

## Placental findings of IUGR and non-IUGR

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This study aims to define the placental findings in intrauterine growth restriction (IUGR). The study group consisted of 40 neonates without IUGR and 24 neonates with IUGR, including their placentas.

The cases were separated into three groups according to gestational age. Group A (n=21): 37 ≤ weeks, Group B (n=27): 32 ≤ - <37 weeks, Group C (n=16): < 32 weeks. Each group had two subgroups, IUGR and non-IUGR.

The placentas from the non-IUGR subgroup were heavier than the IUGR subgroup placentas in the term group (p<0.05). Infarct (over 5%), increased syncytial knots and histiocytic intervillitis were more common in the IUGR cases (p<0.05).

This study shows that chronic patterns of injury are significantly increased in placentas from pregnancies complicated by IUGR. If the injury in the placenta is acute or mild, fetal adaptation can compensate and prevent fetal growth restriction.

**Key words:** IUGR, placental findings, gestational age.

Fetal weight is currently the most important marker of intrauterine growth<sup>1</sup>. Fetal growth is related to the interactions of epigenetic and genetic factors operating in an environment of fetal, maternal and placental impressions<sup>2</sup>. Intrauterine growth restriction (IUGR) results from influences of these factors that inhibit the optimal growth potential of the fetus.

Conventionally, the term small for gestational age (SGA) has been applied to the neonate whose weight is at least 2 SD below the mean for the infant's gestational age<sup>3</sup>. SGA infants may be born at term or preterm. The term IUGR is commonly used to refer to the growth of the fetus, while the term SGA is used for neonates. The incidence of SGA births differs among races and countries. It has been estimated that approximately 10% of all infants are born with IUGR<sup>4</sup>.

Babies with IUGR have a higher risk of death or disability in the perinatal period and may be predisposed to lifelong increased risk

for cardiovascular disorders, hypertension, diabetes mellitus and other disorders<sup>2,5-9</sup>. Recent studies have shown that children who were born with IUGR and showed no major neuropsychological deficit at birth could have adverse neurodevelopment outcomes, cognitive impairments, attention problems and learning difficulties at school<sup>10</sup>.

The placenta is a vital organ for the fetus: it provides oxygen and other nutrients through exchange, and behaves exactly like an endocrine organ<sup>11,12</sup>. The origin of the placenta is the embryo. It connects the fetus to the mother.

Common causes of fetal growth restriction are chromosomal abnormalities, metabolic or nutritional factors, infections and placental disorders<sup>13</sup>. The major cause of IUGR in developed countries is placental insufficiency.

The five most prominent placental findings associated with fetal growth restriction are maternal vascular obstruction, fetal vascular obstruction, advanced idiopathic chronic villitis,

perivillous fibrinoid deposition and chronic ablation<sup>14,15</sup>.

We aimed to compare the placental findings of both preterm and term IUGR neonates with non-IUGR neonates.

### Material and Methods

Placentas of neonates born to mothers who were followed during pregnancy in the Obstetrics and Gynecology Department of the Hacettepe University Faculty of Medicine in Ankara between February and August 2009 were included in the study. The study group consisted of placentas of infants who were diagnosed as IUGR in the prenatal period. The control group placentas were chosen from gestational age-matched non-IUGR and noncomplicated pregnancies. None of the cases featured collagen diseases, cardiac diseases, diabetes mellitus, tobacco or alcohol use, eclampsia or premature rupture of the membranes. Similarly, none had hypercoagulable status (methylenetetrahydrofolate reductase homozygote defect or prothrombin 20210 A mutation and factor V Leiden mutation). Study and control groups were allocated into three categories according to gestational age, as follows: Group A:  $\geq 37$  weeks, Group B:  $\geq 32 - < 37$  weeks, Group C:  $< 32$  weeks. Cases with congenital anomalies or findings of intrauterine infection were excluded from the study. Antenatal care was given to all cases.

Placentas were collected soon after delivery and gross examination of the umbilical cord and placenta was performed. All of the placentas were weighed after removal of the umbilical cord and membranes. Each sample was kept in 10% neutral buffered formalin. After fixation, each of them was cut into slices at approximately 1 cm intervals. At least four sections were randomly gathered from each placental disk, with additional sections obtained from the umbilical cord and the membranes. Placental samples were examined on a light microscope according to standard procedure, all by the same pathologist, who was blinded to the clinical history.

The findings were grouped under five headings: 1- Fetal vascular pathology (intervillous thrombohematoma or feto-maternal hemorrhage, fetal vascular obstruction, developmental disorders, chorangioma,

chorangioma); 2- Maternal malperfusion (infarct over 5%, massive perivillous fibrinoid deposition, increased syncytial knots); 3- Chronic placentitis (histiocytic intervillitis/villitis, chronic deciduitis); 4- Chorioamnionitis (mild-moderate or severe); 5- Other, unclassified findings (diffuse dystrophic calcification). Statistical comparison between groups was performed using OpenEpi Version 2.3.1. and  $p < 0.05$  was accepted as statistically significant. The study was approved by the Hacettepe University Ethics Board.

### Results

Placentas of 24 neonates with IUGR (study group) and 40 neonates without IUGR (control group) were included in this prospective study.

The mean birth weight and gestational age of the neonates were  $2105.2 \pm 899.4$  (630-3500) g and  $34.9 \pm 3.8$  (27-42) weeks respectively.

When the neonates were divided into groups according to gestational age, Group A included 21 infants (7 IUGR/14 non-IUGR); Group B, 27 infants (9 IUGR/18 non-IUGR); and Group C, 16 infants (8 IUGR/8 non-IUGR) (Fig. 1). All of the cases diagnosed as IUGR during the prenatal period were diagnosed as SGA after birth. All of the infants in the control group were appropriate for gestational age (AGA). Eight prominent findings were seen in the histopathology examination. These were infarct (more than 5%), histiocytic intervillitis/villitis, increased syncytial knots, chronic deciduitis, perivillous fibrinoid deposition, acute chorioamnionitis, intervillous thrombohematoma and diffuse dystrophic calcification (Fig. 2). The other findings, such as fetal vascular obstruction, chorangioma and chorangioma, were rarely seen.

The mean placental weights of IUGR infants were lighter than those of non-IUGR infants in all three groups. However, there was statistical difference for term babies only ( $p < 0.05$ ) (Table I).

There were more pathological findings in the placentas of IUGR infants than those without IUGR ( $p < 0.05$ ). All but one of the placentas with IUGR had one or more pathologic findings, while 13 of 40 cases in the non-IUGR group showed no pathological findings (Table II).

Infarct (over 5%) was observed in 8 of the placentas (33%) of the IUGR infants; it was

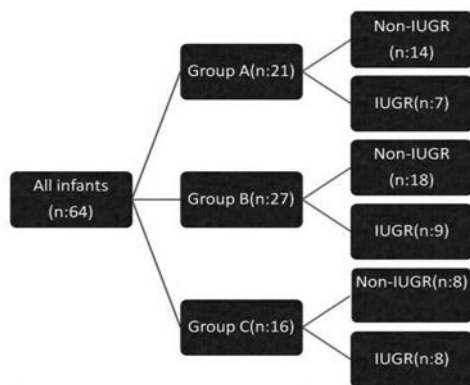


Fig. 1. Distribution of the infants according to gestational ages

present in only two placentas (5%) in the control group ( $p < 0.05$ ). Increased syncytial knots were shown in 4 placentas (16%) of infants with IUGR, and in only one placenta (2.5%) in the control group ( $p < 0.05$ ). Histiocytic intervillitis/villitis was demonstrated in 7 placentas (29%) in the study group and in 4 placentas (10%) in the control group ( $p < 0.05$ ). Chronic deciduitis was detected in 3 placentas (12.5%) in the study group and in two placentas (2.5%) in the control group ( $p > 0.05$ ). Diffuse dystrophic calcification and chorioamnionitis were displayed more often in the non-IUGR group than in the IUGR group, but this difference was not statistically significant ( $p > 0.05$ ).

Intervillous thrombohematoma and perivillous fibrinoid deposition were both observed at a similar rate ( $p > 0.05$ ) in the study and control groups. Fetal vascular obstruction was shown in only one placenta of each group.

Other pathological findings, such as chorangioma and chorangioma, were rarely observed in our study. Chorangioma was seen in a preterm placenta in the control group, and chorangioma

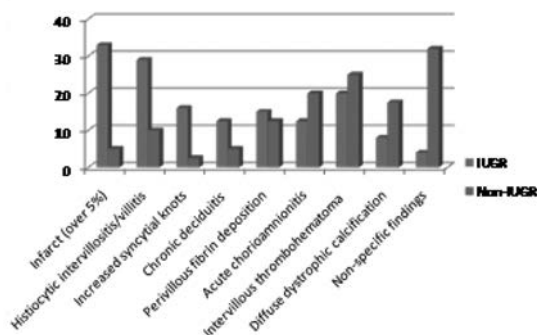


Fig. 2. Placental findings of the study and control groups

in a term placenta in the study group.

We obtained similar results when we compared pathologic findings in placentas of IUGR and non-IUGR cases grouped according to gestational age. Pathological findings in placentas of preterm IUGR infants did not differ significantly from those of term ones.

**Discussion**

In this study, we investigated macroscopic and microscopic pathologic findings of the placentas of IUGR and non-IUGR infants. Additionally, we tried to find out the differences in the placental pathology of term and preterm IUGR infants.

This study showed that placental weights were lower in the IUGR group than in the control group. This is a common finding of studies investigating placental differences between IUGR and normal infants<sup>16</sup>.

Infarct of the maternal floor and patchy diffuse villitis are the most frequent placental findings associated with IUGR in the literature<sup>15,17-20</sup>. Similarly, infarct of more than 5% was more common in the IUGR group in the present study.

Infarct results from ischemia, and reperfusion

Table I. Mean Placental Weights of IUGR and non-IUGR Infants Grouped According to Gestational age

Groups Gestational age in (weeks)	IUGR (n=24) Mean weight of the placentas (g)±SD	Non-IUGR (n=40) Mean weight of the placentas (g)±SD	p
Group A (≥ 37)	395.7±29.3	570.7±116.6	<0.05
Group B (≥ 32 - < 37)	300.5±80.3	494.7±90	>0.05
Group C (< 32)	231.9±76	343.8±68.6	>0.05

injury is often accompanied by this process. The main consequence of the ischemic process is endothelial damage or obstructive thrombus into the lumen. Infarct is a pathologic finding which can also be observed in the placentas of otherwise normal infants<sup>21</sup>; however, the size and width of the infarct are important factors affecting the growth of infant.

In the non-pathologic placenta, the anatomical integrity of the syncytiotrophoblast is crucial in providing maternal-fetal exchange<sup>22</sup>. The trophoblasts surround the villi ("plugging")<sup>2,23</sup>. If there is any defect in the plugging process, this results in abnormal dispersion of the trophoblasts surrounding the villi, and the fetomaternal membrane thickens. This event may cause disperfusion and eventually ischemia.

Syncytial knots are defined as accumulations of degenerating syncytiotrophoblast nuclei, which may protrude slightly from the villous trophoblastic surface. The increase of syncytial knots is related to the imbalance between proliferation and apoptosis of the syncytiotrophoblasts. Syncytial knots, though not a fully understood phenomenon, are accepted as an indicator for placental ischemia. Heazell et al.<sup>24</sup> concluded that an increase in syncytial knots is due to oxidative stresses such as hypoxia, hyperoxia and excess production of reactive oxygen species.

In the present study, we showed that increased syncytial knots were more common in the placentas of IUGR fetuses. We also showed

that this finding was common in term and preterm placentas of IUGR infants regardless of gestational age.

Also in this study, histiocytic intervillitis/villitis was observed more often in the placentas. Intervillitis/villitis may be due to infectious or noninfectious factors. We did not show any causative infectious agent in our cases either serologically or histologically. Idiopathic mild villitis was found in approximately 10% of term placentas by microscopy in several studies and is characterized by lymphohistiocytic infiltration of the villous tree<sup>25-27</sup>. Severe villitis was found to be associated with IUGR or recurrent abortion<sup>28</sup>. Follow-up studies showed that there is a relationship between the inflammation and neurologic disability in the infant<sup>17,29</sup>.

Chronic deciduitis was more common in the placentas with IUGR compared to those in the control group, but the difference was not statistically significant ( $p > 0.05$ ). Infectious agents such as *Toxoplasma gondii*, CMV, syphilis and the herpes simplex virus are regarded as possible etiologies<sup>18</sup>; however there was no evidence of these agents in our cases. Chronic deciduitis is characterized by histological lymphoplasmacytic infiltration of the decidua. It may be associated with recurrent preterm delivery<sup>18</sup>.

In the present study, acute chorioamnionitis was seen more often in the non-IUGR group placentas than in those of the IUGR group, but the difference was not statistically significant

**Table II.** Histological Findings of IUGR/non-IUGR Groups

Histological Findings	IUGR (n=24) n (%)	Non-IUGR (n=40) n (%)	p
Infarct (over 5%)	8 (33)	2 (5)	<0.05
Increased syncytial knots	4 (16)	1 (2.5)	<0.05
Histiocytic intervillitis/villitis	7 (29)	4 (10)	<0.05
Chronic deciduitis	3 (12.5)	2 (5)	>0.05
Diffuse dystrophic calcification	2 (8)	7 (17.5)	>0.05
Acute chorioamnionitis	3 (12.5)	8 (20)	>0.05
Intervillous thrombohematoma	5 (20)	10 (25)	>0.05
Perivillous fibrinoid deposition	4 (16)	5 (12.5)	>0.05
Nonspecific findings	1 (4)	13 (32)	<0.05



( $p > 0.05$ ). There was no variability according to gestational age. Acute chorioamnionitis causes preterm delivery and is associated with perinatal mortality and morbidity and neurological sequel<sup>30-34</sup>. This may be the reason that we saw acute chorioamnionitis more often in the non-IUGR group, since it ends the pregnancy.

Fetal vascular pathology can appear in various forms. The most common forms are intervillous thrombohematoma and fetal obstructive vasculopathy. Fetal obstructive vasculopathy is the more serious of the two. In our study, intervillous thrombohematoma was more commonly observed than fetal obstructive vasculopathy. The latter was observed in only one placenta from each group (IUGR and non-IUGR). A few other studies have also mentioned that it is associated with lower biophysical profile, IUGR, neonatal encephalopathy, cerebral palsy, recurrent fetal loss or preterm labor<sup>35,36</sup>. In this study, intervillous thrombohematoma was more often observed in the term than in the preterm non-IUGR babies ( $p < 0.05$ ). This may point to the "aging of the placenta."

Hyperplastic capillary lesions of the placenta appear in forms such as focal nodular lesions (chorangioma) and generalized increase in villous capillaries (chorangiosis). In the present study, chorangioma (0.3 cm) was found in one placenta delivered with a term IUGR infant, and chorangiosis was observed in a placenta of a near-term non-IUGR infant. These cases had no history of maternal diabetes mellitus, but the pregnant women had lived at an altitude of approximately 1000 meters (m). This could be the predisposing factor.

The rates of perivillous fibrin deposition in both groups were similar ( $p > 0.05$ ). We did not use any strict grading, but the pathological evaluation revealed that perivillous fibrinoid deposits were more massive in the placentas of the IUGR group. This result was the same for preterm and term infants. Our findings suggest that perivillous fibrinoid deposition may not be directly associated with preterm delivery or IUGR. It is probably a nonspecific sign of the placenta.

In our study, diffuse dystrophic calcification was more common in the non-IUGR group, but the difference was not statistically significant ( $p > 0.05$ ). Additionally, it occurred in only one placenta delivered at less than 32 weeks.

Based on available knowledge and experience, it can be said that dystrophic calcification often occurs in mature placentas and reflects the "aging of the placenta"<sup>37</sup>. We could not find any relationship between IUGR and diffuse dystrophic calcification; the present results are consistent with the literature<sup>38</sup>.

This study shows that certain chronic patterns of injury are significantly increased in placentas from pregnancies complicated by IUGR. These are maternal floor infarct, histiocytic intervillitis and increased syncytial knots. Variations in the intensity of perivillous fibrinoid deposition can also be associated with IUGR. However, intervillous thrombohematoma, acute mild chorioamnionitis and mild perivillous fibrinoid deposition may be related to fetal adaptation against placental insufficiency. The pathogenesis of these lesions is poorly understood and needs further research.

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