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MATERNAL-FETAL MEDICINE

Pregnancy outcomes in correlation with placental histopathology in pregnancies complicated by fetal growth restriction with vs. without reduced fetal movements

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Abstract

Purpose Fetal movements are crucial indicators of fetal well-being, with reduced fetal movements (RFM) suggesting potential fetal compromise. Fetal growth restriction (FGR), often linked to placental insufficiency, is a major cause of perinatal morbidity and mortality. This study aimed to investigate the neonatal, labor, and placental outcomes of FGR pregnancies with and without RFM at term.

Methods In this retrospective study, data from all term, singleton deliveries with FGR and concomitant RFM were obtained and compared to an equal control group of FGR without RFM. Maternal characteristics, pregnancy and neonatal outcomes, and placental histology were compared. The primary outcome was a composite of adverse neonatal outcomes. A multivariable regression analysis was performed to identify independent associations with adverse neonatal outcomes.

Results During the study period, 250 FGR neonates with concomitant RFM and an equal control group were identified. The groups did not differ in maternal demographics aside from significantly higher rates of maternal smoking in the RFM group ($p < 0.001$). Polyhydramnios and oligohydramnios ($p = 0.032$ and $p = 0.007$, respectively) and meconium-stained amniotic fluid ($p < 0.001$) were more prevalent in the FGR+RFM group. Additionally, the RFM group showed higher rates of adverse neonatal outcomes despite having larger neonates ($p = 0.047$ and $p < 0.001$, respectively). No significant differences were observed in placental findings. Logistic regression identified RFM as an independent predictor of adverse neonatal outcomes (aOR 2.45, 95% CI 1.27–4.73, $p = 0.008$).

Conclusion Reduced fetal movements are significant and independent predictors of worse neonatal outcomes in FGR pregnancies, suggesting an additional acute insult on top of underlying placental insufficiency.

Keywords Fetal growth restriction · Reduced fetal movements · Placental pathology · Neonatal outcomes

What does this study add to the clinical work

This study aimed to investigate the outcomes of Intra-uterine growth restriction (IUGR) pregnancies with and without Reduced Fetal Movements (RFM) at term. The study showed that RFM are significant and independent predictors of worse neonatal outcomes in IUGR pregnancies, suggesting an additional acute insult on top of underlying placental insufficiency.

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Introduction

The main objective of antenatal care in the third trimester is to ensure the delivery of a healthy baby and to reduce the risk of stillbirth. Regular fetal movements have long been considered an indicator of fetal well-being [1, 2]. A sudden decrease in the number of fetal movements is suggestive of fetal compromise [1, 3, 4], though the risk for worse neonatal outcomes upon reduced fetal movements (RFM) perception alone is debated [5].

Fetal growth restriction (FGR) is one of the leading causes of perinatal morbidity and mortality [6, 7]. When placental insufficiency is the presumed cause of FGR, impaired placentation leads to placental vascular compromise, and an increase in uteroplacental malperfusion lesions constitutes the main etiology of placental-associated FGR [8–10].

Moreover, a recent study published by Calis et al. showed that placentas of small for gestational age (SGA) fetuses, which are usually considered constitutionally small, have similar pathologies with FGR placentas. These pathologies weren't demonstrated among appropriate for gestational age (AGA) placentas, suggesting a possible shared pathomechanism in both SGA and FGR [11].

Fetuses experiencing intrauterine growth restriction exhibit reduced fetal movement when compared to healthy controls, as documented in previous investigations [12, 13]. This phenomenon can be attributed, in part, to the diminished body mass and overall presence of these growth-restricted fetuses. However, it is important to note that some research findings have indicated that FGR, in conjunction with RFM, can independently predict unfavorable neonatal outcomes, thereby necessitating meticulous monitoring and management strategies [14].

Our group has recently concluded that RFM is associated with a higher rate of placental weight < 10th percentile and placental maternal vascular malperfusion lesions vs. controls. These findings strongly suggest the involvement of the placenta in the complex association between RFM at term and adverse pregnancy outcomes [15].

Our study aims to determine if there are differing neonatal outcomes between FGR pregnancies with and without maternal perception of RFM at term and whether these distinctions are evident in placental histopathology. To investigate the influence of RFM in FGR pregnancies, we conducted a comparative analysis of placental histopathology reports and neonatal outcomes between FGR pregnancies with RFM and those without RFM.

Methods

Patient selection

The computerized files of all women who presented to the fetal assessment unit with a primary complaint of reduced fetal movement from 2010 to 2021 at our university-affiliated tertiary center were reviewed. Only cases of FGR neonates with concomitant reduced fetal movements reported within the last 2 weeks were included in the study group—termed the FGR+RFM group. The comparison group consisted of singleton pregnancies with FGR who gave birth between 37 and 42 gestational weeks during the same period, matched for maternal age (± 1 year) and gestational age (± 2 days until delivery). FGR was diagnosed at term, either upon arrival or shortly thereafter, and defined as a birth weight below the 10th percentile according to local population growth charts [16].

Exclusion criteria included pregnancies in the placenta that were not sent for pathological examination, multiple pregnancies, and pregnancies complicated by major fetal malformation, genetic disorders, or infection.

For the purpose of the study, maternal characteristics, pregnancy outcome, and placental histology reports were compared between FGR pregnancy with delivery within the following 2 weeks after RFM complaint (FGR and RFM group) and FGR pregnancy with normal maternal perception of fetal movements (FGR group).

Approval was obtained from the Local Ethics Committee number 0238-21-WOMC.

Data collection

The following data were collected from the women's medical and surgical files: 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, preeclampsia as defined by the American College of Obstetricians and Gynecologists (ACOG) Task Force [17], thrombophilia (defined as any thrombophilia, inherited or acquired, which required thrombo-prophylaxis) [18, 19], oligo or polyhydramnios, maternal fever during labor and meconium-stained amniotic fluid.

Immediately after birth, all neonates were examined by pediatricians. The birthweight percentile for gestational age was assigned using the local growth charts [16]. The following data were collected from the neonatal charts: birthweight, Apgar scores, neonatal intensive care unit (NICU) admission, mechanical ventilation, respiratory distress syndrome (RDS), neurological morbidity (including seizures, intra-ventricular hemorrhage and hypoxic-ischemic encephalopathy), phototherapy, hypoglycemia (defined as basal glucose < 40 mg/dL), sepsis (positive blood or cerebrospinal fluid culture) and blood transfusion. The primary outcome- a composite of adverse neonatal outcomes included any one or more of the following

severe neonatal outcomes: NICU admission, ventilation, RDS, neurological morbidity, sepsis or blood transfusion.

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) [9, 20] as previously reported by us [21, 22]. Briefly, placental weight was determined 24 h after delivery (trimmed and fixed), and the percentile was determined according to placental weight charts [23] after correction for fixation [24]. 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 the umbilical cord was sampled.

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

Fetal vascular supply (FVM) lesions included vascular lesions associated with fetal malperfusion (including thrombosis of the chorionic plate and large fetal-vessel fibrin deposition) and villous lesions (including avascular villi, villous intramural fibrin deposition, villous stromal-vascular karyorrhexis, stem vessel obliteration, and vascular ectasia). Composite FVM lesions are composed of any of the above lesions.

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).

Placentas from either group were collected during the same time period, and an identical sampling strategy was used.

Statistical analysis

Data were analyzed with SPSS, version 28 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). 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. A multivariable logistic regression analysis was performed in order to detect factors associated with a composite of adverse neonatal outcomes in which the composite neonatal outcomes served as the dependent variable, while maternal age, gestational age at delivery, smoking, pregestational and gestational diabetes mellitus, hypertensive disorders, thrombophilia, cesarean section RFM and neonatal weight served as the independent variables.

Results

During the study period, 250 eligible patients delivered a neonate diagnosed with FGR in our institution with a recent reduction in fetal movements. These patients were matched to an even control group of 250 patients with FGR neonates but no decrease in fetal movements perception.

The demographic characteristics of the study groups are detailed in Table 1. The matching technique ensured no significant differences between the groups in terms of maternal age, and similarly, there were no significant differences in regard to gravidity, parity, rate of nulliparity, pre-pregnancy BMI, pregestational and gestational diabetes, chronic and gestational hypertension, rates of preeclampsia and rates of thrombophilia. A significantly larger portion of the patients in the FGR+RFM group smoked compared to patients in the FGR with no RFM (17.2% vs. 3.2%, p < 0.001).

Table 2 demonstrates the labor course and delivery outcomes of the groups. The FGR with RFM group were characterized by significantly higher rates of oligohydramnios (9.6% vs. 3.6%, p = 0.007), polyhydramnios (2.8% vs. 0.4%, p = 0.032), and meconium-stained amniotic fluid (30% vs. 10.4%, p < 0.001).

Neonatal outcomes of the study groups are presented in Table 3. Neonates of the FGR with RFM group had higher birth weight compared to those of the FGR with no RFM

Table 1 Maternal demographics characteristics of the study groups

	FGR with RFM (n = 250)	FGR without RFM (n = 250)	*p*-value
Maternal age (years)	32.14 ± 6.32	31.12 ± 5.69	0.099
Gravidity	2.12 ± 1.47	2.34 ± 1.60	0.119
Parity	0.76 ± 1.18	0.81 ± 1.11	0.647
Nulliparity (%)	148 (59.2)	128 (51.2)	0.072
Pre-pregnancy BMI (kg/m^2)	23.55 ± 4.99	22.45 ± 4.63	0.053
Pregestational and gestational diabetes	20 (8)	21 (8.4)	0.871
Chronic and gestational hypertension	12 (4.8)	6 (2.4)	0.152
Preeclampsia	14 (5.6)	11 (4.4)	0.538
Smoking	43 (17.2)	8 (3.2)	**< 0.001**
Thrombophilia	1 (0.4)	5 (2)	0.100

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant

FGR fetal growth restriction, *RFM* reduced fetal movements, *BMI* body mass index

Table 2 Labor course and delivery outcomes in the study groups

	FGR with RFM (n = 250)	FGR without RFM (n = 250)	*p*-value
GA at delivery (weeks)	39.63 ± 1.12	39.47 ± 0.80	0.066
Vaginal delivery	176 (70.4)	169 (67.6)	0.561
Cesarean delivery	74 (29.6)	82 (32.8)	0.499
Indications: NRFHR	50 (67.5)	47 (58.7)	0.247
Dysfunctional labor	2 (2.7)	4 (4.8)	0.683
Malpresentation	7 (9.4)	8 (9.7)	1.0
Repeat CS	7 (9.4)	11 (13.4)	0.465
Other indications	8 (10.8)	12 (14.6)	0.632
Oligohydramnios	24 (9.6)	9 (3.6)	**0.007**
Polyhydramnios	7 (2.8)	1 (0.4)	**0.032**
Maternal fever during labor	11 (4.4)	5 (2)	0.127
Meconium-stained amniotic fluid	75 (30)	26 (10.4)	**< 0.001**

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant. Other indications of CS included severe preeclampsia, previous myomectomy, placenta and vasa previa, cord prolapse and maternal request

FGR fetal growth restriction, *RFM* reduced fetal movements, *GA* gestational age, *NRFHR* non -eassuring fetal heart rate, *CS* cesarean section

Table 3 Neonatal outcomes in the study groups

	FGR with RFM (n = 250)	FGR without RFM (n = 250)	*p*-value
Birthweight (grams)	2651 ± 206	2512.12 ± 205	**< 0.001**
Apgar 5 min ≤ 7	2 (0.8)	2 (0.8)	1
NICU admissions	24 (9.6)	10 (4)	**0.013**
Ventilation	8 (3.2)	14 (5.6)	0.191
RDS	4 (1.6)	0	**0.045**
Neurological morbidity	5 (2)	0	**0.025**
Phototherapy	8 (3.2)	14 (5.6)	0.191
Hypoglycemia	7 (2.8)	10 (4)	0.459
Sepsis	2 (0.8)	0	0.156
Blood transfusion	2 (0.8)	0	0.156
Composite adverse neonatal outcome	35 (14)	21 (8.4)	**0.047**

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant. Composite adverse neonatal outcome refers to one or more of the following complications: NICU admission, ventilation, RDS, neurological morbidity, sepsis or blood transfusion

FGR fetal growth restriction, *RFM* reduced fetal movements, *NICU* Neonatal intensive care unit, *RDS* respiratory distress syndrome

(2651 ± 206 vs. 2512 ± 205, p < 0.001) yet the neonatal outcomes of this group were worse, including increased rates of NICU admissions (9.6% vs. 4%, p = 0.013), RDS (4% vs. 0%, p = 0.045) and neurological morbidity (5% vs. 0, p = 0.025). Accordingly, the composite adverse neonatal outcomes were also significantly higher in the group presenting with RFM compared to patients with intact fetal estimation (14% vs. 8.4%, p = 0.047).

Table 4 presents the placental characteristics of the study groups, demonstrating no significant differences between the groups in terms of placental weight or histological lesions.

Table 5 displays the results of a logistic regression analysis performed to detect factors independently associated with adverse neonatal outcomes. Reduced fetal movements were found to be significantly and independently associated with worse neonatal outcomes (aOR 2.45, 95%CI 1.27–4.73, p = 0.008), and so was increased gestational age at delivery (aOR 1.55, 95%CI 1.06–2.25, p = 0.021). However, increased maternal age and neonatal birth weight seemed to

Table 4 Placental histopathological lesions of the study groups

	FGR with RFM (n = 100)	FGR without RFM (n = 97)	*p*-value
Placental weight (grams)	386 ± 78	373 ± 60	0.182
Fetal to placental weight ratio	6.96 ± 1.43	6.98 ± 1.11	0.932
Placental weight < 10th percentile	88 (88)	77 (79.3)	0.123
Maternal vascular malperfusion lesions			
Retroplacental hemorrhage	7 (7)	2 (2.0)	0.088
Vascular lesions of MVM	9 (9)	7 (7.2)	0.602
Villous lesions of MVM	52 (52)	47 (48.4)	0.473
Composite lesions of MVM	61 (61)	52 (53.6)	0.190
Fetal vascular malperfusion lesions			
Vascular lesions of FVM	5 (5)	8 (8.2)	0.389
Villous lesions of FVM	16 (16)	15 (15.4)	0.845
Composite lesions of FVM	16 (16)	18 (18.5)	0.855
Inflammatory lesions			
MIR 1–3	20 (20)	16 (16.4)	0.460
FIR 1–3	10 (10)	5 (5.1)	0.179

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant.

FGR fetal growth restriction, *RFM* reduced fetal movements, *MVM* maternal vascular malperfusion, *FVM* fetal vascular malperfusion, *MIR* maternal inflammatory response, *FIR* fetal inflammatory response

Table 5 Logistic regression model for composite adverse neonatal outcomes

Variable	aOR	95% CI	*p*-value
Maternal age	**0.92**	**0.87–0.97**	**0.004**
GA at delivery	**1.55**	**1.06–2.25**	**0.021**
Smoking	0.88	0.34–2.29	0.805
Pregestational and gestational diabetes	0.89	0.28–2.83	0.850
Hypertensive disorders	1.20	0.38–3.78	0.750
Thrombophilia	5.32	0.83–33.83	0.076
Cesarean section	0.74	0.39–1.41	0.372
RFM	**2.45**	**1.27–4.73**	**0.008**
Neonatal weight	**0.99**	**0.99–1.00**	**0.015**

Values reflect the results of multivariate logistic regression analysis. The model was adjusted for all the variables listed in the table. Values in bold are statistically significant.

aOR added odds ratio, *CI* confidence interval, *GA* gestational age, *RFM* reduced fetal movements

The values in bold are statistically significant

be protective factors (aOR 0.92, 95% CI 0.87–0.97, p = 0.004 and aOR 0.99, 95%CI 0.99–1.00, p = 0.0015 respectively).

Discussion

Reduced fetal movements are important subjective signs of possible fetal compromise, yet their significance in the context of growth-restricted neonates has not been studied. This study aimed to assess the neonatal outcomes in patients with FGR in conjunction with RFM compared to those without. The main findings are: (1) The FGR+RFM group exhibited significantly higher rates of polyhydramnios or oligohydramnios and a greater incidence of meconium-stained amniotic fluid. (2) Despite having a significantly higher mean birth weight compared to the control group, the RFM group displayed significantly higher rates of adverse neonatal outcomes. (3) No significant differences were observed in terms of placental findings between the two groups.

Reduced fetal movements is a common complaint among patients seeking medical care at term, prevalent in up to 21% of patients [25, 26]. There is no consensus regarding the clinical significance of reduced fetal movements and its assoaciation to adverse neonatal outcomes. Though most cases do not indicate fetal compromise, an additional risk factor for several adverse neonatal outcomes has been demonstrated, including stillbirth [27]. Interestingly, in a recent study by Zamstein et al. reduced fetal movements did not predict adverse perinatal outcome but was associated with an elevated risk for long-term neurological morbidity of the offspring [28].

Owing to the subjective nature of this complaint, defining objective predictors of adverse neonatal outcomes in women with RFM is essential. Sterpu et al. demonstrated that poor perinatal outcomes were significantly associated with FGR and IVF treatment among patients with RFM [26], and Dutton et al. identified abnormal fetal monitoring and elevated maternal diastolic blood pressure as predictors of poor neonatal prognosis [14]. However, all studies to date examined neonatal outcomes in heterogenous populations, among which the significance of FGR is noteworthy. This study represents the first of its kind to exclusively investigate the influence of RFM on neonatal outcomes in FGR neonates.

FGR is known to be associated with a significant burden of perinatal mortality and morbidity [29]. Moreover, in a study that investigated the link between birth-weight centiles in term pregnancies and perinatal outcome, fetuses < 3rd percentile had the highest risk [30]. In our study, all neonates included were diagnosed with FGR at term, defined as birth-weight below the 10th percentile. Surprisingly, despite the RFM group having significantly larger neonates, their neonatal outcomes were worse, suggesting the presence of an additional contributing factor. Possible explanation to this paradox is that our cohort included only late FGR neonates in term pregnancies, with a better prognosis to begin with, and although there was a significant statistical difference in

birth weight, the clinical significance is questionable. Therefore the effect of reduced fetal movements on neonatal outcome between the study groups was more dominant.

In our study, the FGR+RFM group demonstrated significantly higher rates of polyhydramnios or oligohydramnios, along with a greater incidence of meconium-stained amniotic fluid. These findings suggest varied underlying etiologies. Oligohydramnios may be associated with severe placental insufficiency [31], adversely affecting the fetus and manifesting as RFM. Conversely, the association of FGR with polyhydramnios could often indicate a genetic etiology, which might also present with RFM [32].

The debate persists over whether reduced fetal movements represent an acute insult or cumulative damage. While RFM is associated with chronic conditions such as placental dysfunction and increased rates of various placental lesions [15, 27], it has also been shown to be associated with acute events, including hypoxic episodes [33], umbilical cord complications [34] and meconium-stained amniotic fluid [35].

In this study, neonates with RFM suffered from worse neonatal outcomes that might be attributed to amniotic fluid disturbances, meconium-stained amniotic fluid, and higher rates of composite adverse outcomes. Moreover, the groups in this study did not differ in placental characteristics. This may be due to the underlying placental component in the FGR cohort with increased placental lesions compared to the general population, which are prevalent even without RFM. Hence, we speculate that in this specific cohort RFM represent a second and additional "acute on chronic" insult leading to worse neonatal outcomes in this group.

This study is not without limitations. First, the neonatal outcomes compared consist of short-term outcomes only. Second, few labor and neonatal outcomes were not accessible including umbilical cord pH and cardiotocography during labor, which have potential to contribute to the better understanding of the chronic versus acute mechanism. However, the large cohort assessing maternal, pregnancy, neonatal, and placental characteristics reveals significant and important associations with poor neonatal prognosis irrespective of the inaccessible data. Third, while sending placentas to a pathological review in all cases of FGR should be recommended, more than half of the cohort did not have placental pathology reports available. This may represent a selection bias related to the reason these specific cases were sent to pathology, possibly implying a more complex or challenging course.

The strengths of this study should also be noted. First, it is the first study to examine the effect of RFM in this specific subgroup of FGR neonates. Second, it is a fairly large cohort assessing both maternal, neonatal, labor and placental characteristics of the groups. Finally, all pathology reports were done by a single pathologist (author L.S), who was blinded to the initial diagnosis and demographics of the patients and used a standardized classification system [9].

In conclusion, reduced fetal movements are significant and independent predictors of adverse neonatal outcomes in FGR neonates, likely due to an acute insult superimposed on an already compromised placenta with limited compensatory abilities. Therefore, RFM in suspected FGR neonates necessitates thorough medical assessment and supervision, and induction of labor should be considered. Although limitations exist, this study provides valuable insights into managing this specific subgroup of FGR neonates.

Author contributions L Mor: Project development, Data collection, Data analysis, Manuscript writing. T Rabinovitch: Manuscript writing and editing. L Schreiber: Data management, Data analysis. Y Ganor Paz: Data management, Manuscript writing. G Barda: Data management, Manuscript writing. I Kleiner: Data collection, Data analysis, Manuscript writing. E Weiner: Project development, Data management, Manuscript writing. M Levy: Project development, Data collection, Data analysis, Manuscript writing.

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Data availability The authors declare that the data which supports the findings of this study is available from the corresponding author, T. Rabinovitch, upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of The Edith Wolfson Medical Center No. 0238-21-WOMC.

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