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The impact of placental massive perivillous fibrin deposition on neonatal outcome in pregnancies complicated by fetal growth restriction

Arsenio Spinillo[a,*], Barbara Gardella[a], Giulia Muscettola[a], Stefania Cesari[b], Giacomo Fiandrino[b], Chryssoula Tzialla[c]

[a] Department of Obstetrics and Gynecology, University of Pavia, Piazzale Golgi, 19 Pavia, Italy
[b] Department of Pathology, University of Pavia, Piazzale Golgi, 19 Pavia, Italy
[c] Neonatal Intensive Care Unit, IRCCS Fondazione Policlinico San Matteo, University of Pavia, Piazzale Golgi, 19 Pavia, Italy

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ABSTRACT

Introduction: Massive perivillous fibrin deposition (MPDD) is an uncommon placental lesion which has been associated with an increased risk of adverse pregnancy outcome in retrospective series. The purpose of the study was to evaluate the frequency and consequences of MPFD in pregnancies complicated by fetal growth restriction (FGR).

Materials and methods: A cohort study of 355 pregnancies complicated by FGR diagnosed according to standard ultrasonographic criteria, enrolled, followed and delivered at a single obstetric unit. Pathological placental lesions were classified according to the Amsterdam Placental Workshop Consensus. Penalized logistic regression models were used to evaluate the association of MPFD with maternal risk factors, other pathological lesions and neonatal outcome.

Results: The rates of moderate (25–50% of villi) and severe (> 50% of villi) MPFD were 8.7% (31/355) and 3.1% (11/355), respectively. Compared to other FGR cases, MPFD pregnancies were characterized by higher placental volume (450 ± 144.5 SD as compared to 412.2 ± 151 cm^3,p < 0.001) and lower birthweight/placental weight ratio (5.32 ± 1.53 compared to 6.1 ± 1.52,p < 0.001). The rates of abnormal Doppler ultrasound studies of umbilical and middle cerebral artery were similar in MPFD subjects and controls. After correction for gestational age and birthweight, MPFD was associated with an increased risk of neonatal intraventricular hemorrhage (> grade II) (OR = 5.66,95% CI = 1.69–18.97), sepsis (OR = 5.9, 95% CI = 1.27–27.12), proven necrotizing enterocolitis (OR = 9.84,95% CI = 2.49–38.8) and overall severe adverse neonatal outcome (OR = 5.71,95% CI = 2.05–15.87).

Conclusions: Moderate-to-severe MPFD was relatively common among FGR pregnancies and was associated with morphometric modifications of placenta and with an increased risk of severe adverse neonatal outcome.

1. Introduction

Massive perivillous fibrin deposition (MPFD) and maternal floor infarction are closely related placental lesions characterized by the extensive deposition of fibrin or fibrinoid material in the intervillous space, extending from the basal chorionic plate to subchorionic placental area [1–3]. The entrapment of villi, which become fibrotic and avascular, and the distortion of placental architecture associated with MPFD cause a placental dysfunction leading to increased risks of fetal growth restriction (FGR), perinatal mortality and even impaired infant neurodevelopmental outcomes [4,5]. The prevalence of the severe form of MPFD is low (less than 0.5% of deliveries) and, although described for the first time more than 40 years ago, risk factors, pathophysiology and the mechanisms causing the adverse neonatal outcomes associated with the lesion are poorly known [1,6,7]. Retrospective studies on archived material have suggested that antenatal autoimmune maternal diseases could play a causative role; this association could also explain the increased recurrence rate of the lesion in subsequent pregnancies [2,7–9]. The association of MPFD with adverse neonatal outcome has mainly been evaluated in retrospective series [2,7–10]. In a recent retrospective study comparing MPFD cases to healthy controls, pregnancies complicated by MPFD were associated with an increased risk of FGR, perinatal mortality and abnormal umbilical artery Doppler flow, suggesting an impairment of placental function [10]. However, the

* Corresponding author. Department of Obstetrics and Gynecology, IRCCS Policlinico San Matteo Pavia, Italy.
E-mail address: spinillo@smatteo.pv.it (A. Spinillo).

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impact of MPFD in terms of frequency and perinatal consequences among FGR pregnancies remain to be elucidated. The purpose of this study was to evaluate the rates of MPFD, main maternal risk factors, associated placental pathological lesions and neonatal outcomes in a population of singleton pregnancies with the standard ultrasonographic diagnosis of FGR prospectively enrolled, followed and delivered at the same Institution.

2. Patients and methods

2.1. Patients selection

The study was approved by the Institutional Review Board, and all patients gave their informed, written consent. The population enrolled included all singleton pregnancies who had received a definite diagnosis of FGR based on standard ultrasonographic criteria who attended the outpatient clinic of our department for the surveillance of fetal well-being between 2011 and 2016. The eligibility criteria included: (a) singleton pregnancy; (b) absence of fetal malformations, known chromosomal anomalies or congenital infections; (c) enrollment for prenatal care during the first trimester of pregnancy; and (d) pregnancy complicated by FGR deemed eligible for conservative treatment based on antenatal surveillance data. Demographic data of participants were collected at enrollment. Clinical data were collected during subsequent antenatal visits and at discharge, and stored in a computer database.

FGR was diagnosed when the estimated fetal weight, assessed by ultrasonographic (US) examination, fell below the 10th percentile of the reference curves, confirmed on at least two consecutive measurements taken 2 weeks apart after the standard ultrasonography performed at 18–22 weeks of pregnancy [11,12]. A conservative management plan for FGR was adopted according to a predefined protocol, which included antenatal visits, US surveillance and cardiotocographic monitoring. US evaluation included weekly monitoring of amniotic fluid volume and fortnightly fetal biometry. Doppler studies of fetal circulation included weekly or biweekly measurements of blood flow velocity waveforms of the umbilical artery, middle cerebral artery and ductus venosus depending on the severity of blood flow abnormalities. Amniotic fluid volume was expressed using the amniotic fluid index (AFI) and measured sonographically as the sum of the deepest vertical pool in each of the four maternal abdominal quadrants. FGR pregnancies were classified as early-onset when the diagnosis of fetal growth failure was made at < 32 weeks of pregnancy, and as late-onset when the diagnosis was made thereafter. To evaluate the severity of the growth deficit, the birthweight z-score was computed for each case by comparing the actual birthweight to the standard Italian birthweight for gestational age, adjusted for maternal parity and fetal sex [13].

2.2. Pathologic examination of placenta

Placentas were sent to Department of Pathology for standard histological evaluation. At the time of sectioning, type, number, location, size and percentage of placental involvement of all grossly visible lesions were recorded. At least one sample was taken for each type of lesion. Additionally, at least three full-thickness blocks of normal-appearing parenchyma were submitted, as well as two additional blocks containing cross sections of umbilical cord and two rolls of the extraplacental membranes, respectively. For each case, all available slides were reviewed by two pathologists experienced in placental pathology using a predefined set of variables. Pathologists were blinded to FGR, only gestational age was known at the time of revision. According to Katzman and Genest [3] MPFD was defined as *severe* if meeting the criteria of classic maternal floor infarction (basal villi embedded in fibrin ≥3 mm in thickness, on at least one slide) and/or of transmural MPFD (≥50% of villi encased by fibrin from maternal to fetal surface, on at least one slide), *moderate* for borderline cases (25–50% of villi encased by fibrin with nearly transmural distribution, on at least one slide), and *negative* for placentas lacking moderate or severe deposits. For the purposes of this study, the severity of MPFD was always established by microscopy, but in all cases perivillous deposition involved at least 25% of placental volume. By definition, chronic villitis and histiocytic intervillositis were either absent or represented only focally [2] [Fig. 1.]. The other pathological variables assessed and classified according to the Amsterdam Placental Workshop Group Consensus Statement [14] were: placental inflammatory-immune processes including maternal and fetal acute inflammatory responses (stage and grade); noninfectious chronic villitis distinguishing between low grade (more than 1 focus, each involving < 10 contiguous villi, either focal if seen on only one slide, or multifocal if seen on two or more slides) and high grade (patchy in case of multiple foci, at least one affecting > 10 contiguous villi; diffuse when more than 30% distal villi were involved); fetal-stromal vascular lesions including obstructive lesions of the umbilical cord, proximal (chorionic or stem vessels) villous thrombosis; avascular villi, reserving the term *high-grade fetal vascular malperfusion* for severe cases (≥45 avascular villi in three disc sections, two or more thrombi in the proximal fetal vessels, or multiple non occlusive thrombi); maternal stromal-vascular lesions including accelerated villous maturation and distal villous hypoplasia, infarcts, abruptio placentae (arterial), marginal abruptio (acute vs chronic), decidual vasculopathy (persistence of arterial smooth muscle, fibrinoid necrosis, atherosis, lymphocytic/plasmacytic vasculitis or thrombosis in any location).

Gross data were verified by microscopy when the nature of the lesions was not clear by macroscopy (e.g., hemorrhagic infarcts vs. intervillous thrombi, peripheral atrophy vs. infarction). For microscopic lesions, quantification was made by visual inspection of the slides by the trained pathologists. Histological lesions associated with FGR were subsequently grouped according to the Amsterdam Placental Workshop Group Consensus Statement [14]. According to this classification system, lesions were divided into two categories lesions: (a) maternal vascular malperfusion, including early and late infarctions (yes, no), retroplacental hemorrhage (no, mild, severe), massive perivillous fibrinoid deposition (no, 25–50% of villi, > 50% of villi), distal villous hypoplasia (yes, no), accelerated villous maturation (yes,no), decidual arteriopathy as evidenced by the presence of mural hypertrophy (yes, no), muscularized arteries (yes, no), and acute atherosis (yes, no); or (b) fetal vascular malperfusion, including vascular lesions/abnormalities of cord (yes, no), fetal vascular thrombosis (no, mild, moderate/severe), intramural fibrin deposition (yes, no), and presence of avascular villi (no, mild, moderate/severe) and karyorrhexis (yes, no) [14,15].

Placental volumes were derived from measurements of major and minor diameters and thickness (largest diameter × smallest diameter × thickness). Placental area was calculated by assuming an elliptical surface (largest diameter × smallest diameter × π/4). To evaluate placental efficiency (grams of the fetus produced per gram of placenta), we used both fetal/placental ratio and a fetal/placental weight score obtained by standardized residuals from linear regression of fetal weight on placental weight [16].

2.3. Neonatal outcomes

The severity of neonatal intracranial hemorrhage, periventricular leukomalacia and necrotizing enterocolitis (NEC) was classified according to standard criteria; bronchopulmonary dysplasia was defined as the need for oxygen treatment at 36 weeks corrected for gestational age [17–19]. Overall, severe adverse neonatal outcome included intrauterine or neonatal death, bronchopulmonary dysplasia, intraventricular hemorrhage (> grade II), NEC (> grade IIB), and periventricular leukomalacia (≥grade II).

2.4. Statistical analysis

Comparisons of continuous variables between multiple groups were

performed by Kruskal–Wallis analysis of variance (ANOVA) with Bonferroni correction for pairwise comparisons. Chi-square analysis was used to compare categorical variables. Chi-square for trend was used to test for linear trend with ordinal data. Interobserver reproducibility was calculated with unweighted kappa statistics. Associations between MPFD, maternal, fetal and pathological variables were evaluated using penalized logistic regression analysis with odds ratios (ORs) and 95% confidence intervals (95% CIs), adjusted for gestational age and birthweight (Stata 13.0 for Windows). Penalized maximum likelihood estimation has been proposed as a suitable method of regression analysis for uncommon events [20]. MPFD was used as outcome variable in the study of the association with pathological variables and as an explanatory variable in the study of the association with fetal outcomes.

3. Results

During the period of study, 417 singleton pregnancies with a diagnosis of FGR followed or referred to our unit for the evaluation of fetal growth and well-being were potentially eligible for the study. We excluded from the analysis 7 (1.7%) subjects due to undetected serious fetal malformation, 9 (2.2%) as a result of abnormal fetal karyotype, 8 (1.9%) because of delivery at other institutions, 7 (1.7%) due to uncertain gestational age and 31 (7.4%) because the diagnosis of FGR was not confirmed during follow-up; this left 355 (85.1%) subjects for final analysis.

The overall agreement between the two pathologists, as expressed by k values, for the diagnosis of MPFD and severe villitis were 0.67 (95%CI = 0.56–0.77) and 0.76 (95% CI = 0.67–0.86), respectively. After a careful reevaluation and discussion of all potential cases, out of the 355 placentas analyzed, a diagnosis of moderate or severe MPFD was made in 31 (8.7%) and 11 (3.1%) subjects, respectively. Placental volume involvement ranged from 25 to 90%; all severe MPFD cases showed > 30% of placental parenchymal involvement [Fig. 1].

The sociodemographic characteristics and risk factors for FGR are reported in Table 1. There were no significant differences in the rates of the most common risk factors for FGR, such as sociodemographic variables, complications of pregnancy, type of FGR, placental and fetal Doppler evaluations between cases and controls. Idiopathic FGR included all the cases of fetal growth failure without a known cause (e.g. chronic hypertension, preeclampsia, autoimmune mechanism, maternal diseases, placenta praevia, etc).

Table 1
Maternal sociodemographic and pregnancy characteristics among fetal growth restricted (FGR) pregnancies complicated by moderate (25–50% of villi) and severe (> 50% of villi) placental massive perivillous fibrin deposition (MPFD) and controls.

	MPFD Absent (n = 313)	MPFD Moderate (n = 31)	MPFD Severe (n = 11)	MPFD Overall (n = 42)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Maternal age (ys)	32.8 (5.4)	31.9 (4.9)	31.9 (3.9)	32.1 (4.7)
Pre-pregnancy body mass index (kg/m2)	23.4 (5.6)	21 (6.9)	25.4 (5.1)	23 (6.3)
Gestational age at diagnosis (wks)	32.1 (4.1)	32.9(4.1)	33.7 (4.2)	33.1 (4.1)
Gestational age at delivery (wks)	35.5 (3.4)	35.7 (3.8)	36.1 (2.9)	35.5 (3.6)
	n. (%)	n. (%)	n. (%)	n. (%)
Nulliparity	212 (67.7)	22 (71)	8 (72.7)	30 (71.4)
Smoking in pregnancy	10 (3.2)	1 (3.1)	1 (9.1)	2 (4.8)
Idiopatic FGR	77 (24.7)	5 (15.6)	1 (9.1)	6 (13.9)
Preclampsia	96 (30.7)	6 (19.4)	2 (18.2)	8 (19)
Early FGR	111 (35.5)	10 (32.2)	4 (36.4)	14 (33.3)
Diabetes	27 (8.6)	2 (6.5)	1 (0.91)	3 (7.1)
Autoantibodies	23 (7.3)	3 (9.7)	3(27.3)#	6 (14.3)
Abnormal cardiotocogram	55 (17.6)	7 (22.6)	3 (27.3)	10 (23.8)
Cesarean section	228 (72.8)	25 (80.6)	9 (81.8)	34 (80.9)
Abruptio	6 (1.9)	0	0	0
Placenta praevia	7 (2.2)	0	0	0
umbilical artery Doppler Pi				
Increased	97 (31)	7 (22.6)	4 (36.4)	11 (26.2)
Absent/reversed	47 (15)	4 (12.9)	1 (9.1)	5 (12.2)
Cerebroplacental index < 5th pct	153 (48.9)	16 (51.6)	6 (54.5)	22 (52.4)
Middle cerebral artery PI < 5th pct	104 (33.2)	8 (25.8)	6 (54.5)	14 (33.3)
Oligo/anydramnios	185 (59.1)	17 (54.8)	4 (36.4)	21 (50)

PI = Pulsatility index. #p < 0.05 Chi square for trend.

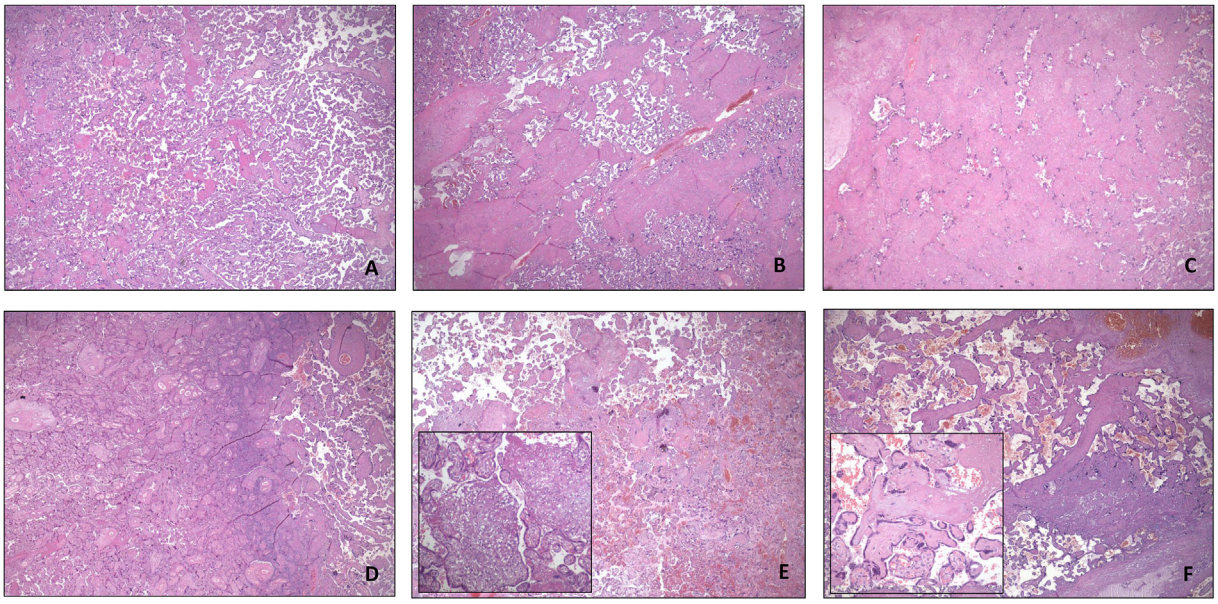

Fig. 1. (A) Negative for MPFD: preterm placenta showing accelerated villous maturation and mild increase in perivillous fibrin (H&E, 2X). (B) Borderline MPFD, characterized by moderate perivillous fibrin deposition with transmural distribution (H&E, 2X). (C) Transmural MPFD with encasement of > 50% of villi, corresponding to the severe form (H&E, 2X). (D, E, F) The differential diagnosis of MPFD includes infarction (D)(H&E, 2X), chronic villitis of unknown etiology (E)(H&E, 2X; inset: H&E, 10X), chronic histiocytic intervillositis, and long-standing high-grade fetal vascular malperfusion (F)(H&E, 2X; inset: H&E, 10X).

Table 2
Neonatal characteristics and outcomes among fetal growth restricted pregnancies complicated by moderate (25–50% of villi) and severe (> 50% of villi) placental massive perivillous fibrin deposition (MPFD) and controls.

	MPFD Absent (n. = 313)	MPFD Moderate (n = 31)	MPFD Severe (n = 11)	MPFD Overall (n = 42)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Birthweight (gm)	1808 (571)	1717 (581)	1818 (566)	1729 (580)
Cord pH	7.29 (0.07)	7.29 (0.07)	7.29 (0.08)	7.29 (0.07)
Cord base excess	−3.1 (2.7)	−2.9 (2.7)	−3.2 (3.4)	−3 (2.8)
Z score birthweight	−2.58 (1.2)	−2.1 (0.7)	−2.1 (0.6)*	−2.1 (0.68)**
	n. (%)	n. (%)	n. (%)	n. (%)
Male sex	155(49.5)	14 (45.2)	6 (54.5)	20 (47.6)
Birthweight < 1500 gm	94 (30)	11 (35.5)	3 (27.3)	14 (33.3)
Gestational age < 32 wks	52 (16.6)	6 (19.4)	1 (9.1)	87(16.7)
Cord pH < 7	2 (0.6)	0	1 (9.1)	1 (2.4)
Severe RDS	51 (16.3)	7 (22.6)	2 (18.2)	9 (21.4)
Surfactant use	30 (9.6)	4 (12.9)	0	4 (9.5)
Mechanical ventilation	36 (11.5)	6 (19.4)	0	6 (14.3)
BPD	11 (3.5)	2 (6.5)	0	2 (4.7)
Sepsis	6 (1.9)	3 (9.7)	0	3(7.1)**
IVH > IInd stage	8 (2.6)	2 (6.5)	3(27.3)*	5 (11.9)**
Leukomalacia	3 (1)	0	0	0
NEC	5 (1.6)	4 (12.9)	1(9.1)*	5(11.9)**
Intrauterine fetal death	1 (0.3)	0	1 (9.1)	1 (2.4)
Neonatal death	6 (1.9)	1 (3.2)	0	1 (2.4)
Overall severe adverse outcome	29 (9.3)	8 (25.8)	3 (27.3)*	11(26.2)**

BPD = Bronchopulmonary dysplasia. IVH: Intraventricular hemorrhage. NEC: Necrotizing enterocolitis.
*p < 0.05 in overall three groups analysis.**P < 0.05 in a two groups analysis.

The rates of detection of maternal autoantibodies (lupus anticoagulant, anticardiolipin and/or anti-β2 glycoprotein 1 antibodies) suggesting complete or incomplete anti-phospholipid syndrome increased progressively with the severity of MPFD (chi-square for trend = 4.3, p = 0.04) and this trend was confirmed in logistic regression after correction for gestational age and birthweight (chi-square = 4.2, p = 0.034). Diabetes included subjects with gestational diabetes (23/313 as compared to 2/42, p = 0.7) and type 1 diabetes preexisting pregnancy (4/313 as compared to 1/42, p = 0.5).

Among multiparas, the rate of a previous low birthweight (< 2500 gm) birth was 45.5% (5/11) among MPFD cases and 17.9% (38/212) in the controls (p = 0.04). Data on subsequent pregnancies outcomes were too sparse to make precise inferences on reproductive consequences of a previous diagnosis of MPFD.

Table 2 reports neonatal variables and outcomes in MPFD and controls. Although crude birthweight was similar across the categories studied, birthweight z-scores (p = 0.008) were significantly higher among newborns delivered after MPFD than in controls. We had one case of intrauterine fetal death during the surveillance of subjects without MPFD and 7 cases of neonatal death. Neonatal sepsis included 3 cases of early (one among MPFD cases and two among controls) and 6 cases of late infection. MPFD was associated with significantly increased rates of neonatal sepsis, intraventricular hemorrhage (> stage II), proven NEC (stage IIB or above), and overall severe adverse neonatal outcome. All cases of NEC, intraventricular hemorrhage and neonatal death occurred before the 33rd week of gestation.

Placental weight and volume were higher and the birthweight/placental weight ratio was lower among FGR pregnancies complicated by overall MPFD than in controls (p < 0.001) (Table 3). Post-hoc results indicated that placental weight and volume were higher among subjects with severe forms of MPFD than in other cases of FGR. Among placental pathological variables suggesting maternal vascular underperfusion only accelerated villous maturation, as expressed by an increased count of syncytial knots, was associated with MPFD. Maternal lesions such as atherosis and distal villous hypoplasia were absent in severe forms of MPFD. The rates of low grade and high grade fetal vascular malperfusion as judged by the frequency of obstructive lesions, thrombosis, intramural fibrin deposition, avascular villi and stromal-

Table 3
Placental plathological lesions among fetal growth restricted pregnancies complicated by moderate (25–50% of villi) and severe (> 50% of villi) placental massive perivillous fibrin deposition (MPFD) and controls.

	MPFD Absent (n. = 313)	MPFD Moderate (n = 31)	MPFD Severe (n = 11)	MPFD Overall (n = 42)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Placental morphometry				
Weight (gm)	300.1 (84.5)	326.5 (91)	358.5 (70.4)*#	328.8 (84.5)**
Area (cm^2)	150.7 (51.6)	141.9 (36.6)	148.4 (42)	143.1 (37.7)
Volume (cm^3)	412.2 (151)	438.7 (139.8)	491.6 (156)*#	450 (144.5)**
Birthweight/placenta weight ratio	6.1 (1.52)	5.34 (1.53)	5.13 (1.59)*#	5.32 (1.53)**
	n. (%)	n. (%)	n.(%)	n.(%)
Birthweigth/placental weight tertile score				
Central (5.9 ± 0.3)	110 (35.1)	6 (19.4)	3 (27.3)	9 (21.4)
High (7.7 ± 0.9)	109 (34.8)	7 (22.6)	2 (18.2)	9 (21.4)
Low (4.3 ± 0.7)	94 (30)	18 (58.1)	6 (54.5)	24 (57.1)**
Maternal vascular malperfusion				
Retroplacental hemorrhage	17 (5.4)	0	1 (9.1)	1 (2.4)
Accelerated villous maturation	94 (30)	18 (58.1)	7 (63.6)*	25 (59.5)**
Distal villous hypoplasia	55 (17.6)	10 (32.3)	0*	10 (23.8)
Recent infarcts	33 (10.5)	1 (3.2)	1 (9.1)	2 (4.8)
Late infarcts	125 (40)	9 (29)	4 (36.4)	13 (31)
Decidual arteriopathy	147 (47)	20 (64.5)	4 (36.4)	24 (57.1)
Fetal vascular malperfusion				
No	147 (47)	1 (3.2)	1 (9.1)	2 (4.8)
Low grade	119 (38)	20 (64.5)	7 (63.6)	27 (64.2)
High grade	47 (15)	10 (32.3)	3 (27.3)*	13 (31)**
Others				
Chronic villitis				
No	238 (76)	21 (67.7)	8 (72.7)	29 (69)
Low grade	60 (19.2)	10 (32.2)	3 (27.3)	13 (31)
High grade	12 (3.8)	0	0	0

*p < 0.05 in overall three groups analysis. **p < 0.05 in a two groups analysis. #P < 0.05 test for linear trend.

Table 4
Placental pathological lesions among early and late fetal growth restricted pregnancies complicated by moderate (25–50% of villi) and severe (> 50% of villi) placental massive perivillous fibrin deposition (MPFD) and controls.

	Early FGR		Late FGR	
	Controls (n = 111)	MFPD (n = 14)	Controls (n = 202)	MFPD (n = 28)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Placental morphometry				
Weight (gm)	245 (76.5)	302.9 (96.9)*	331.7 (72.1)	350.8 (76.3)
Area (cm^2)	123.5 (41.8)	120.1 (28.7)	165.6 (50.4)	154.9 (36.7)
Volume (cm^3)	325 (121)	395.2 (167.8)*	456.6 (145.5)	481.2 (124.7)
Birthweight/placenta weight ratio	5.2 (1.1)	4 (1.1)*	6.5 (1.4)	5.9 (1.4)*
	n. (%)			
Birthweigth/placental weight tertile score				
Central (5.9 ± 0.3)	29 (26.1)	1 (7.1)	81 (40.1)	8 (26.8)
High (7.7 ± 0.9)	19 (17.1)	0	90 (44.6)	9 (32.1)
Low (4.3 ± 0.7)	63 (56.8)	9 (92.9)*	31 (15.3)	11 (39.3)*
Maternal vascular malperfusion				
Retroplacental hemorrhage	9 (8.1)	0	8 (4)	1 (3.6)
Accelerated villous maturation	46 (41.4)	8 (57.1)	48 (23.8)	17 (60.7)*
Distal villous hypoplasia	29 (26.1)	5 (35.7)	26 (12.9)	5 (17.9)
Recent infarcts	17 (15.3)	0	16 (7.9)	2 (7.1)
Late infarcts	54 (48.6)	4 (28.6)	71 (35.1)	9 (32.1)
Decidual arteriopathy	62 (55.9)	8 (57.1)	85 (42.1)	16 (57.1)
Fetal vascular malperfusion				
No	58 (52.3)	0	89 (44.1)	2 (7.1)
Low grade	31 (27.9)	10 (71.4)	88 (43.6)	17 (60.7)
High grade	22 (19.8)	4 (28.6)*	25 (12.4)	9 (32.1)*
Others				
Chronic villitis				
No	95 (85.6)	9 (64.3)	143 (70.8)	19 (70.4)
Low grade	12 (10.8)	5 (35.7)	48 (23.8)	8 (28.6)
High grade	4 (3.6)	0	11 (5.4)	1 (3.6)

*p < 0.05 compared to controls.

vascular kariorrhexis were significantly associated with increased rates of MPFD. Low-grade chronic non specific villitis was diagnosed in 31% of cases (13/42) and in 19.1% of controls (p = 0.1). On the other hand, representing one of the main exclusion criteria of MPFD, high grade villitis, either patchy (n = 9) or diffuse (n = 3), was seen only in non-MPFD placentas.

Table 4 reports placental morphometric and pathological data in MPFD and controls stratified by early and late FGR. Birthweight/placental ratio was lower and the rates of fetal vascular malperfusion pattern were higher among MPFD compared to controls both in early and late FGR. Among early FGR MPFD was also associated with increased placental weight and volume compared to controls. On the other hand, rates of accelerated villous maturation were significantly higher among MPFD than in controls only in the subgroup of late FGR.

Table 5 reports the results of penalized logistic regression analysis. After adjustment for gestational age and birthweight, the association between MPFD and increasing placental weight and volume, a low birthweight/placental weight ratio, increased rates of accelerated villous maturation and fetal vascular malperfusion remained significant. In addition, after adjustment for gestational age and birthweight, the odds ratios of neonatal sepsis, intraventricular hemorrhage, proven NEC and overall severe adverse neonatal outcome were significantly higher in FGR pregnancies complicated by MPFD than in FGR without this lesion.

Table 5
Associations between massive perivillous fibrin deposition, placental morphometric and pathological characteristics and neonatal outcomes after correction for gestational age and birthweight.

Factors associated with massive perivillous fibrin deposition	OR (95% CI)	P value
Birthweight/placental weight tertile[a]		
Central	Reference	
High	0.85 (0.34–2.2)	0.75
Low	4.9 (2.05–11.6)	< .001
Placental weight (×10 gm increment)	1.08 (1.03–1.01)	< .001
Placental volume (×10 cm^3 increment)	1.03 (1.01–1.05)	0.014
Accelerated villous maturation	3.62 (1.78–7.35)	< .001
Fetal vascular malperfusion		
No	Reference	
Low grade	15.67 (3.64–67.61)	< .001
High grade	18.12 (3.91–83.97)	< .001
Neonatal outcome		
Sepsis	5.9 (1.27–27.12)	0.02
IVH (> IInd stage)	5.66 (1.69–18.97)	0.005
NEC (≥IIB stage)	9.84 (2.49–38.8)	0.001
Overall severe neonatal outcome	5.71 (2.05–15.87)	0.001

IVH: Intraventricular hemorrhage. NEC: Necrotizing enterocolitis.
Odds Ratios (OR) and 95% confidence intervals were obtained by penalized logistic regression including each pathological variables as independent variables and MPFD as outcome or by neonatal outcome as dependent and MPFD as independent variable. Gestational age and birthweight (continuous) were added as confounders.
[a] Corrected by gestational age alone.

4. Discussion

The results of this study suggest that the diagnosis of moderate and severe MPFD in placental pathological examination from pregnancies complicated by FGR is more common (11.8%) than previously reported. Previous studies on the incidence of MFDP have shown that this condition is uncommon (0.1% of deliveries) in general population but is strongly associated with FGR, preeclampsia and adverse perinatal outcome [3,6,7,21]. Most previous epidemiologic data included mainly pathological samples extracted from archive material of pregnancies with adverse outcomes; thus, the inferences were carried out only in a small proportion of all histological placental examinations and in a highly selected population of pregnancies [6,8,9]. In addition it is likely that retrospective, selected data were skewed toward the inclusion of more severe form of the pathological lesion and/or included preferentially pregnancies with severe maternal or fetal complications, when the request for placental pathological examination is increasingly common [3,6,10]. Confirming previous findings, among prenatal factors, only the presence of maternal autoantibodies suggesting complete or incomplete anti-phospholipid syndrome was associated with an increased severity of MPFD [3,7,8]. Although the perinatal outcome of pregnancies complicated by MPFD was worse than that of other FGR, we were unable to find other differences among maternal and pregnancy variables such as type of FGR, Doppler evaluation of fetal vessels, cerebroplacental ratio, abnormal fetal heart rate pattern, signs of perinatal hypoxia, and type of delivery between cases and controls. The lack of a strong relationship between abnormalities of Doppler studies of placental circulation and the occurrence of MPFD among growth restricted fetuses has already been reported in other studies and suggest that the excess risk of adverse perinatal events associated with MPFD is unrelated to low uteroplacental blood flow [22,23].

Compared to other FGR pregnancies, MPFD cases were characterized by heavier placentas, similar placental area, increasing volume and a lower birthweight/placental weight ratio both in early and late fetal growth failure. It has been suggested that increased placental weight in MPFD can be due to the excess weight associated with extensive fibrin deposition and with increased proliferation of extravillous throphoblast [2]. Our results confirm these findings, suggesting that the occurrence

of MPFD is accompanied by a morphometric modification of placenta without a significant modification of placental area. Birthweight/placental weight ratio has been considered a proxy for placental efficiency, and low values of this ratio are associated with increased risks of adverse pregnancy outcomes [16]. Since birthweight/placental weight ratio is typically lower in preterm deliveries, it has been recommended to take into account gestational age into the evaluation of the relationship of this ratio with other risk factors [16]. In our study, after correction for gestational age, birthweight/placental weight ratio was markedly lower, and placental volume was higher, among pregnancies with MFDP than in other FGR-associated placental lesions, confirming that massive perivillous fibrin deposition could reflect a distortion in placental architecture.

Most of the pathological data of this study suggest that the main differences between MPFD cases and other FGR subjects involved the occurrence of fetal rather than maternal vascular malperfusion placental lesions. According to previous studies, we found that the rates of lesions such as decidual arteriopathy or distal villous hypoplasia were lower among MPFD, especially when severe, compared to other placental lesions [2]. Fetal vascular malperfusion lesions associated with MPFD included fibrin deposition in the wall of fetal vessels, the presence of avascular villi and of villous stromal-vascular karyorrhexis. The simultaneous occurrence of these features, representing fetal thrombotic vasculopathy, suggests that MPFD is accompanied by a severe form of fetal vascular malperfusion that is potentially causative of adverse perinatal outcomes.

Although, given the small number of cases, the results should be interpreted with caution, MPFD in this study was associated with an increased risk of neonatal sepsis, moderate-to-severe intraventricular hemorrhage, proven necrotizing enterocolitis and overall severe neonatal adverse events. The absence in this and other studies of a definite relationship between MPFD, Doppler abnormalities of maternal and fetal circulation, and neonatal acidosis at birth suggest that the mechanism leading to increased neonatal complications is different from simple perinatal hypoxia but is more probably associated with chronic fetal malperfusion [3,22,23].

Antenatal risk factors for NEC include prematurity, hypoglycemia, fetal growth restriction, maternal infection and neonatal sepsis [17]. Previous studies have found that among preterm and growth restricted infants placental lesions such as fetal thrombotic vasculopathy or placental lesions correlated with maternal coagulation disorders are associated with a four-fold increased risk of NEC (24–25). It has been hypothesized that in growth restricted infants, NEC can be favored by a reperfusion and inflammatory damage of intestinal mucosa following mesenteric ischemia associated with centralization of blood flow and/or with obstructive fetal vascular lesions [24]. The high rates of fetal vascular malperfusion among MPFD cases in this study could easily explain the association between perivillous deposition and NEC.

Maternal floor infarction of the placenta and fetal thrombotic vasculopathy have been associated with increased rates of abnormalities of infant cranial ultrasound, central nervous system injury and subsequent cerebral palsy in previous studies of FGR pregnancies [25,26]. These data support the association between MPFD and IVH found in the present series.

The precise pathophysiology mechanisms linking MPFD features to adverse neonatal outcome remain in most cases to be elucidated. Severe MPFD has been associated with an early imbalance of maternal angiogenic/antiangiogenic factors with a significant midgestation reduction of maternal blood placental growth factor (PIGF) and an increase of soluble vascular endothelial growth factor receptor (sVEGFr) [27]. In addition, compared to healthy controls, subjects with MPFD had higher plasma maternal anti-HLA-I and II antibodies and interferon gamma-induced protein 10 (IP-10), signaling a strong immune anti-fetal rejection and a chronic maternal inflammatory status [28]. Interestingly, an imbalance between angiogenic and antiangiogenic factors and a proinflammatory maternal and fetal status have been demonstrated to play a key role in intraventricular hemorrhage and NEC in preterm infants [24,29]. Increased neonatal blood levels of IP-10 are early markers of neonatal sepsis and NEC and are inversely related to the severity of the diseases [30]. All of these data suggest that alterations of maternal plasma concentrations of mediators of immune response, a proinflammatory status and a dysregulation of angiogenic/antiangiogenic factors could influence the rates of neonatal complications in FGR infants after MPFD [28,29].

The main strengths of the present study were the design, the protocol used for placental examination, the inclusion of all cases of FGR and of both moderate and severe forms of MPFD. On the other hand, the study was carried out on a cohort of FGR pregnancies attending a single obstetric center, so the design is inappropriate to make inferences about the incidence or risks associated with MPFD in the general population. An additional limitation of the present study resides in the definition of MPFD, which remains problematic and subjective, and has not been the focus of the Amsterdam Consensus Statement [14]. Additionally, most of our cases were oversampled at the time of gross sectioning (> 3 samples of normal appearing parenchyma) due to the notion of FGR. For the diagnosis of MPFD we relied on the semiquantitative and fairly broad criteria originally proposed by Katzman and Genest [3]. Accordingly, a necessary and sufficient condition to render a diagnosis of MPFD, any pattern, was the presence of significantly increased perivillous fibrin on at least one slide. However, more recently, some authors advocated that a considerable percentage ($\geq 25\%$) of placental volume should be occupied by MPFD in order to confirm the diagnosis [21].

In conclusion, the results of this study have shown that moderate-to-severe MPFD was relatively common in a cohort of FGR pregnancies. MPFD was associated with morphometric modifications of placenta and with an increased risk of severe adverse neonatal outcome unrelated to umbilical artery or middle cerebral artery Doppler abnormalities.

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