

Evaluation of the Relationship Between Prenatal Doppler Findings and Hematological Profile in Neonates with Intrauterine Growth Restriction at 32 to 36 Weeks of Gestation

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ABSTRACT

Background & Objective: Neonates with birth weights below the 10th percentile of gestational age- and sex-specific reference are known as neonates with intrauterine growth restriction (IUGR). Neonates with IUGR are more prone to diseases, infections, respiratory failure, and neonatal mortality. This study aimed to evaluate the association between perinatal Doppler findings and hematological indices in neonates with intrauterine growth restriction at gestational ages of 32 to 36 weeks.

Materials & Methods: In this analytical cross-sectional study conducted at Akbarabadi Hospital from 2016 to 2017, 90 neonates with IUGR who underwent umbilical artery Doppler ultrasound during pregnancy were haphazardly selected and the umbilical artery Doppler velocity was compared with neonatal hematological indices.

Results: Results indicated that 48, 25, and 17 neonates had normal, absent, and reverse Doppler, respectively. A decreased umbilical artery Doppler velocity was associated with a reduction in platelet level ($P=0.004$) and an increase in NRBC level ($P=0.002$). Considering a P -value >0.05 , white blood cell and hemoglobin levels had no associations with umbilical artery Doppler. However, IVH was correlated with the severity of abnormal umbilical artery Doppler ($P=0.001$). There was no significant relationship between hyperbilirubinemia and abnormal umbilical artery Doppler ($P<0.05$).

Conclusion: The severity of thrombocytopenia and the level of NRBC in IUGR neonates are directly related to abnormal umbilical artery Doppler and consequently, chronic hypoxia in these neonates. Furthermore, IVH is more likely to occur in neonates with chronic hypoxia. Early and perinatal diagnoses of these abnormalities can help us treat them faster and reduce long-term morbidities.

Keywords: Color Doppler sonography, Hematologic disorders, Intrauterine growth restriction (IUGR)



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Introduction

Various studies have indicated that birth weight is one of the key determinants of a child's survival and his/her future physical and brain development and is a valid indication of intrauterine growth (1,2). Since low birth weight leads to death, several disabilities, and childhood diseases, it is very important to identify the factors affecting low birth weight and eliminate them (3). According to the results obtained by a group of researchers, age, maternal weight, number of

pregnancies, maternal occupation, history of smoking, birth rate, duration of pregnancy, and history of giving birth to low-birth-weight neonates have direct relationships with birth weight (3,4). During pregnancy, fetal growth is determined by its anthropometric measures, especially weight. Indeed, a neonate's birth weight is the most important determinant of neonatal morbidity and mortality. According to the World Health Organization (WHO),

low birth weight annually leads to 9.1 million neonatal deaths (5). Neonates born with low birth weight are divided into two groups: the first group includes preterm neonates who did not have sufficient time to fully develop and the second group consists of term neonates whose gestation period was equivalent to or more than 37 weeks. These neonates, despite having enough time to grow, are very small at birth and weigh less than 2,500 gr. This group of neonates is called IUGR (intrauterine growth restriction). However, some preterm infants may also be IUGR (6). By percentile, IUGR is defined as a fetal weight of less than the 10th percentile estimated by ultrasound (7). Neonates with IUGR are more inclined to diseases, infections, respiratory failure, and neonatal mortality. Moreover, these infants have more difficulties with learning and training compared to normal infants. Besides, IUGR, as a risk factor, plays a role in developing adult health problems, such as diabetes, hypertension, and cardiovascular diseases (6). Therefore, due to the increasing number of IUGR neonates and considering the importance of preventing hematological disorders in these neonates and reducing morbidity and mortality in IUGR neonates by using an effective and economical method, this study aimed to evaluate the association between prenatal Doppler findings and hematological disorders in neonates with intrauterine growth restriction at 32 to 36 weeks of gestation.

Materials and Methods

A total of 90 pregnant women referred to Akbarabadi Hospital from 2016 to 2017 were studied. Inclusion criteria: singleton pregnancy, gestational age between 32 to 36 weeks, IUGR confirmation with Abdominal circumference $< 5\%$ or UA PI $>$ two standard deviation. Exclusion criteria: chromosomal abnormality, patient who didn't have the above criteria. This was an analytical cross-sectional study. Inclusion criteria were single pregnancy, gestational age matching the LMP and ultrasound before a gestational age of 20 weeks, gestational age between 32 and 36 weeks, the presence of IUGR based on the abdominal circumference below 5% percentile, and/or increased umbilical artery (UA) pulsatility index (PI) more than 2 standard deviations.

Patients who did not have the abovementioned conditions or had chromosomal abnormalities were excluded. Maternal history, including hypertension or diabetes, was not regarded as an exclusion criterion.

Umbilical artery Doppler velocity was evaluated by Doppler ultrasound. Considering a previously carried out study (8), the patients were divided into three groups, i.e., normal, absent, and reverse. Immediately after giving birth, umbilical cord blood samples were taken to determine pH. In the neonatal ward, neonatal intravenous blood samples were taken to assess the blood parameters. Neonates were subjected to cerebral ultrasound for examining IVH between the third and fifth days after birth. Additionally, to measure bilirubin level and jaundice,

intravenous blood samples were taken between the third and fifth days after birth. In addition to the aforementioned variables, a checklist, including the delivery characteristics, the Apgar score at birth with a complete blood cell count (CBC), that is counting the white blood cells, platelets, nucleated red blood cells, and the hemoglobin level in peripheral blood and umbilical cord pH, measuring the neonatal bilirubin level between the third and fifth days after birth, and examining the incidence of IVH at day 3 to 5 after birth, was completed for the patients. In the current study, a platelet count of less than 150,000 was considered as thrombocytopenia. Serum platelet counts ranged from 100,000 to 150,000 were regarded as mild, the range from 50,000 to 100,000 were considered as moderate, and below 50,000 were considered as severe. Afterward, the obtained data were entered in pre-prepared forms and analyzed by SPSS 21 (SPSS Inc., Chicago, Ill. USA). All ethical considerations adopted by the Ministry of Health and Medical Education were observed at all stages of carrying out this study.

Regarding the Declaration of Helsinki on ethical principles, all the ethical standards were considered in this study. Moreover, the patients' names remained confidential when publishing the results of the current study. Besides, the research proposal was submitted to the Medical Ethics Committee of Iran University of Medical Sciences to be approved.

The data were analyzed by SPSS. Percentages and means were used as central indices for describing the variables and standard deviations were applied as an index of dispersion. The Chi-square test and frequency percentages were used to compare the qualitative variables. To compare the quantitative variables in different groups, the one-way ANOVA was used in case of having the parametric conditions and the Kruskal-Wallis H test was employed in case of not having the parametric conditions. A P-value of less than 0.05 was considered.

Results

In the present study, 90 pregnant mothers and their neonates born prematurely were examined. The mean age of the mothers who participated in the current study was 30.82 (± 6.93) years, their mean weight was 87.72 (± 11.59) kg, and their neonatal mean birth weight was 1576.64 (± 447.26) gr. Among these mothers, 25 women experienced their first pregnancy, 34 women had their second pregnancy, 28 women had their third pregnancy, and 3 women experienced their fourth pregnancy (67 women had no previous abortions, while 19 women had one abortion and 4 women had two abortions). Out of these 90 pregnant mothers, 33 women (36.7%) had a normal vaginal delivery and 57 women (63.3%) had a cesarean section. When examining the umbilical artery Doppler, 48 women (53.3%) had a normal Doppler, 25 women (27.8%) had an absent Doppler, and 17 women (18.9%) had a reverse Doppler. Among the 33 neonates born by

normal vaginal delivery, 26 neonates (78.7%) had a normal Doppler and 7 neonates (21.3%) had an absent Doppler. None of the neonates had a reverse Doppler. Out of the 57 neonates born by cesarean section, 22 neonates (38.5%) had a normal Doppler, 18 neonates (31.5%) had an absent Doppler, and 17 neonates (30%) had a reverse Doppler. The mean platelet count was 237170, 108000, and 67000 in the normal group, the absent group, and the reverse group, respectively (Table 1). The P-value analysis revealed a value of less than 0.05 ($P=0.004$); therefore, it can be concluded that the neonates' mean platelet counts were different in various sonographic indices.

The mean hemoglobin level was 17.17, 17.59, and 18.42 in the normal, absent, and reverse Doppler groups, respectively (Table 1). The P-value analysis indicated a value of greater than 0.05; therefore, it can be concluded that the neonates' mean hemoglobin levels did not differ in various sonographic indices. The mean white blood cell (WBC) count was 14.81, 9.36, and 5.58 in the normal, absent, and reverse Doppler groups, respectively (Table 1). The P-value analysis showed a value of greater than 0.05; therefore, it can be concluded that the neonates' mean WBC counts did not differ in various sonographic indices. The mean NRBC was 92.68, 399.71, and 511.67 in the normal, absent, and reverse Doppler groups, respectively (Table 1). The P-value analysis indicated a value of less than 0.05 ($P=0.002$); therefore, it can be concluded that the neonates' mean NRBC blood levels were different in various sonographic indices. Assessing the arterial blood gases showed that the

mean pH was 7.29, 7.01, and 6.89 in the normal, absent, and reverse Doppler groups, respectively (Table 1). The P-value analysis showed a value of less than 0.05 ($P=0.001$), demonstrating a significant association between the levels of blood pH and sonographic indices of umbilical artery Doppler. Five neonates died before the third day after birth and before performing the cerebral ultrasound. Of the remaining 85 neonates, 1 neonate was born by normal vaginal delivery and 15 neonates were born by cesarean section developed IVH. Of these 16 neonates with IVH, 13 neonates (81.3%) were in the reverse Doppler group and 3 neonates (18.7%) were in the absent Doppler group (Table 1). None of the neonates in the normal Doppler group developed IVH. The P-value analysis showed a value of less than 0.05 ($P=0.001$); therefore, it can be concluded that there was a correlation between the incidence of IVH and Doppler sonographic indices.

Five neonates died before the third day after birth and before measuring their bilirubin levels. Of the remaining 85 neonates, 20 neonates born by normal vaginal delivery and 21 neonates born by cesarean section developed hyperbilirubinemia. Of the 41 neonates with hyperbilirubinemia, 15 neonates were in the reverse Doppler group (36.6%), 12 neonates were in the absent Doppler group (29.3%), and 14 neonates were in the normal Doppler group (34.1%) (Table 1). The P-value analysis revealed a value of more than 0.05; therefore, it can be concluded that there was no difference between hyperbilirubinemia and Doppler sonographic indices.

Table 1.

	Normal doppler	Absent doppler	Reverse doppler
Mean platelet count	237170	108000	67000
Mean Hb	17.17	17.59	18.42
Mean WBC count	14.81	9.36	5.58
Mean NRBC count	92.68	399.71	511.67
Mean PH	7.29	7.01	6.89
IVH incidence	-	3 (18.7%)	13 (81.3%)
Hyperbilirubinemia	14 (34.1%)	12 (29.3%)	15 (36.6%)

Discussion

This study aimed to evaluate blood cells and hematological indices in the neonates with IUGR and examine their associations with prenatal Doppler ultrasound findings.

The analyses performed revealed that there was a correlation between decreased platelet count and Doppler sonographic findings and the platelet counts decreased in the IUGR neonates who had an abnormal umbilical artery Doppler ultrasound (absent and/or reverse). Moreover, there was a direct relationship between the severity of thrombocytopenia and the

severity of umbilical artery Doppler. Severe (<50,000) and moderate (<100,000) thrombocytopenia were prevalent in the neonates with reverse Doppler, while mild thrombocytopenia (<150,000) was common in the neonates with absent Doppler.

Considering the NRBC count, there was a direct relationship between increased NRBC count and abnormal umbilical artery Doppler. The NRBC count were higher in the neonates with abnormal Doppler. However, there was no significant relationship between

the severity of Doppler ultrasound (reverse or absent) and increased NRBC.

As has been shown in previous studies (9,10), fetal erythropoiesis and increased NRBC count in the fetal blood circulation are markers for intrauterine hypoxia. With increase umbilical artery resistance and fetal blood flow slowing and chronic hypoxia platelet production increased in the liver and bone marrow. This finding is similar to previous studies (9,10,11,12,13). Increased NRBC count can also differentiate between hypoxia and acute neurologic injury or neurological injury following chronic hypoxia so that in chronic lesions, NRBC count increase.

About WBC count and Hb level there was no significant difference between different groups. These findings were different from those of previous studies (9,10,11,12) but similar with one study (13). This difference may be due to genetic differences in the Iranian neonates. The other reason that can explain this result is a decrease in RBC life time in the IUGR neonate with absent or reverse Doppler. Despite the increase of NRBC count, because of RBC lysis, Hb level do not increase with hypoxia. This may explain hyperbilirubinemia in IUGR neonates.

About IVH incidence we found significant difference between neonates with Absent or Reverse Doppler and neonates with normal Doppler. These findings are consistent with an increase severity of thrombocytopenia concurrently with an increase severity of Doppler disorder.

There is no obvious relationship between hyperbilirubinemia and absent or reverse Doppler in our study. This finding is different with previous studies (9,11,15). The reason for this difference may be the low Hb level in neonates in our study.

Conclusion

Modern perinatology tries to reduce perinatal mortality and morbidity but every year many neonates are born with cerebral pulsus and hypoxic-ischemic disorders. IUGR is the common problem in perinatology and one of the main reason for perinatal mortality and morbidity. One of The main challenge for perinatologists is to reduce this mortality and morbidity like intra uterine fetal death and neurological problem.

Increase NRBC level and decrease platelet level in fetus can predict IUGR before birth and even before Doppler sonography. In animal models, NRBC levels increase 2 to 3 days after hypoxia; therefore, the increase may indicate hypoxia before the labor initiation.

Increased NRBC levels are associated with adverse neonatal outcomes, including increased ICU admission, respiratory distress, and increased need for mechanical ventilation.

The incidence of thrombocytopenia is associated with an increased rate of neurological complications. The presence of placental pathology in IUGR fetus and increased resistance to fetal blood flow lead to platelet aggregation, decreased platelet levels, increased placental microthrombosis, and exacerbation of placental insufficiency. Therefore, early diagnosis of this abnormality and initiation of treatment with drugs, such as aspirin, which inhibit thromboxane A₂, improve placental blood circulation, prevent IUGR progress, and improve pregnancy outcomes.

Furthermore, we found that the rate of IVH incidence increased significantly as the abnormal umbilical artery Doppler (reverse compared to absent) got severe. This finding is consistent with the fact that an increase in the severity of thrombocytopenia concurrently occurred with an increase in the severity of abnormal Doppler. As the severity of thrombocytopenia got worse, the incidence of IVH increased in the neonates.

One of the major problems seen in IUGR neonates which can have long-term consequences is IVH. It is clear that identifying risk factors for its occurrence before delivery can have significant benefits, including administering prenatal treatments (such as magnesium sulfate), choosing the type of delivery and pregnancy termination time, and providing quick postpartum care. The present and previous studies have shown that prenatal Doppler ultrasound can be a strong predictor of IVH. Finally, finding the relationship of uterine-placental blood circulation with hematological indices and perinatal outcomes plays an important role in managing the pregnancy, considering the proper time for pregnancy termination, and providing postpartum care.

Limitations of the Study

1. The absence of control group in our study because some complications may be due to prematurity in neonates
2. Mother disease like preeclampsia, hypertension and diabetes are not included in our study.

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Conflict of Interest

Authors declared no conflict of interests.

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