Placental lesions in small for gestational age fetuses with and without clinical features of fetal growth restriction: a secondary analysis of the Doppler Ratio In fetal Growth restriction Intervention Trial At (near) Term (DRIGITAT) study

Marijnen, M.C.; Meeren, L.E. van der; Schoots, M.H.; Freedman, A.A.; Ernst, L.M.; Bazyleva, E.; ... ; DRIGITAT Trial Grp

OBSTETRICS

Placental lesions in small for gestational age fetuses with and without clinical features of fetal growth restriction: a secondary analysis of the Doppler Ratio In fetal Growth restriction Intervention Trial At (near) Term (DRIGITAT) study

M. C. Marijnen, MD; L. E. van der Meeren, MD, PhD; M. H. Schoots, MD, PhD; A. A. Freedman, PhD; L. M. Ernst, MD, PhD; E. Bazyleva; W. Ganzevoort, MD, PhD; S. J. Gordijn, MD, PhD; DRIGITAT Trial Group*

OBJECTIVE: The primary pathophysiological mechanism underlying fetal growth restriction is placental insufficiency, which can be attributed to various placental lesions. It is unknown if ultrasound markers can antenatally detect and distinguish between different placental lesions and their grading. This study aimed to investigate the association between placental lesions, clinical markers, including Doppler velocimetry, and birth outcome.

STUDY DESIGN: This study was a secondary analysis of the DRIGITAT study, a multicenter prospective cohort with nested randomized controlled trial of late preterm small for gestational age pregnancies. Placental slides were independently revised, scored, and classified using a digital synoptic reporting tool, according to the Amsterdam Consensus criteria and the Freedman-Ernst subclassification, by 2 perinatal pathologists blinded to clinical data, except for gestational age. Pregnancy characteristics and birth outcomes of cases with placental pathology available were compared to those without. Within the group with pathology available, participants were classified as fetal growth restriction (2 consecutive abnormal Doppler measurements: umbilicocerebral ratio>0.8 or umbilical artery pulsatility index>p90 or both abnormal), potential fetal growth restriction (once or intermittent abnormal umbilicocerebral ratio or umbilical artery pulsatility index or both abnormal), or small for gestational age not otherwise specified (never-abnormal umbilicocerebral ratio or umbilical artery pulsatility index). Placental lesion prevalence and grading were analyzed in relation to Doppler ultrasound findings (umbilicocerebral ratio>0.8 or umbilical artery pulsatility index>p90), biomarkers (placental growth factor, and the soluble fms-like tyrosine kinase-1 placental growth factor ratio), birthweight percentiles, and composite adverse perinatal outcome. The potential relation between grading of maternal vascular malperfusion, fetal vascular malperfusion, and chronic inflammation (CI) and Doppler ultrasound and composite adverse perinatal outcome were calculated by performing a multinomial logistic regression analysis yielding a likelihood in terms of an odds ratio and 95% confidence intervals (95% CI). We used inverse probability weighting to account for selection bias in the pathology sample and adjusted odds ratios were calculated.

RESULTS: Of the 690 participants, 294 placentas (42.6%) were available for this analysis, while placental pathology was unavailable for 396 participants (57.4%). Prelabor caesarean for suspected fetal distress was significantly more frequent in the group with pathology available (37.2%) compared to the group without pathology available (11.4%). In the fetal growth restriction group, 37.8% of placentas showed high-grade maternal vascular malperfusion, vs 18.2% in the small for gestational age not otherwise specified group; high-grade fetal vascular malperfusion was found in 28.9% and 15.1%, respectively. High-grade maternal vascular malperfusion was associated with the greatest odds of fetal growth restriction, with an adjusted odds ratio of 2.6 (95% CI, 1.7—4.2; p<.001). The adjusted odds ratio for high-grade fetal vascular malperfusion was 1.9 (95% CI, 1.2—3.0; p .01). Both high-grade maternal vascular malperfusion and high-grade fetal vascular malperfusion were significantly associated with composite adverse perinatal outcome. High-grade maternal vascular malperfusion was significantly more frequent if maternal serum placental growth factor and soluble fms-like tyrosine kinase-1:placental growth factor ratio were abnormal.

CONCLUSION: Among the small for gestational age infants, clinical features of fetal growth restriction are associated with high-grade maternal vascular malperfusion and high-grade fetal vascular malperfusion and the combined presence of these lesions. Both lesions may manifest antenatally with Doppler abnormalities (umbilicocerebral ratio>0.8 or umbilical artery pulsatility index>p90).

Key words: cerebroplacental ratio, Doppler velocimetry, fetal growth restriction, placenta pathology, small for gestational age, umbilicocerebral ratio

Introduction

Placental insufficiency is the primary pathophysiologic mechanism resulting in fetal growth restriction (FGR), where the fetus fails to reach its intrinsic growth potential.[1,2] FGR significantly contributes to (preventable) stillbirths, adverse neurodevelopmental outcomes, and long-term cardiovascular risks.[3–6]

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AJOG at a Glance

Why was this study conducted?

To investigate the association of placental lesions with clinical features, Doppler ultrasound, biomarkers, and birthweight percentiles in small for gestational age (SGA) or fetal growth restriction (FGR) pregnancies.

Key findings

High-grade maternal vascular malperfusion (MVM) and high-grade fetal vascular malperfusion (FVM) are markedly more frequent in FGR than in SGA not otherwise specified. Both lesion categories are associated with abnormal Doppler antenatally. High-grade MVM is associated with abnormal serum biomarkers. Clinicians should be aware of increased perinatal risks in cases of high-grade lesions, as indicated by abnormal Doppler findings.

What does this add to what is known?

Clinical FGR features are associated not only with high-grade MVM but also with high-grade FVM, and combined presence. High-grade lesions can be antenatally detected by Doppler ultrasound. Standardized and structured reporting of placental lesions by perinatal pathologists using a digital synoptic reporting tool leads to comprehensiveness of the pathology report which enables data comparison.

Small for gestational age (SGA) is often used as a proxy for FGR. As there is no measure of individual growth potential, fetuses are compared to population statistics to define small size. Typically, SGA is defined as an estimated fetal weight (EFW) or birthweight below the 10th percentile (p10).[7] SGA indicates smallness but does not discriminate between pathological or constitutional smallness. The 2016 FGR consensus definition aimed to better identify FGR, incorporating not only (severe) smallness but also functional placental parameters, including the cerebroplacental ratio (CPR) and crossing growth percentiles, indicating redistribution of the fetal circulation and slow fetal growth velocity, respectively.[8]

Maternal serum biomarkers including placental growth factor (PlGF) and the soluble fms-like tyrosine kinase-1:PlGF (sFlt-1:PlGF) ratio, help differentiate risk profiles for adverse outcomes in SGA not otherwise specified (NOS) and FGR, mainly related to maternal hypertensive disorders of pregnancy.[9–13] Initial DRIGITAT analyses showed that low PlGF (99 pg/mL) and high sFlt-1:PlGF ratio (>33) in the third trimester were associated with adverse neonatal outcomes.[13]

Placental lesions underlying placental insufficiency vary, and the relation with clinical (ultrasound) markers remains incompletely understood. According to the Amsterdam Consensus criteria, lesions are grouped into 4 categories: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), acute inflammation (AI), and chronic inflammation (CI).[14–16] Additionally, some placental lesions are classified under a separate category termed other significant pathology. Many studies have linked obstetric conditions to individual lesions. Combining placental lesions may reveal more detailed underlying pathophysiologic mechanisms related to clinical features and adverse outcomes.[14] Understanding the etiology and interaction of placental lesions, incorporating severity and multiplicity, can help personalize monitoring and management for individual patients and inform management for subsequent pregnancies.

We hypothesized that distinct placental lesions would correlate with different ultrasound markers. MVM is characterized by high-resistance vasculature in both maternal and fetal vessels, making it clinically detectable. In FVM, this association had not been identified and the study team feared that FVM fetuses, also with increased risk of stillbirth, may be underdetected. Chronic inflammation has previously not been linked to Doppler abnormalities.[17] This study aimed to investigate associations of placental lesions with clinical features, Doppler ultrasound, maternal biomarkers, and birthweight in a secondary analysis of the DRIGITAT study.[13]

Materials and methods

Study setting

This was a secondary analysis of the DRIGITAT study, a multicenter prospective cohort of late preterm SGA pregnancies with nested randomized controlled trial comparing expedited birth to expectant monitoring in SGA fetuses with recurrent abnormal Doppler measurements until term age. The study protocol and primary outcomes have been previously published and are summarized below.[13,18]

Participants

Pregnant women from 32+0 to 36+6 weeks with a singleton pregnancy were eligible for cohort inclusion if their fetus had an EFW or fetal abdominal circumference <p10.[19–21] Gestational age and the estimated date of delivery were established using crown-rump length measured during the first-trimester dating scan before study enrollment.

Procedures

Participants underwent routine care per local protocol, including at least two weekly biometry and weekly Doppler ultrasound scans, in which the pulsatility indices (PIs) of the umbilical artery (UmbA) and middle cerebral artery (MCA) were measured. Doppler percentiles were calculated according to Arduini and Rizzo.[22] The umbilicocerebral ratio (UCR), which is the inverse of the CPR, was calculated by dividing PI values of the UmbA and MCA. Guidance and safety net criteria were given regarding the timing of birth.[18]

Biomarkers

Maternal blood samples were drawn at enrollment and stored for biomarker

analysis. sFlt-1 and PlGF levels were measured using Roche Elecsys assays on the Cobas e601-module (Roche Diagnostics, Basel, Switzerland). Abnormal sFlt-1:PlGF ratio was defined as >33, and abnormal PlGF as ≤99.[23–25]

Clinical difference between small for gestational age and fetal growth restriction

We grouped participants as FGR, potential FGR, or SGA NOS based on Doppler ultrasound findings. If the UCR (>0.8) or UmbA PI (>p90) or both were abnormal twice consecutively, participants were labeled FGR. Participants with inconsistent Doppler abnormalities (once or intermittent abnormal) were labeled potential FGR. Participants grouped as SGA NOS had no Doppler abnormalities. Participants with FGR were eligible for randomization. In this exploratory analysis, we included all randomized participants (immediate birth vs expectant monitoring) and eligible participants who declined randomization but consented to cohort follow-up.

Placental examination

Clinicians were encouraged to submit placentas for histopathologic examination.[16,18] In the Netherlands, routine indications include (severe) FGR, stillbirth, asphyxia, suspected infection, and macroscopic abnormalities.[26] Placentas were sampled according to the Amsterdam Consensus criteria sampling routine; therefore at least 4 blocks were available.[16] Each perinatal pathologist reviewed half of the cases independently. In instances of uncertainty, cases were discussed jointly by both perinatal pathologists until consensus was reached. Both pathologists were trained to use the Amsterdam Consensus criteria.

All placental slides (hematoxylin and eosin and additionally immunohistochemistry when available) were prospectively collected. Two perinatal pathologists (L.M. and M.S.), blinded for clinical data except for gestational age, scored and classified placentas. Main categories of placental pathology included MVM, FVM, CI, and AI, graded as absent, low-grade or high-grade. Staging and grading for FVM and AI were based on the Amsterdam Consensus criteria, while grading for MVM and CI was derived from the Freedman-Ernst subclassification.[14,16] A synoptic (digital) reporting tool for placenta pathology according to the Amsterdam Consensus criteria and Freedman-Ernst subclassification generated phenotypes of overlapping placental lesions.[14,16,27] Table 1 outlines major categories and included lesions.

Outcomes

Birthweight percentiles were based on sex-specific Hoftiezer charts.[28] A composite adverse perinatal outcome (CAPO) was defined by 1) adverse condition at birth or 2) major neonatal morbidity or mortality:

1. Adverse condition at birth: fetal death or signs of asphyxia: a 5-minute Apgar score<7, an UmbA pH<7.0, or a venous pH<7.1, or neonatal resuscitation by ventilation, thoracic compressions, or need for vasoactive medication.
2. Major neonatal morbidity: cerebral morbidity (intracranial hemorrhage grade≥3, periventricular leukomalacia grade≥2, convulsions), respiratory morbidity necessitating respiratory support, circulatory morbidity, sepsis, necrotizing enterocolitis, or perinatal mortality (defined as neonatal death within the first 28 days).

TABLE 1
Major categories of placental lesions

Major category	Lesions included
Acute inflammation	Maternal: acute subchorionitis, acute chorionitis, acute chorioamnionitis, acute necrotizing amnionitis Fetal: acute chorionic vasculitis, phlebitis, arteritis or panvasculitis, acute funisitis
Chronic inflammation	Membranes or chorionic plate: chronic chorionitis, chronic chorioamnionitis Basal plate: chronic deciduitis with or without plasma cells, chronic decidual perivasculitis Villi: chronic villitis Intervillous space: chronic histiocytic intervillositis Fetal: chronic eosinophilic T-cell vasculitis, chronic inflammation fetal vessels
Fetal vascular malperfusion	Thrombi or intramural fibrin deposition in chorionic vessel, velamentous vessel, stem villous vessel and/or umbilical vessel; avascular villi, villous stromal vascular karyorrhexis
Maternal vascular malperfusion	Fibrinoid necrosis or acute atherosis, muscularization of basal plate arterioles, mural hypertrophy of membrane arterioles, basal decidual vascular thrombus, single infarct or multiple infarcts, increased syncytial knots, villous agglutination, increased perivillous fibrin deposition[a], distal villous hypoplasia, retroplacental blood or hematoma, retroplacental hematoma with hemosiderin or infarct, placental hypoplasia (in presence of one other maternal vascular lesion)
Other significant pathology	Hemosiderosis, massive perivillous fibrin deposition[b], myonecrosis, amnion nodosum, delayed villous maturation, chorangiosis, isolated low placental weight (placental hypoplasia)

[a] According to the Freedman-Ernst criteria, categorized as maternal vascular malperfusion; [b] According to the Freedman-Ernst criteria, categorized as other significant pathology. While recent studies suggest that these lesions may represent chronic thrombo-inflammatory disorders, we adhered to our predefined classification criteria.

Statistical analysis

Categorical baseline characteristics were summarized as numbers and percentages based on observations available and compared using chi-square tests. Continuous variables were presented as medians with interquartile ranges and compared using Kruskal-Wallis test. Frequencies of MVM, FVM, and CI and their grading (high-grade, low-grade, none) were calculated and compared using chi-square test, for different subgroups:

1. FGR classification based on Doppler (FGR, potential FGR, SGA NOS);
2. Birthweight percentile (<p3; p3−p10; ≥p10);
3. CAPO (present; absent);
4. PlGF (abnormal: ≤99; normal: >99);
5. sFlt-1:PlGF ratio (sFlt-1:PlGF>33; sFlt-1:PlGF≤33).

For the FGR classification, birthweight percentile and CAPO groups, a subanalysis was performed for chronic villitis (high-grade, low-grade, none).

Multinomial logistic regression analyses were performed to assess the association between placental lesions and FGR classification, with odds ratios (ORs) and 95% confidence intervals (CI). To correct for selection bias in the pathology sample, we applied inverse probability weighting (IPW),[14,29,30] modeling the probability of selection into the pathology sample based on maternal age, gestational diabetes, hypertensive disorders or pregnancy, preterm birth, birthweight percentile, mode of birth, and year of birth. Cases overrepresented in the pathology sample relative to the full study population (high probability of selection) were assigned lower weights, while underrepresented cases (low probability of selection) were given higher weights. This ensures that cases are proportionally represented based on their probability of inclusion, thereby reducing the effects of selection bias. ORs were also calculated for CAPO groups.

Venn diagrams were created to visually represent overlap and distinction of placental lesions in the FGR and SGA NOS groups (MVM, FVM, CI, no lesions).

Also, analyses were performed for all placental phenotypes according to the Freedman-Ernst subclassification generated by the synoptic reporting tool for FGR classification groups.[15]

Differences with P values <.05 were considered statistically significant. Analyses were performed using SPSS software.[31]

Results

Enrolment ran from January 1st, 2018, until April 25th, 2022, across 19 centers (12 secondary and 7 tertiary care centers). Of 692 women included, 2 were excluded because of missing biometry and Doppler data. Despite the general study advice to submit placentas for examination, only 294 placentas (42.6%) were examined, with the highest rates in the FGR group (65.2%), followed by potential FGR (40.5%) and SGA NOS (36.1%) (Supplemental Figure 1). Among examined placentas, 39.1% were from secondary care centers and 60.9% from tertiary care centers (Supplemental Table 1).

Supplemental Table 2 compares pregnancy characteristics and birth outcomes between those with (n=294) and without (n=396) placental pathology available. The group with placental pathology available showed more severe features of FGR (elevated UmbA PI, low MCA PI, high UCR, abnormal PlGF, and sFlt-1:PlGF ratio) and worse outcomes, including higher rates of prelabor caesareans for fetal distress (37.2% vs 11.4%), birthweight<p3 (67.0% vs 38.1%), and CAPO (37.4% vs 14.1%).

Table 2 presents placental lesion grading in FGR classification groups. Only 21 (7.1%) of all examined placentas were histologically normal. High-grade MVM and high-grade FVM were significantly more frequent in the FGR group compared to the SGA NOS group (37.8% vs 18.2% for MVM (p .001) and 28.9% vs 15.1% for FVM; p .009). The high-grade FVM lesions driving the association are presented in Supplemental Table 3. CI or chronic villitis did not differ significantly between groups.

Table 3 shows placental lesions in birthweight percentile groups. Placentas from neonates with birthweights <p3 were overrepresented in the pathology sample (67.0%) compared to those not reviewed (38.1%) (Supplemental Table 2). High-grade FVM was significantly more frequent in <p3 (23.4%) compared to p3 to p10 (9.1%; p .012). Low-grade FVM was significantly less frequent in <p3 compared to >p10 (18.3 vs 38.7%, p .009). No significant differences were found for MVM, CI, or chronic villitis.

Table 4 presents adjusted ORs (aORs) and 95% CIs of FGR and potential FGR. High-grade MVM and high-grade FVM were associated with an increased odds of FGR. High-grade MVM was associated with the greatest odds of FGR based on Doppler abnormalities (UCR>0.8 or UmbA PI>p90), with an aOR of 2.6 (95% CI, 1.7−4.2). The aOR for high-grade FVM was 1.9 (95% CI, 1.2−3.0).

MVM, FVM, CI, and their grading related to CAPO is presented in Supplemental Table 4. High-grade MVM and high-grade FVM were significantly more frequent in the CAPO group. The aOR for high-grade MVM was 1.8 (95% CI, 1.2−2.7; p 0.006) and for high-grade FVM 2.1 (95% CI, 1.4−3.3; p<.001). The most frequently observed adverse outcome contributing to CAPO was metabolic morbidity, defined as hypoglycemia or jaundice requiring treatment, occurring in 61.8% of cases. This was followed by respiratory morbidity, with 34.6% of newborns requiring respiratory support (Supplemental Table 5).

Supplemental Tables 6 and 7 show MVM, FVM, and CI in relation to PlGF and sFlt-1:PlGF ratio. High-grade MVM was significantly more frequent in the abnormal PlGF group (42.2%) compared to the normal group (15.6%; p<.001). High-grade MVM was significantly more frequent in the abnormal sFlt-1:PlGF ratio group (40.3%) compared to the normal group (14.2%; p<.001).

Supplemental Figures 2 and 3 illustrate overlapping placental lesions across the FGR and SGA NOS groups. In FGR,

TABLE 2
Placental lesions in FGR classification groups (N = 294)

Placental pathology	FGR (n=90)	Potential FGR (n=45)	SGA NOS (n=159)
Histologically normal	3 (3.3%)	3 (6.7%)	15 (9.4%)
Maternal vascular malperfusion[a]			
Total (all grades)	57 (63.3%)	26 (57.8%)	87 (54.7%)
High-grade	34 (37.8%)[b]	14 (31.1%)	29 (18.2%)
Low-grade	23 (25.6%)	12 (26.7%)	58 (36.5%)
None	33 (36.7%)	19 (42.2%)	72 (45.3%)
Fetal vascular malperfusion			
Total (all grades)	42 (46.7%)	17 (37.8%)	65 (40.9%)
High-grade	26 (28.9%)[c]	7 (15.6%)	24 (15.1%)
Low-grade	16 (17.8%)	10 (22.2%)	41 (25.8%)
None	48 (53.3%)	28 (62.2%)	94 (59.1%)
Chronic inflammation			
Total (all grades)	39 (43.3%)	23 (51.1%)	67 (42.1%)
High-grade	16 (17.8%)	9 (20.0%)	24 (15.1%)
Low-grade	23 (25.6%)	14 (31.1%)	43 (27.0%)
None	51 (56.7%)	22 (48.9%)	92 (57.9%)
Chronic villitis			
Total (all grades)	24 (26.7%)	13 (28.9%)	34 (21.4%)
High-grade	10 (11.1%)	4 (8.9%)	14 (8.8%)
Low-grade	14 (15.6%)	9 (20.0%)	20 (12.6%)
None	66 (73.3%)	32 (71.1%)	125 (78.6%)

FGR, fetal growth restriction, *SGA NOS*, small for gestational age not otherwise specified.

[a] Pearson chi-square test p 0.014; [b] Difference with group never-abnormal Doppler p 0.001; [c] Difference with group never-abnormal Doppler p 0.009.

MVM was found in 75.0%, with frequent overlap: MVM+FVM in 19.7% and all 3 lesions in 25.0%. FVM alone was uncommon (5.3%) (Supplemental Figure 2). In SGA NOS, MVM occurred in 61.3%, FVM in 45.8% and CI in 47.2% (Supplemental Figure 3).

Supplemental Table 8 presents patterns of overlapping lesions by Freedman-Ernst classification in the FGR groups. Low-grade lesions only (group 6a, 7a, 7b) were observed in 26.7% of the FGR group. All 3 high-grade pathologies occurred in 5.6% of the FGR group compared to 0.0% in the SGA NOS group. Other overlapping lesions did not differ significantly between groups.

Comments

Principal findings

Among near-term and term SGA pregnancies, high-grade MVM and high-grade FVM were markedly more frequent in FGR than in SGA NOS. High-grade MVM was more frequent with abnormal maternal serum biomarkers. The main finding is that high-grade MVM and high-grade FVM were associated with abnormal Doppler measurements (UCR>0.8 or UmbA PI>p90) and that severity of lesions is important in risk classification.

The contrast between the FGR and SGA NOS groups suggests that Doppler abnormalities (UCR>0.8 or UmbA PI>p90) may possibly serve as an effective tool to identify placental dysfunction due to high-grade MVM and high-grade FVM. The lack of significant differences in low-grade MVM, FVM, CI, or chronic villitis indicates that Dopplers are less effective at detecting these lesions.

Results in the context of what is known

In a previous study by Freedman et al[14], investigating associations of placental phenotypes with birthweight, the prevalence of SGA infants (not specified for Doppler abnormalities) varied with grade and type of pathology. In the group characterized by ≥2 multiple high-grade pathologies (MVM, FVM, or CI), up to 48.7% were SGA, with an average of 39.0%.[14] In the "triple threat" subgroup, including all 3 high-grade pathologies, the percentage of SGA infant was 38.2%.[14] Our study, including Doppler measurements (UCR and UmbA PI) as a clinical feature of FGR, showed significant differences in high-grade MVM and high-grade FVM in FGR compared to SGA NOS. Overlapping lesions in the FGR group most often involved MVM, FVM, and CI. Our results align with the findings of Freedman et al, that severity and multiplicity of lesions are important in risk association in SGA, and extend this previous work by demonstrating the utility of Doppler measurements in improving risk stratification.

A well-known moderate association exists between MVM and abnormal Doppler PIs of the uterine artery and UmbA.[32,33] However, the association of FVM with Dopplers is less well-established.[34,35] A recent study by Shmueli et al[36] found that an abnormal CPR was an independent risk factor for both MVM and FVM. Our study not only confirms these results but also builds upon them by incorporating a grading system, further enhancing the scope of previous findings.

Our findings also align with the recently published consensus-based near-miss criteria for stillbirth, which recognize high-grade placental lesions as a significant marker of stillbirth risk.[37]

TABLE 3
Placental lesions in birthweight percentile groups (N = 294)*

Placental pathology	<p3 (n=197)	p3–p10 (n=66)	≥p10 (n=31)
Histologically normal	16 (8.1%)	4 (6.1%)	1 (3.2%)
Maternal vascular malperfusion			
Total (all grades)	114 (57.9%)	27 (40.9%)	19 (61.3%)
High-grade	60 (30.5%)	12 (18.2%)	5 (16.1%)
Low-grade	54 (27.4%)	25 (37.9%)	14 (45.2%)
None	83 (42.1%)	29 (43.9%)	12 (38.7%)
Fetal vascular malperfusion[a]			
Total (all grades)	82 (41.6%)	25 (37.9%)	17 (54.8%)
High-grade	46 (23.4%)[b]	6 (9.1%)	5 (16.1%)
Low-grade	36 (18.3%)[c]	19 (28.8%)	12 (38.7%)
None	115 (58.4%)	41 (62.1%)	14 (45.2%)
Chronic inflammation			
Total (all grades)	90 (45.7%)	26 (39.4%)	13 (41.9%)
High-grade	36 (18.3%)	9 (13.6%)	4 (12.9%)
Low-grade	54 (27.4%)	17 (25.8%)	9 (29.0%)
None	107 (54.3%)	40 (60.6%)	18 (58.1%)
Chronic villitis			
Total (all grades)	50 (25.4%)	13 (19.7%)	8 (25.8%)
High-grade	22 (11.2%)	3 (4.5%)	5 (16.1%)
Low-grade	28 (14.2%)	10 (15.2%)	3 (9.7%)
None	147 (74.6%)	53 (80.3%)	23 (74.2%)

[a] Pearson chi-square test p 0.013; [b] Difference with group p3 to p10 p 0.012; [c] Difference with group >p10 p 0.009; * Missing placentas: in birthweight <p3 group, 151/348 (43.4%) placentas were missing. In birthweight p3 to p10 group, 144/210 (68.6%) placentas were missing. In birthweight >p10 group, 101/132 (76.5%) placentas were missing.

These criteria were developed in the context of stillbirth research to account for intervention bias and the Hawthorne effect (change in behavior of doctors and patients due to increased awareness of risks).[37,38] By identifying high-grade placental lesions as a contributing factor in cases where adverse outcomes may have been averted by timely intervention, our results support its inclusion in near-miss definitions. Moreover, because many of these placental lesions have a high risk of recurrence, their identification is clinically relevant for guiding management in subsequent pregnancies.

The finding that high-grade MVM is more frequent with abnormal PlGF value or sFlt-1:PlGF ratio supports previous research linking these biomarkers to placental insufficiency and hypertensive disorders of pregnancy.[25,39,40] Our study further demonstrates that the occurrence of MVM is also associated with the studied maternal serum biomarkers. Thus, MVM may drive associations between these biomarkers and hypertensive disorders of pregnancy.

Placental examination remains debated.[41] Critics argue that lesion sensitivity for adverse outcomes is low and examination should be limited to stillbirth or asphyxia cases.[42] Advocates emphasize that examination is essential to understand the biology of pregnancy outcomes, to improve neonatal and maternal outcomes, and to guide care in subsequent pregnancies, though more research is needed.[43,44] Our study supports a more liberal approach to placental examination. First, our results confirmed the differentiation between low-risk SGA NOS and high-risk FGR. High-grade lesions were more frequent in FGR, identified by abnormal Doppler ultrasound. This strengthens the reliability of Doppler as a diagnostic tool to differentiate between FGR and SGA NOS. Second, identifying lesions following complicated pregnancies helps in recurrence risk calculation and can guide care in subsequent pregnancies, such as determining the need for low-dose aspirin (LDA) prophylaxis or timely birth. However, while LDA is known to prevent preterm preeclampsia and the associated MVM, its efficacy in preventing CI and FVM lesions remains unproven, although the benefit can be hypothesized for these lesions as well by immune modulation and mild antithrombotic effect.[32,45–47] To further elucidate LDA efficacy in other lesion categories, studies should perform stratified analyses of women in perinatal trials based on placental pathology (type and grade).[48] Third, generating a comprehensive pathology report allows pathology findings to be effectively communicated, enabling obstetricians to better inform patients about potential risks.

Strengths

A unique feature of this study is that placentas were prospectively collected with detailed clinical, ultrasound, and biomarker data. Two experienced perinatal pathologists (L.M. and M.S.) independently reviewed all placentas. Their expertise reduced the likelihood of missed lesions and ensures accurate lesion grading, minimizing interobserver variability.[41] A synoptic web-based reporting tool, recently developed through international collaboration, was used to promote uniform placental examination.[27] It generates a comprehensive pathology report, including phenotype classification based on the Amsterdam Consensus and Freedman-Ernst subclassification. A distinction is made between high-grade and low-grade lesions, expanding research possibilities. Using this tool reduces variability in

TABLE 4
ORs and IPW-adjusted ORs for FGR and potential FGR (N = 135)

	FGR (n=90)						Potential FGR (n=45)					
Placental pathology	OR	*P* value	95% CI	aOR	*P* value	95% CI	OR	*P* value	95% CI	aOR	*P* value	95% CI
MVM												
High-grade	2.6	.004	1.3–4.9	2.6	<.001	1.7–4.2	1.8	.15	0.81–4.1	1.7	.06	1.0–2.9
Low-grade	0.87	.65	0.46–1.6	0.77	.25	0.49–1.2	0.78	.55	0.35–1.8	0.69	.14	0.42–1.1
FVM												
High-grade	2.1	.02	1.1–4.1	1.9	.01	1.2–3.0	0.98	.97	0.38–2.5	0.92	.79	0.50–1.7
Low-grade	0.76	.43	0.39–1.5	0.75	.23	0.46–1.2	0.82	.63	0.36–1.8	0.83	.45	0.50–1.4
CI												
High-grade	1.2	.62	0.59–2.5	1.2	.58	0.69–2.0	1.6	.33	0.64–3.8	1.2	.62	0.64–2.1
Low-grade	0.96	.91	0.52–1.8	1.1	.81	0.68–1.6	1.4	.43	0.64–2.9	1.4	.14	0.89–2.3

aOR, adjusted odds ratio; *CI*, chronic inflammation; *FGR*, fetal growth restriction; *FVM*, fetal vascular malperfusion; *IPW*, inverse probability weighting; *MVM*, maternal vascular malperfusion; *OR*, odds ratio; *95% CI*, 95% confidence interval.

reporting. Additionally, we addressed selection bias in the pathology sample and the results remained consistent, confirming our associations.

Limitations

Our study also has limitations. The main limitation is selection bias toward abnormal clinical features, as mainly placentas from neonates with low birthweight or CAPO have been examined. Although sensitivity analyses following IPW were performed, the results should still be interpreted with caution due to potential residual selection bias. However, a recent study by Odom-Konja et al[49] found that selection bias has only a modest impact when using clinical pathology samples, even when only 50% of placentas undergo clinical examination. Low adherence to placental histologic examination might be the result of local protocol variations or costs.[26] In a study examining Dutch FGR protocols, 80% of protocols did not include any recommendation to perform pathological examination of the placenta.[26] This underscores the variability in routine clinical practice and likely contributed to the number of missing placental pathology reports in our study. Missing data, specifically in the SGA NOS group, may have hampered findings. The placentas of the SGA NOS group would have served as a control group assuming that these fetuses were constitutionally small. Unfortunately, a case-control analysis is hampered by the apparent selection bias. Selection bias towards placental examination in case of FGR and the low number of placentas without placental lesions likely resulted in a bias toward the null for all Freedman-Ernst phenotypes.

Clinical implications

Our findings demonstrate that both high-grade MVM and FVM are associated with Doppler abnormalities in FGR, improving risk stratification. While Dopplers (UCR and UmbA PI) may not differentiate between these lesion categories, they may provide a step toward more individualized care in pregnancies complicated by placental insufficiency. The sequence of placental changes and the time required for Doppler abnormalities to manifest remain unknown. It is also unclear whether SGA cases with high-grade lesions would develop Doppler abnormalities if the pregnancy were prolonged. This study highlights the clinical value of placental examination following complicated pregnancies. It emphasizes the importance of grading placental lesions for better risk assessment, as we found distinct associations with Doppler measurements. LDA may be considered in subsequent pregnancies following high-grade MVM.

Research implications

Future studies should compare study participants with abnormal and normal Dopplers, specifically UCR and UmbA PI, incorporating a larger number of control placentas of SGA NOS and appropriate for gestational age pregnancies to strengthen findings. In our opinion, structured placental pathology reporting, preferably using a uniform and globally available synoptic tool should be adopted in clinical practice to standardize and enhance the comprehensiveness of pathology reports and to improve data harmonization and comparison. Future trials should stratify women by placental pathology findings to evaluate the efficacy of interventions such as LDA across different lesion categories. A predictive model integrating Doppler measurements and placental lesions is needed for individualized risk assessment of high-risk FGR and low-risk SGA.

Conclusions

High-grade MVM and high-grade FVM are associated with Doppler abnormalities and increased neonatal risks. High-grade MVM was markedly more frequent in case of abnormal maternal serum biomarkers.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Initial ethical board approval for the execution of this trial was obtained from the Medical Research Ethics Committee (MREC) of the Amsterdam UMC—location AMC on 18 January 2018 (NL62923.018.17). The study was approved by the institutional review boards (IRB) of all participating centers prior to patient enrollment. Written, informed consent to participate was obtained from all participants. The trial was registered in the Netherlands Trial Register, registration number NTR6663, on 14 August 2017. ■

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Author and article information

From the Department of Obstetrics and Gynecology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands (Marijnen and Ganzevoort); Amsterdam Reproduction & Development Research Institute, Amsterdam, The Netherlands (Marijnen and Ganzevoort); Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (Marijnen and Gordijn); Department of Pathology, Leiden University Medical Center Leiden, Leiden, The Netherlands (van der Meeren); Department of Pathology, Erasmus Medical Center, University Medical Center, Rotterdam, The Netherlands (van der Meeren); Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (Schoots); Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA (Freedman); Department of Pathology and Laboratory Medicine, NorthShore/Endeavor Health, Evanston, Illinois, USA (Ernst); Department of Pathology, University of Chicago Pritzker School of Medicine, Chicago, Illinois, USA (Ernst); Belgian Society of Pathology, Brussel, Belgium (Bazyleva); and Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium (Bazyleva).

DRIGITAT Trial Group: J.M. Schaaf (Department of Obstetrics and Gynaecology, Flevo Hospital, Almere, The Netherlands; M.A. de Boer (Department of Obstetrics and Gynaecology, Amsterdam University Medical Centers, Amsterdam, The Netherlands); J.J. Zwart (Department of Obstetrics and Gynaecology, Deventer Hospital, Deventer, The Netherlands); A.J.M. Huisjes (Department of Obstetrics and Gynaecology, Gelre Hospital, Apeldoorn, The Netherlands); J.H.W. Veerbeek (Department of Obstetrics and Gynaecology, Diakonessenhuis, Utrecht, The Netherlands); J.O.E.H. van Laar (Department of Obstetrics and Gynaecology, Máxima Medical Center, Eindhoven, The Netherlands); S. Al-Nasiry (Department of Obstetrics and Gynaecology, Maastricht UMC+, Maastricht, The Netherlands); H.A. Bremer (Department of Obstetrics and Gynaecology, Reinier de Graaf Hospital, Delft, The Netherlands); B.B.J. Hermsen (Department of Obstetrics and Gynaecology, OLVG, Amsterdam, The Netherlands); H.P. van de Nieuwenhof (Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands); M. Sueters (Department of Obstetrics and Gynaecology, Leiden University Medical Center, Leiden, The Netherlands); D.P. van der Ham (Department of Obstetrics and Gynaecology, Martini Hospital, Groningen, The Netherlands), M.S. Post (Department of Obstetrics and Gynaecology, Medical Center Leeuwarden, Leeuwarden, The Netherlands); J. Baalman (Department of Obstetrics and Gynaecology, Medisch Spectrum Twente, Enschede, The Netherlands); J.B. Derks (Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht, The Netherlands); J.M. Sikkema (Department of Obstetrics and Gynaecology, Ziekenhuisgroep Twente, Almelo, The Netherlands); J.W. de Leeuw (Department of Obstetrics and Gynaecology, Ikazia Hospital, Rotterdam, The Netherlands).

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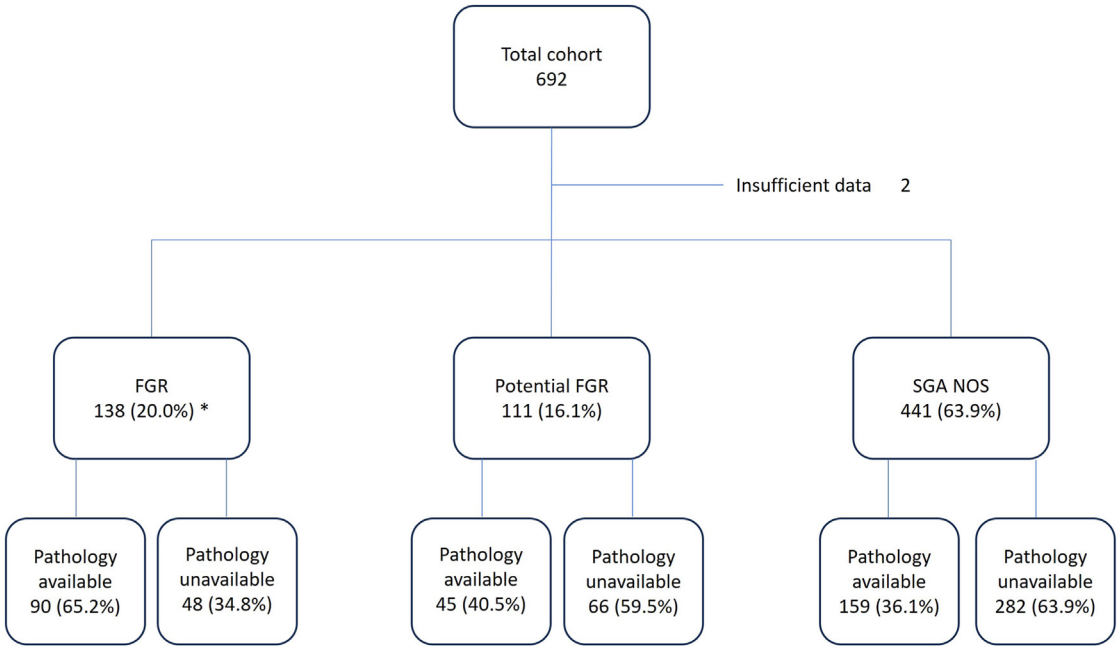
Corresponding author: M.C. Marijnen, MD. m.c.marijnen@amsterdamumc.nl

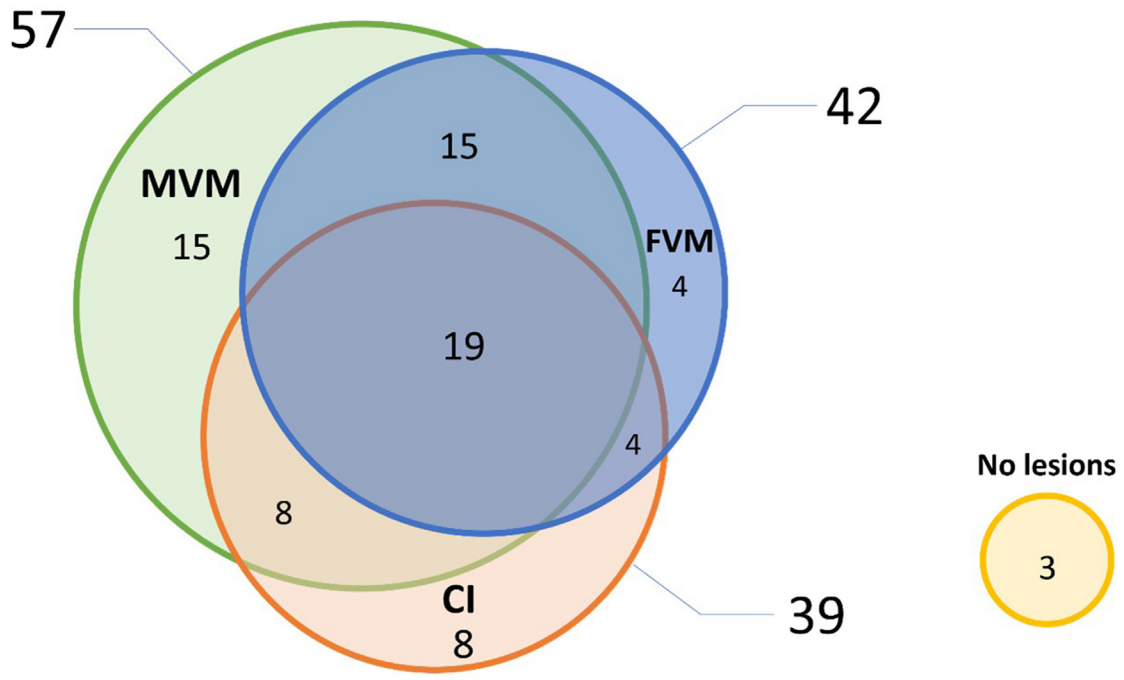
SUPPLEMENTAL FIGURE 1
Flowchart of cohort study population with different subgroups



FGR: Doppler abnormal twice consecutive. Potential FGR: Doppler abnormal once or intermittent. SGA NOS: Doppler never abnormal. Abnormal Doppler: umbilical artery pulsatility index above the 90th percentile or umbilicocerebral ratio>0.8 and EFW below the third percentile at 32 to 35 weeks or EFW below the 10th percentile at 36 weeks.

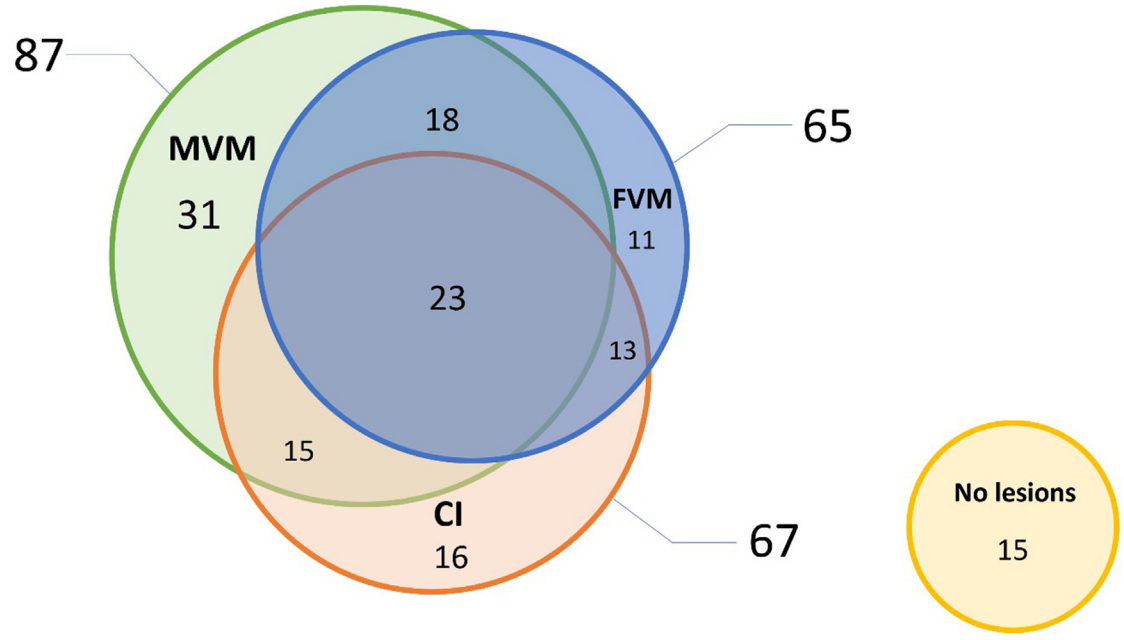
EFW, estimated fetal weight; *FGR*, fetal growth restriction; *SGA NOS*, small for gestational age not otherwise specified. *Including 6 women with absent or reverse end-diastolic flow in the umbilical artery.

SUPPLEMENTAL FIGURE 2
Venn diagram of overlapping lesions in FGR (n = 76)



CI, chronic inflammation; *FVM*, fetal vascular malperfusion; *MVM*, maternal vascular malperfusion.

SUPPLEMENTAL FIGURE 3
Venn diagram of overlapping lesions in SGA NOS (n = 142)



CI, chronic inflammation; *FVM*, fetal vascular malperfusion; *MVM*, maternal vascular malperfusion.

SUPPLEMENTAL TABLE 1
Distribution of examined placentas among secondary and tertiary care centers (n = 294)

Center	N, % of total (N=294)
Secondary care centers (n=12)	115, 39.1%
Tertiary care centers (n=7)	179, 60.9%

SUPPLEMENTAL TABLE 2
Pregnancy characteristics and birth outcomes study population (N = 690)

Characteristics	Pathology available	No pathology available	Total study population
General demographic and obstetric data			
N (%)	294 (42.6%)	396 (57.4%)	690
Maternal age (years)	31.0 (28.0–34.0)	31.0 (28.0–34.0)	31.0 (28.0–34.0)
BMI (kg/m^2)	23.7 (21.3–26.6)[a]	22.3 (20.4–25.7)	23.0 (20.8–26.0)
Smoking (2nd half of pregnancy)	19 (7.4%)	14 (4.1%)	33 (5.5%)
Low-dose aspirin use	27 (9.2%)	33 (8.3%)	60 (8.7%)
Nulliparous[b]	183 (62.2%)[c]	206 (52.0%)	389 (56.4%)
(Development of) gestational HT	22 (7.5%)	17 (4.3%)	39 (5.7%)
(Development of) preeclampsia[d]	52 (17.7%)[e]	35 (8.8%)	87 (12.6%)
Gestational diabetes	18 (6.1%)	18 (4.5%)	36 (5.2%)
At inclusion in cohort			
Gestational age (weeks)	34.0 (32.9–35.3)	34.3 (33.0–35.7)	34.1 (33.0–35.6)
EFW (grams)	1651.5 (1428.5–1921.5)[f]	17,560 (1566.0–1982.8)	1716.5 (1525.8–1960.3)
EFW<p3[d]	165 (56.1%)[e]	135 (34.1%)	300 (43.5%)
EFW MoM	0.76 (0.71–0.80)[f]	0.78 (0.75–0.81)	0.77 (0.73–0.81)
Umbilical artery PI	1.1 (0.90–1.3)[f]	0.98 (0.87–1.1)	1.01 (0.88–1.2)
Umbilical artery PI>p90 and PEDF[d]	50 (17.0%)[e]	34 (8.6%)	84 (12.2%)
Middle cerebral artery PI	1.7 (1.4–2.0)[g]	1.7 (1.5–2.0)	1.7 (1.4–2.0)
Middle cerebral artery PI<p5[h]	70 (25.3%)[i]	66 (18.1%)	136 (21.2%)
UCR	0.64 (0.49–0.82)[f]	0.56 (0.46–0.69)	0.59 (0.48–0.74)
UCR>0.8[d]	73 (26.4%)[f]	50 (13.7%)	123 (19.2%)
Abnormal Doppler twice consecutive	90/138	48/138	138
Percentage of abnormal Doppler twice group	65.2%	34.8%	N/A
Abnormal Doppler once or intermittent	45/111	66/111	111
Percentage of abnormal Doppler once or intermittent group	45.5%	54.5%	N/A
Never-abnormal Doppler	159/441	282/441	441
Percentage of never-abnormal Doppler group	36.1%	63.9%	N/A
PIGF≤99[d]	109/237 (46.0%)[f]	66/238 (27.7%)	175/475 (36.8%)
PIGF≤99 (without PE)[j]	69/194 (35.6%)[a]	46/214 (21.5%)	115/408 (28.2%)

(continued)

SUPPLEMENTAL TABLE 2

Pregnancy characteristics and birth outcomes study population (N = 690) *(continued)*

Characteristics	Pathology available	No pathology available	Total study population
sFlt-1:PlGF ratio>33[d]	124/237 (52.3%)[f]	81/238 (34.0%)	175/475 (36.8%)
sFlt-1:PlGF ratio>33 (without PE)[k]	83/194 (42.8%)[e]	59/214 (27.6%)	142/408 (34.8%)
Birth outcomes			
Spontaneous birth			
Total	173/294 (58.8%)	284/396 (71.7%)	457/690 (66.2%)
Spontaneous onset	36/173 (20.8%)	81/284 (28.5%)	117/457 (25.6%)
Induction of labor	137/173 (79.2%)	203/284 (71.5%)	340/457 (74.4%)
Instrumental vaginal			
Total	10/294 (3.4%)	16/396 (4.0%)	26/690 (3.8%)
Secondary presumed fetal distress	9/10 (90.0%)	14/16 (87.5%)	23/26 (88.5%)
Obstruction or prolonged labor	1/10 (10.0%)	2/16 (12.5%)	3/26 (11.5%)
Caesarean delivery			
Total	111/294 (37.8%)	96/396 (24.2%)	207/690 (30.0%)
Prelabor CS[l]	43/294 (14.6%)	44/396 (11.1%)	
Total	16/43 (37.2%)[m]	5/44 (11.4%)	87/690 (12.6%)
Fetal condition (CTG)	7/43 (16.3%)	1/44 (2.3%)	21/87 (24.1%)
Fetal condition (Doppler/EFW)	8/43 (18.6%)	15/44 (34.1%)	8/87 (9.2%)
Fetal presentation	7/43 (16.3%)	10/44 (22.7%)	23/87 (26.4%)
Maternal condition	2/43 (4.7%)	3/44 (6.8%)	17/87 (19.5%)
Maternal and fetal	3/43 (7.0%)[n]	10/44 (22.7%)	5/87 (5.7%)
Other			13/87 (14.9%)
Secondary CS	68/294 (23.1%)	52/396 (14.7%)	120/690 (17.4%)
Total	68/251 (27.1%)	52/352 (14.8%)	120/603 (19.9%)
Total (without prelabor CS)	35/251 (13.9%)	21/352 (6.0%)	56/603 (9.3%)
Fetal condition (CTG) (in group without prelabor CS)			
Fetal condition (CTG)	35/68 (51.5%)	21/52 (40.4%)	56/120 (46.7%)
Fetal condition (Doppler/EFW)	2/68 (2.9%)	2/52 (3.8%)	4/120 (3.3%)
Fetal presentation	10/68 (14.7%)	12/52 (23.1%)	22/120 (18.3%)
Prolonged labor or obstruction	5/68 (7.4%)	7/52 (13.5%)	12/120 (10.0%)

(continued)

SUPPLEMENTAL TABLE 2

Pregnancy characteristics and birth outcomes study population (N = 690) *(continued)*

Characteristics	Pathology available	No pathology available	Total study population
Maternal condition	4/68 (5.8%)	4/52 (7.7%)	8/120 (6.7%)
Maternal and fetal	3/68 (4.4%)	2/52 (3.8%)	5/120 (4.2%)
Other	9/68 (13.2%)	4/52 (7.7%)	13/120 (10.8%)
Gestational age at birth (weeks)	37.3 (36.3–38.4)[f]	38.3 (37.3–39.1)	38.0 (37.0–39.0)
Birthweight (grams)	2242.5 (1867.0–2550.0)[f]	2590.0 (2285.0–2890.0)	2457.5 (2055.0–2770.0)
Birthweight MoM	0.72 (0.65–0.78)[f]	0.79 (0.73–0.84)	0.76 (0.69–0.82)
Birth weight percentile			
≥p10	31 (10.5%)	101 (25.5%)	132 (19.1%)
p3–p10[d]	66 (22.4%)[f]	144 (36.4%)	210 (30.4%)
<p3[d]	197 (67.0%)[f]	151 (38.1%)	348 (50.4%)
Live birth	294 (100%)	396 (100%)	690 (100%)
Death shortly after birth (<24 h)	1 (0.34%)	0 (0.0%)	1 (0.14%)
Death >24 h after birth	2 (0.68%)	1 (0.3%)	3 (0.43%)
Fetal sex			
Female	159 (54.1%)	245 (61.9%)	404 (58.6%)
Male	135 (45.9%)	151 (38.1%)	286 (41.4%)
Apgar score 5' <7	7 (2.4%)	10 (2.5%)	16 (2.3%)
Composite adverse neonatal outcome[d]	110 (37.4%)[f]	56 (14.1%)	166 (24.1%)
Neonatal hospital days	5 (4–14)[f]	2 (2–4)	3 (2–7)
Placental weight (grams)	310.0 (266.0–367.0)	N/A	N/A

Abnormal Doppler = umbilical artery pulsatility index above the 90th percentile or umbilicocerebral ratio>0.8 and EFW below the third percentile at 32 to 35 wk or EFW below the 10th centile at 36 wk.

BMI, body mass index; *CS*, caesarean section; *CTG*, cardiotocography; *EFW*, estimated fetal weight; *HT*, hypertension; *MoM*, multiple of the median; *PE*, preeclampsia, *PEDF*, positive end-diastolic flow; *PI*, pulsatility index; *PlGF*, placental growth factor; *sFlt-1:PlGF*, soluble fms-like tyrosine kinase-1:placental growth factor; *UCR*, umbilicocerebral ratio.

[a] Difference with group no placental pathology p 0.002; [b] Pearson chi-square test p 0.007; [c] Difference with group no placental pathology p 0.007; [d] Pearson chi-square test $P<0.001$; [e] Difference with group no placental pathology p 0.001; [f] Difference with group no placental pathology $P<0.001$; [g] Difference with group no placental pathology p 0.022; [h] Pearson chi-square test p 0.029; [i] Difference with group no placental pathology p 0.029; [j] Pearson chi-square test p 0.002; [k] Pearson chi-square test p 0.001; [l] Pearson chi-square test p 0.026; [m] Difference with group no placental pathology p 0.005; [n] Difference with group no placental pathology p 0.039 BMI: 21 values (3.0%) missing, smoking: 90 values (13.0%) missing, middle cerebral artery: 49 values (7.1%) missing, UCR: 49 values (7.1%) missing, PlGF: 215 values (31.2%) missing, Flt-1:PlGF: 215 values (31.2%) missing, neonatal hospital days: 12 (1.7%) missing values, Placental weight: 31 (10.5%) missing values.

SUPPLEMENTAL TABLE 3
High-grade fetal vascular malperfusion lesions

High-grade FVM	N (%)
Avascular villi	24 (42.1%)
Avascular villi, villous stromal-vascular karyorrhexis	4 (7.0%)
Thrombi or intramural fibrin deposition in small stem vessels	2 (3.5%)
Thrombi or intramural fibrin deposition in small stem vessels, avascular villi	22 (38.6%)
Thrombi or intramural fibrin deposition in small stem vessels, avascular villi, villous stromal-vascular karyorrhexis	4 (7.0%)
Villous stromal-vascular karyorrhexis	1 (1.8%)
Total	57 (100%)

FVM, fetal vascular malperfusion.

SUPPLEMENTAL TABLE 4
Placental lesions in CAPO groups (N = 294)

Placental pathology	CAPO present (n=110)	CAPO absent (n=184)
Histologically normal	2 (1.8%)	19 (10.3%)
Maternal vascular malperfusion[a]		
Total (all grades)	68 (61.8%)	102 (55.4%)
High-grade	39 (35.5%)[b]	38 (20.7%)
Low-grade	29 (26.4%)	64 (34.8%)
None	42 (38.2%)	82 (44.6%)
Fetal vascular malperfusion		
Total (all grades)	52 (47.3%)	72 (39.1%)
High-grade	28 (25.5%)[c]	29 (15.8%)
Low-grade	24 (21.8%)	43 (23.4%)
None	58 (52.7%)	112 (60.9%)
Chronic inflammation		
Total (all grades)	53 (48.2%)	76 (41.3%)
High-grade	19 (17.3%)	30 (16.3%)
Low-grade	34 (30.9%)	46 (25.0%)
None	57 (51.8%)	108 (58.7%)
Chronic villitis		
Total (all grades)	31 (28.2%)	40 (21.7%)
High-grade	11 (10.0%)	17 (9.2%)
Low-grade	20 (18.2%)	23 (12.5%)
None	79 (71.8%)	144 (78.3%)

MVM high-grade odds ratio (OR), 2.0 (95% CI, 1.1–3.6; p 0.02); adjusted OR, 1.8 (95% CI, 1.2–2.7; p 0.006). FVM high-grade OR, 1.9 (95% CI, 1.0–3.4; p 0.045); adjusted OR, 2.1 (95% CI, 1.4–3.3; $P<.001$).

CAPO, composite adverse perinatal outcome.

[a] Pearson chi-square test p 0.019; [b] Difference with group CAPO absent p 0.005; [c] Difference with group CAPO absent p 0.042.

SUPPLEMENTAL TABLE 5
Individual adverse perinatal outcomes

Adverse outcome	N (110)	% (110)
Fetal death	0	0.0
Arterial pH<7.0 or venous pH<7.1	5	4.6
5-min Apgar score<7	7	6.4
Neonatal resuscitation	14	12.7
Respiratory morbidity	38	34.6
Cerebral morbidity	13	11.8
Circulatory morbidity	9	8.2
Metabolic morbidity	68	61.8
Sepsis	19	17.3
Necrotizing enterocolitis	0	0.0
Neonatal death within 28 d	3	2.7

SUPPLEMENTAL TABLE 6
Placental lesions in PlGF subgroups (N=237)[a]

Placental pathology	PlGF≤99 (n=109)	PlGF>99 (n=128)
Histologically normal	5 (4.6%)	11 (8.6%)
Maternal vascular malperfusion[b]		
Total (all grades)	77 (70.6%)	67 (52.3%)
High-grade	46 (42.2%)[c]	20 (15.6%)
Low-grade	31 (28.4%)	47 (36.7%)
None	32 (29.4%)[d]	61 (47.7%)
Fetal vascular malperfusion		
Total (all grades)	51 (46.8%)	54 (42.2%)
High-grade	26 (23.9%)	24 (18.8%)
Low-grade	25 (22.9%)	30 (23.4%)
None	58 (53.2%)	74 (57.8%)
Chronic inflammation		
Total (all grades)	58 (53.2%)	54 (42.2%)
High-grade	18 (16.5%)	23 (18.0%)
Low-grade	40 (36.7%)[e]	31 (24.2%)
None	51 (46.8%)	74 (57.8%)

PlGF, placental growth factor.

[a] 57 missing; [b] Pearson chi-square $P<.001$; [c] Difference with group PlGF>99 group $P<.001$; [d] Difference with group PlGF>99 group p 0.004; [e] Difference with group PlGF>99 group p 0.037.

SUPPLEMENTAL TABLE 7
Placental lesions in sFlt-1:PlGF ratio subgroups (N = 237)[a]

Placental pathology	sFlt-1:PlGF ratio>33 (n=124)	sFlt-1:PlGF ratio≤33 (n=113)
Histologically normal	5 (4.0%)	11 (9.7%)
Maternal vascular malperfusion[b]		
Total (all grades)	87 (70.2%)	57 (50.4%)
High-grade	50 (40.3%)[c]	16 (14.2%)
Low-grade	37 (29.8%)	41 (36.3%)
None	37 (29.8%)[d]	56 (49.6%)
Fetal vascular malperfusion		
Total (all grades)	58 (46.8%)	47 (41.6%)
High-grade	30 (24.2%)	20 (17.7%)
Low-grade	28 (22.6%)	27 (23.9%)
None	66 (53.2%)	66 (58.4%)
Chronic inflammation		
Total (all grades)	62 (50.0%)	50 (44.2%)
High-grade	20 (16.1%)	21 (18.6%)
Low-grade	42 (33.9%)	29 (25.7%)
None	62 (50.0%)	63 (55.8%)

sFlt-1:PlGF, soluble Fms-like tyrosine kinase 1:placental growth factor ratio.

[a] 57 missing; [b] Pearson chi-square $P<.001$; [c] Difference with group sFlt-1:PlGF≤33 group $P<.001$; [d] Difference with group sFlt-1:PlGF≤33 group p 0.002.

SUPPLEMENTAL TABLE 8

Prevalence of pathology phenotypes by Doppler classification groups (N = 294)

Group name and description	Group number	Included phenotypes	FGR (n=90)	Potential FGR (n=45)	Constitutional SGA (n=159)
Multiple high-grade pathologies (C, F, M)	1				
All 3 high-grade pathologies (triple threat)	1a	CFM, aCFM, ACFM	**5 (5.6%)**[a]	1 (2.2%)	0 (0.0%)
High-grade fetal AND maternal vascular pathology	1b	FM, cFM, aFM, acFM, AFM, AcFM	5 (5.6%)	3 (6.7%)	3 (1.9%)
High-grade maternal vascular pathology AND high-grade chronic inflammation	1c	CM, CfM, aCM, ACfM, ACM, ACfM	3 (3.3%)	2 (4.4%)	6 (3.8%)
High-grade fetal vascular pathology AND high-grade chronic inflammation	1d	FC, CFm, aFC, aCFm	4 (4.4%)	0 (0.0%)	8 (5.0%)
High-grade acute inflammation AND high-grade fetal vascular pathology (with or without chronic inflammation and/or low-grade maternal vascular pathology)	2	AF, AFm, AcF, AcFm, ACF, ACFm	0 (0.0%)	0 (0.0%)	4 (2.5%)
High-grade fetal vascular pathology					
With or without low-grade acute inflammation	3a	F, aF	2 (2.2%)	1 (2.2%)	4 (2.5%)
WITH low-grade chronic inflammation AND/OR low-grade maternal vascular pathology (with or without low-grade acute inflammation)	3b	cF, Fm, cFm, acF, aFm, acFm	9 (10.0%)	2 (4.4%)	5 (3.1%)
High-grade chronic inflammation					
With or without low-grade fetal vascular pathology	4a	C, Cf	1 (1.1%)	2 (4.4%)	3 (1.9%)
WITH any acute inflammation (with or without low-grade fetal vascular pathology)	4b	aC, aCf, AC, ACf	3 (3.3%)	1 (2.2%)	2 (1.3%)
WITH low-grade maternal vascular pathology (with or without low-grade fetal vascular pathology)	4c	Cm, Cfm	0 (0.0%)	1 (2.2%)	3 (1.9%)
WITH low-grade maternal vascular pathology AND any acute inflammation	4d	aCm, aCfm, ACm, ACfm	0 (0.0%)	**2 (4.4%)**[a]	0 (0.0%)
High-grade maternal vascular pathology (with or without any acute inflammation and/or other low-grade pathology)	5	M, cM, fM, cfM, aM, acM, afM, acfM, AM, AcM, AfM, AcfM	21 (23.3%)	8 (17.8%)	20 (12.6%)
Low-grade fetal vascular pathology OR chronic inflammation					
With or without low-grade acute inflammation	6a	c, f, ac, af	6 (6.7%)	8 (17.8%)	20 (12.6%)
WITH high-grade acute inflammation	6b	Ac, Af	1 (1.1%)	0 (0.0%)	2 (1.3%)

(continued)

SUPPLEMENTAL TABLE 8

Prevalence of pathology phenotypes by Doppler classification groups (N = 294) *(continued)*

Group name and description	Group number	Included phenotypes	FGR (n=90)	Potential FGR (n=45)	Constitutional SGA (n=159)
Low-grade maternal vascular pathology OR any combination of low-grade chronic inflammation and fetal vascular malperfusion					
Without acute inflammation	7a	m, cm, cf., fm, cfm	14 (15.6%)	4 (8.9%)	33 (20.8%)
WITH low-grade acute inflammation	7b	am, acm, acf, afm, acfm	4 (4.4%)	2 (4.4%)	12 (7.5%)
WITH high-grade acute inflammation	7c	Am, Acm, Acf, Afm, Acfm	3 (3.3%)	2 (4.4%)	3 (1.9%)
Other significant pathology	8		3 (3.3%)	0 (0.0%)	2 (1.3%)
Acute inflammation alone					
High-grade acute inflammation	9a	A	1 (1.1%)	3 (6.7%)	5 (3.1%)
Low-grade acute inflammation	9b	a	2 (2.2%)	0 (0.0%)	8 (5.0%)
Histologically normal	10		3 (3.3%)	3 (6.7%)	15 (9.4%)

A, high-grade acute inflammation; *a*, low-grade acute inflammation; *C*, high-grade chronic inflammation; *c*, low-grade chronic inflammation; *F*, high-grade fetal vascular malperfusion; *f*, low-grade fetal vascular malperfusion; *FGR*, fetal growth restriction; *M*, high-grade maternal vascular malperfusion; *m*, low-grade maternal vascular malperfusion; *SGA*, small for gestational age.

[a] Difference with constitutional SGA group p 0.015 (indicated in bold values).