

## Original Article

### Comparison of Placental Morphology and Histopathology of Intrauterine Growth Restriction and Normal Infants

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#### ABSTRACT

**Background and Objectives:** Birth of healthy term infant depends on normal placenta development with its disturbance causing problems like Intrauterine Growth Restriction (IUGR). The aim of this research was to evaluate morphologic and histopathologic changes of placenta in normal and IUGR infants to improve the management of the future pregnancies.

**Methods:** This cross-sectional study was conducted on 23 pregnant women with IUGR and 23 normal fetus referred to Imam Reza Hospital between 2007 and 2009. Mother, newborn and placenta data were recorded after delivery. Inclusion criteria were material age of 18-35 yr and gestational period of 32-42w with IUGR or normal embryo. The subjects were matched for age, height, weight, social status. Exclusion criteria were twin pregnancy, gestational age <32w, preeclampsia or chronic hypertension during pregnancy and diabetes. Data were analyzed using SPSS software version 11.5.

**Results:** Infarction rate, thrombosis, tissue ischemia, increased thickness of membranes and intervillous fibrin were significantly higher in IUGR group. Mean placenta weight was lower in IUGR group (440 vs. 585g).

**Conclusion:** Placenta of IUGR newborns were smaller with more microscopic infarction. Fetal placental weight ratio in IUGR group was lower than controls. The gross and microscopic measurements of a placenta are more objective and seem to offer a good way to get proper information about IUGR.

**Keywords:** IUGR, Placenta, Pathology

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Received: 26/December/2012

Accepted: 05/May/ 2013

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## Introduction

**T**he newborns with low birth weight, who are small for their gestational age and their weight are below the 10th percentile to their gestational age (SGA) are considered as infants with fetal growth restriction (FGR) and is the common manifestation of aberrant process that may impede fetal growth (1). A health term birth depends on normal placenta development. Disturbance in its development causes a large group of pregnancy complications including miscarriage, unsuccessful pregnancy, fetal death in the second trimester, third trimester classic symptoms like IUGR, preeclampsia and placental abruption (2).

A close relationship between IUGR and placental qualitative changes was shown and the main pathological findings in placenta were prematurity and hypoplasia (3).

Multiple placental infarctions may cause placental failure. Infarction in the base of maternal placenta is associated with IUGR, miscarriage and stillbirth. Furthermore, it seems that the incidence of central nervous system damages and neural development complications increase in these infant. Placental vascular thrombosis is associated with IUGR and stillbirth (1).

In a histopathological evaluation of placenta in IUGR pregnancies, the weight of IUGR placenta was less than normal placenta. Infarction and intervillous fibrinoid deposition were higher in IUGR placenta. In addition thickening of basal membrane and cytotrophoblast hyperplasia were more common among IUGR placenta. All the main histopathological findings pointed to placental blood flow reduction and fetal blood flow restriction (4).

Abnormal utero-placental or feto-placental blood flow may have side effects on intrauterine growth and increase the risk of neurological impairment (deficit)(5). This study may be useful in deciding and managing future pregnancies (4). Prevention of these perinatal complications in fetuses with growth restriction is possible by effective

prenatal identification and management (6).

The aim of this research was to evaluate infarction, thrombosis, tissue ischemia, increased thickness of membranes, mean placental weight and fetal placental weight ratio in IUGR and normal infants that can explain IUGR and lead to preventive care.

## Materials and Methods

This research was cross-sectional study conducted on pregnant women with IUGR fetuses referred to Imam Reza Hospital between 2007 and 2009. During this period of time similar number of pregnant women with normal singleton fetus (pregnancies without IUGR fetus and the mothers had not diabetes and hypertension) were recruited into a control group. The two groups were similar in terms of age, BMI (body mass index), and educational level. Upon IUGR suspicion (based on comparing gestational age with fundal height and ultrasound series) Doppler sonography was done by a radiologist to examine placenta, umbilical cord, uterine and middle cerebral arteries resistance to confirm the diagnosis. Inclusion criteria was all pregnant women between the ages 18 to 35 and gestational age 32 to 42 weeks who were diagnosed with fetal IUGR. Exclusion criteria were twin pregnancy, gestational age less than 32 week, gestational hypertension or chronic hypertension, diabetes, congenital anomaly and smoking. Written informed consent was obtained from pregnant mothers.

After delivery, all the necessary information on pregnancy, mother, newborn and morphologic assessment of placenta (i.e. placental weight, cord insertion and number of the umbilical vessels, embryonic membranes, color of the maternal & fetal surfaces of placenta, and the probable rate of infarction) were collected and recorded using a questionnaire. The placenta were kept in formalin solution and sent to a laboratory, where they would be evaluated by a pathologist after one day. To avoid bias, the pathologist was blind to all samples (cases or controls). After macro-

scopic evaluation multiple samples of each likely pathologic tissue and a random sample of parenchyma of placenta, umbilical cord and placental membranes were taken for tissue processing. Samples were processed for 18 hours in tissue processor and in various solutions (Alcohol, Xylol). Microscopic sections of 3-4 microns thickness were prepared from each block and were stained with Hematoxylin-Eosin. After studying these samples the pathologist would fill the microscopic section of the questionnaire with information such as hemorrhage and necrosis of parenchyma, Intervillous fibrin, hypervascularization of intervillous vessels, number of intervillous vessels.

Placenta with infarction were divided into two categories include coagulative necrosis in less than 50 percent of tissue and more than 50 percent. Intervillous fibrin was classified to 3 groups: Less than 5% of tissue sample, between 5-10%, more than 10%. The first group was considered normal placenta (7).

Data were classified and analyzed using SPSS 11.5 software. Tables and appropriate statistical

parameters were used. Chi-square test was conducted to compare placental pathological changes between case and control groups. After ensuring normality of the variables, independent *t*-test was used to compare quantitative variables, such as placental weight. Otherwise, appropriate nonparametric tests such as Kendall or Friedman test was used for qualitative variables. The correlation between placental weight and birth weight was determined. Fisher test was also used for variables with small number.

This study was approved by the Ethical Committee of Research of Mashhad University of Medical Sciences with ethics code “86295”.

### Results

Of 46 placentas, 23 came from the IUGR pregnancies (case group) and 23 of them were related to normal pregnancies (control group). Variables were divided into two groups: quantitative and qualitative, which are shown in Table 1 and 2 respectively.

**Table 1-** Statistical indicators of quantitative variables in the case and control groups

Variable		Number		Mean ± SD	P value	
Maternal	Age (yr)	Case	23	27.6 ± 5.3	0.955	
		Control	23	27.5 ± 6.1		
	BMI(Kg/m <sup>2</sup> )	Case	23	24.3 ± 3	0.841	
		Control	23	24.5 ± 3.3		
	Parity	Case	23	2.4 ± 1.4	0.90	
		Control	23	2.4 ± 1.5		
Fetal	Birth weight (gr)	Case	23	2122.7 ± 380.4	0.025	
		Control	23	3212.6 ± 406.1		
	Gestational age (weeks)	Case	23	37.7 ± 1.9	0.001	
		Control	23	39.1 ± 1		
	Placental	Placenta weight (g)	Case	23	440 ± 64.5	0.001
			Control	23	585.7 ± 149.4	
Placenta volume (ml)		Case	23	501.6 ± 384.5	0.144	
		Control	23	640 ± 212		
Number of cord vessels		Case	23	3 ± 0	1.000	
		Control	23	3 ± 0.2		

**Table 2-** Evaluation of pathologic qualitative variables in IUGR and normal groups

variable		Case		Control		P value
		Number	Percentage	Number	Percentage	
<b>Umbilical cord Insertion</b>	Central	9	39.1	5	21.7	0.337
	Eccentric	14	60.9	18	78.3	
<b>Number of abnormal Umbilical cord vessels</b>		0	0	0	0	-
<b>Membrane Insertion</b>	Marginal	22	96.5	23	100	0.489
	Circummarginate	1	4.5	0	0	
<b>Acute infarction with less than 50% ischemia</b>		9	39.1	2	8.7	0.009*
<b>Chronic infarction with less than 50% Ischemia</b>		3	13	2	8.6	0.109
<b>Microscopic infarction</b>		12	52.1	2	8.6	0.036*
<b>Thrombosis</b>		8	34.7	1	6	0.001*
<b>Avascular villi</b>		7	30.4	0	0	0.009*
<b>Microscopic tissue ischemia</b>		5	21.7	2	8.6	0.007*
<b>Abnormal thickness of placental membrane</b>		5	21.7	0	0	0.049*
<b>Intervillous fibrinoid deposition</b>	5%<	8	34.8	17	73.9	0.014*
	5-10%	5	21.7	2	8.7	
	> 10%	10	43.5	4	17.4	
<b>Cord vasculitis</b>		1	4.3	0	0	1.000
<b>Membranit</b>		1	4.3	0	0	0.498
<b>Chorioamnionitis</b>		1	4.3	0	0	1.000
<b>Intervillous hemorrhage</b>		2	8.6	1	4.3	0.550
<b>Amnion nodosum</b>		1	4.3	1	4.3	0.489
<b>Intravillous Hemosiderin</b>		2	8.6	1	4.3	0.243
<b>Trofoblastic fusion disturbance</b>		2	8.6	1	4.3	1.000
<b>Stromal collagenisation</b>		1	4.3	0	0	1.000
<b>Chorioangioma</b>		1	4.3	0	0	1.000

In the assessment of abnormalities of placenta it was determined that in the IUGR group only two placenta were bilobate and one was succenturiate. In the control group, the entire placentas were normal. Considering this low frequency, there was no possibility of statistical analysis.

Table 3 summarizes the fetal placental weight

ratio in both groups. The mean ratio for the IUGR group was 0.22 (standard deviation=0.06) with the minimum of 0.15 and the maximum of 0.35. In the control group the mean was 0.18 (standard deviation=0.04) with the minimum and maximum being 0.06 and 0.26 respectively.

**Table 3-** Statistical values of fetal-placental weight ratio in all cases

Group	Number	Mean±SD
Case	21	0.22±0.06
Control	23	0.18±0.04

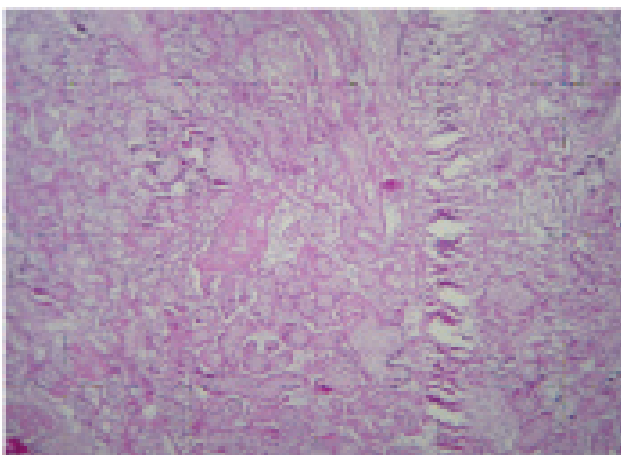
PValue=0.025

Normal distribution of the fetal placental weight ratio was determined by Kolmogorov–Smirnov test ( $P$  value=0.640) and the differences between the control and case groups were statistically significant ( $P$  value=0.025).

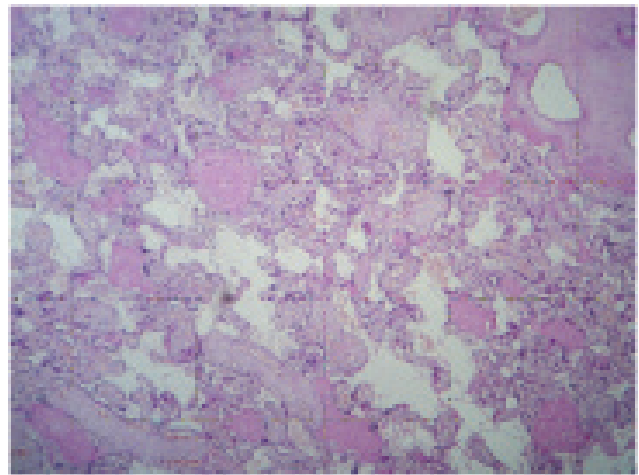
Since the placental and birth weights are quantitative variables with normal distribution, the Pearson correlation test was used to examine the correlations ( $r=0.585$ ,  $P= 0.001$ ). For all the cases in both groups, there was a linear correlation between birth weight and placental weight in level 99%.

In the IUGR group, the  $r$ -value was 0.119 and the  $P$  Value was 0.606; therefore no linear correlation existed between placental and birth weights. Similarly, no linear correlation was discovered in the control group ( $r=0.406$ ,  $P= 0.055$ ). There is not non linear correlation between placental weight and birth weight in each group. Nonlinear regression analysis used to determine this correlation.

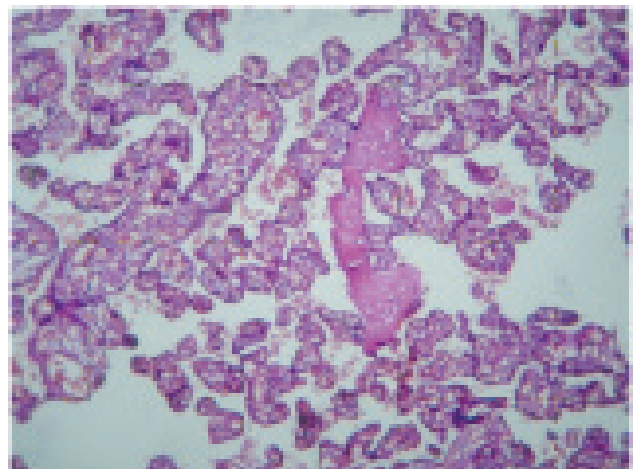
Figures 1, 2, 3 were shown pathological findings in IUGR placenta.



**Fig.1:** Coagulative necrosis. (H&E ×200)



**Fig.2:** Coagulative necrosis and intervillous fibrin deposition.(H&E ×400)



**Fig.3:** Hypervascularity and chorangioma. (H&E ×200)

### Discussion

Most previous studies on IUGR have not differentiated between constitutionally and pathologically small fetuses. Additionally, studies on the pathogenesis of IUGR have been limited by the concept that IUGR fetuses represent a homogenous group. This has created some confusion and has hampered our understanding of the mechanisms causing IUGR. The findings of the current study demonstrate several different placental histopathologic lesions in IUGR-related placenta.

According to abnormal placental shapes, the frequency of bilobate and succenturiate placenta

in the IUGR group were 2 and 1, respectively. No such incidences were found among the control group ( $P=0.27$ ). Considering the low frequency of these abnormal placental shapes, it was not statistically possible to compare. In studies conducted by Benirschke & Faye-Petersen & Fox & Maulik & Salafia *et al.*, circumvallate placenta, circummarginate, velamentous insertion of the cord and placenta previa were suggested as possible causes of IUGR. In their study, these types of placenta were not found in cases. It is recommended that in the future studies types of placental shapes be studied based on etiology of IUGR (7- 11).

Regarding the cord insertion being central or marginal, there were no statistically significant differences. Salafia *et al.* (2006) suggested that abnormal cord insertion rarely showed general fetal defects (11).

In a study by Sharma and Mardi (2003) placental infarction on macroscopic and microscopic surfaces as well as ischemic necrosis was higher in the IUGR placenta compared to those normal (3). Curtin (2007) compared IUGR and normal placenta and found an association between the vascular reduction of fetoplacental and loss of functional placental tissue that these lesions being matched with IUGR (4).

In this study, statistically significant differences were found between the IUGR and normal group regarding the pathologic changes, macroscopic infarction, acute infarction with less than 50% ischemia, microscopic infarction, thrombosis, thickness of placental membranes, avascular villi and tissue ischemia. Infarction is seen as a compressed layer of fibrinoid deposition in the base of placenta and it causes disturbance of normal maternal blood flow. These infarctions are associated with IUGR, miscarriage, preterm labor and intrauterine fetal death. Pathophysiological mechanisms appear to be caused by maternal

platelet aggregation and placental thrombosis (12, 13). Sometimes it reoccurs in the next pregnancy. Its etiology is not well known, but it may be associated with maternal thrombophilia (14- 17).

In our study, mothers with vascular diseases, hypertension or diabetes were excluded from cases. It was confirmed in IUGR fetuses with other etiologies except above, the vascular pathology is observed yet. This result is suggested by Salafia (2006) (11).

Intervillous fibrinoid deposition of less than 5% was observed more frequently in the control group. But intervillous fibrinoid deposition of more than 10% was more common in the case group. Therefore, high amount of intervillous fibrinoid deposition is a pathological finding in IUGR-related placenta. Mardi and Sharma's study (2003) confirms our study(3).

Although Redline and Pappin suggested the association between chronic villitis and growth restriction (18) no evidence of villitis was found in either group in our study. This could be due to the small sample size combined with the rarity of villitis; therefore, it is recommended such pathological findings be examined in a larger sample size in future studies.

Placental weight and the fetal-placental weight ratio in IUGR group were significantly lower than controls, which similar to earlier studies (19). Average placental weights were 440 g and 585 g in the IUGR and control groups respectively ( $P=0.000$ ). Maulik *et al.* (2006) found placental weights to be 631 g in the control group and 409 g in the IUGR group with the differences being statistically significant (10).

Salafia's *et al.* (2006), reported fetal-placental weight ratio decreased due to placental insufficiency (11). In our study, this reduction was also confirmed. In the case group, the average placental volume was 501 ml and in the control group

it was 640 ml. However, volume of placenta in comparison between the two groups was smaller in the IUGR group. Especially the standard deviation was more.

Based on our inclusion/exclusion criteria cases with preeclampsia and diabetes that causes a large percentage of IUGR cases in the medical centers were excluded; hence morphological evaluation of placenta in specific etiologies of IUGR was not possible. It is suggested that multi-central extensive studies will be carried on larger sample sizes in order to be able to study the relationship between placental morphology and various causes of IUGR.

Because of many etiologic roots, outcomes, treatment and management of this complication of pregnancy is unrecognized yet, more extensive pathological and morphological researches on placenta can be more successful in identifying factors causing IUGR and consequently the treatment and prevention of that.

### Conclusion

The placenta of the IUGR group was smaller than the normal group. Fetal-placental weight ratio in IUGR group was lower than controls. Important pathologic findings were infarction, thrombosis, ischemia, avascular villi, increased placental membranes thickness and intervillous fibrosis. The gross and microscopic measurement of a placenta is more objective and seems to offer a good way to get proper information about IUGR.

### Acknowledgment

This article is concluded from the thesis of Dr. Taraneh Arbabzadeh, number 2047-T, degree of PhD in Obstetrics and Gynecology. The authors would like to thank to Mashhad University of Medical Sciences for its financial support.

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