Histopathological analysis of the placental lesions in pregnancies complicated with IUGR and stillbirths in comparison with noncomplicated pregnancies

İUGR ve ölü doğumlarla komplike olmuş gebeliklerde plasental lezyonların histopatolojik analizi ve nonkomplike gebeliklerle karşılaştırılması

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Abstract

Objective: Placental factors and hypoxemia are the keys to intrauterine growth restriction (IUGR) and stillbirth. The aim of the study is to analyze histological changes in placentas of IUGR fetuses in pregnancies with no apparent etiologic factor and unexplained intrauterine fetal deaths.

Material and Methods: A total of 110 placentas were collected; 26 placentas of IUGR fetuses with no apparent cause, 58 placentas from unexplained intrauterine deaths over 20 weeks of gestation, and 26 placentas from uncomplicated pregnancies who delivered a healthy live baby. Microscopic examinations of placentas were performed for histopathological analyzes.

Results: Gestational age at delivery was 33.67±4.37 weeks, 29.15±8.36 weeks, and 39.0±1.52 weeks in women in group I, group II and group III, respectively ($p<0.01$). Infarction and intervillous thrombosis are significantly more frequent in placentas of Group I and group II. Chronic villitis occurred in 69%, 63% and 30% of group I, group II, and group III, respectively. Placental intravascular thrombi (Group I, 31% and group II, 26%), perivillous fibrin deposition and fibrinoid necrosis (65% in Group I and 53% in group II), infarction, intervillous thrombosis, chronic villitis, hemorrhagic endovasculitis, placental intravascular thrombi, perivillous fibrin deposition, fibrinoid necrosis, erythroblastosis and villous edema were found in the study group.

Conclusion: The results reported here indicate that a relationship exists between morphological changes in the placentas of IUGR and intrauterine fetal deaths (J Turkish-German Gynecol Assoc 2011; 12: 75-9)

Key words: Stillbirth, intrauterine growth restriction, histopathology, placenta, light microscopy

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Özet

Amaç: Plasental faktörler ve hipoksemi, intrauterine gelişme geriliği (İUGR) ve intrauterine eksituslar da ana nedenlerdir. Çalışmanın amacı etyolojik nedeni tespit edilemeyen IUGR'li fetüslerin ve açıklanamayan intrauterine ölümlerin plasentalarındaki histolojik değişikliklerin analizini yapmaktır.

Gereç ve Yöntemler: Bilinen bir sebebi olmayan 26 İUGR'lı fetüsün plasentası, 20 haftanın üzerinde 58 açıklanamayan intrauterine eksituslu fetüsün plasentası ve 26 sağlıklı nonkomp-like canlı yenidoğanın plasentası olmak üzere toplam 110 plasenta toplandı. Histopatolojik analiz için plasentaların mikroskopik incelemesi yapıldı.

Bulgular: Grup I, grup II ve grup III'ün doğum anındaki gestasyonel haftaları, sırasıyla, 33.67±4.37 hafta, 29.15±8.36 hafta ve 39.0±1.52 hafta idi. İUGR'li fetüsler ve ölü bebek-lerin plasentalarında enfarktüs ve intervillöz trombozis anlamlı olarak daha fazlaydı. Kronik villitis, grup I, Grup II ve grup III'de sırasıyla %69, %63 and %30 oranında idi. Çalışma grubunda plasental intravasküler trombüs (Grup I'de %31, grup II'de %26), perivillöz fibrin depozitleri ve fibrinoid nekroz (Grup I'de %65 ve grup II'de %53) ve ayrıca enfarktüs, in-tervillöz tromboz, kronik villitis, hemorajik endovaskülitis, plasental intravasküler thrombus, perivillöz fibrin depozitleri, fibrinoid nekrozis, eritroblastozis ve villöz ödem varlığı tespit edildi.

Sonuç: Çalışmamızın sonuçları, intrauterin gelişme gerilikli fetüsler ile intrauterine ölüm olan fetüslerin plasentalarındaki morfolojik değişiklikler arasında ilişki olduğunu göstermektedir.

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Anahtar kelimeler: Ölü doğum, intra uterin gelişme geriliği, histopatoloji, plasenta, ışık mikroskopi

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Introduction

Fetal growth and viability depends on the maternal supply of nutrients and oxygen through the placenta into the umbilical circulation. Placental factors and hypoxemia are keys to intrauterine growth restriction (IUGR) and fetal death. IUGR is a condition associated with placental insufficiency (1). Adaptive changes in IUGR may fail at some point, leading to fetal death. Conditions resulting in placental dysfunction can be recurrent. The placental complications may manifest in different ways in different pregnancies; IUGR in one pregnancy and fetal death in another pregnancy (2, 3). Faulty placentation has been linked to the pathogenesis of preeclampsia, preterm births, abortions, IUGR and intrauterine death (4, 5). IUGR may be caused by fetal, placental, or maternal factors. These factors are usually multiple and overlapping.

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The most common causes of stillbirth between 24 and 27 weeks of gestation are infection, abruption and fetal anomalies. Unexplained stillbirth is a fetal death that cannot be attributed to an identifiable fetal, placental, maternal, or obstetrical etiology, and accounts for 60% of fetal deaths (6, 7). The most frequent cause of stillbirth after 28 gestational weeks is unexplained fetal loss. Unexplained fetal loss includes stillbirths associated with growth restriction and placental abruption (6). Information on placental abnormalities may reveal the presence of chronic fetal insults and allow their differentiation from acute (peripartum) stresses (8). The aim of the present study is to analyze histological changes in placentas of IUGR fetuses, in placentas of unexplained intrauterine death fetuses and in uncomplicated pregnancies.

Material and Methods

Patients

A total of 110 placentas were collected; 26 placentas of IUGR fetuses (Group I) with no apparent cause, 58 placentas from unexplained intrauterine deaths over 20 weeks of gestation (Group II) and 26 placentas from uncomplicated term pregnancies in whom a healthy live baby was delivered (Group III). Gestational ages were 33.67±4.37 weeks, 29.15±8.36 weeks, and 39.0±1.52 weeks in women with group I, group II and group III, respectively ($p<0.01$). (Table 1). The study was approved by the Institutional Review Board and informed consent has been obtained from all the patients.

Multiple pregnancies, fetuses with a chromosomal anomaly or congenital anomaly, and fetuses with hydrops fetalis were excluded from this study. Maternal exclusion criteria were preeclampsia, diabetes mellitus, infection, placental tumors and trauma. In addition, women with antenatal hemorrhage (placental abruption, vasa previa and placenta previa), and women diagnosed with any systemic disorder were excluded from the study. Fetal death was defined as a lack of fetal heart activity diagnosed by ultrasound examination. IUGR was defined on the basis of an estimated fetal weight of less than the third percentile for gestational age (9), reduced amniotic fluid volume or Doppler ultrasound of the umbilical artery demonstrating absent end diastolic flow velocity. The diagnosis of IUGR was established by serial ultrasonographic examination of fetal biometric measurements (weight, biparietal diameter, head circumference, femur length, and abdominal circumference).

Sample collection and histological analyses

Immediately after delivery, placentas were fixed with 10% formalin for 24 hours and processed for routine paraffin embeding. Multiple random samples were taken from each placenta from a macroscopically normal central portion of the placenta, including two samples of umbilical cord (one close to the distal end and one from within 10 cm of the insertion on the chorionic plate), two samples of the extra placental membranes (one from the edge of the site of rupture when identifiable, one from a membrane roll extending from the site of rupture to the placental margin), and at least one sample of chorionic plate consisting of chorionic vessels. For all cases, 4 sections of 4 μm thickness were cut on a rotary microtome from the middle of each specimen, and were mounted on clean gelatinized slides, and stained with H & E. Sections were analyzed by light microscopy and in each of the placental slides, the 10 smallest terminal villi (each less than 80 μm in diameter) in 10 different fields were examined (magnification ×400). The observations were recorded by digital camera (Olympus® DP70, Japan). Microscopic evaluation of placentas included non-inflammatory changes of amnion, acute inflammatory changes, infarction, intervillous thrombosis, chorionic villitis, hemorrhagic endovasculitis, placental intravascular thrombi, trophoblast degenerative knots, perivillous fibrin deposition and fibrinoid necrosis, erythroblastosis and villous edema (Table 2) (8). (Fig. 1, 2). The researchers examining the tissue sections were blinded to the clinical details of the cases.

Table 1. Demographic and obstetric characteristics of patients

	Group 1	Group 2	Group 3	p
Mean of age	26.5±6.05	26.77±6.08	25.8±4.94	p>0.05
Gravida	2.27±1.64	2.60±1.90	2.58±1.38	
Parity	0.81±1.2	1.1±1.35	1.66±1.08	
Gestational age at delivery	33.67±4.37	29.15±8.36	39.0±1.52	p<0.01

Statistical analysis

Statistical analyses were performed using the chi-square test for categorical variables. Continuous variables were compared by the Student's t-test. $p<0.05$ was considered significant. All computations were carried out with SPSS software 13.0 (SPSS inc. Chicago, Illinois, USA).

Results

Means of age, gravida and parity of patients were similar in group I, group II and group III. Gestational age at delivery was 33.67±4.37 weeks, 29.15±8.36 weeks, and 39.0±1.52 weeks in women in group I, group II and group III, respectively ($p<0.01$). (Table 1).

Microscopic examination revealed no significant difference between the three groups in respect to non-inflammatory changes of amnion, acute inflammatory changes and trophoblastic degenerative knots ($p>0.05$). Statistically significant light microscopy findings are shown in Table 3. Infarction and intervillous thrombosis are significantly more frequent in placental cotyledons of group I and group II fetuses. The most common associated pathologic condition with infarction and thrombosis was chronic villitis in both groups (Fig. 2).

Chorionic villitis occurred in 69%, 63% and 30% of group I, group II, and group III, respectively. There was one case (3.8%) of hemorrhagic endovasculitis in the control group ($p<0.05$). Thirty one percent of placentas in group I and 28% of placentas in group II had hemorrhagic endovasculitis. The volume of affected tissue was similar in group I and group II.

There was no case of intravascular thrombi in the control group. However, 31% and 26% of placentas of group I and group II had placental intravascular thrombi ($p<0.01$). Thrombi were only detected in chorionic vessels (Fig. 2). The number of affected vessels is shown in Table 3. Perivillous fibrin deposition and fibrinoid necrosis was more common in group I (65%) and group II (53%) compared to group III (11%, $p<0.01$). (Fig.1). The incidence of erythroblastosis and villous edema were significantly higher in the group I and group II than the control one ($p=0.01$).

Table 2. Parameters for microscopic evaluation of placenta (8) (Figure 1 and 2)

Non-inflammatory changes of amnion
amnion nodosum
meconium histiocytosis
Acute inflammatory changes
pattern of spread of organism extra amniotic or intraamniotic
maternal vs. fetal inflammatory response
discordance btw. maternal-fetal inflammatory responses
Infarction, intervillous thrombosis
age
associated pathologic condition [chorionic villitis, decidual thrombosis]
Chorionic villitis
type of cellular infiltrate
presence of intervillositis
volume of affected tissue [grade]
associated features [vasculitis, intravascular thrombi, hemorrhagic endovasculitis]
Hemorrhagic endovasculitis
type of vessel[s] involved [chorionic, major stem]
volume of affected tissue [grade]
associated changes[chronic villitis, placental intravascular thrombi]
Placental intravascular thrombi
type of vessel[s] involved [chorionic, major stem]
number of involved vessels
associated features [vasculitis, hemorrhagic endovasculitis]
Trophoblast degenerative knots
proportion normal, increased or decreased relative to gestational age
diffuse or focal
associated changes [abnormal villous fibrosis or vascularity, decidual vasculopathy]
Perivillous fibrin deposition and fibrinoid necrosis
proportion normal, increased or decreased relative to gestational age
diffuse or focal
associated changes [X-cell proliferation, acute inflammation, villous and decidual pathologic conditions]
Erythroblastosis and villous edema
proportion of nucleated-anucleate erythrocytes relative to gestational age
proportion of affected villi [edema]
severity of edema [diameter of affected relative to gestational age]
associated changes [acute or chronic inflammation, decidual vasculopathy, abruptio placenta]

Discussion

Placental pathology in intrauterine growth restriction and fetal demise after 20 weeks of gestation are investigated in this study. In this analysis, we intentionally did not include any women with a particular clinical risk factor (such as preeclampsia, or gestational diabetes) along with intrauterine death or intrauterine growth restriction. Although gestational ages of the groups were different, this study provides important results in placentas of IUGR fetuses and intrauterine death fetuses. Amnion nodosum is commonly regarded as a placental hallmark of severe and prolonged oligohydramniosis (10). Meconium histiocytosis reflects the duration of exposure to meconium before delivery. Acute placental inflammation is usually related to clinical situations such as premature rupture of the membranes and preterm delivery. Although these lesions are associated with chronic uterine vascular insufficiency, neither of them was found to be significantly different among the groups.

Placental infarction can be observed in many normal pregnancies. It is usually of no significance unless it affects more than 10-20% of the placental volume (11). The existence of a relation between fetal hypoxia and placental infarction has been shown (12). In the present study, placental infarction was detected in 58% and 62%, 4% of group I, group II and group III, respectively. Intervillous thrombosis was only observed in placentas of intrauterine death fetuses and may be feature of intrauterine death (Fig. 2).

It is reported that fetal thrombotic vasculopathy and fetal stem vessel thrombosis are common findings in women with adverse pregnancy outcomes (13). In the present study, no major stem occlusion was found in the placentas of group I or group II fetuses. Thirty-one percent of group I fetuses and 26% of group II fetuses had chorionic vessel occlusion. However, none of the placentas from healthy babies had placental intravascular thrombi ($p<0.05$). In contrast, occlusion of <50% of the lumen are not uncommon at term and this is reported to be a preparation for parturition (8).

Table 3. Statistically significant light microscopy findings in placentas of fetuses with intrauterine growth restriction (Group I) and placentas of stillbirths (Group II), and healthy live babies (Group III) (Student's t-test)

Comparision of Histopathological Analyses	Group I n [%]	Group II n [%]	Group III n [%]	P value
Infarction, intervillous thrombosis	15 [58]	39 [67]	1 [4]	<0.01
Infarction	15 [57.7]	36 [62]	1 [4]	
intervillous thrombosis	- -	2 [3]	-	
Infarction and intervillous thrombosis	- -	1 [2]	-	
associated pathologic condition	14 [54]	34 [59]	1 [4]	
chorionic villitis	10 [39]	21 [36]	1 [4]	
decidual thrombosis	4 [15]	9 [16]	- -	
chorionic villitis and decidual thrombosis	- -	4 [7]	- -	
Chorionic villitis	18 [69]	37 [64]	8 [31]	<0.5
Hemorrhagic endovasculitis	8 [31]	16 [28]	1 [4]	<0.5
type of vessel[s] involved				
chorionic	8 [31]	15 [26]	1 [4]	
major stem	- -	1 [2]	- -	
volume of affected tissue[grade]				
grade 1	1 [4]	4 [7]	1 [4]	
grade 2	6 [23]	10 [17]	-	
grade 3	1 [4]	2 [3]	-	
Placental intravascular thrombi	8 [31]	15 [26]	- -	<0.5
type of vessel[s] involved				
chorionic	8 [31]	15 [26]		
major stem	- -	- -		
number of involved vessels				
1	2 [8]	2 [3]		
2	5 [19]	12 [21]		
more than 2	1 [4]	1 [2]		
Perivillous fibrin deposition / fibrinoid necrosis	17 [65]	31 [53]	3 [12]	<0.01
Perivillous fibrin deposition	16 [62]	29 [50]	- -	
fibrinoid necrosis	1 [4]	2 [3]	3 [12]	
Perivillous fibrin deposition with fibrinoid necrosis	- -	- -	- -	
proportion relative to gestational age				
normal	8 [31]	16 [28]	2 [8]	
increased	8 [31]	12 [21]	1 [4]	
decreased	1 [4]	3 [5]	- -	
diffuse or focal				
diffuse	12 [46]	18 [31]	2 [8]	
focal	5 [19]	13 [22]	1 [4]	
Erythroblastosis / villous edema	12 [46]	28 [48]	7 [27]	<0.01
Erythroblastosis	5 [19]	5 [9]	- -	
villous edema	3 [12]	7 [12]	6 [23]	
Erythroblastosis and villous edema	4 [16]	16 [28]	1 [4]	

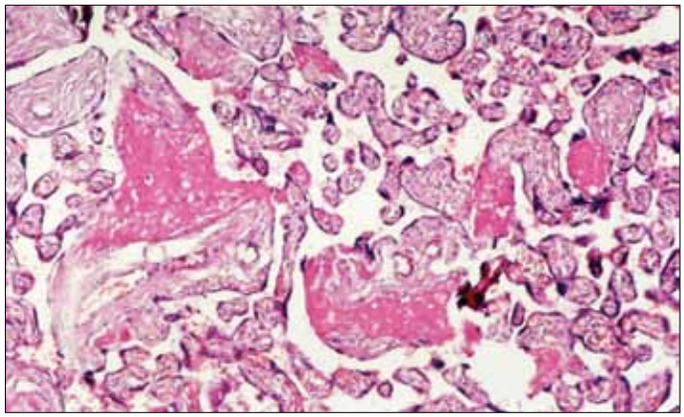

Figure 1. Histopathological section of perivillous fibrin deposits in placenta of IUGR fetus. H&E, x400

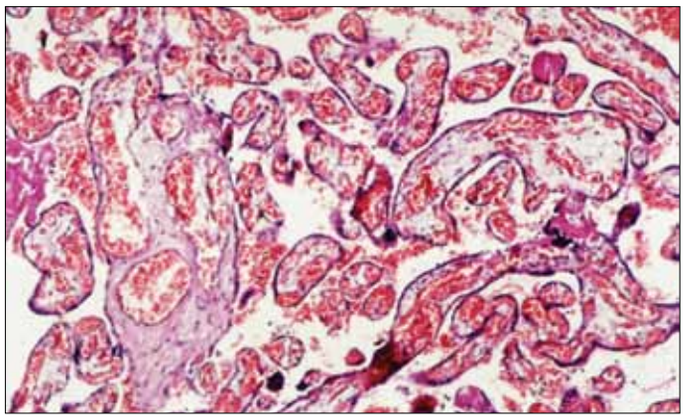

Figure 2. Histopathological section of villous thrombosis in intrauterine death fetus pla-centas. H&E, x400

Large areas of the placenta may be affected by different lesions without any obvious danger to the fetus. It is evident that the number of different types of lesions that are seen is far more strongly associated with fetal growth restriction or intrauterine death than the presence or severity of any one lesion (14). It is more likely that accumulation of placental injury for a sufficient duration leads to IUGR and fetal death (15).

Fibrinoid necrosis and perivillous fibrin deposition are associated with IUGR, autoimmune processes, infection, toxic insult, a known abnormal host-placenta interaction, genetic disorders and confined placental mosaicism (16-19). Perivillous fibrin deposition and fibrinoid necrosis were significantly more frequent in group I and group II compared to group III (Fig. 1). The presence of excess erythroblasts in the placental circulation suggests a response to hematopoietic stress (14). Villous edema may be observed in several situations like hydrops fetalis and acute intraamniotic infection (20). In this study erythroblastosis together with villous edema were found to be significantly more common in complicated pregnancies.

Infarction, intervillous thrombosis, chorionic villitis, hemorrhagic endovasculitis, placental intravascular thrombi, perivillous fibrin deposition, fibrinoid necrosis, erythroblastosis and villous edema were found to be the types of lesions that cause a normal fetus to become growth restricted or die (Fig. 1, 2). However, the extent of these lesions and clinical outcomes could not be clearly defined. The results reported here indicate that a relationship exists between morphological changes in the placentas of IUGR fetuses and intrauterine death fetuses.

Conflict of interest

No conflict of interest was declared by the authors.

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