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Original Article

The Association Between Placental Pathology in Fetuses with Fetal Growth Restriction and Maternal and Neonatal Outcomes Post-Delivery

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Abstract

Background and aims: Placental insufficiency causes many pregnancy complications, including fetal growth retardation (FGR), and may be related to placental pathology. This study investigated the relationship between the placental pathology of different FGR grades and pregnancy outcomes.

Methods: In this prospective study, 67 patients diagnosed with FGR during pregnancy with different grades were included in the study. After birth, their final placental pathology was examined, and the relationship between final placental pathology and fetal and maternal outcomes was investigated. Data were analyzed by SPSS version 26.

Results: A significant relationship was observed between accelerated villus maturation pathology and FGR grading, birth weight, postnatal placental weight, and neonatal outcome one month after birth. Accordingly, the cases with accelerated villous maturation had a higher death rate at the end of one month in their babies ($P=0.02$).

Conclusion: Placental pathology is an applicable tool for predicting pregnancy and maternal and neonatal outcomes.

Keywords: Placental pathology, FGR, Maternal, Neonatal, Outcome

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Introduction

Fetal growth retardation (FGR) is defined as the failure of the fetus to achieve its potential genetic growth (1). FGR is defined as an estimated fetal weight of less than the 10th percentile for gestational age (2). Small for gestational age (SGA) newborns represent approximately 10% of births worldwide, and the incidence reaches 45% in some countries (3). The prevalence of SGA varies geographically and according to the term or prematurity of the fetus (4, 5). The highest prevalence of SGA was found in Southeast Asia (6). SGA increases adverse pregnancy for mothers and lifelong outcomes, such as hypertension, metabolic syndrome, type 2 diabetes, and so on for the babies (7, 8). Ultrasonography is the best method for diagnosing FGR. Doppler ultrasonography is performed if the estimated fetal weight at sonography is less than 10% (9). Low levels of umbilical vein blood flow were associated with an increased risk among SGA fetuses to be delivered by cesarean section (10). Delivery timing should be based on the severity of fetal growth restriction and umbilical artery Doppler velocimetry (11). Placental dysfunction is the most common cause of FGR (12). The placenta plays a critical role in transporting oxygen and nutrients to the fetus (13). A wide range of placental response patterns can be induced to complete the development of the fetus. Chronic patterns of placental damage in FGR placental pathology include obstructive lesions of maternal vessels (the most common cause), villitis of unknown etiology (VUE), per villous fibrinous deposition and chronic abruption. Maternal vascular disorders were the most common finding in preterm infants and maternal hypertension with FGR, while VUE was the most common finding in term pregnancies with normal blood pressure with FGR. Pathological lesions of the placenta of FGR cases can be divided into vascular or non-vascular, macroscopic or microscopic, and congenital or acquired types (14-16). The pathogenesis of early FGR, which is diagnosed before 33 weeks, is different from late FGR, and the pregnancy outcome in late FGR is better than in early FGR. Early FGR is often associated with preeclampsia, abnormal umbilical artery Doppler, and poor perinatal outcomes. In contrast, late FGR is associated with milder degrees of placental dysfunction and is less likely to be associated with preeclampsia and umbilical artery Doppler changes (17).

The Amsterdam Consensus provides diagnostic criteria for 4 major patterns of placental injury: 2 inflammatory processes, including acute chorioamnionitis (ACA) and villitis of unknown etiology (VUE), and 2 types of placental vascular insufficiency, including fetal vascular malperfusion (FVM) and maternal vascular malperfusion (MVM) (18). Loverro et al examined the relationship between placental pathology based on the Amsterdam criteria and maternal and fetal outcomes. They showed that retrospective awareness of placental damage helps prevent complications in future pregnancies and that their identification in recent pregnancies can effectively diagnose complications early (19). The present study aimed to investigate the relationship between final placental pathology based on the Amsterdam criteria in FGR fetuses, the cause of termination of pregnancy in these fetuses, and the outcome of one-month-old babies.

Materials and Methods

Study Type and Samples Characteristics

In this prospective study, a total of 67 pregnant women were included based on the sample size formula considering a prevalence of 5% and an acceptable error (d) equal to 0.05. The patients with FGR below the 3% percentile who had indications for termination of pregnancy between 28 and 37 weeks of pregnancy were included in the study. The exclusion criteria were multiple pregnancies, gestational age of less than 27 weeks and 6 days at birth, congenital or genetic abnormalities of the fetus, and loss of data related to placental pathology.

Procedure

Cases were identified using the institutional perinatal database. The medical records of eligible women for demographic and obstetrical data, validation of gestational age with first-trimester ultrasound, and pregnancy complications were recorded. After biometrics, if FGR was diagnosed, a Doppler ultrasound was performed on them. FGR grade at the time of termination of pregnancy, age at birth, birth weight, the reason for termination of pregnancy, and short-term neonatal outcomes were examined. After termination of pregnancy, the placenta was separated spontaneously and sent in formalin for pathology examination. Pathological examinations of the placenta were performed using a standard protocol. In short, the weight of the placenta was determined within 24 hours after delivery with a digital scale. Macroscopic assessment of the placenta, membrane, and umbilical cord, including detection of macroscopic parenchymal lesions or adherent clots, the number of umbilical cord vessels, the location of the umbilical cord connection to the placenta (central, paracentral, eccentric, marginal, or velamentous) and hyper coiled or hypo coiled umbilical cord (the ratio of the total number of coils to the length of the umbilical cord: hypercoiled cord is defined as more than 3 coils per 10 cm and hypocoiled cord represents 1 coil per 10 cm) was defined (20). Four placenta samples (including umbilical cord and fetal membranes, marginal area of the placenta, the central area of the placenta adjacent to the umbilical cord, and the central area of the placenta at a distance from the umbilical cord) and additional slices of any macroscopic lesions of the placenta were prepared, and their paraffin blocks were provided. Placental lesions were classified according to the criteria proposed by Redline and the 2014 Amsterdam Placental Workshop Group (18,19). Other placental pathologies, such as sub-amniotic cysts, were also recorded. The cause of termination of pregnancy and Apgar score at 1, 5, and 10 minutes, and PH at birth, as well as the status of the newborn in the follow-up at the end of infancy in terms of survival, were recorded in the questionnaire.

Statistical Analysis

Numerical variables were expressed as mean ± SD (standard deviation). Numbers and percentages were used for categorical variables. The Kolmogorov–Smirnov test was used to evaluate the distribution of each variable. The statistical analysis was performed using an independent samples *t*-test and Fisher's exact test. A P-value < 0.05 was considered statistically significant. SPSS version 26.0 was used to analyze the data.

Results

This study examined 67 pregnant women with FGR fetuses with a mean age of 31.4 ± 5.56 and a mean gestational age of 34.52 ± 2.65 in the third trimester of pregnancy from 28 to 37. The mean weight of the fetus at birth was 1728 ± 618 g. The mean weight of the placenta in the pathological examination was 250 ± 92.1 g, and the mean placental thickness was 29.8 ± 9.11. In the evaluation of placental calcification by the pathologist, the lowest score reported was 0, and the highest score was 18, with a mean of 4.22 ± 4.59. The mean Apgar score at 1, 5, and 10 minutes was reported to be 6.76 ± 1.65, 7.49 ± 1.76, and 7.49 ± 1.90, respectively (Table 1).

The fetuses of 2 subjects under study (3%) had a single-artery umbilical cord. The other 65 (97%) had two arteries and one vein in the umbilical cord, which was also confirmed in the pathological examination. There were no positive points in the ultrasound reports

Table 1. Descriptive Statistics of the Quantitative Variables of the Study

Variable	N	Mean ± SD	Min	Max
Mother's age (years)	67	31.10 ± 5.56	20	42
Gestational age (weeks)	67	34.53 ± 2.65	28	37
Birth weight (g)	67	1728.0 ± 618.78	385	2700
Placental weight (g)	67	250.49 ± 92.10	100	570
Placental thickness at birth (mm)	67	29.83 ± 9.11	15	70
Calcification score at birth	67	4.22 ± 4.59	0	18
Apgar 1	67	6.76 ± 1.65	1	9
Apgar 5	67	7.49 ± 1.76	0	10
Apgar 10	67	7.94 ± 1.90	0	10

except for 2 cases of the single umbilical artery, 1 case of a subchorionic hematoma, and 2 cases of sub-amniotic cyst. Fifty-six cases (83.6%) had a central or paracentral connection of the umbilical cord in pathology, examining the location of the connection of the umbilical cord to the placenta. Nine cases (13.4%) had a marginal connection, and 2 (3%) had a connection of the umbilical cord to the velamentous placenta.

Twenty-eight cases (41.9%) had normal pathology, and 39 (58.2%) had abnormal pathology results when examining the final pathology results. There was a significant relationship between cases of abnormal placental pathology and death at the end of the neonatal period in the Pearson Chi-square analysis ($P \leq 0.05$). In examining the outcome of newborns after birth, 66 newborns were transferred to the NICU and 1 newborn who was born due to preeclampsia and severe FGR with a very low weight at 28 weeks after initial resuscitation died in the operating room. Generally, 58 babies (86.6%) were alive, and 9 babies (13.4%) died at the end of one month. Table 2 shows the frequency of newborn outcomes after one month, causes of termination of pregnancy, and abnormal pathology of the placenta and umbilical cord.

Table 2. Frequency of Qualitative Variables

Variable	Qualitative study	Number	Percentage
FGR grade	1	42	62.7
	2	19	28.4
	3	6	9.0
Neonatal outcome after 1 month	Alive	58	86.6
	Dead	9	13.4
Placental calcification score (pathology)	NR	22	32.8
	≤5	20	29.9
	5–10	15	22.4
	≥10	10	14.9
Cause of termination of pregnancy	FGR	34	50.7
	Preeclampsia	12	17.9
	Fetal distress	13	19.4
	Bleeding	3	4.5
	Other	5	7.5
Pathology of the placenta and umbilical cord	Placental infarction	21	31.3
	Cholangitis	9	13.4
	Placental congestion	12	17.9
	Accelerated villous maturation	5	7.5
	Intervillous thrombosis	3	4.5
	Concomitant infarction + cholangitis	3	4.5
	Concomitant infarction + cholangitis + villous maturation	3	4.5
	Sub-amniotic cyst	2	3.0
	Hypercoiled umbilical cord	7	10.4
	Single umbilical artery	2	3.0
	False knot of the umbilical cord	1	1.5
Total		67	100

First, this variable is classified as normal and abnormal to determine the relationship between placental pathology and pregnancy outcome. Then, the relationship between its subgroups including infarction, cholangitis, congestion, intervillous thrombosis, and other results (hypercoiled umbilical cord, accelerated villous maturation, single umbilical artery, sub-amniotic cyst, and false umbilical cord knot) and neonatal outcome variables (alive and dead), newborn Apgar score at 1, 5, and 10 minutes after birth, FGR grade, reasons for termination of pregnancy (pre-eclampsia, fetal distress, vaginal bleeding, and FGR), and the location of the placenta (anterior, posterior, and fundal) was studied. Then, the analysis was performed. In examining the relationship between the placental pathology and neonatal outcome, Fisher's exact test (1-sided) showed that there was a significant relationship between these two variables ($P = 0.045$), and the death rate was higher in cases of abnormal pathology (Table 3).

In examining placental pathology subgroup variables, Fisher's exact test (2-sided) showed that only the relationship between accelerated villous maturation and the neonatal outcome was significant. Therefore, out of 5 cases with this pathology, 3 (60%) died. In comparison, the death rate was 9.6% (6 deaths out of 62 cases) without this type of pathology ($P = 0.028$) (Table 4).

In examining the relationship between placental pathology and newborn Apgar score, the independent *t*-test showed that in cases with abnormal pathology, the mean Apgar score at 1, 5, and 10 minutes was significantly lower than in cases with normal placental pathology ($P < 0.05$) (Table 5).

In examining the relationship between placental pathology, FGR grade, reasons for termination of pregnancy, placenta location, and umbilical cord location, Fisher's exact test showed that there was no significant relationship between the placental pathology variable and its subgroups and FGR grade, pregnancy termination reasons, placenta location, and umbilical cord location ($P > 0.05$). The relationship between neonatal outcome and FGR grade was examined using Fisher's exact test

Table 3. The Association between Placental Pathology and Neonatal Outcome

Placental pathology		Normal, N (%)	Abnormal, N (%)	Total (100%)	*P* value
Neonatal outcome	Alive	27 (46.6%)	31 (53.4%)	58 (100%)	
	Dead	1 (11.1%)	8 (88.9%)	9 (100%)	0.045
Total		28	39	67	

Table 4. Correlation between Accelerated Villous Maturation and Neonatal Outcome

Accelerated villous maturation		No N (%)	Yes N (%)	Total (100%)	*P* value
Neonatal outcome	Alive	56 (96.5%)	2 (3.4%)	58 (100%)	
	Dead	6 (66.7%)	3 (33.3%)	9 (100%)	0.02
Total		62	5	67	

(2-sided) and it was found that the relationship between these two variables was significant, and the rate of mortality increased with the increase in FGR grade ($P<0.05$) (Table 6).

In examining the relationship between neonatal outcome and the reasons for termination of pregnancy, placenta location, and umbilical cord location, Fisher's exact test showed that there was no significant relationship between neonatal outcome, the reasons for termination of pregnancy, placenta location, and umbilical cord location ($P>0.05$). Although the highest number of deaths was assigned to the fundal placenta (3 deaths occurred (30%) out of 10 fundal placenta cases), 5 deaths (17.2%) and 1 death (3.5%) occurred in 29 posterior and 28 anterior placenta cases, respectively. The highest number of deaths occurred due to the marginal type regarding the location of the umbilical cord, which occurred in 3 out of 9 cases (33.3%). There were 2 cases of velamentous cord insertion, with a zero death rate. There were 56 central and paracentral cases, 6 of whom died (10.7%).

The relationship between reasons for termination of pregnancy and FGR grade was examined using Fisher's exact test (2-sided) and a significant relationship was found between these two variables. Therefore, in grade 1, FGR was the most common reason for pregnancy termination; in grade 2, fetal distress was the most common reason for pregnancy termination; and in grade 3, preeclampsia was the most common reason for pregnancy termination (Table 7).

Discussion

The placenta is the interface between maternal and fetal blood circulation. Inefficient placental growth underlies a wide range of pregnancy complications, including FGR. The FGR placentas are characterized by abnormalities in the villous and vascular network of the placenta, as well as changes in the function and growth of trophoblast cells (21, 22). FGR is often accompanied by preeclampsia, which may result in increased perinatal mortality (16, 23). Pathologic evaluation of the placenta allows one to identify causes that could lead to major obstetric complications (24). Recognizing placental pathology findings is essential for patient management in future pregnancies (25). For example, acetylsalicylic acid (ASA) reduces obstetric complications related to maternal vascular malperfusion (MVM) (26). Recent studies have provided good evidence of specific structural and tissue abnormalities of the placenta in FGR fetuses. Loverro et al performed pathological examination of the placenta from 439 pregnancies, including 282 pathological and 157 normal pregnancies over 33 weeks of gestation. A normal placenta was present in 57.5% of normal and 42.5% of pathological pregnancies, and placental pathology was present in 26.2% of normal and 73.8% of pathological pregnancies. In the study of the relationship between neonatal health and pregnancy outcomes, among 191 normal infants, 98 infants (51.3%) were born from normal pregnancies, and 93 infants (48.7%) were born from mothers with pathological pregnancies. Among 248 pathological infants, 59 (23.8%) were born from normal pregnancies, while 189 (76.2%) were born from pathological pregnancies (19). In this study, 28 cases (41.9%) were normal, and 39 cases (58.2%) were abnormal in the final pathological examination of FGR fetuses. The mean Apgar score at 1, 5, and 10 minutes in abnormal placental pathology was lower than in normal placental pathology.

On the other hand, the outcome of the newborn worsens both at birth and at the end of the neonatal period in cases of placental pathology. In the present study, the rate of fetal mortality increased with the increase of FGR grade. However, there was no significant relationship between placental pathology and its subgroups and FGR grades,

Table 5. Correlation between Apgar Score and Placental Pathology

Placental pathology	Apgar	N	Mean ± SD	*t*-test	*P* value
Normal	1	28	7.25 ± 1.17	2.1	0.03
Abnormal	1	39	6.41 ± 1.85		
Normal	5	28	8.10 ± 1.03	2.7	0.007
Abnormal	5	39	7.05 ± 2.03		
Normal	10	28	8.60 ± 1.22	2.5	0.01
Abnormal	10	39	7.46 ± 2.10		

Table 6. Correlation of Neonatal Outcome with FGR Grade

FGR grade		1	2	3	Total (100%)	*P* value
Neonatal outcome	Alive	41 (71.9%)	15 (26.3%)	2 (3.4%)	58 (100%)	0.0001
	Dead	1 (11.1%)	4 (44.4%)	4 (44.4%)	9 (100%)	
Total		42	19	6	67	

Table 7. The Relationship between Reasons for Termination of Pregnancy and FGR Grade

Reasons for termination of pregnancy		FGR (N, %)	Preeclampsia (N, %)	Fetal distress (N, %)	Vaginal bleeding (N, %)	Other (N, %)	Total (N, %)	*P* value
FGR Grade	Grade 1	27 (64.3%)	5 (11.9%)	3 (7.1%)	2 (4.8%)	5 (11.9%)	42 (100%)	0.004
	Grade 2	5 (26.3%)	5 (26.3%)	9 (47.4%)	0 (0%)	0 (0%)	19 (100%)	
	Grade 3	1 (20%)	2 (40%)	1 (20%)	1 (20%)	1 (20%)	6 (100%)	
Total		33	12	13	3	6	67	

FGR: Fetal Growth Retardation

which may be justified by the small number of cases with FGR grades 2 and 3 investigated in this study.

According to the Amsterdam classification, placental pathology in 80 abnormal pregnancies was examined and divided into 4 groups, including two types of placental vascular insufficiency (maternal and fetal) and two types of placental inflammatory process (acute chorioamnionitis and villitis of unknown etiology). Accelerated villous maturation is challenging to detect in term placentas but is a repeatable pattern for preterm diagnosis (18). The present study examined placental pathology only in FGR fetuses. In this study, most pathological cases were in group 1 of the Amsterdam classification. They were related to maternal vascular malperfusion, including placental infarction. This issue may be related to the most common cause of FGR, but this finding aligns with studies conducted by Malmberg and Smolich. In the study of placental pathology in infants with hypoxic encephalopathy, there was a subacute or chronic placental abnormality in most of them, for example, FVM in late pregnancy (27, 28). This suggests a common pathophysiology for FGR and a higher incidence of hypoxic encephalopathy in these infants. Accelerated villous maturation is defined as small or too short villi for gestational age, which is usually seen in term pregnancy. However, it can be a repeatable pattern for preterm diagnosis. That may be seen in mild, moderate, or severe forms of placental insufficiency, including FGR, preeclampsia, and preterm labor (18). In our study, only the relationship between accelerated villous maturation and neonatal outcome was significant, and the pregnancy outcome at the end of one month with this pathology was worse. This reinforces the theory of more significant maturation of FGR fetuses than fetuses of similar gestational age. Villitis of unknown etiology (VUE) is defined as local lymphocytic inflammation in the stroma of terminal villi (29). VUE has been associated with FGR with variable incidence (30). According to Redline, VUE is a possible cause of fetal vascular damage in FGR (31). Unlike this study, Park observed a few cases of IUGR with VUE without a significant difference in the incidence compared to AGA (32). The present study did not report any cases of VUE in pathology. Vedmedovska et al performed macroscopic and microscopic examination of singleton placentas of 50 consecutive neonates with FGR and compared them to 50 normal fetuses (control group) born next to an FGR case. They found that intervillous thrombosis and villous infarction were more common in the FGR group, which can reduce placental blood flow (33). In our study, placental infarction was the most common finding in FGR fetuses. The pathophysiology of preeclampsia and FGR was similar and associated with placental insufficiency. In the study conducted by Loverro et al, the most common causes of termination of pregnancy were premature rupture of membranes before week 37 (25.5%), IUGR (19.5%), high blood pressure (15.6%), oligohydramnios (9.6%), gestational diabetes (8.2%), placenta previa (5.3%) preeclampsia (4.6%), tic meconium (4.6%), abruption (4.3%), and intrauterine fetal death (2.8%) (19). However, in this study, the most common causes were FGR, preeclampsia, fetal distress, and bleeding, respectively. There was a significant relationship between FGR grade and the cause of pregnancy termination. In grade 1, FGR, in grade 2, fetal distress, and in grade 3, preeclampsia was the most common cause of termination justified considering the common pathophysiology of them, which is in line with the study conducted by Youssef et al (34). Reasons for delivery at 34 to 37 weeks of pregnancy in women with mild hypertension or preeclampsia can be due to high blood pressure or preeclampsia, premature PROM, IUGR, or obstetric concerns (35). Revising the International Classification of Diseases (ICD) codes for placental pathology could facilitate the development of relevant health data to study long-term health outcomes further. A placenta with a specific pathology requires a community health assessment and risk factors such as malnutrition and obesity (36).

Conclusion

According to the Amsterdam Declaration, placental pathology leads to maternal, obstetric, and neonatal outcomes. Retrospective knowledge of placental pathology helps prevent complications in subsequent pregnancies. However, the detection of placental abnormalities in recent pregnancies by ultrasound can affect the result of the current pregnancy. The recent study can be the beginning of new studies of placental therapy based on ultrasound in pathological pregnancies with FGR fetuses. Therefore, based on FGR grade and the possibility of effective pathology in this field, measures can be taken to improve the maternal or fetal outcome of pregnancy. It was suggested that this study be conducted in a larger sample size with different FGR grades compared to normal pregnancies.

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Authors' Contribution

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Competing Interests

The authors reported no potential conflict of interests.

Ethical Approval

Ethical considerations in this study included obtaining approval from the Ethics Committee of[University Name] (IR.MUI.MED.

REC.1401.112) and written consent from the participants. The researchers would like to express their gratitude to the patients who participated in this study.

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