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MATERNAL-FETAL MEDICINE

Recurrent intrauterine growth restriction: characteristic placental histopathological features and association with prenatal vascular Doppler

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Abstract

Purpose Intrauterine growth restriction (IUGR) is a leading cause of perinatal morbidity and mortality, carrying a 20% recurrence rate. The placental disease is a cardinal factor among IUGR underlying processes. This study describes placental histopathological features (HPf) characteristic of recurrent IUGR (rIUGR) and assesses association with antenatal Doppler studies.

Methods We conducted a retrospective case–control study, between the years 2005–2016, evaluating 34 placentae of 17 women with rIUGR, and 59 placentae of a gestational age-matched control. Doppler studies within a week prior to delivery were analyzed for the rIUGR group.

Results Placental HPf characteristic of rIUGR is maternal and fetal vascular malperfusion lesions; maternal accelerated villous maturation and villous infarcts, repetitive feature rate 88.8% (95% CI 37.2–97), and fetal chorionic plate/stem villous thrombi, repetitive feature rate 66.6% (95% CI 30–90.3). Among women with abnormal Doppler, 83.3% had a placenta HPf of maternal vascular malperfusion lesions and 66.7% presented with a hypertensive disorder.

Conclusions Women with rIUGR are a unique group of patients characterized by repetitive placental HPf of both maternal and fetal vascular malperfusion lesions. Specifically, maternal vascular malperfusion lesions are associated with abnormal Doppler findings. In conclusion, characteristic placental HPf may serve as predictors of future IUGR recurrence, thus offering early recognition of pregnancies that require "high-risk" antenatal care.

Keywords Placenta · Recurrent IUGR · Histopathological features · Vascular malperfusion

Introduction

Intrauterine growth restriction (IUGR) is commonly defined as fetal growth less than the 10th percentile for gestational age. It is a leading cause of perinatal morbidity and mortality as well as later life health consequences [1–4]. Furthermore, 26–53% of term and preterm stillbirths are diagnosed with IUGR. The overall recurrence rate of IUGR has been estimated at 20%. However, prediction tools for future pregnancies are scarce [3, 5–9].

The placenta is a cardinal organ responsible for fetal growth and well-being. Thus, placental features may serve as a predictor for the recurrence of IUGR in future pregnancies [10, 11]. Numerous studies describe placental morphological and histopathological findings characteristic of IUGR [11–13], but only a few studies report histopathological features (HPf) of recurrent IUGR (rIUGR) placentae [14, 15].

The objective of the present study is to describe repetitive placental histopathological findings (HPf) characteristic to recurrent IUGR (rIUGR) and present association with antenatal sonographic Doppler studies.

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Methods

We conducted a retrospective single-center case–control study between the years 2005–2016. For the study, we reviewed all IUGR placentae samples obtained from women who delivered more than one singleton IUGR live-born, > 24 weeks gestation, with more than one placenta available for pathology reevaluation. IUGR was defined as neonatal birth weight below the 10th percentile for gestational age (population-based) [16]. Excluded from the study are known fetal genetic or structural malformations, CMV or clinically overt bacterial intrauterine infection. Placental findings were compared to those obtained from a group of gestational age-matched appropriate for gestational age (AGA) neonates of women with no known risk factors for IUGR (ratio 1:2). Maternal demographics, data regarding delivery, fetal and maternal outcomes were obtained from validated computerized medical records.

Placentae analysis and sample preparation

Placentae sampling and preparation for the initial HPf analysis was performed according to the institutional protocol [17]. Briefly, each placenta was fixed in formaldehyde 4% following removal of membranes and cord. Placentae were weighted; percentile was determined by specific placental weight charts [18]. For each placenta, at least five full-thickness disk samples were taken. Additional samples were obtained from the membrane roll, the umbilical cord, and any other abnormal area. Samples were embedded in paraffin blocks. Five-micrometer-thick slices were than H&E stained for microscopic assessment.

All histopathological reassessments were performed by a single pathologist (LS). Analyses were based on the latest classification for placental lesions revised by Redline 2015 (incorporating the 2014 Amsterdam placental group criteria) and classification of placental lesions revised according to the Amsterdam placental workshop group consensus statement [11, 19]. Repetitive feature rate was calculated using the following formula: $\frac{N \text{ of recurring placentae with specific HPf}}{\text{total} N \text{ placentae with specific HPf}}$.

Ultrasonographic fetal Doppler flow measurements

Biometrical and Doppler flow measurements of the umbilical artery (UA) and middle cerebral artery (MCA) data, within a week prior to delivery, were analyzed. Doppler studies were performed in accordance with the antenatal care follow-up protocol of IUGR, thus not available for the AGA group. The Doppler flow measurements of UA and MCA were obtained by ultrasound Voluson E8 (GE Healthcare) using a convex probe (frequency 3.5–5 MHz). Doppler blood flow was assessed by pulsatility index (PI) measurement based on Gosling et al. pattern: $\text{PI} = \frac{(\text{maximal systolic velocity} - \text{minimal diastolic velocity})}{\text{mean velocity}}$ [20].

For the purpose of the study, the results of Doppler studies were classified as normal/abnormal either by the Cerebral-placental ratio (CPR), when PI values were obtained, or by UA or MCA systolic/diastolic ratio, when the PI value was not recorded [20–22].

Statistics

Description of demographic, clinical, and placental pathology data was by numbers and percentages for categorical variables and by mean values ± standard deviations or by a median with interquartile ranges for continuous variables.

Relations between categorical variables were evaluated by Chi-square and Fisher's exact tests. The effect of categorical variables on continuous measurements was tested by unpaired student *t* and Mann–Whitney tests. The choice of a parametric or nonparametric test depended on the distribution of a continuous variable. The *p* values presented are 2-sided when *p* values < 0.05 were denoted statistically significant.

Analyses were carried out using IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.

Results

We identified 34 rIUGR placentae obtained from 17 women and 59 placentae of AGA fetuses provided by 55 women. The groups were similar for maternal age, education, and parity. Inherent to group definition, the two groups differed significantly for mean birth weight, 1963 ± 486 s versus 2624 ± 853 g in the rIUGR and AGA groups, respectively, $p < 0.001$. A total of 77% of rIUGR infants were under the 5th percentile for gestational age. The rIUGR group was characterized by an increased rate of hypertensive disorders 29.4% versus 3.4%, $p < 0.001$. Women of the rIUGR group had a significantly higher rate of both inductions of labor and cesarean deliveries with no trial of labor in comparison with the AGA group, 23.5% versus 11.9% and 32.4% versus 11.9%, respectively, $p = 0.007$ (Table 1).

Placental macroscopic characteristics of all samples were assessed. Placental weight differed significantly between the two groups, 331.5 ± 113 versus 490 ± 136.3 in the rIUGR and AGA group, respectively, $p < 0.001$. A total of 52.9% of rIUGR placentae were under the 10th percentile for gestational age as compared to 3.4% in the AGA group. Overall, HPf that were most prevalent in the rIUGR group in comparison with the AGA group were maternal and fetal vascular malperfusion lesions (Table 2).

Table 1 Study population characteristics: maternal and neonatal

	rIUGR	AGA	*p* value
	N = 17 women	*N* = 55 women	
Maternal characteristics			
Maternal age (years), mean ± SD	28.5 ± 5	28.7 ± 6	0.92
Maternal age > 35 years, *n* (%)	1 (5.9%)	11 (20%)	0.16
Education* > 12 years, *n* (%)	15 (100%)	50 (96.2%)	0.4
	N = 34 deliveries	*N* = 59 deliveries	
Obstetric history			
Parity, mean ± SD	3.7 ± 3.4	3.1 ± 2.5	0.34
Prior early pregnancy loss, mean ± SD	0.8 ± 1	0.5 ± 1	0.09
Maternal morbidity			
Pre/gestational diabetes mellitus, *n* (%)	0	3(5%)	0.25
Hypertensive disorder, *n* (%)	10 (29.4%)	2 (3.4%)	**< 0.001**
Index pregnancies			
Pregnancy following in vitro fertilization, *n* (%)	2 (5.9%)	2 (3.4%)	0.56
Gestational age at delivery (weeks), mean ± SD	36.4 ± 3.4	35.3 ± 4.2	0.4
Preterm (< 37 weeks), *n* (%)	14 (46.7%)	27 (45.8%)	0.93
Mode of labor initiation			
Spontaneous, *n* (%)	15 (44.1%)	45 (76.2%)	**0.007**
Induction, *n* (%)	8 (23.5%)	7 (11.9%)	
Cesarean delivery w/o trial of labor, *n* (%)	11 (32.4%)	7 (11.9%)	
Mode of delivery			
Spontaneous vaginal delivery, *n* (%)	15 (44.1%)	27 (45.8%)	0.5
Instrumental vaginal delivery, *n* (%)	4 (11.8%)	3 (5.1%)	0.87
Cesarean delivery, *n* (%)	15 (44.1%)	29 (49.2%)	0.64
Neonatal outcome			
Birth weight (g), mean ± SD	1963 ± 486	2624 ± 853	**< 0.001**
Male gender, *n* (%)	15 (44.1%)	37 (62.7%)	0.08
Neonatal intensive care unit admission, *n* (%)	16 (53.3%)	31 (52.5%)	0.94
Apgar score 5′ < 7, *n* (%)	2 (6.7%)	8 (17%)	0.16

Bold values represents the statistically significant results

*rIUGR—Recurrent intrauterine growth restriction. This group includes 17 women in 34 deliveries

*AGA—Appropriate for gestational age. This group includes 55 women in 59 deliveries

*Education information is available for 15 and 52 women in rIUGR and AGA groups, respectively

Table 2 Significant differences in placental histopathological features characteristic of rIUGR compared to AGA placentae

Placental classification	Histopathological feature	rIUGR *N* = 34 deliveries	AGA *N* = 59 deliveries	***p* value**
Macroscopic description	Placental weight (g), mean ± SD	331.5 ± 113.0	490 ± 136.3	**< 0.001**
	Placental weight < 10th percentile for gestational age, *n* (%)	18 (52.9%)	2 (3.4%)	**< 0.001**
Maternal stromal-vascular lesions—malperfusion	Global/partial—late: accelerated villous maturation, *n* (%)	9 (26.5%)	5 (8.5%)	**0.019**
	Segmental/complete—villous infarct(s), *n* (%)	10 (29.4%)	3 (5.1%)	**0.002**
	Global/partial or segmental/complete, *n* (%)	18 (52.9%)[a]	8 (13.6%)	**< 0.0001**
Fetal stromal-vascular lesions—malperfusion	Segmental/complete—chorionic plate or stem villous thrombi, *n* (%)	6 (17.6%)	1 (1.7%)	**0.009**
	Global/partial or segmental/complete, *n* (%)	12 (35.3%)	6 (10.2%)	**0.003**

Bold values represents the statistically significant results

Based on Redline classification of placental lesions 2015, incorporating the 2014 Amsterdam Placental Workshop Group criteria. HPf found statistically significant are listed in the table

[a]One placenta presented with both pathologies

We performed additional analyses to evaluate the repetitive placental HPf characteristic of rIUGR of the same maternal origin. Notably, we found the following repetitive lesions: maternal malperfusion lesions—accelerated villous maturation and villous infarcts with a total repetitive feature rate for malperfusion features of 88.8% (95% CI 37.2–97) and fetal malperfusion lesions—chorionic plate/stem villous thrombi with a repetitive feature rate of 66.6% (95% CI 30–90.3). Other repetitive abnormalities were the abnormal placental shape or umbilical insertion site, meconium-associated changes, and hypercoiled cord (Table 3).

A valid fetal sonographic evaluation taken within a week prior to delivery was obtained for revision for 18 fetuses within the rIUGR group. Six Doppler studies were classified as abnormal and indicative of fetal blood redistribution. Among woman with an abnormal Doppler, 66.7% had hypertensive disorders compared to 8.3% in the normal Doppler group. Notably, abnormal Doppler studies were characteristic of pregnancies with repetitive placental HPf of maternal vascular malperfusion lesions; 83.3% maternal vascular malperfusion lesions in the abnormal Doppler versus 25% in the normal Doppler group, $p = 0.032$.

Discussion

As morbidity and mortality are increasingly prevalent in IUGR neonates, strategies to predict and prevent recurrence are critical for obstetric management and neonatal outcomes. Pathological assessment of placentae in IUGR pregnancies is a common practice, and HPf have been described extensively in the literature [23, 24]. In this study, focused on recurrent IUGR, in addition to baseline placental pathology indicative of IUGR previously described in cases of single isolated IUGR, we found a significant rate of repetitive placental HPf of maternal and fetal stromal-vascular malperfusion lesions. Nevertheless, abnormal Doppler studies indicative of fetal vascular redistribution were common in placentae characterized by maternal malperfusion rather than by fetal lesions.

Normal fetal development is dependent on adequate cell growth and differentiation [25]. Throughout pregnancy, the placenta undergoes several stages of maturation in adaptation to gestational age demands and development [25]. An insult in these processes can lead to IUGR with or without changes in the head to abdomen ratio-the "head sparing" effect [9, 10]. There are various etiologies for IUGR that can be broadly categorized into maternal, fetal, or placental origin [5, 6, 8]. Placenta-related IUGR is postulated to be influenced by an abnormal remodeling of the uterine spiral arteries that are responsible for supplying the placenta during early pregnancy [26]. A deficiency in their function may lead to placental malperfusion, associated with hypoxic cell stress within the placental tissue [27]. While the placental involvement consists of either maternal or fetal vascular compromise, both result in a decrease of maternal blood flow to the growing fetus.

There are few placental HPf associated with IUGR. Such features include global or partial maternal malperfusion (accelerated maturation), chronic villitis, complete or segmental fetal vascular malperfusion (fetal thrombotic vasculopathy), and fetal stromal–vascular developmental

Table 3 Repetitive feature rate of placental HPf in rIUGR group

Placental classification	Histopathological feature	Number of participants with specific HPf in both placentae, *N* (%)	Repetitive feature rate[a], % (95% CI for proportion)
Maternal stromal-vascular lesions—malperfusion	Global/partial—late: accelerated villous maturation, *n* (%)	2 (11.8)	44.4 (18.9–73.3)
	Segmental/complete—villous infarct(s), *n* (%)	3 (17.6)	60 (31.3–81.2)
	Global/partial or segmental/complete, *n* (%)	8 (47.1)	88.8 (67.2–97.0)
Fetal stromal-vascular lesions—malperfusion	Global/partial, *n* (%)	1 (5.9)	40 (11.7–77.0)
	Segmental/complete—chorionic plate or stem villous thrombi, *n* (%)	2 (11.8)	66.6 (30.0–90.3)
	Global/partial or segmental/complete, *n* (%)	3 (17.6)	50.0 (25.4–74.6)
Other placental processes	Abnormal placental shape or umbilical insertion site	1 (5.9)	22.2 (6.3–54.7)
	Meconium-associated changes	4 (23.5)	53.3 (30.1–75.2)
	Hypercoiled cord	1 (5.9)	14.3 (4.0–40.0)

[a]Repetitive feature rate was calculated using the following formula: $\frac{N \text{ of recurring placentae with specific HPf}}{\text{total } N \text{ placentae with specific HPf}}$

lesions [11]. A review of placental pathology from pregnancies complicated by IUGR showed a mixture of maternal as well as abnormal fetal features; the most common HPf was chorangiosis—increased number of blood vessels in the chorionic villi (39%), followed by placental ischemia (18%), villitis of unknown etiology (13%), fetal thrombotic vasculopathy (8%), and less commonly, velamentous umbilical cord insertion, maternal sickle cell trait, and placenta accreta [10, 28].

Particularly, in the present study, we demonstrate that a similar repetitive pattern of combined maternal and fetal lesions is characteristic of rIUGR. Moreover, we present a higher impact of the placental maternal pathology with lesions that are similar to previously reported by others, however of higher magnitude; 52.9% versus 25–35% as reported by others for IUGR in general, while 47% of women had such findings in both placentae [11, 23, 29, 30]. These lesions include accelerated villous maturation and villous infarcts. Interestingly, similar changes were described for placentae originating from pregnancies complicated by placental insufficiency including IUGR, preeclampsia and idiopathic spontaneous preterm labor [19, 24, 31]. Some reports point to the association between similar placental histopathological findings and adverse pregnancies' outcomes, such as intrauterine fetal demise [14, 15].

Similar to other studies, we found an association of the abnormal placental shapes with rIUGR as compared with the AGA neonates [32]. The pathophysiology remains unknown, but one hypothesis is the underdevelopment of the uteroplacental circulation [33]. The higher rate of rIUGR from a single maternal origin may be associated with a common genetic determinant of the implantation site, placental shape, and fetal growth.

There are known angiogenic factors that contribute to the placental formation; few are highly expressed during embryonic and fetal development, especially in the first trimester. Abnormal expression of these angiogenic factors, determined by genetic heritage, may be involved in the higher magnitude of fetal as well as maternal vascular pathology of the placentae from rIUGR pregnancies in our study [34–36].

Doppler findings may suggest placental insufficiency, further identifying fetuses that are at highest risk for adverse outcomes and that may benefit from an early intervention [9, 37, 38]. The most commonly used sonographic assessment of fetal well-being in pregnancies complicated by IUGR is the velocimetry/resistance in the umbilical and middle cerebral arteries. It has been estimated that a measurement of elevated vessels' resistance to blood flow is obtained when there is a 30% compromise of fetal placental vascularization. As the number or compromised vessels increase, reaching 60–70% of placental vascularization, reversed or absence of end-diastolic blood flow (REDF/AEDF) in the placenta is apparent. These pathological patterns of blood flow to the placenta are also associated with fetal acidosis and intrauterine fetal demise in IUGR fetuses [9, 39]. Little has been reported on the association between the placental pathology and antenatal Doppler studies. The current study found that the abnormal Doppler was significantly more common in pregnancies with placental HPf of malperfusion vascular lesions and in particular—villous infarcts. Abnormal Doppler was also significantly more common in pregnancies complicated by hypertensive disorders. These findings are in accord with reports of poorer outcomes in IUGR neonates of mothers with pregnancies complicated with hypertensive disorders, and with findings of placental maternal vascular lesions in women with IUGR complicated with hypertensive disorders compared with normotensive IUGR [40].

We did not find an increased rate of placental features that are associated with meconium pathology. As opposed to HPf that represent an underlying fetal and maternal vascular placental pathology, features as changes associated with meconium exposure and increased circulating nucleated red blood cells are reactive pathologies reflecting episodes of acute fetal distress [41–43].

This study is unique for several reasons, mainly as we assess the pathological analysis of placentae of recurrent pregnancies complicated by IUGR. Second, well-characterized cohort of patients, as standardized population-specific growth curves were used to define IUGR. Third, the AGA group was included to discriminate the characteristic features associated solely with recurrent IUGR; since some of the histopathological features of the placenta may be nonspecific, especially since some of the IUGR neonates were preterm, we aimed to present robust data by comparison with gestational age-matched AGA neonates. Fourth, the study is among the few linking antenatal vascular Doppler assessment to maternal rather than fetal vascular pathology. Fifth, the use of uniform and consistent criteria for the definition and classification of the placental HPf. Last, collection and processing of the placentae were performed in a single center by a strict protocol for the study period and the re-assessment performed by one dedicated perinatal pathologist, thus avoiding preparation and observer variance.

The current study bares few limitations. First, small sample size; in our institution, similar to others, placentae of pathological pregnancies, including those complicated by IUGR, often do not reach pathological evaluation [44]. Additionally, due to the small sample size, we were unable to perform correlation analysis. Second, selection bias of the AGA neonates; routine pathological assessment of placentae from normal pregnancies is not performed. Thus, we used placentae of AGA fetuses obtained from complicated rather than normal pregnancies; however, the final analysis showed that the placental histologic assessment of this group was similar to that reported for normal, uncomplicated pregnancies, with no infectious or

other pathognomonic features. Third, this study did not include the order of pregnancies complicated by IUGR; the mean parity was 3.7 ± 3.4, thus limiting the sequencing order. Fourth, we used the actual birth weight, thus SGA; however, because the aim and implication of the study is for placental pathology as a predictor for future antenatal diagnosis of IUGR we used the term for the present study. Furthermore, our national guidelines recommend the antenatal definition of IUGR according to BW curves and not sonographic curves [45]. Fifth, we lack information regarding the baseline placental HPf in cases of abnormal Doppler findings. However, as data in this field are scarce, our study is among the few describing the association of HPf, specifically in recurrent IUGR, and Doppler findings.

Sixth, the database contains no information on the paternal origin of the pregnancy. Thus, conclusions are limited to repetitive maternal contribution alone. Last, the database lacks information regarding smoking habits and maternal BMI, thus limiting environmental influence assessment.

In conclusion, repetitive fetal and maternal vascular malperfusion lesions are the characteristic placental HPf that are associated with rIUGR. The search for early common pathogenesis, mostly related to the implantation process, may explain the later placental and fetal pathologies and refine the estimation of the individual recurrence risk for IUGR. Recognition of the characteristic placenta histopathological features described by the present study for rIUGR may in future pregnancy optimize the definition of a population at risk, for careful fetal surveillance associated with favorable outcomes and guide therapeutic interventions [46]. Additionally, this group may be assessed for a genetic fingerprinting as a step toward precision medicine.

Author contributions KR-O helped in research performance and authored the manuscript. JM authored the manuscript, was involved in the critical review, and was corresponding author. NS assisted in research performance and critically reviewed the manuscript. ST and LS assisted in research performance. RF helped in statistical analysis. SGG contributed to research concept, statistical analysis, manuscript review, and critical appraisal.

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Compliance with ethical standards

Conflict of interest All authors declare they have no conflict of interest.

Ethics approval The study was approved by the Institutional Review Board for clinical studies of Shaare Zedek Medical Center, Affiliated with the Hebrew University Hadassah School of Medicine, Jerusalem, Israel. Approval ID: 0173-16-SZMC.

Informed consent Informed consent was obtained from all individual participants included in the study.

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