Placenta 80 (2019) 36–41

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Pregnancy outcomes in correlation with placental histopathology in subsequent pregnancies complicated by fetal growth restriction

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ARTICLE INFO

Keywords:
Fetal growth restriction
Placental pathology
Neonatal outcome
Maternal malperfusion lesions

ABSTRACT

Objective: In attempt to shed new light on the etiopathogenesis of fetal growth restriction (FGR) we aimed to compare pregnancy outcomes and placental histopathology in cases of first vs. subsequent FGR occurrence.
Study design: Pregnancy and placental reports of FGR pregnancies (defined by birth weight < 10th percentile), born between 2008 and 2018 were reviewed. Included only cases with recurrent FGR, in two consecutive pregnancies, thus each subject served as her own control in two FGRs consecutive pregnancies. Neonatal outcome and placental histopathology were compared between the first FGR delivery (first FGR group) and the subsequent FGR delivery (subsequent FGR group). Composite adverse neonatal outcome was defined as one or more early neonatal complications.
Results: Included in the study a total of 96 cases with recurrence of FGR pregnancies. Placentas from the first FGR group were characterized by higher rate of maternal vascular malperfusion (MVM) lesions as compared with the subsequent FGR group (71.8% versus 55.2%, respectively, p = 0 .02). Adverse neonatal outcome was more prevalent in the first FGR group as compared to the recurrent FGR group (41.6% versus 25%, respectively, p = 0.02). After controlling for confounders, using multivariate regression analysis, placental MVM lesions (aOR = 1.36, 95% CI = 1.12–1.45) and composite adverse neonatal outcome (aOR = 1.18 95% CI = 1.09–1.55) were found to be independently associated with the first FGR group.
Conclusion: First event of FGR is associated with a higher rate of placental MVM lesions and adverse neonatal outcome as compared to FGR in subsequent pregnancies.

1. Introduction

Fetal growth restriction (FGR) is one of the leading causes of perinatal morbidity and mortality [1,2]. When “placental insufficiency” is the presumed cause of FGR, impaired placentation leads to placental vascular compromise and an increase in utero-placental malperfusion lesions constitute the main etiology of placental associated FGR [3–5].

In cases of growth restricted fetuses, as with most maternal and fetal conditions, careful evaluation of the placenta may help in the diagnosis of an underlying condition or pathophysiology [6,7]. As compared to appropriate for gestational age, placentas from FGR pregnancies are characterized by lower mean weight, lower fetal to placental weight ratio, increased thrombi or hematomas, villous infarction, and thickening of the villous trophoblastic basal membrane [7,8]. Existing evidence links specific placental lesions to FGR. According to Redline et al., the typical placental findings in cases of FGR include: global/partial maternal vascular malperfusion (MVM) lesions (accelerated maturation), villitis of unknown etiology (VUE) or chronic villitis, complete/segmental fetal vascular malperfusion (FVM) lesions (fetal thrombotic vasculopathy), fetal stromal-vascular developmental lesions, and perivillous fibrinoid deposition [3,8,9].

Salafia et al. studied placental lesions in 128 FGR cases. They found placental infarction, VUE, hemorrhagic endovasculitis, and placental vascular thromboses are more frequent in the FGR cases, compared to the non-FGR cases (55% versus 32%). Relationships of all placental lesions to FGR were independent of each other. In addition, FGR infants had multiple types of lesions in their placentas more frequently [10].

Placental-mediated complications, with FGR being the most common, are known to have a high recurrence rate in subsequent pregnancies [11].

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https://doi.org/10.1016/j.placenta.2019.04.001
Received 18 January 2019; Received in revised form 13 March 2019; Accepted 1 April 2019

The “Immune maladaptation theory” claims that the fetus and the placenta both act as the graft or foreign body while the mother, plays the role of the host. In the subsequent pregnancy, according to this theory, it would be reasonable to assume that the maternal immune system will recognize the fetus and therefore, the rejection reaction tends to be less severe [12]. We hypothesized that placental histopathology and neonatal outcome will differ between the first occurrence of FGR and the recurrent case of FGR in the same patient in a way that the former will be more severe than the later. In order to test our hypothesis, we compared the detailed placental histopathology reports and neonatal outcomes between subsequent pregnancies complicated by FGR in the same patient.

2. Materials and methods

2.1. Patients selection

Our departmental protocol routinely performs a full placental analysis in all complicated pregnancies, as in cases of FGR pregnancies. The computerized files of all women who gave birth at 24–42 gestational weeks, to a singleton neonate with FGR, in our university affiliated tertiary centre, from January 2008 to November 2018, were reviewed. Exclusion criteria included pregnancies for which the placenta was not sent for pathological examination, pregnancy termination, pregnancies complicated by major fetal malformation, genetic disorder, or clinically diagnosed maternal infection. The study group included all women who delivered a subsequent singleton FGR pregnancy, in our institution. FGR was defined as birth-weight below the 10th percentile according to the updated local population growth charts [13].

For the purpose of the study maternal characteristics, pregnancy outcomes, and placental histopathology reports were compared between the first pregnancies complicated with FGR (first FGR group) and the recurrent/subsequent FGR pregnancies (subsequent FGR group). In this manner each subject served as her own control in two consecutive pregnancies.

Approval was obtained from the Local Ethics Committee.

2.2. Data collection

The following data were collected from the women's medical and surgical files of their pair pregnancies: age, gestational age at delivery, gravidity, parity, mode of delivery, pre-pregnancy, Body Mass Index (BMI kg/m^2), pre-gestational diabetes mellitus (PGDM), gestational diabetes mellitus (GDM), smoking status, hypertensive morbidity, pre-eclampsia as defined by the American College of Obstetricians and Gynecologists (ACOG) Task Force [14], anti-hypertension therapy during pregnancy, Low Molecular Weight Heparin (LMWH) and acetylsalicylic acid (Aspirin) treatment during pregnancy (dosage of 100 mg), abnormal umbilical artery Doppler studies (defined as pulsatility index > 95th percentile or absent/reverse diastolic flow before delivery), thrombophilia (defined as any thrombophilia, inherited or acquired, which required thrombo-prophylaxis) [15,16], and magnesium-sulphate therapy during labor. In all participants, gestational age was confirmed by first-trimester ultrasonography.

Immediately after birth, all neonates were examined by pediatricians. Birth-weight percentile for gestational age was assigned using the updated local growth charts [13]. The following data were collected from the neonatal charts: birthweight, Apgar scores, cord blood Ph, neonatal intensive care unit (NICU) admission, hypoglycemia (defined as basal glucose < 40 mg/dL), seizures, mechanical ventilation, respiratory distress syndrome, necrotizing enterocolitis (NEC), phototherapy, sepsis (positive blood or cerebrospinal fluid culture), blood transfusion, and death.

2.3. Placental histopathology

Placental histopathology examinations were performed using our standard protocol by a single pathologist (author L.S). Placental lesions were classified according to the criteria adopted by the Society for Pediatric Pathology (SPP) [4,9] as previously reported by us [17,18]. Briefly, placental weight was determined 24 h after delivery (trimmed and fixed) and the percentile was determined according to placental weight charts [19] after correction for fixation [20]. From each placenta, six tissue samples were embedded in paraffin blocks for microscopic assessment: one role of the free membranes, (chorion and amnion with attached decidua capsularis), one at the cord insertion, one from central tissue that appeared abnormal on gross examination, two from normally appearing central tissue, and one at the margin visible abnormal areas on gross examination. In addition, a section of umbilical cord was sampled.

Lesions of maternal vascular supply included: retroplacental hemorrhages, vascular changes associated with maternal malperfusion including acute atherosis, chronic perivasculitis, mural hypertrophy, fibrinoid necrosis, absence of spiral artery remodelling, arterial thrombosis, and persistence of intramural endovascular trophoblast in the third trimester (decidual arteriopathy), and villous changes associated with maternal malperfusion (increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, distal villous hypoplasia, and villous infarcts).

Lesions of fetal vascular supply included: thrombosis of the chorionic plate and stem villous vessels, avascular villi, intramural fibrin deposition, villous stromal-vascular karyorrhexis, stem vessel obliteration, and vascular ectasia.

Findings consistent with chorioamnionitis were defined by the presence of an inflammatory neutrophil infiltrate at two or more sites on the chorionic plate and extra-placental membrane. Maternal inflammatory response (MIR) was divided into three stages; stage 1 – characterized by the presence of a few scattered neutrophils in the subchorionic space; stage 2 – characterized by many neutrophils [11–30 per high power field (HPF)] in the lower half of the chorionic plate; and stage 3 – characterized by dense infiltrates of neutrophils (> 30 per HPF) throughout the chorionic plate. Fetal inflammatory response (FIR) was also divided into three stages: umbilical arteritis; and stage 3 – concentric umbilical perivasculitis (necrotizing funisitis).

Viillitis of unknown etiology (VUE), defined as lymphohistiocytic inflammation localized to the stroma of terminal villi, but often extending to the small vessels of upstream villi, was recorded separately. Low grade VUE is defined as the presence of inflammation affecting fewer than 10 contiguous villi in any one focus, with more than one focus required for the diagnosis. High grade is defined as the presence of multiple foci, on more than one section, at least one of which shows inflammation affecting more than 10 contiguous villi.

Chronic histiocytic intervillositis is a rare idiopathic inflammatory lesion distinct from VUE and associated lesions. It is characterized by a monomorphic maternal histiocytic infiltrate in the intervillous space without accompanying VUE. Massive perivillous fibrin deposition (maternal floor infarction) characterized by large amounts of fibrin and fibrinoid matrix surrounding a significant proportion of the distal villous tree.

All the placental lesions mentioned above, were compared between the study groups (the placentas from the first pregnancy vs. the placentas from the subsequent pregnancy). Each placenta could, therefore, express none, one, or more than one type (combination) of lesion.

2.4. Statistical analysis

Data were analyzed with Epi Info, version 7.0 (Centers for Disease Control and Prevention, Atlanta, GA). Continuous variables were calculated as mean ± standard deviation (SD) and compared using the Student's t-test or the non-parametric Mann-Whitney test as

appropriate. Categorical variables were calculated as rate (percentage) and compared with Chi square or Fisher's exact test as appropriate. All tests were two tailed, and the threshold for statistical significance was defined as p-value < 0.05.

Composite MVM lesions was defined as one or more of lesions resulting from loss of integrity of the maternal circulation as retroplacental hemorrhages, vascular changes associated with maternal malperfusion as acute atherosis and mural hypertrophy, and villous changes associated with maternal malperfusion as increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, and villous infarcts.

Composite FVM lesions were defined as one or more lesions: thrombosis of the chorionic plate and stem villous vessels, avascular villi, intramural fibrin deposition, villous stromal-vascular karyorrhexis, stem vessel obliteration, and vascular ectasia.

Composite adverse neonatal outcome was defined as one or more of the following early neonatal complications: cord blood Ph < 7.1, hypoglycemia, seizures, mechanical ventilation, respiratory distress syndrome, NEC, phototherapy, sepsis, blood transfusion, or death.

Multivariate regression analyses were performed to identify independent associations with composite MVM lesions and composite adverse neonatal outcome. Those lesions served (separately) as the dependent variables while the study groups (first vs. subsequent FGR), maternal age, diabetes mellitus, hypertensive diseases, acetylsalicylic acid (Aspirin) use, and LMWH use served as independent variables.

3. Results

During the study period, 34,825 deliveries occurred. Of them 2786 (8%) were complicated by singleton FGR neonates, of whom only 1254 (45.0%) cases had placental pathology examination. Ninety-six patients had two subsequent singleton FGR pregnancies and met the inclusion criteria. The first FGR event constituted the 'first FGR group' (n = 96), and the subsequent FGR pregnancy constituted the 'subsequent FGR group' (n = 96). (Fig. 1).

Maternal and pregnancy characteristics of the first and subsequent FGR groups are presented in Table 1. Gestational age, pre-gestational BMI, any diabetes during pregnancy, any hypertension morbidity, antihypertension therapy during pregnancy, LMWH and acetylsalicylic acid (Aspirin) treatment during pregnancy (dosage of 100 mg), magnesium-sulfate therapy during labor, umbilical artery Doppler studies, smoking status, thrombophilia and Cesarean delivery rates were similar between both groups. Maternal age was (as per the study design) more advanced in the subsequent FGR group (32.4 ± 4.5 years versus 29.5 ± 4.1 years, respectively; p < 0.001). Nulliparous women, as expected from the study design, were only present in the first FGR group and they constituted 61.4% of that group.

Placental characteristics are presented in Table 2. Composite placental MVM lesions were significantly more common in placentas from the first FGR group, as compared to the subsequent FGR group, (71.8% versus 55.2%, respectively; p = 0.02). Placental hemorrhage as part of MVM lesions displayed a trend for higher prevalence among the first FGR group, (12.5% versus 4.1%, p = 0.06). FVM lesions and inflammatory lesions were equally prevalent among the groups.

Table 3 presents neonatal outcomes of the study groups. Mean birthweight, the rate of FGR < 5th percentile and Apgar score at 5 min < 7 were not significantly different among the groups. Umbilical artery Ph ≤ 7.1 was significantly more prevalent among the first FGR group (23.9% versus 9.3%, p = 0.01).

Composite adverse neonatal outcome was found in 41.6% of the neonates in the first FGR group as compared to 25.0% of the subsequent FGR group, (p = 0.02).

Using multivariate logistic regression analysis, after adjustment was performed for maternal age, diabetes mellitus, hypertensive diseases, acetylsalicylic acid (Aspirin) use, and LMWH use, placental maternal malperfusion lesions (aOR = 1.36, 95% CI = 1.12–1.45) and composite adverse neonatal outcome (aOR = 1.18 95% CI = 1.09–1.55) were found to be independently associated with the first FGR group (Table 4).

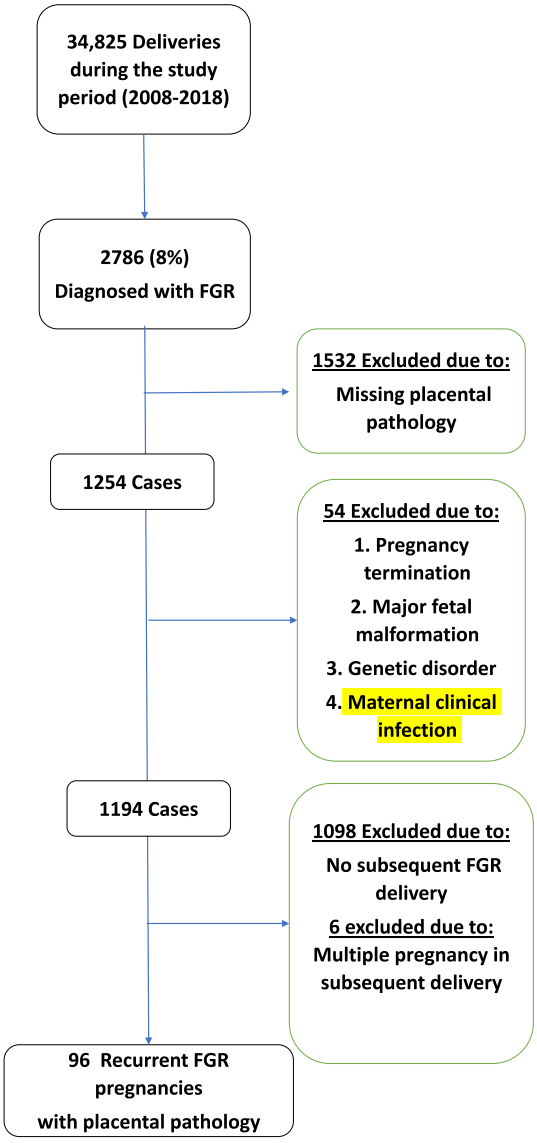

Fig. 1. Participant flow diagram.

4. Discussion

This study aimed to compare pregnancy outcomes and placental histopathology in cases of first versus subsequent FGR occurrence, in the same woman. Our main findings were: 1) Placental MVM lesions were significantly more common in placentas from the first FGR group, as compared to the subsequent FGR group while there was no significant difference between the groups regarding the rate of FVM nor inflammatory lesions. 2) Adverse neonatal outcome was found to be more prevalent in the first occurrence of FGR as compared to the subsequent occurrence. 3) These two findings were found to be independently associated with the first FGR occurrence after adjustment for potential confounders including acetylsalicylic acid (Aspirin) and LMWH treatment during the subsequent pregnancy.

Impaired placental function or uteroplacental insufficiency has various manifestations during pregnancy, primarily FGR and pre-eclampsia [5]. Moreover, a placental disease may present itself differently in subsequent pregnancies [21,22]. The main pathophysiological

Table 1
Maternal demographics and pregnancy characteristics of the study groups.

	First FGR (n = 96)	Subsequent FGR (n = 96)	*p* value
Maternal age (years)	29.5 ± 4.1	32.4 ± 4.5	< **0.001**
GA at delivery (weeks)	36.6 ± 3.0	37.0 ± 3.2	0.30
Nulliparity (%)	59 (61.4%)	0	< **0.001**
BMI (kg/m^2)	23.65 ± 4.5	24.42 ± 4.7	1.00
PGDM (%)	0	1 (1.0%)	1.00
GDM (%)	6 (6.2%)	9 (9.3%)	0.59
Any DM (%)	6 (6.2%)	10 (10.4%)	0.43
Chronic HTN (%)	3 (3.1%)	3 (3.1%)	1.00
Gestational HTN (%)	7 (7.2%)	7 (7.2%)	1.00
Preeclampsia mild or severe (%)	10 (10.4%)	8 (8.3%)	0.80
Any HTN disorder during pregnancy (%)	15 (15.6%)	16 (16.6%)	1.00
Acetylsalicylic acid treatment (%)	5 (5.2%)	10 (10.4%)	0.28
Low molecular weight Heparin (%)	4 (4.1%)	12 (12.5%)	0.06
Hypertensive therapy during pregnancy (%)	4 (4.1%)	4 (4.1%)	1.00
Magnesium Sulfate during labor (%)	5 (5.2%)	6 (6.2%)	1.00
Smoking (%)	24 (25%)	29 (30.2%)	0.51
Pathological Doppler studies (%)	7 (7.2%)	9 (9.3%)	0.79
Thrombophilia (%)	6 (6.2%)	12 (12.5%)	0.21
Induction of labor	49 (51.0%)	58 (60.4%)	0.24
Cesarean delivery	52 (54.1%)	55 (57.2%)	0.77

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant. GA-gestational age, BMI – body mass index, PGDM - pregestational diabetes mellitus GDM – gestational diabetes mellitus, DM-diabetes mellitus, HTN-hypertension.

Table 2
Placental histopathological lesions in the study groups.

	First FGR n = 96	subsequent FGR n = 96	p-value
Placental weight, grams	338.3 ± 89	360.6 ± 97	0.09
Placental weight < 10th percentile	85 (88.5)	76 (79.2)	0.11
Birth-weight to placental-weight ratio	6.50 ± 1.5	6.12 ± 1.5	0.08
Maternal vascular malperfusion lesions			
Placental hemorrhage	12 (12.5%)	4 (4.1%)	0.06
Vascular lesions of maternal malperfusion	18 (18.7%)	11 (11.4%)	0.22
Villous lesions of maternal malperfusion	64 (66.6%)	51 (53.1%)	0.07
Composite maternal malperfusion lesions	69 (71.8%)	53 (55.2%)	**0.02**
Fetal vascular malperfusion lesions			
Composite fetal malperfusion lesions	17 (17.7%)	22 (22.9%)	0.47
Inflammatory lesions			
MIR (stage 1–3)	10 (10.4%)	10 (10.4%)	1.00
FIR (stage 1–3)	2 (2.0%)	2 (2.0%)	1.00
Villitis of unknown etiology (both grades)	10 (10.4%)	5 (5.2%)	0.28
Low grade	4 (4.2%)	2 (2.1%)	0.68
High grade	6 (6.3%)	3 (3.1%)	0.50
Chronic histiocytic intervillositis	2 (2.0%)	1 (1.0%)	1.00
Other lesions			
Perivillous fibrin deposition	1 (1.0%)	1 (1.0%)	1.00

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant. FTOD, fetal thrombo-occlusive disease; MIR, maternal inflammatory response; FIR, fetal inflammatory response.

Table 3
Neonatal outcomes in the study groups.

	First FGR (n = 96)	subsequentFGR (n = 96)	*p* value
Birthweight (grams)	2151.8 ± 521	2207.2 ± 529	0.46
FGR < 5th percentile (%)	41 (42.7%)	31 (32.3%)	0.17
Umbilical Ph ≤ 7.1 (%)	23 (23.9%)	9 (9.3%)	**0.01**
Apgar 5 < 7 (%)	6 (6.2%)	5 (5.2%)	1.00
NICU (%)	36 (37.5%)	37 (38.5%)	1.00
Seizures (%)	0	1 (1.0%)	1.00
Hypoglycemia (%)	8 (8.3%)	7 (7.2%)	1.00
Mechanical ventilation (%)	6 (6.2%)	2 (2.0%)	0.27
Respiratory distress syndrome (%)	5 (5.2%)	1 (1.0%)	0.21
Necrotizing enterocolitis (%)	0	0	1.00
Phototherapy (%)	12 (12.5%)	13 (13.5%)	1.00
Sepsis (%)	1 (1.0%)	0	1.00
Transfusion (%)	3 (3/1%)	1 (1.0%)	0.62
Composite adverse neonatal outcome (%)	40 (41.6%)	24 (25%)	**0.02**

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant. FGR- Fetal growth restriction; NICU - Neonatal intensive care unit.

Table 4
Independent associations with First FGR pregnancy – multivariate analysis [a].

	aOR	95% CI
Composite maternal malperfusion lesions	1.36	1.12–1.45
Composite adverse neonatal outcome	1.18	1.09–1.55

[a] Adjusted for: maternal age, diabetes mellitus, hypertensive diseases, Aspirin use, and Low Molecular Heparin use.

factors differentiating FGR and preeclampsia placentas from normotensive, appropriate for gestational age pregnancies, are the presence of lesions related to the maternal and fetal vascular supply [7,23].

The tendency for uteroplacental insufficiency to reoccur is evidenced by the fact that the birth of an FGR neonate in the first pregnancy increases the risk of recurrence by more than sevenfold [24,25]. Recently we have studied the role of placental histopathology in the prediction of fetal growth restriction (FGR) recurrence [17]. Some evidence shows that the first occurrence of preeclampsia manifests earlier and more severe in nature than the recurrence [26,27]. One of the evidence regarding more severe manifestation in the first occurrence, is the increased risk of FGR and also preeclampsia in primiparous compared with multiparous women [28,29]. As in our study, both pathological placental histopathology and neonatal adverse outcome were more common in the first FGR occurrence. Although placental pathological findings are significantly less common in subsequent pregnancies compared to the first FGR occurrence, the difference did not manifest in the birthweight that was similar between groups.

This finding of a more severe nature of placental disease in the first

occurrence or a decrease in the incidence of adverse outcomes with subsequent pregnancies may be explained by the "Immune maladaptation theory" [30,31]. The theory suggests that intolerance between the mother and the fetus, resembles chronic graft versus host disease seen in transplantation when the fetus and placenta act as a graft and the mother is naturally playing the host [32,33]. This reaction involving the interaction between innate immune cells, NK cells and trophoblast antigens, play an essential role in the pathogenesis of preeclampsia and possibly also in FGR [12,34]. There would, therefore, have to be an "immune tolerance" in the next pregnancy [35,36], that can explain the less severe placental histopathology and neonatal outcome in the subsequent pregnancies, as in our study. The milder presentation in subsequent pregnancies occurred despite a more advanced maternal age. A word of caution should be mentioned - An immune response could theoretically be more pronounced in the second encounter [37], However, the results in the current study demonstrated the opposite: a milder immunological response in the second encounter with pregnancy.

Importantly, FVM lesions are known to closely be associated with FGR. Most of FVM lesions are not the consequence of immune-mediated process (rather result from umbilical blood flow obstruction) [38]. That could explain why we found no significant difference regarding FVM between the groups of FGR in subsequent pregnancies. In addition, all the inflammatory lesions including MIR, FIR, VUE and chronic histiocytic intervillositis, did not differ between groups. This can be explained by their relative rarity (at least for chronic histiocytic intervillositis), and due to our limited cohort size. We intend to re-evaluate this in a few years again as our cohort is growing.

We are aware of the study limitations. First, due to its retrospective design, which limited, among the rest, our ability to follow patients that delivered their subsequent pregnancy in different institutes. Second, we included only pregnancies whose placentas were initially sent for histopathological examination, and although a standard protocol exists in our department suggests the evaluation of FGR placentas, this is not always performed due to postnatal recognition of low birth weight. This is reflected by the fact that only in 45.0% of pregnancies complicated by FGR neonates, placentas were sent to histopathology examination. As such, patients for which placental examination exists are most probably a representation of the more severe cases - which introduces selection bias to our study.

Third, although all fetuses had Doppler flow assessment only a small part of our cohort had abnormal Doppler studies. This implies that at least part of our cohort represents "constitutional" FGR, however doe to the study design (each patient serves as her own control) we do not think that constitutional FGR biased our results. Fourth, the pathologist was not necessarily blinded to the suspected diagnosis of FGR, which could have led to observer bias. Lastly, in some cases of FGR in the subsequent pregnancy, the mother was treated with acetylsalicylic acid (Aspirin) (dosage of 100 mg) and LMWH as preventive therapy that could interfere with placental pathology [39,40]. Notably, all of our major findings were associated with the first FGR pregnancy after controlling for all confounders including acetylsalicylic acid (Aspirin) and LMWH use in the recurrent pregnancy.

Our study has several notable strengths. It is the first study that compares recurrent FGR pregnancies in the same woman in correlation with placental histopathology. Our study includes a relatively large cohort of patients with consecutive FGR pregnancies managed in a single university centre. Additionally, the use of our electronic medical records, as opposed to birth certificates or patient recall, increases accuracy and diminishes recall bias. In addition, exclusion of twin pregnancies and all cases of non-placenta-mediated FGR, allows for a better estimation of placental lesions and adverse neonatal outcome. Lastly, we were able to control for all major background confounders.

In conclusion, our study shows that the first event of FGR is associated with a higher rate of placental MVM lesions and a higher rate of adverse neonatal outcome, compared to FGR in subsequent pregnancies. These findings imply that the "immune tolerance" hypothesis of preeclampsia might be relevant to other placenta-mediated complications, including FGR. Future studies should prospectively evaluate this hypothesis on larger scale populations.

Disclosure

There is not any financial relationship with any organization or any conflict of interest to report.

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