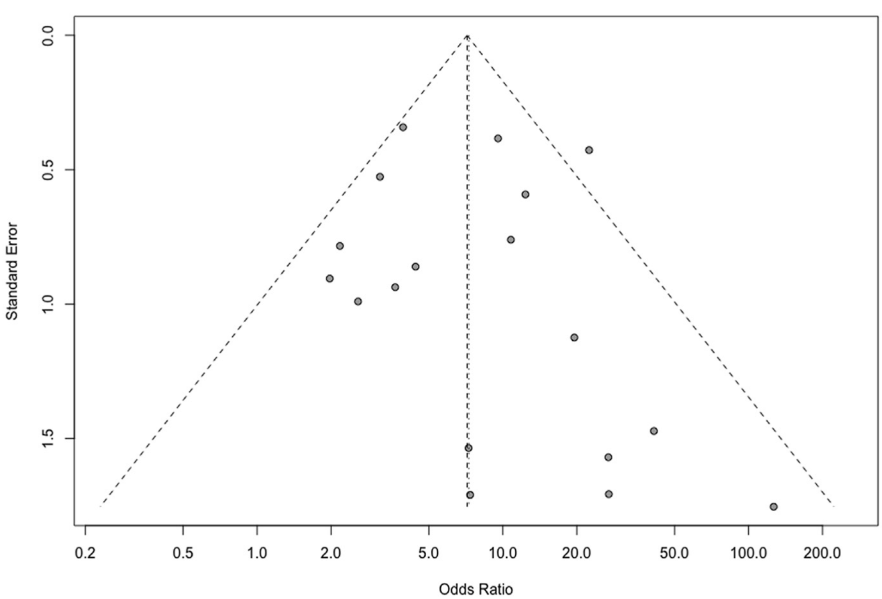
Forest plot of the odds ratio of umbilical artery absent end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; *GRIT*, Growth Restriction Intervention Trial; *OR*, odds ratio.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 6

Funnel plot for umbilical artery reverse end-diastolic velocity

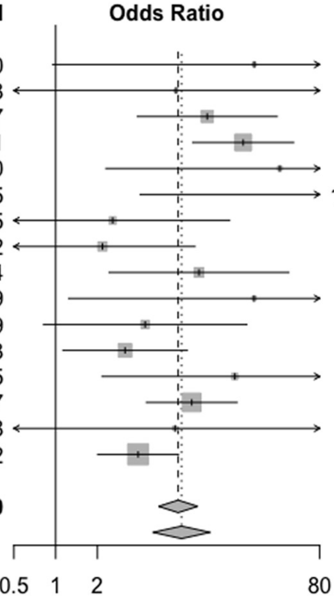


Funnel plot with pseudo 95% confidence limits for umbilical artery reverse end diastolic velocity.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 7

Forest plot of umbilical artery reverse end-diastolic velocity for fetal death



Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight (fixed)	Weight (random)
Valcamonico A. (1994)	1	5	0	40	27.00	[0.95; 766.12]	1.0%	1.9%
Ozcan T. (1998)	1	6	0	13	7.36	[0.26; 210.02]	0.9%	1.8%
Hofstaetter C. (2002)	12	37	4	117	12.36	[3.88; 39.44]	7.9%	9.2%
Soregaroli M. (2002)	14	37	14	541	22.45	[9.72; 51.84]	15.2%	12.5%
Ertan A.K. (2003)	12	30	0	30	41.22	[2.30; 737.99]	1.3%	2.4%
Figueras F. (2004)	1	3	0	105	126.60	[4.07; 3938.69]	0.9%	1.8%
Cosmi E. (2005)	3	70	1	75	2.58	[0.37; 17.94]	2.8%	4.7%
Schwarze A. (2005)	6	42	2	32	2.17	[0.47; 10.09]	4.5%	6.5%
Crispi F. (2008)	9	27	2	54	10.78	[2.43; 47.88]	4.8%	6.8%
Shand A.W. (2009)	2	20	0	99	26.89	[1.24; 583.17]	1.1%	2.2%
Benavides-Serralde A. (2011)	2	11	4	79	4.42	[0.82; 23.85]	3.7%	5.7%
Cruz-lemini M. (2012)	8	60	7	153	3.16	[1.13; 8.87]	10.0%	10.4%
Abdelhalim E.M. (2014)	2	7	1	65	19.55	[2.16; 177.02]	2.2%	3.8%
Crimmins S. (2014)	27	108	10	307	9.56	[4.51; 20.28]	18.8%	13.5%
Frauenschuh I. (2015)	3	30	0	28	7.25	[0.36; 147.05]	1.2%	2.2%
Monier I. (2017)	19	106	19	362	3.93	[2.01; 7.67]	23.7%	14.5%
Fixed effect model		**599**		**2100**	**7.63**	**[5.51; 10.58]**	**100.0%**	**--**
Random effects model					**8.07**	**[5.00; 13.01]**	**--**	**100.0%**

Heterogeneity: $I^2 = 38\%$, $\tau^2 = 0.2934$, $p = 0.06$

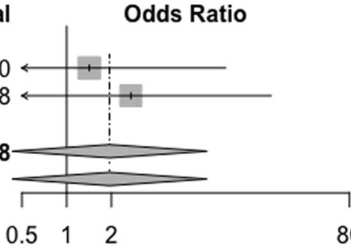
Forest plot of the odds ratio of umbilical artery reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; *OR*, odds ratio.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 8

OR of umbilical artery reverse end-diastolic velocity for fetal death



Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight (fixed)	Weight (random)
GRIT study group. (2003)	1	32	8	360	1.42	[0.17; 11.72]	51.4%	51.4%
Ganzevoort W. (2017)	1	19	6	298	2.70	[0.31; 23.68]	48.6%	48.6%
Fixed effect model		**51**		**658**	**1.94**	**[0.43; 8.82]**	**100.0%**	**--**
Random effects model					**1.94**	**[0.43; 8.82]**	**--**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.68$

Forest plot of the odds ratio of umbilical artery reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; *GRIT*, Growth Restriction Intervention Trial; *OR*, odds ratio.

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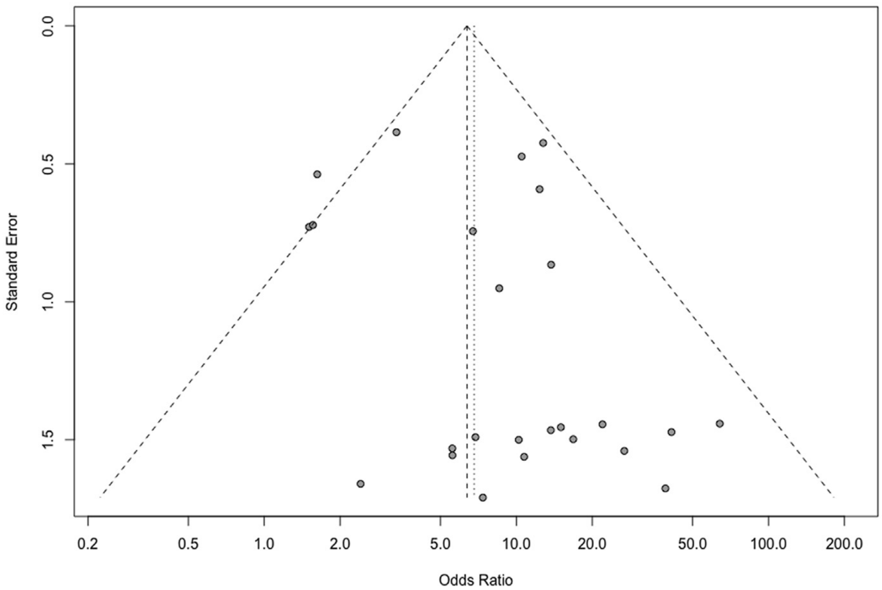
SUPPLEMENTAL FIGURE 9

Funnel plot for umbilical artery absent or reverse end-diastolic velocity



This shows a funnel plot with pseudo 95% confidence limits for umbilical artery absent or reverse end-diastolic velocity.

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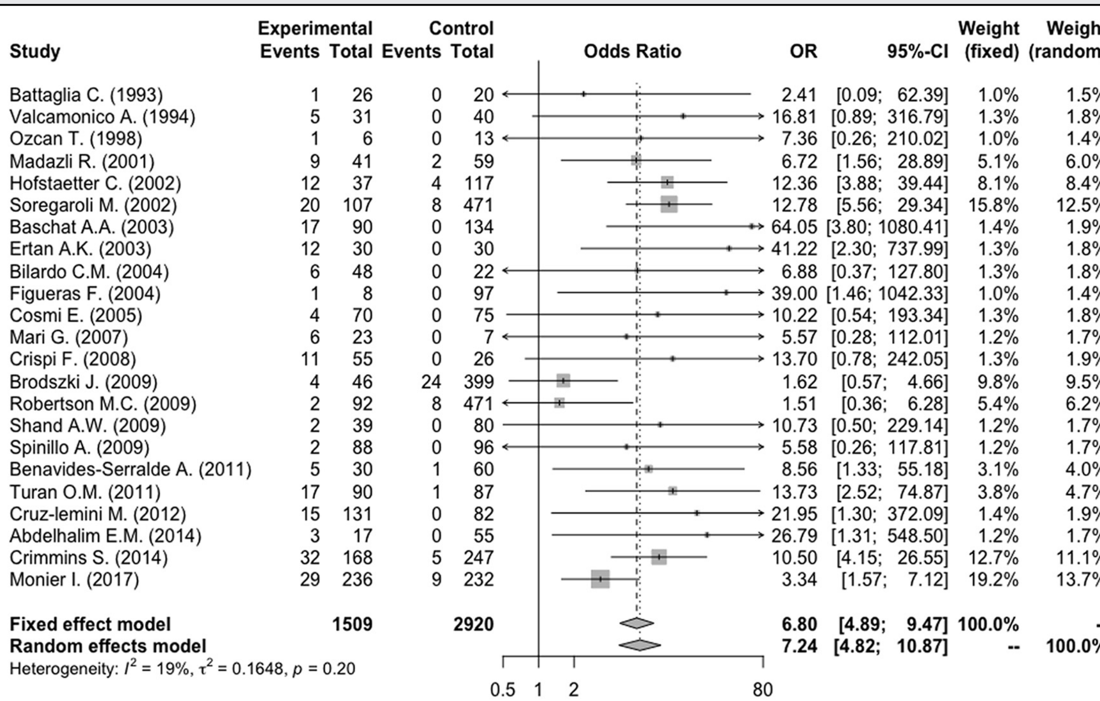
SUPPLEMENTAL FIGURE 10

Forest plot of umbilical artery absent or reverse end-diastolic velocity



Forest plot of the odds ratio of umbilical artery absent or reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; *OR*, odds ratio.

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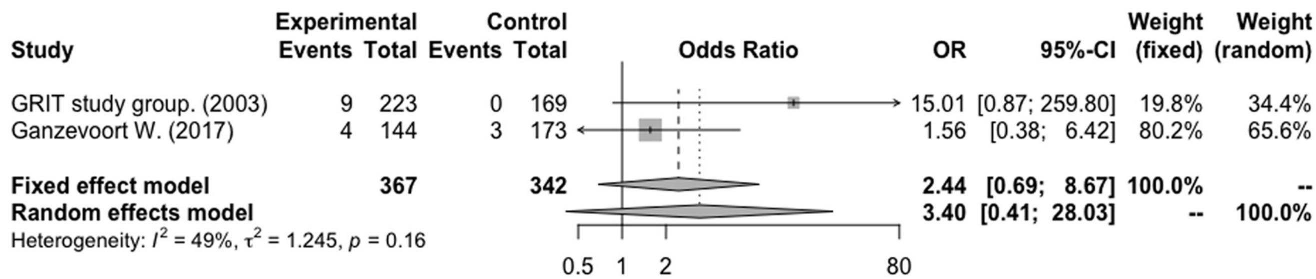
SUPPLEMENTAL FIGURE 11

Forest plot umbilical artery absent or reverse end-diastolic velocity



This figure shows a forest plot of the odds ratio of umbilical artery absent or reverse end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; *GRIT*, Growth Restriction Intervention Trial; *OR*, odds ratio.

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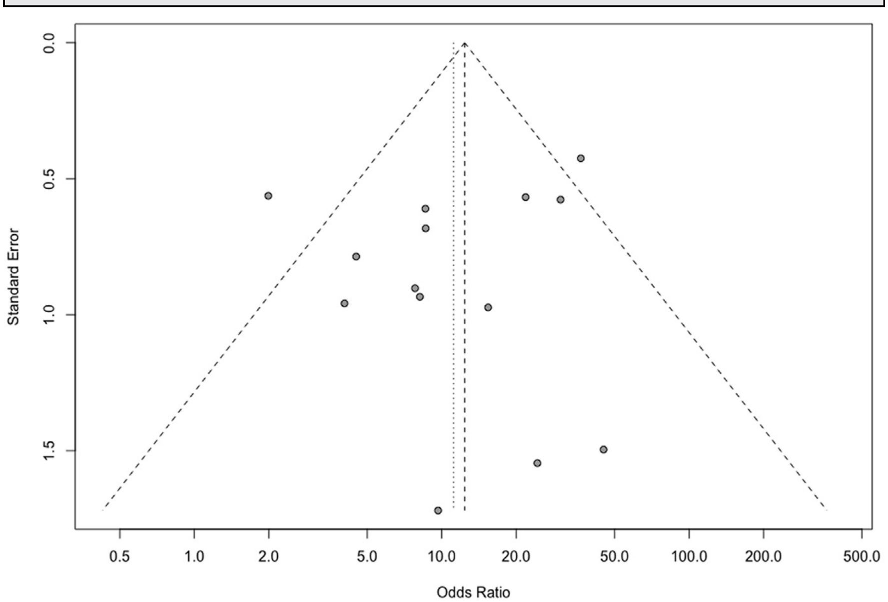
SUPPLEMENTAL FIGURE 12

Funnel plot for ductus venosus absent or reverse end-diastolic velocity

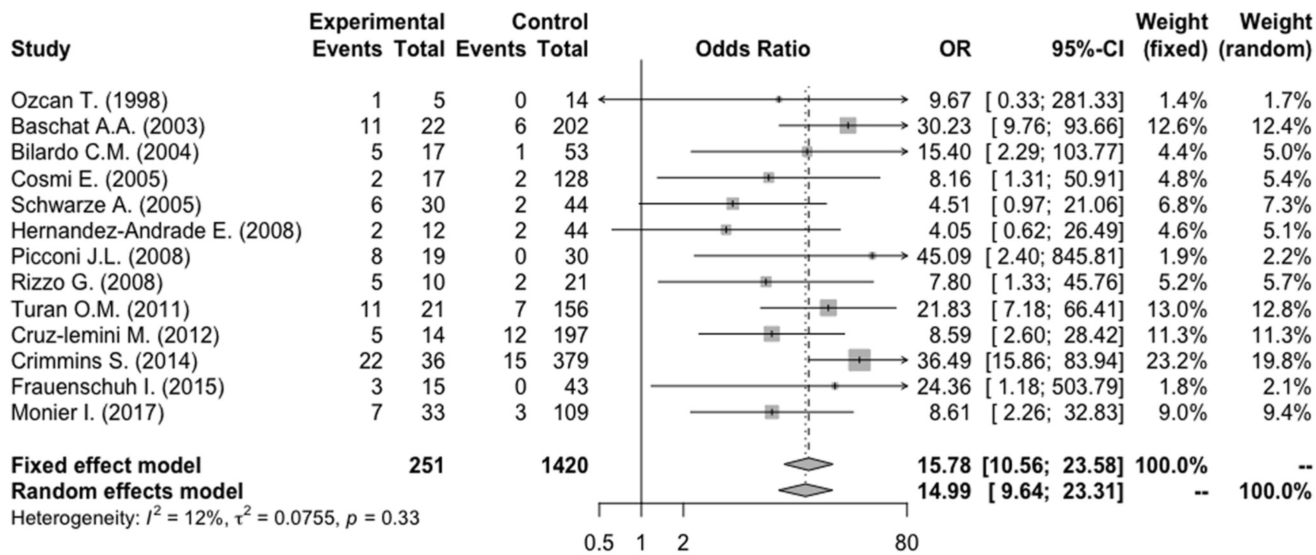


Funnel plot with pseudo 95% confidence limits for ductus venosus absent or reverse end diastolic velocity.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 13

Forest plot of ductus venosus absent or reverse end-diastolic velocity



Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight (fixed)	Weight (random)
Ozcan T. (1998)	1	5	0	14	9.67	[0.33; 281.33]	1.4%	1.7%
Baschat A.A. (2003)	11	22	6	202	30.23	[9.76; 93.66]	12.6%	12.4%
Bilardo C.M. (2004)	5	17	1	53	15.40	[2.29; 103.77]	4.4%	5.0%
Cosmi E. (2005)	2	17	2	128	8.16	[1.31; 50.91]	4.8%	5.4%
Schwarze A. (2005)	6	30	2	44	4.51	[0.97; 21.06]	6.8%	7.3%
Hernandez-Andrade E. (2008)	2	12	2	44	4.05	[0.62; 26.49]	4.6%	5.1%
Picconi J.L. (2008)	8	19	0	30	45.09	[2.40; 845.81]	1.9%	2.2%
Rizzo G. (2008)	5	10	2	21	7.80	[1.33; 45.76]	5.2%	5.7%
Turan O.M. (2011)	11	21	7	156	21.83	[7.18; 66.41]	13.0%	12.8%
Cruz-lemini M. (2012)	5	14	12	197	8.59	[2.60; 28.42]	11.3%	11.3%
Crimmins S. (2014)	22	36	15	379	36.49	[15.86; 83.94]	23.2%	19.8%
Frauenschuh I. (2015)	3	15	0	43	24.36	[1.18; 503.79]	1.8%	2.1%
Monier I. (2017)	7	33	3	109	8.61	[2.26; 32.83]	9.0%	9.4%
Fixed effect model		**251**		**1420**	**15.78**	**[10.56; 23.58]**	**100.0%**	**--**
Random effects model					**14.99**	**[9.64; 23.31]**	**--**	**100.0%**

Heterogeneity: $I^2 = 12\%$, $\tau^2 = 0.0755$, $p = 0.33$

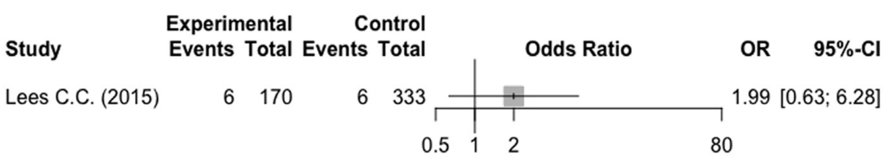
Forest plot of the odds ratio of ductus venosus absent or reverse end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; *OR*, odds ratio.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 14

Forest plot of ductus venosus absent or reverse end-diastolic velocity



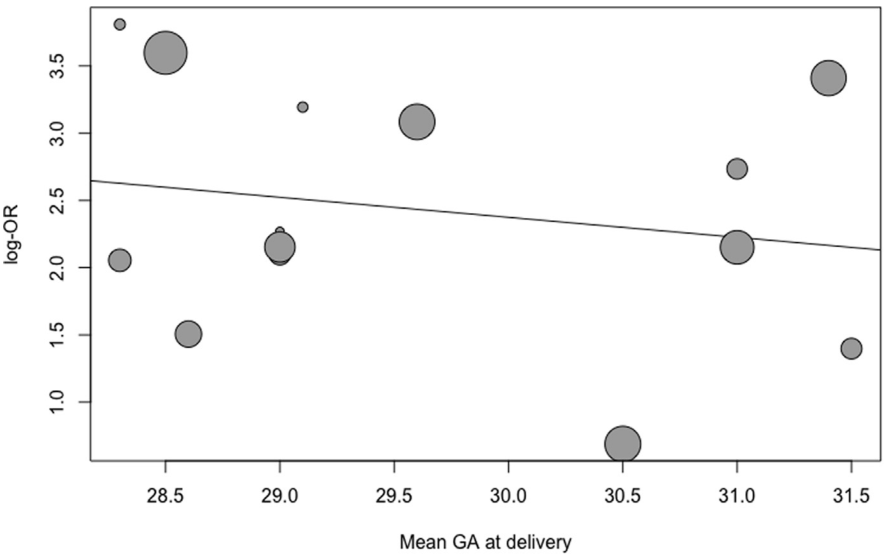
Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI
Lees C.C. (2015)	6	170	6	333	1.99	[0.63; 6.28]

The figure shows the forest plot of the odds ratio of ductus venosus absent or reverse end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; *OR*, odds ratio.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL FIGURE 15
Bubble of gestational age on diastolic velocity



Bubble graph with the fitted meta-regression line of the mean gestational age at delivery against the OR for fetal death of the studies on ductus venosus absent or reverse end diastolic velocity.

GA, gestational age; *OR*, odds ratio.

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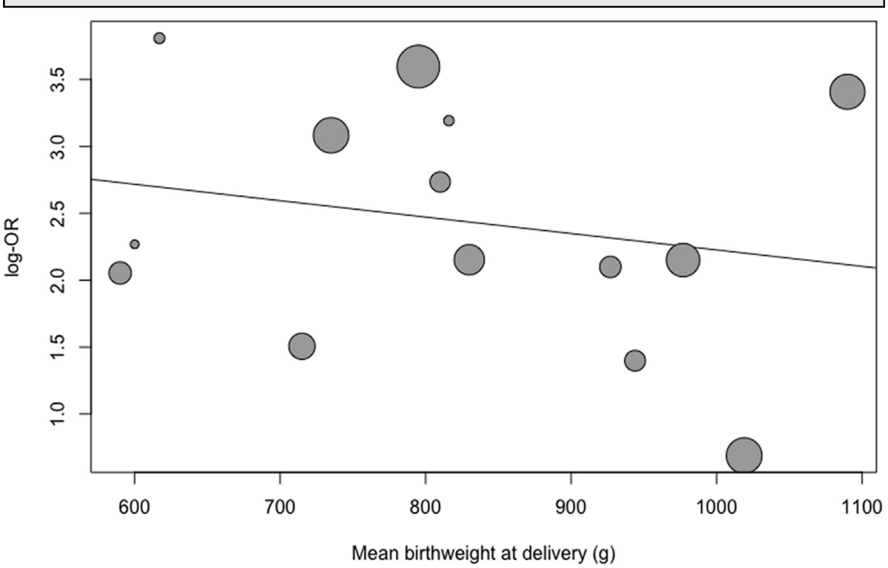
SUPPLEMENTAL FIGURE 16
Bubble graph of birthweight on diastolic velocity



This figure shows the bubble graph with the fitted meta-regression line of the mean birthweight against the OR for fetal death of the studies on ductus venosus absent or reverse end-diastolic velocity.

OR, odds ratio.

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SUPPLEMENTAL TABLE 1

Characteristics of the studies included in the meta-analysis

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Battaglia et al[30]	1993	Italy	Prospective cohort	January 1988 to November 1991	• Singleton pregnancies • Amniotic fluid <2 cm • >2 SD in umbilical artery Doppler flow velocity-waveforms • Abdominal circumference <5th centile	• Fetal structural or chromosomal abnormalities • Maternal diabetes	46	Umbilical artery
Valcamonico et al[31]	1994	Italy	Prospective cohort	January 1989 to June 1990	• Estimated fetal weight < 2 SD • Information on Doppler flow evaluation	• x	31	Umbilical artery
Ozcan et al[32]	1998	United States	Prospective cohort	June 1994 to February 1997	• Normal fetal anatomy • Fetal weight <5th centile • Doppler waveform estimations within 2 weeks from delivery	• Neonates with a birthweight >5th centile • Fetal structural or chromosomal abnormalities after delivery	19	Umbilical artery/ductus venosus
Madazli et al[33]	2001	Turkey	Prospective cohort	.	• Singleton pregnancies • Fetal abdominal circumference <2 SD	• Fetal structural or chromosomal abnormalities	100	Umbilical artery
Hofstaetter et al[34]	2002	Germany	Prospective cohort	5.5 years	• Singleton pregnancies • Estimated fetal weight below 10th centile	• Fetal structural or chromosomal abnormalities	146	Umbilical artery
Soregaroli et al[34]	2002	Italy	Retrospective cohort	1991–1999	• Singleton pregnancies • Fetal abdominal circumference <2 SD • Information of fetal biometry, amniotic fluid and fetal-maternal Doppler velocimetry	• x	578	Umbilical artery
Baschat et al[36]	2003	United States	Prospective cohort	December 1994 to June 2001	• Delivery prior to 37 completed weeks of gestation • Birthweight <10th percentile • Pulsatility index umbilical artery >2 SD above the mean for gestational age	• Maternal diabetes • Fetal structural or chromosomal abnormalities • Twin gestation	224	Umbilical artery/ductus venosus
Ertan et al[37]	2003	Germany	Cohort	10 year period	• Umbilical artery or fetal aorta absent or reverse end diastolic velocity at the time of delivery • Perinatal outcome	• Fetal structural or chromosomal abnormalities	30	Umbilical artery

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

(continued)

SUPPLEMENTAL TABLE 1
Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
GRIT Study Group[20]	2003	Belgium	RCT	.	• Singleton or multiple pregnancies where the responsible clinician was uncertain whether to deliver the baby immediately • Gestational age between 24 and 36 weeks • Recorded waveform of umbilical artery Doppler	• x	392	Umbilical artery
Bilardo et al[38]	2004	The Netherlands/ United Kingdom	Cohort	.	• Singleton pregnancies • $<$ 33 weeks of gestation • Abdominal circumference $<$5th centile	• x	70	Umbilical artery / Ductus venosus
Figueras et al[39]	2004	Spain	Prospective cohort	June 1998 to December 1999	• Pregnancies $>$ 26 weeks • Fetal weight $<$5th centile	• x	108	Umbilical artery
Cosmi et al[12]	2005	Italy	Prospective cohort	2001 to 2004	• Fetal weight $<$10th centile • Umbilical artery pulsatility index $>$2 • Normal fetal anatomy • Absence of maternal pathology • Delivery before 32 weeks of gestation • Forward umbilical artery diastole • Forward ductus venous diastolic flow • At least 3 consecutive Doppler measurements before delivery • Last Doppler measurement obtained within 24 hours from delivery	• Abnormal fetal anatomy • Maternal pathology • Pulsation in umbilical vein • Amniotic fluid index $<$5 cm	145	Umbilical artery/ductus venosus
Schwarze et al[40]	2005	Germany	Retrospective cohort	1999–2004	• Birthweight $<$10th centile • Absent or reverse end-diastolic velocity in umbilical artery • Delivered before 34 weeks of gestation	• Multiple pregnancies • Fetal structural abnormalities	74	Umbilical artery/ductus venosus

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

(continued)

SUPPLEMENTAL TABLE 1

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

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Mari et al[40]	2007	Italy	Retrospective cross-sectional	.	• Fetal weight <3rd centile • Umbilical artery pulsatility index >95th centile Normal anatomy • Middle cerebral artery examination within 8 days before delivery of fetal demise • Deliveries before 33 weeks of gestation	• Fetal structural or chromosomal abnormalities	30	Umbilical artery
Crispi et al[42]	2008	United Kingdom	Cohort		• Fetal weight <10th centile • Umbilical artery pulsatility index >2 SD • Fetal death between 24 and 34 weeks	• Evidence of fetal infection • Structural/ chromosomal abnormalities	81	Umbilical artery
Hernandez-Andrade et al[43]	2008	Spain	Cohort	.	• Fetal weight <10th centile • Umbilical artery pulsatility index >2 SD • Information from ductus venosus, umbilical artery, and middle cerebral artery	• x	56	Ductus venosus
Picconi et al[44]	2008	United States	Retrospective cohort	.	• Fetal weight < 10th centile • Umbilical artery pulsatility index >95th centile • Normal anatomy • Doppler assessment of the ductus venosus	• Fetal infection • Fetal structural or chromosomal abnormalities	49	Ductus venosus
Rizzo et al[45]	2008	Italy	Prospective cohort	March 2006 to May 2008	• Fetal weight <10th centile • Abnormal umbilical artery velocity waveforms during and diastole • Successful recordings from both ductus venosus and aortic isthmus	• Fetal structural or chromosomal abnormalities • Maternal disease	31	Ductus venosus
Brodszki et al[46]	2009	Sweden	Retrospective cohort	1998–2004	• Fetuses with absent or reverse end-diastolic velocity in umbilical artery before 30 weeks of gestation • Fetal weight <2 SD • Live-born delivery before 30 weeks of gestation	• Fetal structural or chromosomal abnormalities • Absence of twin-to-twin transfusion syndrome	46	Umbilical artery

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

(continued)

SUPPLEMENTAL TABLE 1

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

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Robertson et al[47]	2009	Australia	Retrospective cohort	July 1998 to January 2006	• Singleton pregnancies • Growth-restricted fetuses • Absent end-diastolic flow • Subsequent administration of betamethasone and poststeroid umbilical artery Doppler studies	• x	92	Umbilical artery
Shand et al[48]	2009	Australia	Retrospective cohort	January 2001 to December 2004	• Birthweight ratio of less than 0.85 • Umbilical artery Doppler assessment within 7 days of birth	• x	119	Umbilical artery
Spinillo et al[49]	2009	Italy	Prospective cohort	1997–2006	• Fetal abdominal circumference <10th centile • Umbilical artery pulsatility >95th centile • Umbilical artery absent/reversed end-diastolic velocities	• Fetal structural or chromosomal abnormalities	184	Umbilical artery
Benavides-Serralde et al[50]	2011	Spain	Prospective cohort	April 2007 to December 2009	• Singleton pregnancies • Fetal weight <10th centile • High-risk pregnancies	• x	72	Umbilical artery
Turan et al[51]	2011	United States/ Germany/Italy/The Netherlands/United Kingdom	Prospective cohort	January 2000 to March 2006	• Singleton pregnancies • Abdominal circumference <5th percentile • Umbilical artery pulsatility index >2 SD • At least 3 Doppler examinations before delivery	• Fetal structural or chromosomal abnormalities	177	Umbilical artery/ductus venosus
Cruz-Lemini et al[52]	2012	Spain/Belgium/Chile	Prospective cohort	2 year period	• Fetal weight <10th centile • Umbilical artery pulsatility index >95th centile	• Twin pregnancies • Fetal infection • Fetal structural or chromosomal abnormalities	222	Umbilical artery
Abdelhalim et al[53]	2014	Egypt	Prospective cohort	May 2010 to February 2013	• Singleton pregnancies • Scan at 28–38 weeks • High-risk pregnancies for IUGR	• Low-risk pregnancies • Fetal structural or chromosomal abnormalities	72	Umbilical artery

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

(continued)

SUPPLEMENTAL TABLE 1
Characteristics of the studies included in the meta-analysis *(continued)*

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Crimmins et al[54]	2014	United States/ Germany	Retrospective cohort	January 2000 to December 2002	• High-risk pregnancies • Fetal weight <10th centile	• Fetal structural or chromosomal abnormalities • Multiple gestation • Fetal infection • Unavailability of outcome variables	987	Umbilical artery/ductus venosus
Frauenschuh et al[55]	2015	Germany	Cohort	1996–2004	• High-risk singleton pregnancy • Growth-restricted fetuses <32 weeks • Umbilical artery absent/reversed end-diastolic velocities	• Multiple pregnancies • Fetal structural or chromosomal abnormalities	58	Umbilical artery/ductus venosus
Lees et al[57] (TRUFFLE)	2015	Europe (United Kingdom, The Netherlands, Germany, Austria, Italy)	Randomized control trial	January 2005 to October 2010	• Singleton pregnancies • Fetal abdominal circumference <10th centile • Umbilical artery pulsatility index >95th centile, with or without reversed or absent end-diastolic velocities • Gestational age between 26 and 31.9 weeks • Fetal weight >500 g • Normal ductus venosus waveform with pulsatility index <95th centile	• Delivery known, planned, or impending • Women younger than 18 years old • Fetal structural or chromosomal abnormalities	503	Ductus venosus
Ganzevoort et al[58] (TRUFFLE)	2017	Swiss	Retrospective cohort	1998–2004	• Fetal weigh <2 SD • Umbilical artery absent/reversed end-diastolic velocities • Delivery <30 weeks of gestation	• Fetal structural or chromosomal abnormalities • Twin-to-twin transfusion syndrome	317	Umbilical artery
Monier et al[56]	2017	France	Prospective cohort	2011–2017	• All deliveries between 22 and 31 weeks • Information on Doppler and fetal outcome	• Patients with no inform consent or incomplete data	636	Umbilical artery/ductus venosus

IUGR, intrauterine growth restriction; *RCT*, randomized controlled trial.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL TABLE 2

Influence analysis on umbilical artery absent end-diastolic velocity

Study deleted	IoV random effect model estimation if the study is deleted						Relative weights IoV REM, %
	OR	95% CI		OR change (%)	Heterogeneity		
					I^2,%	*P* value	
Valcamonico et al[31] (1994)	3.54	2.19	5.72	−2.9	0	NS	2.9
Madazli et al[33] (2001)	3.37	2.05	5.55	−7.4	0	NS	8.8
Soregaroli et al[35] (2002)	3.58	2.14	5.99	−1.8	0	NS	15.1
GRIT Study Group[20] (2003)	3.50	2.16	5.66	−4.0	0	NS	2.6
Crispi et al[42] (2008)	3.61	2.24	5.84	−0.8	0	NS	2.3
Robertson et al[47] (2009)	4.05	2.45	6.65	11.1	0	NS	9.1
Benavides-Serralde et al[50] (2011)	3.47	3.47	5.64	−4.7	0	NS	4.1
Cruz-Lemini et al[52] (2012)	3.48	2.15	5.62	−4.6	0	NS	2.9
Abdelhalim et al[53] (2014)	3.66	2.25	5.92	0.3	0	NS	3.6
Crimmins et al[54] (2014)	3.33	2.00	5.55	−8.6	0	NS	13.9
Ganzevoort et al[58] (2017)	3.99	2.43	6.55	9.5	0	NS	8.6
Monier et al[56] (2017)	4.45	2.57	7.73	22.2	0	NS	26.1

Umbilical artery absent end-diastolic velocity Egger publication bias: _cons, 1.30, SE, 0.641; t = 2.04, p = .069 (−1.12to 2.73).

CI, confidence interval; *NS*, not significant; *OR*, odds ratio; *IoV*, Inverse of Variance; *REM*, Random Effect Model.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL TABLE 3

Influence analysis on umbilical artery reverse end-diastolic velocity

Study deleted	IoV random effect model estimation if the study is deleted				Heterogeneity		Relative weights IoV REM (%)
	OR	95% CI		OR change, %	I^2, %	*P* value	
Valcamonico et al[31] (1994)	7.36	4.62	11.71	−1.1	0	.583	2.1
Ozcan et al[32] (1998)	7.50	4.72	11.94	0.8	0	.582	1.9
Hofstaetter et al[34] (2002)	7.04	4.37	11.34	−5.4	0	.609	8.4
Soregaroli et al[35] (2002)	6.11	4.23	8.83	−17.8	0	.490	12.2
Ertan et al[37] (2003)	7.17	4.57	11.24	−3.7	0	.612	2.2
GRIT Study Group[20] (2003)	7.92	5.10	12.30	6.4	0	.627	3.7
Figueras et al[39] (2004)	7.17	4.59	11.19	−3.7	0	.618	1.9
Cosmi et al[12] (2005)	7.65	4.81	12.17	2.8	0	.595	3.3
Schwarze et al[40] (2005)	7.92	5.02	12.49	6.4	0	.613	5.4
Crispi et al[42] (2008)	7.19	4.48	11.54	−3.3	0	.599	5.6
Shand et al[48] (2009)	7.31	4.59	11.63	−1.8	0	.588	2.7
Benavides-Serralde et al[50] (2011)	7.66	4.79	12.26	2.9	0	.596	4.7
Cruz-Lemini et al[52] (2012)	8.16	5.15	12.93	9.7	0	.602	9.8
Abdelhalim et al[53] (2014)	7.19	4.55	11.36	−3.4	0	.602	2.7
Crimmins et al[54] (2014)	7.14	4.31	11.84	−4.0	0	.630	13.4
Frauenschuh et al[55] (2015)	7.44	4.68	11.85	0	0	.580	2.0
Ganzevoort et al[58] (2017)	7.73	4.88	12.25	3.9	0	.602	3.6
Monier et al[56] (2017)	8.40	5.31	13.30	12.8	0	.535	14.6

Umbilical artery reverse end-diastolic velocity Egger Publication Bias, _cons 0.100, SE, 0.597, t = 0.17, $P = .868$ (−1.16 to 1.36).

CI, confidence interval; *OR*, odds ratio; *IoV*, Inverse of Variance; *REM*, Random Effect Model.

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SUPPLEMENTAL TABLE 4
Influence analysis on umbilical artery absent or reverse end-diastolic velocity

Study deleted	IoV random-effect model estimation if the study is deleted						Relative weights IoV REM (%)
	OR	95% CI		OR change, %	Heterogeneity		
					I^2, %	*P* value	
Battaglia et al[33] (1993)	7.31	4.72	11.32	2.0	0	NS	1.4
Valcamonico et al[31] (1994)	7.10	4.58	11.00	−1.0	0	NS	2.1
Ozcan et al[32] (1998)	7.27	4.68	11.29	1.5	0	NS	1.7
Madazli et al[33] (2001)	7.20	4.58	11.30	0.4	0	NS	5.3
Hofstaetter et al[34] (2002)	6.81	4.36	10.63	−5.0	0	NS	7.7
Soregaroli et al[35] (2002)	6.56	4.21	10.21	−8.5	0	NS	11.3
Baschat et al[36] (2003)	6.77	4.46	10.27	−5.6	0	NS	2.4
Ertan et al[37] (2003)	6.90	4.51	10.57	−3.7	0	NS	2.0
GRIT Study Group[20] (2003)	7.09	4.58	10.97	−1.1	0	NS	1.8
Bilardo et al[38] (2004)	7.18	4.63	11.13	0.1	0	NS	1.3
Figueras et al[39] (2004)	7.09	4.57	10.98	−1.1	0	NS	2.0
Cosmi et al[12] (2005)	7.18	4.62	11.15	0.1	0	NS	2.0
Mari et al[41] (2007)	7.18	4.64	11.12	0.2	0	NS	1.0
Crispi et al[42] (2008)	7.09	4.59	10.96	−1.1	0	NS	1.4
Brodszki et al[46] (2009)	7.85	5.50	11.22	9.5	0	NS	8.6
Robertson et al[47] (2009)	7.67	5.13	11.45	6.9	0	NS	5.4
Shand et al[48] (2009)	7.22	4.64	11.23	0.7	0	NS	2.2
Spinillo et al[49] (2009)	7.27	4.68	11.29	1.4	0	NS	1.8
Benavides-Serralde et al[50] (2011)	7.10	4.56	11.05	−1.1	0	NS	3.2
Turan et al[51] (2009)	6.90	4.47	10.66	−3.7	0	NS	3.6
Cruz-Lemini et al[52] (2012)	7.02	4.55	10.82	−2.1	0	NS	1.6
Abdelhalim et al[53] (2014)	7.05	4.55	10.92	−1.6	0	NS	2.4
Crimmins et al[54] (2014)	6.85	4.34	10.81	−4.4	0	NS	10.0
Ganzevoort et al[58] (2017)	7.68	5.08	11.62	7.2	0	NS	5.7
Monier et al[56] (2017)	7.89	5.08	12.27	10.1	0	NS	12.3

Umbilical artery absent or reverse end-diastolic velocity Egger Publication Bias. _cons, 0.678, SE, 0.451, t = 1.50, $P = .147$ (−0.25 to 1.61).

CI, confidence interval; *IoV*, inverse of variance; *NS*, not significant; *OR*, odds ratio; *REM*, random effect model.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

SUPPLEMENTAL TABLE 5

Influence analysis on ductus venosus absent or reverse end-diastolic velocity

Study deleted	IoV random-effect model estimation if the study is deleted						Relative weights IoV REM, %
					Heterogeneity		
	OR	95% CI		OR change, %	I^2, %	*P* value	
Ozcan et al[32] (1998)	12.11	6.67	21.99	1.9	0	NS	2.9
Baschat et al[36] (2003)	10.62	5.79	19.45	−10.7	0	NS	10.1
Bilardo et al[38] (2004)	11.48	6.26	21.05	−3.4	0	NS	4.8
Cosmi et al[12] (2005)	12.08	6.57	22.22	1.6	0	NS	5.5
Schwarze et al[40] (2005)	12.62	6.90	23.08	6.2	0	NS	7.0
Hernández-Andrade et al[43] (2008)	12.59	6.95	22.83	5.9	0	NS	5.3
Picconi et al[44] (2008)	11.35	6.26	20.61	−4.5	0	NS	3.6
Rizzo et al[45] (2008)	12.00	6.50	22.15	1.0	0	NS	5.9
Turan et al[51] (2009)	10.96	5.84	20.53	−7.8	0	NS	10.3
Cruz-Lemini et al[52] (2012)	12.23	6.51	22.95	2.8	0	NS	9.6
Crimmins et al[54] (2014)	10.04	5.82	17.30	−15.5	0	NS	12.6
Frauenschuh et al[55] (2015)	11.70	6.40	21.45	−1.5	0	NS	3.8
Lees et al[57] (2015)	17.17	11.28	26.16	44.4	0	NS	10.2
Monier et al[56] (2017)	12.06	6.45	22.55	1.4	0	NS	8.4

Ductus venosus absent or reverse end-diastolic velocity Egger Publication Bias, _cons, −1.01, SE, 1.02, t = −0.99, $P = .341$ (−3.25 to 1.22).

CI, confidence interval; *NS*, not significant; *OR*, odds ratio; *IoV*, Inverse of Variance; *REM*, Random Effect Model.

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