



Maternal vascular malformation in the placenta is an indicator for fetal growth restriction irrespective of neonatal birthweight

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ABSTRACT

Introduction: To study the association between placental pathology and neonatal birthweight and outcomes, and whether a combination of first trimester biomarkers and fetal growth velocity can predict placental lesions.

Methods: The presence of maternal vascular malperfusion (MVM) lesions (Amsterdam criteria) was recorded in a retrospective cohort of singleton pregnancies in the Maastricht University Medical Centre, 2011–2018. First trimester maternal characteristics and PAPP-A, PlGF and sFlt-1 levels were collected. Fetal growth velocities were calculated (mm/week) from 20 to 32 weeks for abdominal circumference, biparietal diameter, head circumference and femur length. Data were compared between neonates with ‘small for gestational age’ (SGA < p10) and different categories of ‘appropriate for gestational age (AGA)’ AGAp10-30, AGAp30-50 and AGA > p50 (reference), using one-way ANOVA and post hoc test.

Results: There were significantly more MVM lesions in the SGA group (94.6% $p < .0001$), but also in the AGAp10-30 (67.3% $p < .0001$) and AGAp30-50 (41.6% $p = 0.002$), compared to the reference AGA group (19.3%). The prediction of MVM for a 20% false-positive rate, with maternal characteristics was 25.2%. The addition of birthweight percentile gave a prediction of 51.7% for MVM. However adding placental biomarkers and fetal growth velocities (instead of birthweight percentile) to the maternal characteristics, gave a prediction of 81.8% (PPV 49.5%, NPV 53.7%).

Discussion: Placental MVM lesions correlated inversely with birthweight even in AGA neonates, and was associated with slower fetal growth and more adverse outcome in SGA neonates. A combination of first trimester biomarkers and fetal growth velocity had good prediction of placental MVM lesions, as an indicator of fetal growth restriction irrespective of neonatal weight.

1. Introduction

Adequate fetal growth is a prerequisite for a successful pregnancy and for long-term health and well-being of the offspring. When fetal growth fails to meet its genetically predetermined potential, a pathological condition, fetal growth restriction (FGR) ensues [1,2]. FGR complicates up to 3–6% of all pregnancies and is a major obstetric problem causing significant perinatal morbidity and mortality [3–5]. Whilst FGR can occur as a direct consequence of a maternal disease or a fetal anomaly, the majority of FGR is caused by placental dysfunction [6]. Placental dysfunction results in insufficient supply of oxygen and nutrients to the fetus, which, if prolonged, leads to restriction of its

growth and, ultimately in reduced size. Due to lack of consensus on what constitutes normal intrauterine growth, estimated fetal weight is used as proxy. Hence, growth restriction is most commonly defined as estimated fetal weight (EFW) or birthweight below the 10th percentile, also called fetal growth restriction (FGR) or small-for-gestational age (SGA), respectively [7,8]. Conversely, a fetus that grows or has a birthweight above the 10th percentile is considered to be appropriate-for-gestational age (AGA). However, it is conceivable that a number of AGA fetuses have decreased growth velocity during second and third trimester but not severe enough to cause smallness, and they, thereby, fall outside of the contemporary definition of FGR. These “relatively” growth restricted fetuses remain unrecognized, receive suboptimal

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monitoring, and are consequently at increased risk of morbidity and mortality [9,10]. We and others have recently published on the added value of measuring fetal growth velocity in the diagnosis and management of late fetal growth restriction [11]. Reduced fetal growth velocity is currently part of the consensus definition of late fetal growth restriction. The mechanism underlying the late mild phenotype of fetal growth restriction is still not fully understood. It is possible that this phenotype is associated with a milder placental disease, resulting from a disbalance in the production and secretion of angiogenic factors in the placenta. Angiogenic factors such as placental growth factor (PlGF) and its inhibitor, the anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) are believed to be a key regulator of placental angiogenesis and vasculogenesis [12,13]. They are secreted in a balanced way by villous syncytiotrophoblast into the maternal circulation in response to hypoxic stimuli in the first trimester [14]. The balance of the pro- and anti-angiogenic effects of these biomarkers on maternal endothelial cell and leukocyte functions is essential for normal vascular adaptation of pregnancy and its dysregulation is well-described in preeclampsia [15]. Alternatively, PlGF is also secreted by extravillous trophoblast, as well as the endometrial epithelial cells and leukocytes at the fetomaternal interface indicating the potential modulatory functions during implantation and maternal spiral artery remodeling [16]. Low maternal serum levels of PlGF and high levels of sFlt-1 are seen in FGR fetuses and their levels are linked to the severity of growth restriction and placental pathology [17–21]. However, how the dysregulated angiogenic balance is linked to placental pathology in cases of FGR is not well understood [22].

Placental lesions, characteristic of maternal vascular malperfusion (MVM), are thought to be the consequence of this process of defective remodeling of maternal spiral arteries, and are considered the placental hallmark of FGR [23,24]. The birth of an FGR neonate in the first pregnancy increases the risk of a recurrence FGR by more than sevenfold [25]. However, in a cohort of 96 recurrent FGR pregnancies, Levy et al. showed that maternal vascular malperfusion (MVM) lesions and adverse neonatal outcomes were more prevalent in the first FGR pregnancy than in the subsequent FGR delivery [26]. The Amsterdam consensus on the definition of various placental characteristics and lesions provide a reliable and extensive framework to study the placental abnormalities associated with growth restriction [27].

In this study, we investigated if lower birthweight, even if considered appropriate for gestational age (AGA), is correlated with MVM and various other placental lesions. Additionally, we studied whether MVM lesions are more strongly predicted by a model using birthweight percentiles or a combination of angiogenic biomarkers and fetal growth velocities.

2. Methods

2.1. Study population

This was a retrospective cohort study of singleton pregnancies delivered between January 2011 and August 2018 in Maastricht University Medical Centre, a tertiary academic centre in the Netherlands. Pregnant women with a fetus with congenital anomalies were excluded from the study. The study protocol was approved by the medical ethical committee of the Maastricht University Medical Centre (17-4-0.15.1/ab). Procedures followed were in accordance with institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects (revised 13 November 2001, effective 13 December 2001).

2.2. Data collection and definitions

During routine hospital visits, baseline data on maternal health were collected and recorded. These baseline data include maternal age,

data on length, weight, smoking status, general medical and obstetric history and relevant information about the current pregnancy. Body mass index (BMI) was calculated by weight (kg) divided by height (m)-squared. Preeclampsia (PE) was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy [28]. In normotensive women at baseline, PE was defined as the development of hypertension with proteinuria. When a woman was suspected of developing hypertension, blood pressure was recorded for a period of 30 min at 3-min intervals using a semiautomatic oscillometric device in half-sitting position. Median values of 9 subsequent recordings were used for analysis. Gestational hypertension was then defined as a median systolic blood pressure equal to or greater than 140 mmHg, and/or a diastolic blood pressure equal or greater than 90 mmHg. The diagnosis of proteinuria required excretion of albumin/creatinine ratio of more than 30 mg/mmol, without evidence of a urinary tract infection. The neonatal birthweight was calculated in percentiles according to the Dutch reference standard [29].

Based on birthweight four separate study groups were formed, namely birthweight < 10th percentile (considered SGA), birthweight between the 10–30th centile, birthweight between the 30–50th centile and birthweight above the 50th centile (without preeclampsia, hypertensive disease or diabetes), as reference group.

An experienced sonographer, who was not otherwise involved in the study, took fetal biometric measurements on a GE Voluson with a 2–5 MHz curved-array transducer, in accordance with the routine mid-trimester fetal ultrasound scan guidelines [30]. Fetal biometry included measurement of the abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC) and femur length (FL). Fetal growth scans were performed twice, one between 18 and 22 weeks of gestational age and one between 30-and-34 weeks gestational age as a routine third trimester growth scan [10,31]. Fetal growth parameters were recorded in an electronic database (Astraia, GMBH). Estimated fetal weight was calculated using the Hadlock equation [32] [Hadlock C; $\log_{10}$ BW = $1.335 - 0.0034(AC)(FL) + 0.0316(BPD) + 0.0457(AC) + 0.1623(FL)$]. Growth velocities were calculated as the difference in absolute value of the measured fetal growth parameters between the two examination periods, divided by the number of weeks (mm/week) [33]. If multiple scans were performed, the scan with a scan date which was closest to 20 weeks with a maximum range of 18–22 weeks or closest to 32 weeks with a maximum range of 30–34 weeks of gestational age was selected for analysis.

2.3. Sampling of blood serum

Blood samples were collected at week 11–13 of gestational age as part of routine patient care and an extra serum sample was stored at -80° until further analysis. Placental biomarkers (PlGF, sFlt-1, PAPP-A, and β -hCG) were retrospectively measured in serum. Samples were analysed in a certified laboratory using commercially available kits. Measurements of sFlt-1 and PlGF assays were performed according to the manufacturer's instructions on the fully automated BRAHMS KRYPTOR compact PLUS system (ThermoFisher Scientific, Hennigsdorf, Germany). Both assays are immunometric assays based on the Time Resolved Amplified Cryptate Emission (TRACE) technology as described elsewhere [34]. Measurements of PAPP-A and free β -hCG were performed according to the manufacturer's instructions on the (fully automated) Auto-Delfia system (PerkinElmer, Turku, Finland). Both assays are fluoroimmunoassays.

2.4. Neonatal outcome data

All data regarding delivery and neonatal outcome were registered by an obstetrician or paediatrician. Apgar scores of the newborn were assessed at 1 and 5 min after birth. The cut-off point for adverse outcome was an Apgar-score less than 7 at 5 min after birth. NICU admissions were reported and a composite adverse neonatal outcome consisting of asphyxia, sepsis, respiratory distress syndrome [35] and

transient tachypnea [36] was used. All of these complications were recorded in the medical files. Asphyxia was diagnosed if the new-born suffered from intrapartum-related hypoxia-ischemia with multiple organ failure including encephalopathy [37]. Stillbirth and postnatal death during hospitalization were recorded.

2.5. Placental histology evaluation

Placental histological examinations were performed according to a local standard protocol. The pathologist was blinded for dependent and independent variables, like birthweight percentile categories, fetal growth velocities, and biomarker results. The pathologist was not blinded for gestational age and absolute birthweight outcome. After delivery, placentas were placed in 4% buffered formalin and allowed to fix for at least 48 h. The umbilical cord length and diameter was measured and the cord was inspected. In particular, insertion site, number of vessels and number of coils were recorded. The implantation was documented as (para)central, marginal (within 1 cm of the placental disc margin) or velamentous. The umbilical coiling index (UCI) was determined by dividing the total number of coils by the total umbilical cord length in centimeters. Hypocoiling was defined as an UCI < 0.1 and hypercoiling as an UCI > 0.3. Placental membranes were inspected as well and both the cord and membranes were removed from the placental parenchyma. The placental disc was weighed after fixation, without the umbilical cord and placental membranes. Placental weight was compared to reference values for the corresponding gestational age [38]. The placental disc was measured in three dimensions. Subsequently, the placental disc was cut in 1 cm thick slices and the cut surface was grossly inspected. Any macroscopic lesions were documented and sampled, along with standard samples. Standard samples include two cross-sections of the umbilical cord (one at the fetal end and one section at the maternal end), two membrane roll sections and two full-thickness sections of normal appearing placental parenchyma within the central two thirds of the placental disc. The samples were embedded in paraffin and cut into 4 µm thick slides. The slides were stained with H&E (hematoxylin and eosin) and assessed by a pathologist. Findings were documented in the pathology report which was added to the electronic patient record.

Maternal vascular malperfusion (MVM) was diagnosed when certain gross and microscopic findings are present in the placenta. Criteria for gross findings were placental hypoplasia, infarction of more than 5% and retroplacental haemorrhage. Criteria for microscopic findings are distal villous hypoplasia, accelerated villous maturation and decidual arteriopathy (including acute atherosclerosis) [27].

Histological microscopic placental findings are noted and included different abnormalities. Infarction was divided into three categories according to affected percentage in relation to total placental parenchyma (infarct < 5%, infarct 5–15% and infarct 15–30%). Percentages are calculated macroscopically, by determining the percentage of parenchymatous lesions on cut section to the nearest 5 percent. The lesions are then sectioned for microscopic evaluation. If there are different types of microscopic lesions, for instance both infarction and intervillous thrombus, the percentage is adjusted for the degree of infarction (again the nearest 5 percent). Haematoma was noted according to the location. Other findings included thrombosis and avascular villi. Maternal floor infarct was defined as massive perivillous fibrin depositions. Inflammation of the membranes was divided into different categories; inflammation of the decidua, inflammation of the decidua and chorion, inflammation of the decidua, chorion and the amnion.

2.6. Statistical analysis

Differences between two groups were tested using the independent T-test for continuous data. Results were presented as mean and standard deviation (SD). Differences between three or more groups were

calculated with ANOVA and the bonferroni post hoc test. For comparing categorical data between groups, the chi-square test was performed.

Potential predictors of MVM were tested in three models. The first model includes the maternal characteristics: maternal age, conception method (spontaneous vs assisted), smoking during pregnancy (yes/no), maternal BMI. The second model consists of the maternal characteristics (first model) and birthweight percentile. The third model consists of maternal characteristics, serum PlGF, sFlt-1 and sFlt-1/PlGF ratio measured at 12 weeks of gestational age and fetal growth velocities (mm/week) of abdominal circumference (ACv), biparietal diameter (BPDv), head circumference (HCv) and femur length (FLv) between 20 and 32 weeks of gestational age.

3. Results

3.1. General characteristics

Between January 2011 and August 2018, we included 394 women with a singleton pregnancy. The reference group, birthweight > 50th percentile (n = 115), the AGA 30–50th birthweight percentile (n = 126), AGA 10–30th percentile (n = 113) and the SGA group (n = 37). The general characteristics of the study population are represented in Table 1. There were no significant differences for maternal age, BMI and primiparous. In the AGA30–50 group 16.2% of the women smoked, 27.5% in the AGA10–30 group and 17.4% of the SGA group, compared with 17.6% in the reference group. Diabetes was present in 6.3% in the AGA30–50 group and 6.2% in the AGA10–30 group, while it was absent in the SGA group. PE was diagnosed in 11.1% of all the pregnancies in the AGA30–50 group, in 23.9% of the AGA10–30 group and in 29.7% of the SGA group. In the AGA30–50 group 23.4% was diagnosed with gestational hypertension, compared to 50.4% in the AGA10–30 group and 57.1% in the SGA group. Gestational age at birth was significantly lower in the SGA group (217.82 ± 25.96 , $p < .0001$) compared to the reference group (247.54 ± 26.86). There were no significant differences in gestational age at birth between the reference group and AGA10–30 and AGA30–50 groups.

3.2. Neonatal outcome data

Table 2 shows neonatal outcomes in all study groups. There were no significant differences in the percentage of neonates with Apgar < 7 at 5 min, postnatal death or stillbirths between all groups. However, there were significantly more NICU admissions in the SGA group (82.4%, $p < .0001$) compared to the reference group (33%). SGA fetuses were diagnosed with an adverse neonatal outcome significantly more often than the reference group (45.9% versus 12.2%, $p < .0001$). Also, neonates with a birthweight percentile 30–50 had more adverse neonatal outcome than the reference group (23.8% versus 12.2%, $p = 0.018$).

3.3. Differences in placental lesions

Table 3 and Fig. 1 show the differences in placental lesions between the categories of birthweight percentiles. There was a significant trend between birthweight percentile and the existence of MVM lesions ($F = 89.1$, $p < .0001$), distal villous hypoplasia ($F = 8.2$, $p = 0.004$), accelerated villous maturation ($F = 55.9$, $p < .0001$), infarct ($F = 38.4$, $p < .0001$) and placental hypoplasia ($F = 60.8$, $p < .0001$).

There were significantly more MVM lesions in the AGA30–50 (41.6%, $p = 0.002$), AGA10–30 (67.3%, $p < .0001$) and SGA group (94.6%, $p < .0001$), compared with the reference AGA group (19.3%). The different sub-lesions belonging to MVM were compared separately as well. Distal villous hypoplasia was significantly more common in the SGA group (8.1%, $p = 0.025$) compared to the reference group (0%). There was no significant difference in the AGA10–30 and AGA 30–50

Table 1

Maternal and pregnancy baseline characteristics, birthweightpercentiles (bwp) > 50 (reference group) versus bwp30–50, bwp10–30 and bwp < 10.

	Birthweight percentile > 50 (reference group) (n = 115)	Birthweight percentile 30–50 (n = 126)	P-value	Birthweight percentile 10–30 (n = 113)	P-value	Birthweight percentile < 10 (n = 37)	P-value
Maternal age (years)	31.3 ± 4.9 (20–43)	31.0 ± 4.7 (19–44)	1.000	30.4 ± 5.2 (18–43)	1.000	30.3 ± 4.4 (20–39)	1.000
BMI (kg/m ²)	27.9 ± 5.9 (18–46)	27.5 ± 6.6 (17–47)	1.000	26.5 ± 5.7 (17–43)	0.305	26.8 ± 5.1 (19–38)	1.000
Primiparous (%)	50.4 (58/115)	46.8 (59/126)	0.416	57.5 (65/113)	1.000	67.6 (25/37)	1.000
Smoking	71.4(65/91)	79.8 (79/99)	0.217	69.2 (63/91)	0.005	65.2 (15/23)	0.024
Never (%)	10.0 (10/91)	4.0 (4/99)	0.077	3.3 (3/91)	0.036	17.4 (4/23)	0.500
Stopped (%)	17.6 (16/91)	16.2 (16/99)	1.000	27.5 (25/91)	0.351	17.4 (4/23)	1.000
Yes (%)	–	–	–	–	–	–	–
Diabetes (%)	–	6.3 (8/126)	0.010	6.2 (7/113)	0.016	0 (0/37)	1.000
PE (%)	–	11.1 (14/126)	< .0001	23.9 (27/113)	< .0001	29.7 (11/37)	< .0001
Gestational Hypertension (%)	–	23.4 (29/124)	< .0001	50.4 (57/113)	< .0001	57.1 (20/35)	< .0001
GA (days)	247.5 ± 26.9	243.2 ± 31.8 (176–291)	1.000	241.8 ± 29.2 (175–291)	1.000	217.8 ± 26.0 (189–279)	< .0001
GA < 34 weeks (%)	(174–288)	38.1 (48/126)	1.000	40.7 (46/113)	1.000	75.7 (28/37)	< .0001
GA 34–36 weeks (%)	32.2 (37/115)	14.3 (18/126)	0.685	12.4 (14/113)	0.324	13.5 (5/37)	1.000
GA > 36 weeks (%)	21.7 (25/115)	47.6 (60/113)	1.000	46.9 (53/113)	1.000	10.8 (4/37)	0.001
Birthweight (g)	46.1 (53/115)	2661 ± 857.7	0.002	1998.1 ± 786.4 (620–3420)	< .0001	1122 ± 569.8	< .0001
	(810–4350)	2270 ± 851.5 (680–3510)				(638–2694)	
Birthweight percentile	68.0 ± 11.8 (51–100)	40.1 ± 5.9 (30–50)	0.000	20.4 ± 5.5 (10–29)	< .0001	5.3 ± 2.7 (0–9)	< .0001

Data are given as mean ± SD (min-max) or % (n/N). BMI: body mass index (kg/m²); PE: preeclampsia; GA: gestational age.

versus the reference group. Accelerated villous maturation however was significantly higher compared to the reference group (5.2%), with 25.7% in the AGA10–30 ($p < .0001$) and 59.5% in the SGA group ($p < .0001$). AGA10–30 (12.4%, $p = 0.001$) and SGA (27.0%, $p < .0001$) were diagnosed significantly more often with infarct (> 5%) compared to the reference group (1%). Hypoplasia of the placenta was also significantly higher in both the AGA10–30 group (43.4%, $p < .0001$) and the SGA group (67.6%, $p < .0001$) compared to the reference group (11.3%). Vasculopathy was significantly more common in the AGA10–30 group and SGA group with respectively 17.7% ($p = 0.026$) and 27% ($p = 0.003$).

The placentas of the AGA30–50 group were significantly lower in weight compared to the reference group (394.86 ± 141.97 vs 441.76 ± 128.86 , $p = 0.038$). The same trend was seen in the AGA10–30 group (344.11 ± 112.57 vs 441.76 ± 128.86 , $p < .0001$) and in the SGA group (181.93 ± 47.42 , $p < .0001$).

The placenta's showed significantly higher total infarct rates in the AGA10–30 group (40.7%, $p = 0.001$) and the SGA group (59.5%, $p < .0001$) compared to the reference group (18.3%). The SGA group showed more avascular villi in the placenta, with a percentage of 10.8% compared to 1.7% in the reference group ($p < .0001$).

There were no significant differences between all groups in the categories of haematoma, inflammation of the membranes, maternal floor infarcts, delayed villous maturation, umbilical coil index, hyper- or hypo coiling, marginal or velamentous insertion or having a single umbilical artery.

Table 2

Neonatal outcome of the study groups, birthweightpercentile (bwp) > 50 (reference group) versus bwp30–50, bwp10–30 and bwp < 10.

	Birthweight percentile > 50 (reference)(n = 115)	Birthweight percentile 30–50(n = 126)	P-value	Birthweight percentile 10–30(n = 113)	P-value	Birthweight percentile < 10(n = 37)	P-value
APGAR 5min < 7 (%)	13.0 (15/115)	11.9 (15/126)	0.788	8.0 (9/113)	0.205	10.8 (4/37)	0.711
NICU stay	33.0 (38/115)	42.0 (50/126)	0.286	42.3 (47/113)	0.184	82.4 (28/37)	< .0001
Adverse neonatal outcome (%)	12.2 (14/115)	23.8 (30/126)	0.018	23.0 (26/113)	0.032	45.9 (17/37)	< .0001
Neonatal death (%)	0.9 (1/115)	0.8 (1/126)	0.949	1.8 (2/113)	0.554	0 (0/37)	0.319
Stillbirth (%)	2.6 (3/115)	0.8 (1/126)	0.285	0 (0/113)	0.083	2.7 (1/37)	0.975

Data are given as % (n/N). NICU: neonatal intensive care unit. Composite adverse neonatal outcome consists of 4 complications: asphyxia, sepsis, respiratory distress syndrome and transient tachypnoea of the newborn. Asphyxia: intrapartum-related hypoxia-ischemia with multiple organ failure including encephalopathy. Neonatal death: first 28 days of life.

3.4. Predictive performance for MVM

Three models were compared in the prediction of MVM. The discriminative ability of the three different models as quantified by AUC is shown in Table 4. For the prediction of MVM, the maternal characteristics were used in screening model 1 (maternal age, conception method, smoking during pregnancy and parity) and had an AUC of 0.539 (95% CI 0.468–0.609). Adding birthweight percentile to the baseline screening (model 2), improved the prediction of MVM with an AUC of 0.695 (95% CI 0.541–0.849). Model 3 consist of maternal characteristics, biomarkers (PIGF, sFlt-1 and PAPP-a) and growth velocities (abdominal circumference, biparietal diameter, head circumference, femur length velocity), this improved the prediction of MVM with an AUC of 0.855 (95% CI 0.653–1.000). For a 20% false-positive rate (FPR), model 1, maternal characteristics, predicted 25.2% of placental tissues with MVM lesions. The addition of birthweight percentile gave a prediction of 51.7% for MVM. However adding placental biomarkers and fetal growth velocities (instead of birthweight percentile) to the maternal characteristics, gave a prediction of 81.8% (PPV 49.5%, NPV 53.7%).

4. Discussion

4.1. Main findings

The present study demonstrated that the negative correlation between birthweight and placental vascular pathology, as well as adverse

Table 3
Placental characteristics of the different birth weight percentile groups.

	Birthweight percentile > 50 (reference group) (n = 115)	Birthweight percentile 30–50(n = 126)	P-value	Birthweight percentile 10–30(n = 113)	P-value	Birthweight percentile < 10(n = 37)	P-value
Macroscopic placenta characteristics							
Placenta weight (g)	441.8 ± 128.9 (188–784)	394.9 ± 142.0 (128–700)	0.038	344.11 ± 112.57 (103–610)	< .0001	181.9 ± 47.4 (125–253)	< .0001
Placenta weight (percentile)	49.4 ± 27.7(3–97)	38.8 ± 26.5(3–97)	0.003	27.5 ± 26.8(3–97)	< .0001	11.7 ± 13.3(3–50)	< .0001
Placental length (cm)	17.7 ± 3.1 (7.5–26.5)	16.8 ± 3.0 (7–23.5)	0.770	17.0 ± 2.6 (11–24)	1.000	14.3 ± 2.3 (11–17)	< .0001
Placental width (cm)	15.1 ± 2.3 (9–20)	15.1 ± 3.0 (9–21)	1.000	14.1 ± 2.5 (7–21)	0.054	11.9 ± 1.7 (10–15)	< .0001
Placental thickness (cm)	2.5 ± 0.9 (1–6)	2.5 ± 0.8 (1–5)	1.000	2.4 ± 1.3(2–5)	1.000	2.0 ± 0.6 (2–3)	0.002
Macroscopic umbilical cord characteristics							
Umbilical coiling index	0.2 ± 0.12(0.0–0.7)	0.2 ± 0.2 (0.1–0.9)	0.638	0.2 ± 0.1 (0.0–0.7)	1.000	0.3 ± 0.2 (0.1–0.5)	0.187
Hypercoiling (%)	20.0 (14/70)	20.8 (16/77)	0.908	19.1 (13/68)	0.070	46.2 (6/13)	0.106
Hypocoiling (%)	11.4 (8/70)	10.4 (8/77)	0.841	13.2 (9/68)	0.749	8.3 (1/12)	0.755
Marginal or velamentous insertion (%)	25.5 (12/85)	20.7 (23/111)	0.225	16.5 (16/97)	0.658	17.1 (6/35)	0.676
Single umbilical artery (%)	3.1 (3/98)	3.8 (4/104)	0.762	1.1 (1/91)	0.352	5.6 (1/18)	0.598
Microscopic characteristics							
Infarct (%)	21.4 (21/98)	27.8 (35/126)	0.212	40.7 (46/113)	0.001	59.5 (22/37)	< .0001
Infarct < 5% (%)	95.2 (20/21)	91.4 (32/35)	0.600	68.9 (31/45)	0.003	54.4 (12/22)	0.002
Infarct 5–15% (%)	4.8 (1/21)	5.7 (2/35)	0.881	22.2 (10/45)	0.030	40.9 (9/22)	0.005
Infarct 15–30% (%)	0.0 (0/21)	2.9 (1/35)	0.444	6.7 (3/45)	0.083	4.5 (1/22)	0.329
Haematoma (%)	4.2 (4/96)	10.8 (11/102)	0.079	3.6 (3/84)	0.838	18.8 (3/16)	0.206
Thrombosis (%)	20.6 (21/102)	25.7 (27/105)	0.526	18.6 (16/86)	0.603	44.4 (8/18)	0.074
Inflammation membranes-	18.3 (21/115)7.0 (8/115)	19.8 (25/126)	0.927	61.5 (16/26)	0.235	2.7 (1/37)	0.647
deciduitis (%)	1.7 (2/115)	6.3 (8/126)	0.124	2.7 (3/113)	0.891	0 (0/37)	0.479
-chorionitis		5.6 (7/126)	0.967	0.9 (1/113)	0.673	2.7 (1/37)	0.476
(%) -chorioamnionitis (%)							
Avascular villi (%)	1.7 (2/115)	0.8 (1/126)	0.539	1.8 (2/113)	0.903	10.8 (4/37)	0.040
Maternal floor infarct (%)	0.0 (0/115)	0.8(1/126)	0.339	0.9 (1/113)	0.320	0.0 (0/37)	1.000
Villous maturation	1.7 (2/115)	3.4 (4/126)	0.425	6.2 (7/113)	0.067	2.7 (1/37)	0.321
Delayed (%)							
Acute atherosclerosis (%)	0.0 (0/115)	0.8 (1/126)	0.334	4.4 (5/113)	0.025	0.0 (0/37)	1.000

Data are given as mean ± SD (min-max) or % (n/N).

neonatal outcome, is not confined to SGA neonates but is also present across all categories of birthweight of neonates considered appropriate for gestational age. The prediction of placental MVM lesions, a hallmark of placental dysfunction, was higher using a combination of fetal

growth velocities and placental biomarkers, than using birthweight percentiles, suggesting that these ultrasound and blood markers are more related to the pathology of fetal growth restriction than neonatal smallness.

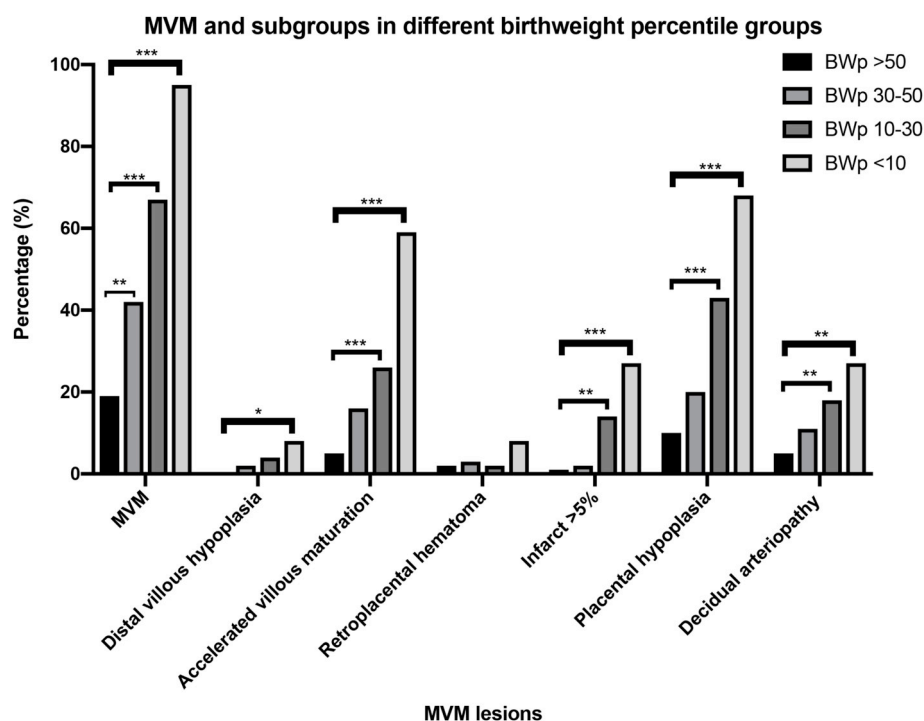


Fig. 1. Maternal vascular malperfusion lesions in different birth weight percentile groups.

Table 4
Predictive performance of three models for the prediction of MVM lesions.

Predictive value	Model 1	Model 2	Model 3
	Maternal characteristics	MC + BWp	MC + FGv + placental biomarkers
AUC	0.539 (0.468–0.609)	0.695 (0.541–0.849)	0.855 (0.653–1.000)
10% FPR	11.0 (6.8–16.6)	13.8 (9.1–19.8)	36.4 (29.4–44.0)
Sensitivity	10.4 (6.5–16.0)	12.8 (8.5–18.6)	28.1 (22.4–34.5)
PPV	10.3 (6.4–16.0)	10.6 (6.6–16.5)	13.8 (8.6–21.3)
NPV			
20% FPR	25.2 (18.5–31.5)	51.7 (44.1–59.2)	81.8 (75.5–87.4)
Sensitivity	23.2 (17.5–29.9)	38.4 (32.2–44.9)	49.5 (43.6–55.4)
PPV	20.9 (15.3–27.9)	29.8 (22.0–38.8)	53.7 (41.2–65.8)
NPV			

Model 1: maternal characteristics (maternal age, conception method, smoking during pregnancy and parity) Model 2: maternal characteristics with birthweight percentile. Model 3: maternal characteristics with fetal growth velocity (FGv) between 20 and 32 weeks of pregnancy and placental biomarkers: PlGF, sFlt-1 and PAPP-a.

4.2. Interpretation

Previous research has mainly described the impact of placental vascular pathology on birthweight and adverse outcome in the SGA population, as the main risk group for placental insufficiency [19]. In this study, we focused in particular on AGA neonates subdivided into categories of birthweight percentiles to investigate the impact of placental lesions on the milder phenotype of FGR. There is little existing literature on the prevalence and influence of placental MVM lesions in AGA neonates, as most studies pooled AGA neonates into one whole group, which was subsequently used as a reference to the SGA group. Our finding of a stepwise increase in MVM lesions in lower birthweight categories of AGA neonates supports the hypothesis that there is a subgroup of placental-mediated FGR fetuses in neonates born as AGA. This challenges the existing paradigm of using neonatal size, and by extrapolation estimated fetal size, as the basis for defining fetal growth restriction. Our findings also highlight the importance of identifying the subgroup of “normal sized” FGR fetuses, as they pose a potential perinatal risk similar to the SGA group.

Despite advances in our understanding of the placental origins of fetal growth restriction [39] the exact contribution of placental lesions to the clinical diagnosis and associated morbidity of fetal growth restriction is not fully understood. It is important to discuss that the association between placental MVM lesions and neonatal morbidity is not a direct or causative one, but rather circumstantial as both are related to decreased birthweight percentile. Previous studies have shown that SGA pregnancies exhibited more MVM lesions compared to AGA pregnancies [18,19]. Only about a fifth of the SGA placentas were totally free of histological abnormalities, while this was the case in about three quarters of the AGA group [40]. After birth, SGA fetuses with MVM lesions were at greater risk of neurodevelopment problems compared to SGA fetuses without placental MVM lesions [41].

It has long been acknowledged that being born small is linked to increased mortality and morbidity, including respiratory distress or intraventricular haemorrhage, as well as lifelong implications [42]. This knowledge translated in clinical practice into a focused attention on monitoring FGR fetuses and the inadvertent negligence of the risks of placental dysfunction to the AGA fetuses [1]. Our results suggest that fetuses with birthweights as high as the 30–50th centile also showed placental lesions characteristic of growth restricted babies and were at risk for adverse neonatal outcome. A recent study involving over 6000 infants confirmed that the majority of adverse perinatal outcomes (including stillbirth, low cord pH, emergency caesarean delivery for fetal distress in labour and neonatal intensive care unit admission) occurred

among AGA fetuses [43]. Our data add evidence to the emerging concept that the placental dysfunction causing FGR is not only restricted to SGA fetuses, but can also occur in different degrees in AGA fetuses [44,45]. We argue that antenatal recognition of FGR fetuses would remain suboptimal unless it incorporates some form of estimation of reduced fetal growth, in addition to fetal size. There is ongoing debate among researchers on whether to use a population-specific curve, a global standard for fetal growth or a customized chart [46]. Our previous research have shown that incorporating fetal growth velocity, measured by relative change in fetal abdominal circumference over time, improves the prediction of neonates with adverse outcome [47]. Identifying these fetuses with the highest risks for perinatal morbidity is the first step towards focusing the resources for antenatal surveillance that utilizes measures of fetal hemodynamic adaptations to reduced placental function. Subsequently, women with suspected fetal growth restriction should be counselled about the optimal timing of delivery, which several guidelines have set at 37–38 weeks [48]. This recommendation is based on the findings of the randomized controlled trial of 650 women with SGA > 36 weeks (DIGITAT study), in which women with expectant management had a 2-fold increase in risk of developing preeclampsia compared to women who had induction of labour, despite no difference in the perinatal outcomes [49].

4.3. Placental function

The intricate mechanisms behind normal placental function are relevant to fetal growth, as they ensure continuous provision of fetal needs of nutrients and oxygen, the elimination of waste products and protection from pathogens. Dysfunction or injury to the placenta disrupts these essential processes and can cause growth impairment and even stillbirth [50,51]. The most common mechanism of injury to the placenta is thought to be caused by hypoxia-reoxygenation insults to the developing placental villi early in pregnancy. This process is initiated by failed physiologic transformation of the spiral arteries, which results in restricted maternal blood flow into the intervillous space. Differences in oxygen tension will lead to oxidative stress and free radical damage to the placental villi, resulting in histologic features of MVM [52–54]. These pathologic lesions are characteristic of severe early placental dysfunction. However, our data suggest that similar lesions develop in a more subtle and insidious manner over time leading to a milder form of FGR. In this study, accelerated villous maturation and placental hypoplasia, two typical MVM lesions seen in early FGR and preeclampsia [55], were seen more with a decrease in birthweight in the AGA group.

The improved prediction of MVM lesions using sFlt-1 and PlGF levels has implications on our understanding of the role of placental angiogenic biomarkers in the pathogenesis of FGR. First, PlGF is suggested to play a role in maternal spiral artery remodeling since it has been expressed by key regulators of this process at the fetomaternal interface including invading extravillous trophoblasts, endometrial epithelial cells and endometrial leukocytes [16]. This would suggest that aberrant production of pro-angiogenic signals is primarily involved in defective spiral artery remodeling leading to placental ischaemic injury and secondary development of MVM lesions. Alternatively, it is more plausible to think of reduced pro-angiogenic factors as a consequence of defective spiral artery remodeling, rather than its cause, and that both disturbed placental angiogenesis and MVM are downstream effects of the ensuing placental ischemia [22]. Previous research have shown that, in placental tissues with MVM lesions, multifocal infarction and formation of syncytial knots will produce and secrete antiangiogenic protein soluble Fms-like tyrosine kinase (sFlt-1) and suppress the secretion of placental growth factor (PlGF) in the maternal blood [56–58]. A prospective cohort study linking longitudinal changes in maternal angiogenic biomarkers and uterine artery doppler measurement (as a proxy to spiral artery adaptation) to postpartum pathological placental lesions of MVM would provide more insight into

the intricate mechanism of placental aetiology of FGR. The use of placental biomarkers in predictive models for FGR can have major implications on our future screening strategies. Although our model of combining first trimester placental biomarkers and third trimester fetal growth velocities significantly improved the prediction of pregnancies with MVM lesions, the applicability of this model is hampered by the relatively low positive and negative predictive value of about 50%. Interestingly, the addition of these biomarkers, together with measuring fetal growth velocity, have been shown to improve the clinical screening strategies and identification of high-risk pregnancies, and allow timely interventions and targeted therapies [11, 59].

4.4. Strengths and limitations

There are certain limitations in the current study that need to be highlighted. First of all, the study has a retrospective design that puts it at risk of selection bias, a part of the cases were not eligible for selection if the placental examination report was not completed. Another limitation is the fact that the study is performed in a tertiary care hospital, confining the selection to a relatively high-risk population and limiting the interpretation of our data and the generalizability to an unselected low-risk population. Strengths of the study included the complete integrated registration of various ultrasound, histological and biochemical parameters, as well as maternal and neonatal outcomes from a large population followed up in a single tertiary care centre. The inclusion of ultrasound measurement of fetal growth velocities is a new and practical method of assessing fetal growth potential within the SGA and AGA group using a simple calculation that can be readily employed and interpreted in low-resource setting without the need of complex mathematical models. Another strength of this study is the availability of an appropriate reference group without preeclampsia, hypertensive disease or diabetes. Also, we used the Amsterdam Placental Workshop Consensus Criteria to classify MVM lesions, this standardized definition will help ensure validity and comparability of findings across different studies [27].

5. Conclusion

This study shows that, in neonates considered appropriate for gestational age, there was a negative correlation between their birth-weight and placental vascular malperfusion lesions and also adverse neonatal outcome. This suggests that a subgroup of normal weight neonates have features of intrauterine growth restriction and are potentially at risk of neonatal complications due to masked placental dysfunction. Further prospective studies are needed to determine if morbidity in AGA neonates could be reduced by screening using a combination of placental biomarkers and fetal growth velocity.

Author contributions

All authors made a significant contribution to this study.

All the authors have accepted responsibility of the entire content of this submitted manuscript and approved submission.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Employment of leadership

None declared.

Honorarium

None declared.

Declarations of interest

None.

Ethics approval and consent to participate

The study protocol was approved by the medical ethical committee of the Maastricht University Medical Centre (17-4-0.15.1/ab). Procedures followed were in accordance with institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects (revised 13 November 2001, effective 13 December 2001).

Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.placenta.2019.09.003>.

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