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The Relationship of Intrauterine Growth Restriction with Placental Pathologic Changes in Newborns

Hossein Dalili[1], Fatemeh Sadat Nayeri[1], Seyed Reza Mirjalili[1,2*], Seyyed Nasrollah Hosseini[3], Alireza Abdollahi[4], Mamak Shariat[1], Sedigheh Hantoushzadeh[5]

[1] Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2] Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran
[3] Faculty of Ministry of Health and Medical Education, Tehran University of Medical Sciences, Tehran, Iran
[4] Department of Pathology, Tehran University of Medical Sciences, Tehran, Iran
[5] Department of obstetrics and gynecology, Tehran University of Medical Sciences, Tehran, Iran

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Corresponding author:
Dr. Seyed Reza Mirjalili

Email:
dr_sr_mirjalili@yahoo.com

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ABSTRACT

Background: Intrauterine growth restriction is a multifaceted problem and is associated with a significant increase in the level of morbidity and perinatal mortality. According to some studies, failure of the placenta is responsible for the most cases of intrauterine growth restriction. The aim of this study was to evaluate the placental pathologic changes in the intrauterine growth restriction (IUGR) samples and compare them with normal cases.

Methods: A study population consisted of 60 intrauterine growth restriction neonates and 60 normalized neonates born at Tehran Imam Khomeini Hospital between June 2016 and July 2017. The placenta was weighed, immediately after delivery, and the umbilical cord was separated, then stored in 10% formalin and sent for pathological examination as soon as possible. Data collection was performed according to the following items: the pathologist's report, the results of the infants' examination, and the data in the neonatal cases.

Results: The intrauterine growth restriction group showed a high frequency of placenta infarction ($P < 0.001$), inflammation of the villous ($P < 0.001$), villous fibrosis ($P = 0.044$), villous vascularization disorder ($P = 0.001$), prevalence of chorioamnionitis ($P = 0.027$), prevalence of Syncytiotrophoblastic knots ($P < 0.001$) and placental necrosis ($P = 0.048$) than normal group. However, the mean weight of the placenta ($P < 0.001$), the length and width of the macroscopic placenta changes was less ($P < 0.001$).

Conclusion: The results of the current study showed that a major part of the macroscopic and histological changes are detectable in the intrauterine growth restriction samples, which are considerably more common than normal, although they are not pathognomonic, but in the future, more accurate results can be obtained from more extensive studies.

Introduction

The intrauterine growth restriction (IUGR) means fetal growth is less than the normal growth potential of a specific infant which is due to genetic or environmental factors. IUGR can be a natural response to nutrient deprivation or oxygen deprivation.[1] Around the world, 30 million infants suffer from the IUGR every year. IUGR mainly occurs in Asia.[2] Pathophysiologically, intrauterine growth disturbances can be related to maternal, placental, or fetal related factors. Nearly one-third of IUGRs are due to maternal factors and two-thirds of them related to placenta and infants.[3] Prenatal diagnosis of IUGR is based on prenatal ultrasound, biophysical profiles and assessment of the fetal acid-base status and Doppler Velocimetry. In the failure of the placenta the umbilical artery resistance increases and diastolic flow in the umbilical artery was decreases or reverses. The findings indicate that in the absent and reversed-end diastolic flow approximately 60 to 70 % of the villous placenta is damaged, and in the severe IUGR, the middle cerebral flow increased.[4]

Intrauterine growth restriction is a problem that is associated with a significant increase in the level of morbidity and perinatal mortality. IUGR infants are at risk for metabolic disorders, polycythemia, and intracranial hemorrhage (IVH), NEC, BPD, and ROP. Early neonatal complications included hypothermia, hypoglycemia, hypocalcemia, polysystemic, jaundice, etc.[5,6] With regard to long-term complications, you can also cite adult problems such as diabetes, hypertension, obesity, cardiovascular disease and dyslipidemia. It also has more problems in terms of learning and education.[6] The placental insufficiency is responsible for most cases of IUGR, and the human placenta is the most reliable control for the infants before and after birth. Similarly, several microscopic abnormalities are commonly identified in the IUGR-related placenta, which, of course, are not pathognomonic for the IUGR-placenta. These changes were included villous infarctions, placental abruption, a variety of abnormal villous morphology, increasing the thickening of basal membranes of trophoblast, villous fibrosis, and the decreasing in the volume of the villi of the nonspecific inflammatory lesions.[7-9]

In the study of Salafia et al., it has been reported that increasing in the placental changes such as infarction and villous fibrosis in IUGR groups were 55% versus 33% in the control group.[10] In spite of the some conducted studies, the relation between placental pathognomonic changes for IUGR or related etiologies has not been confirmed.

Considering the importance of the issue and the lack of studies and information in this regard, especially in developing countries, it was decided to perform a study at the Imam Khomeini Hospital of Tehran to evaluate the relationship between IUGR and placental pathological changes in the neonate born at Imam Khomeini Hospital in Tehran in the years of 2016-2017 and assess the status of these newborns.

Materials and Methods

This cross-sectional or case-control study was performed on 60 IUGR infants and 60 normal infants born at the Imam Khomeini Hospital in Tehran for 13 months during the period of June 2016 to July 2017. In the case group, the inclusion criteria was included selecting IUGR neonates, and exclusion criteria included congenital anomalies, the presence of the fatal genetic syndrome and the history of ARTs syndrome. In the control group, IUGR neonates were not selected and the neonates of the control and experimental groups were selected consecutively. Exclusion criteria included congenital anomalies, the presence of the genetic fatal genetic disease and the history of ARTs syndrome.

Immediately after delivery, the placenta was weighed and after cutting the umbilical cord, the placenta was stored in formalin 10%. Then, the placenta samples were sent to

the pathology lab in the shortest time. The samples were examined by a pathologist with optical microscopes and the pathologic outcome was reported. Infants who were entered the study was examined by a neonatal physician. Then, according to a researcher-made questionnaire the information was collected based on items, including the history of mother, and the cases of mother and neonate's.

The diagnosis of the IUGR was based on the results of an examination of the newborn by a neonatologist and also the report of gynecologists based on prenatal ultrasonography. Chronic maternal diseases were as following: cardiovascular disease, kidney disease, liver disease, diabetes, hypertension, hypothyroidism, autoimmune disease, and maternal infections, including UTI and vaginal infection. The pathology of the placenta was divided into abnormal and abnormal categories. The data collection tool was a researcher-made questionnaire. SPSS 23 software was used to analyze the data. To characterize the qualitative variables, the frequency and percentage were used and to describe the quantitative variables, the mean and standard deviations were administered. To compare qualitative variables Chi-square was used and for quantitative variables, t-test or Mann-Whitney was run. Logistic regression test and Mantel Haenszel test were used. The P-value was less than 0.05.

Results

A total of 120 samples were included in the study, of which 60 neonates with IUGR and 60 neonates were normal. Comparison of baseline data in two groups of healthy infants and IUGR showed that the prevalence of cesarean section in the IUGR group was significantly higher (98.3% vs. 48.3%, $P < 0.001$). The mean of gestational age and neonatal weight in the IUGR neonates compared with the normal neonates was statistically significant ($P < 0.001$). The prevalence of preeclampsia, chronic maternal diseases, the prevalence of pregnancy-related infections and vaginal infections in mothers with the IUGR was significantly higher than that of normal-born mothers (Respondtively $P < 0.032$, $P < 0.006$, $P < 0.001$, and $P < 0.001$) (Table 1).

In examining the pathological examination of the placenta, in many indices, there was a significant difference between the two groups with and without the IUGR. The results were illustrated in Table 2.

On the placental pathology, it was investigated into two categories: natural and abnormal (based on the Throne study).[15] In the IUGR, abnormal pathological abundance was higher and the possibility of the pathologic placenta was 1.76 times (68% versus 42%). To ensure that the gestational age was not considered as interference in the abnormal pathology, the binary logistic regression was used to measure the significant effect of gestational age and placental insufficiency in the IUGR.

The independent variable was considered as an abnormal pathology. The only factor associated with the placental abnormal pathology was the IUGR, and not the preterm, in other words abnormal placenta may increase the prevalence of IUGR for 5.5 times.

However, in comparison with the case and control groups, both the placental pathology and the gestational age were significant, but the regression test showed that the incidence of IUGR was not due to the lower GA, but due to placental insufficiency and the abnormal placental pathology.

Both in the IUGR and preeclampsia, the abnormal placental pathology was higher. The Mantel Haenszel test was run to show that if preeclampsia was interference. Then, it was found out whether or not there was a preeclampsia; the abnormal placental pathology was higher in IUGR. In preeclampsia, all placentas were abnormal, but otherwise, due to the IUGR, the abnormal placentas were significantly higher.

The logistic regression test also showed that in the presence of preeclampsia, IUGR has led to placental abnormalities (about two times), but preeclampsia has not shown such an effect.

Table 1. The underlying and general characteristics of the IUGR and normal infants born in Imam Khomeini Hospital Complex in 2016-2017

Characteristics	Normal Group (%)	IUGR Group (%)	P
Type of delivery			< 0.001
Cesarean section	29 (48.3)	59 (98.3)	
Vaginal Delivery	31 (51.7)	1 (1.7)	
Level of Education			0.144
High School	27 (45.0)	13 (22.0)	
Diploma and Associate Degree	25 (41.7)	27 (45.8)	
Bachelor	8 (13.3)	16 (27.1)	
Master's and Ph.D.	0 (0)	3(5.1)	
Number of Gravities			0.283
One	24 (40.0)	33 (55.0)	
Two	21 (35.0)	18 (30.0)	
Three	11 (18.3)	5 (8.3)	
≤ 3	4 (6.7)	4 (6.7)	
Maternal Chronic Diseases	11 (18)	33 (55)	< 0.001
Pregnancy-Related Infections	8 (13.3)	22 (36.7)	0.006
Vaginal infection	1 (1.7)	8 (13.3)	0.032
Urinary tract infection during pregnancy	7 (11.7)	13 (21.7)	0.142
Underlying disease			
Cardiovascular disease	0 (0)	1 (1.7)	0.999
Kidney disease	0 (0)	2 (3.3)	0.869
Liver disease	0 (0)	1 (1.7)	0.999
Diabetes	1 (1.7)	1 (1.7)	1.000
Hypertension	0 (0)	2 (3.3)	0.869
Hypothyroidism	10 (16.7)	7 (11.7)	0.556
History of smoking	1 (1.7)	1 (1.7)	1.000
Preeclampsia history	0 (0)	13 (21.7)	< 0.001
Sex (male)	31 (51.7)	30 (50.0)	0.855
Mother's age (years)	28.78 ± 6.09	29.83 ± 4.54	0.286
Maternal BMI (kg / m 2)	28.32 ± 4.71	28.18 ± 5.11	0.880
Gestational age (weeks)	38.17 ± 2.21	32.34± 3.11	< 0.001
Baby weight (g)	3120.33 ± 540.58	1428.00 ± 610.26	< 0.001
Pregnancy weight gain	11 ± 4.3	10.2 ± 5.7	< 0.101

Discussion

The findings of this study showed that the majority of pathologic parameters of the placentas in the IUGR samples were significantly different from those of normal ones, the main of which was the reduction of the placental weight (P < 0.001), the reduction of the length and width of the macroscopic placenta (P < 0.001), placental infarction (P < 0.001), villous inflammation (P < 0.001), villous fibrosis (P = 0.044), villous vascularization reduction (P = 0.001), Syncytiotrophoblastic knots (P < 0.001), placental necrosis (P = 0.048) placenta edema (P = 0.003) and villous loss (P = 0.012). The results of other studies have indicated that the most common placental changes include patchy placental infarction, increasing the thickness of the trophoblastic basal membrane, villous fibrosis, terminal villous hypervascularization, decreasing in villous volume, and non-specific inflammatory lesions.[7-9] In the present study, it was shown that these pathogenic changes are not IUGR, and in fact, each of these pathogenic changes can be observed only in a few patients. For example, in our study, the placental infarction, the reduction of the number of villous and the villous fibrosis was considered as the most common pathological changes observed in only half of the patients, while these changes, even in normal samples, were observed in 5 to 23% of the subjects.

Table 2. Placental characteristics in IUGR and normal groups in the Imam Khomeini Hospital in 2016-17

Characteristics	Normal Group (%)	IUGR Group (%)	P
Placental weight (g)	587.02 ±119.15	397.55 ± 192.31	< 0.001
Macroscopic length of placenta	17.42 ± 3.14	14.07 ± 3.31	< 0.001
Macroscopic width	15.09 ± 4.36	11.17 ± 2.32	< 0.001
Macroscopic diameter	3.44 ± 2.51	4.11 ± 3.16	0.203
Placental infarction	5 (8.3)	28 (46.7)	< 0.001
Inflammation of villi	13 (21.7)	35 (58.3)	< 0.001
Villous fibrosis	23 (38.3)	35 (58.3)	0.044
Reduction of Cancio capillary membrane	1 (1.7)	4 (6.7)	0.364
Villous vascularization disorder	1 (1.7)	13 (21.7)	< 0.001
Coriomaniacitis	2 (3.3)	9 (15.0)	0.027
Calcification	8 (13.3)	4 (6.7)	0.224
Syncytiotrophoblastic knots	3 (5.0)	20 (33.3)	< 0.001
Placental necrosis	2 (3.3)	8 (13.3)	0.048
Presence of cytotrophoblast cells	0 (0)	1 (1.7)	0.999
Localized necrosis points	3 (5.0)	10 (17)	0.04
Presence of umbilical vein and artery	59 (98)	60 (100)	0.315
Placenta edema	7 (12)	21 (21)	0.003
Villous loss	0 (0)	6 (10)	0.012

This suggests that although these changes are apparent in most of the patients with the IUGR, they may have a diagnostic value and differentiation among the patients with the IUGR and the normal ones.

However, is the importance is that similar frequencies of pathological changes reported in other studies. In the study of Stallmach et al., Macroscopic lesions such as placental necrosis were observed in 92% of cases.[11] In another study, Salafia and colleagues suggested that villous infarction and fibrosis in the IUGR group were 55% versus 33% of the control group, [10] which was consistent with the results of the study. Sato et al. also observed that infarction and embryonic vascular thrombosis were more prevalent in the IUGR than normal ones.[12] The results of Zhonghua and colleagues showed that the low birth weight of the IUGR neonates compared to the normal ones was due to the decrease in the level of placental villous and capillary level of the embryo.[13] In the study done by Aherne, in the placental premature, the decrease in size and volume of the placenta was quite evident. In addition, decreasing the placenta parenchyma, the decrease in average villi surface, especially the capillary surface, was quite evident in IUGR cases, which was consistent with the current study.[14]

According to the Thorne study, there were two categories of placentas if there were some abnormal parameters in placentas then they were considered as an abnormal one. In the present study, it was used the same category and then the comparison was done between the two groups. Comparing the groups together, in the IUGR, the frequency of abnormal pathology is significantly more (41-68% versus 42% -25) (P = 0.003 and IUGR 1.76, respectively) (P < 0.001).

Conclusion

In a general conclusion, it can be said that, firstly, a large part of the macroscopic and histologic pathological changes are detectable in the IUGR sample, which is significantly more common than normal, although not pathognomonic, and the same is true in the similar studies. In the vast majority of studies, there was no control group and, given the high cost, these limitations were created and descriptive studies were conducted. In our study, the advantage was having a control group that has produced a higher level of evidence. Our study limitation was lower GA. In the future, with the wider studies, we would eliminate this limitation, and certainly better results in studies can be achieved by eliminating this disruptive effect.

Conflict of Interests

Authors have no conflict of interests.

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