Original Article

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Cerebroplacental Ratio During the Third Trimester of Pregnancy: A Prospective Case-Control Study

Gebeliğin Üçüncü Trimesterinde Maternal Demir Eksikliği Anemisi ve Şiddetinin Serebroplasental Oran ile İlişkisi

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ABSTRACT

Objective: The aim of this study is to evaluate iron deficiency anemia and its severity in relation to the cerebroplacental ratio (CPR) in the third trimester of pregnancy.

Methods: The research was planned as a prospective study. The World Health Organization (WHO) recommends that hemoglobin (Hb) level should remain above 11.0 g/dL during pregnancy. The WHO guidelines define Hb values between 10 and 10.9 g/dL as mild anemia, and between 7 and 9.9 g/dL as moderate anemia. The CPR was calculated by dividing the middle cerebral artery pulsatility index (MCA PI) by the umbilical artery (UA) PI.

Results: Of the 108 pregnant women in this study, 40 were grouped as moderately anemic, 34 as mild anemic, and 34 as healthy. Demographic characteristics were similar between the groups. MCA PI values were 1.89±0.34 in the moderate anemia group, 1.63±0.32 in the mild anemia group, and 1.57±0.39 in the control group, and there was a significant difference among the groups (p<0.001). UA PI values were 0.92±0.18 in the moderate anemia group, 1.01±0.15 in the mild anemia group, and 1.01±0.14 in the control group (p=0.013). While the MCA resistance index (RI) values were similar between the groups (p=0.836), there was a significant difference between the groups in terms of UA RI (p=0.042). CPR PI values were 2.11±0.43 in the moderate anemia group, 1.62±0.22 in the mild anemia group, and 1.56±0.4 in the control group (p<0.001).

ÖZ

Amaç: Bu çalışmanın amacı, gebeliğin üçüncü trimesterinde demir eksikliği anemisi ve şiddeti ile serebroplasental oran (CPR) ilişkisini değerlendirmektir.

Yöntemler: Araştırma prospektif olarak planlanmıştır. Dünya Sağlık Örgütü (DSÖ), hamilelik sırasında hemoglobin (Hb) düzeylerinin 11,0 g/dL'nin üzerinde kalmasını önermektedir. DSÖ kılavuzları, 10 ila 10,9 g/dL arasındaki Hb değerlerini hafif anemi, 7 ila 9,9 g/dL arasındaki değerleri orta derecede anemi olarak tanımlar. CPR, orta serebral arter pulsatilite indeksinin (MCA PI) umbilikal arter (UA) PI'ya bölünmesi ile hesaplandı.

Bulgular: Bu çalışmadaki 108 gebenin 40'ı orta derecede anemik, 34'ü hafif anemik ve 34'ü sağlıklı olarak gruplandı. Demografik özellikler gruplar arasında benzerdi. Orta dereceli anemi grubunda MCA PI 1,89±0,34, hafif anemi grubunda 1,63±0,32, kontrol grubunda 1,57±0,39 idi ve gruplar arasında anlamlı fark vardı (p<0,001). UA PI değerleri orta dereceli anemi grubunda 0,92±0,18, hafif anemi grubunda 1,01±0,15 ve kontrol grubunda 1,01±0,14 idi (p=0,013). Gruplar arasında MCA direnç indeksi (RI) değerleri benzer iken (p=0,836) UA RI'da gruplar arasında anlamlı fark vardı (p=0,042). CPR PI değerleri orta dereceli anemi grubunda 2,11±0,43, hafif anemi grubunda 1,62±0,22 ve kontrol grubunda 1,56±0,4 idi (p<0,001).

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Conclusion: Our results suggested that MCA PI, UA PI, UA RI, and CPR PI were altered in the presence of iron deficiency anemia in the third trimester of pregnancy.

Keywords: Iron deficiency anemia, third trimester, cerebroplacental ratio, CPR

Sonuç: Sonuçlarımız, gebeliğin üçüncü trimesterinde demir eksikliği anemisi varlığında MCA PI, UA PI, UA RI ve CPR PI'nın değiştiğini göstermektedir.

Anahtar Sözcükler: Demir eksikliği anemisi, üçüncü trimester, serebroplasental oran, CPR

Introduction

Although treatable, iron deficiency anemia is the most widespread nutritional disorder worldwide affecting approximately 40% of pregnancies (1,2). Hemodilution causes anemia in pregnancy after the plasma volume increases beginning in the first trimester of pregnancy. The World Health Organization recommends that hemoglobin (Hb) levels are maintained above 11.0 g/dL in pregnancy and do not fall below 10.5 g/dL in the second trimester (3). A mother requires approximately 1130 mg of total iron in the antepartum and postpartum periods (4). This value changes over time from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester (5).

Anemia in pregnancy can cause severe maternal and perinatal complications. Anemia increases the risks of preterm birth and low birth weight (6). Fetal growth accelerates in the third trimester, increasing the fetal need for iron. If anemia is present, the fetus receives less oxygen transfer causing hypoxemia, which may result in a restructuring of the blood flow in the fetus. Therefore, fetal brain blood flow increases because of a decreased resistance to flow in the fetal middle cerebral artery (MCA) and increased resistance in the umbilical artery (UA) (7,8). Monitoring fetal blood flow using a Doppler ultrasound has significantly improved the perinatal morbidity and mortality rates of pregnancies affected by fetal growth restriction (FGR) caused by this change in blood flow. Furthermore, abnormal Doppler findings in uncomplicated pregnancies without FGR might be associated with adverse perinatal outcomes. In particular, the cerebroplacental ratio (CPR), defined as the MCA pulsatility index (PI)/UA PI, may serve as a reliable indicator of these adverse outcomes (9,10). It is hypothesized that FGR may occur due to insufficient circulation and oxygenation due to maternal iron deficiency anemia in the early third trimester. In order to prevent intrauterine growth retardation in fetuses due to anemia , Doppler can be used in addition to blood tests performed during follow-up. Hence, in the current study, we aimed to evaluate the association between iron deficiency anemia and its severity with CPR during the third trimester of pregnancy.

Methods

This was a prospective study approved by the Marmara University Faculty of Medicine (decision no: 09.2020.1144/ date: 06.11.2020), and conducted at Marmara University, in accordance with the Declaration of Helsinki. An informed consent form was obtained from the participants.

Study Population and Inclusion Criteria

This study was planned as a prospective study to evaluate uncomplicated healthy singleton pregnant women who were admitted to Marmara University, Gynecology and Obstetrics Outpatient Department between 01/12/2020-01/12/2021 and had iron deficiency anemia after 28 weeks of gestation.

The inclusion criterion was pregnant women who delivered singletons between $28^{0/7}$ and $37^{0/7}$ weeks of gestation. The gestation week was determined by the last menstrual period. If the last menstrual period was unknown, the gestational week was determined using ultrasonographic measurements performed in the first trimester. The exclusion criteria were: (1) having multiple pregnancies, (2) preterm delivery prior to 37 weeks of gestation, (3) fetal chromosomal or congenital anomalies, (4) maternal use of tobacco, alcohol, or drugs, (5) Hb <4 mg/dL, and (6) presence of complications such as diabetes (pregestational or gestational), chronic hypertension, gestational hypertension, preeclampsia), preterm premature rupture of membrane, placenta previa, and placental abruption. In addition, pregnant women with thalassemia, sideroblastic anemia or megaloblastic anemia were also excluded from this study. The 108 pregnant women were divided into three groups according to anemia levels based on the WHO cutoffs (12): Hb 7-9.9 mg/dL (n=40), Hb 10-10.9 mg/dL (n=34), and Hb >11 mg/dL (n=34, control group). Iron deficiency anemia was defined when the serum ferritin level was less than 15 mcg/L and there was no infection (11). Anemia was classified as no anemia (Hb >11 mg/dL), mild anemia (Hb 10-10.9 g/dL), and moderate anemia (Hb 7-9.9 g/dL) based on the WHO cutoffs (12).

Ultrasonographic Evaluations

The CPR was measured as previously described (13) by an experienced ultrasonographer. A Mindray DC-7 Ultrasound (Shenzhen Mindray Bio-Medical Electronics Co., Ltd, China) with a 3.5-MHz curvilinear transducer to perform the Doppler measurements. Doppler measurements for the UA was performed in the umbilical cord-free loops. The MCA was measured using a transverse Doppler image of the fetal head taken at the level of the sphenoid bone. The Circle of Willis was visualized using color flow Doppler and measured approximately 1 cm distal to the branching point from the internal carotid artery, with the insonation angle as close to 0 degrees as possible. The PI and resistivity index (RI) for each artery was calculated from the mean of three measurements taken during fetal apnea periods. The CPR was calculated from the MCA PI to UA PI ratio.

Statistical Analysis

Values were analyzed using the SPSS 22.0 package program. Mean, standard deviation, minimum, and maximum values were used for the descriptive variables. The ANOVA test was used to evaluate the difference between groups. The Spearmen correlation test was also used to evaluate the relationship between Hb level and cerebroplacental ratio. p<0.05 was considered statistically significant.

Results

A total of 108 pregnant women, including 40 with moderate anemia, 34 with mild anemia, and 34 that were healthy, were included in the study. The mean Hb value of the pregnant women in the moderate anemia group was 9.1 mg/dL, in the mild anemia group was 10.4 mg/dL, and in the control group was 11.9 mg/dL. Demographic data of the pregnant women included in the study are given in Table 1. Age, gestational week, body mass index, gravidity, parity, abortion, and the number of surviving pregnant women were similar between the groups (p=0.747, p=0.112, p=0.054, p=0.609, p=0.416, p=0.854, and p=0.510, respectively).

The MCA PI was 1.89±0.34 in moderate anemia group, 1.63±0.32 in mild anemia group, and 1.57±0.39 in the control group (p<0.001). MCA RI values were similar between the groups (p=0.836). UA PI values were 0.92±0.18 in the moderate anemia group, 1.01±0.15 in the mild anemia group, and 1.01±0.14 in the control group (p=0.013). There was a significant difference between the groups in terms of UA RI values with 0.60±0.11 in the moderate anemia group, 0.64±0.09 in the mild anemia group, and 0.65±0.07 in the control group (p=0.042).

The CPR PI values were 2.11±0.43 in the moderate anemia group, 1.62±0.22 in the mild anemia group, and 1.56±0.4 in the control group (p<0.001). There was a difference between the groups and CPR PI value and a significant negative correlation was observed (r=-0.472, p<0.001) (Table 2).

Discussion

In the third trimester of pregnancy, iron deficiency anemia is frequently seen due to rapid growth. Preventing iron deficiency in pregnancy is imperative to limiting iron deficiency in the fetus and the associated complications (14). This study aimed to evaluate the effect of iron deficiency anemia on CPR in the third trimester, which is used as a fetal development marker.

In this study, no difference was observed between the groups in terms of demographic characteristics. However, a decrease in Hb level resulted in (1) an increase in MCA PI and CPR PI values, and (2) a decrease in UA PI and UA RI values. Complications during pregnancy can cause acute and chronic hypoxia in the fetus. Acute hypoxia occurs during cord compression or labor, while chronic hypoxia occurs in conditions such as high altitude

Table 1. Comparison of anemia groups and demographic characteristics

	Hemoglobin (mg/dL)			p
	7-9.9	10-10.9	>11	
Patients	40	34	34	
Age (year)	28.60±4.84	28.71±6.88	29.65±7.22	0.747
Gestational age (week)	32.7 (29-36)	32.70 (28-36)	33.35 (30-36)	0.179
BMI (kg/cm²)	28.03±3.65	28.03±4.38	30.32±3.96	0.054
Gravida	2.47 (1-6)	2.5 (1-6)	2.81 (1-7)	0.609
Parity	1.05 (0-3)	1.13 (0-5)	1.44 (0-6)	0.416
Abortions	0.47 (0-4)	0.38 (0-3)	0.38 (0-2)	0.854
Living	1.05 (0-3)	1.13 (0-5)	1.38 (0-5)	0.510

Values were written as mean ± standard deviation or mean (maximum-minimum).
BMI: Body mass index

Table 2. Comparison and correlation of anemia groups and ultrasound parameters

	Hemoglobin (mg/dL)				Correlation	
	7-9.9	10-10.9	>11	p	r	p
MCA PI	1.89±0.34	1.63±0.32	1.57±0.39	**0.000**	-0.285**	**0.003**
MCA RI	0.72±0.12	0.73±0.09	0.73±0.11	0.836	0.081	0.403
UA PI	0.92±0.18	1.01±0.15	1.01±0.14	**0.013**	0.267**	**0.005**
UA RI	0.60±0.11	0.64±0.09	0.65±0.07	**0.042**	0.279**	**0.003**
CPR PI	2.11±0.43	1.62±0.22	1.56±0.4	**0.000**	-0.472**	**0.000**
CPR RI	1.24±0.26	1.16±0.19	1.14±0.18	0.103	-0.215*	0.026

Values were written as mean ± standard deviation
MCA: Middle cerebral artery, PI: Pulsatility index, RI: Resistance index, UA: Umbilical artery, CPR: Cerebroplacental ratio

living, anemia, smoking, maternal respiratory diseases, anemia, and preeclampsia (15). The resistance in the fetal cerebral artery is high in the prenatal period. However, this may change in placental insufficiency and hypoxemia in response to chemoreceptor stimulation or changes in vasodilators or vasoconstrictors (16). There are studies in the literature evaluating maternal iron deficiency anemia and fetal cerebral blood flow. Abdel-meged et al. (7) evaluated the effect of iron deficiency treatment on CPR and found that the mean MCA PI at admission was 1.42 in the control group, 1.41 in mild anemia group, 1.42 in moderate anemia group, and 1.56 in severe anemia group. MCA RI values were 0.821 in the control group, 0.734 in the mild anemia group, 0.81 in the moderate anemia group, and 0.70 in the severe anemia group. In addition, they found that there was an increase in CPR RI and UA RI values with anemia.

In the study conducted by Ali et al. (17) in which they evaluated fetal vascular adaptation before and after treatment in severe anemia, they concluded that the fetuses of individuals with severe maternal anemia showed altered MCA and UA flows, and they showed that vascular adaptation returned to normal after maternal anemia was treated. In their study, the UA PI and UA RI values were higher and the MCA PI and MCA RI values were lower in the anemia group. They showed that CPR RI rates were also lower in the anemia group. They found that after the treatment, MCA RI, MCA PI, UA PI, and UA RI values decreased due to adaptation and CPR RI rates increased. This has been interpreted as the fetus is adapting to anemic conditions by redistributing blood flow to the brain (17). In a study by Abdelsamie et al., (18) the MCA PI value was measured as 1.62±0.15 in the severe anemia group, 1.47±0.16 in the moderate anemia group, and 1.41±0.22 in the mild anemia group. These values showed that there was an increase in the PI value with anemia. The UA RI, UA PI, and MCA RI values also increased with anemia (18). In the current study, MCA PI values were 1.57±0.39 in the control group, 1.63±0.32 in mild anemia group, and 1.89±0.34 in moderate anemia group. The MCA PI and CPR PI values increased with the decrease in the Hb level and there was a decrease in the UA PI and UA RI values. In addition, although the MCA RI values were lower in the anemia group, no significant difference could be found between the groups.

It is well documented that the CPR RI rate decreases in the presence of hypoxia due to increased placental resistance and cerebral vasodilation (19). It may cause cerebral vasodilation due to hypoxia affecting the fetus during maternal anemia. Maternal anemia is a factor that affects the development of the fetus by creating a chronic hypoxic state in the fetus. In the case of anemia, the decrease in cerebral resistance has a protective effect on the brain by redistributing the blood flow to the brain. It stands out as a mechanism to protect the fetus from a hypoxic state by providing more blood flow from the placenta in response to a decrease of resistance in the uterine artery. Maternal anemia in pregnancy is a condition that should constantly be followed up. It can be evaluated biochemically as well as ultrasonographically. Redistribution and changes in UA and MCA are known in anemia. Fetal well-being in anemia in uncomplicated pregnancies can be evaluated with these values. If these parameters, which can be observed during routine follow-up, change, it should be kept in mind that maternal anemia may also be present in addition to FGR.

Study Limitations

Since smoking is a confidential process in society, some of our patients hide their smoking during pregnancy or report it as less than it is. Although uncomplicated pregnancies were included, smoking and altitude that would cause chronic hypoxia were not questioned. In addition, although patients were selected in the last trimester, they were not all in the same week. The effect of severe acute respiratory syndrome coronavirus-2 on Doppler imaging was unknown and patients were not questioned whether they had an infection. The patients were evaluated only during the third-trimester follow-up in the clinic, and the effects of anemia and USG results on pregnancy outcomes were not evaluated. While selecting the groups, iron use during follow-up in the clinic was ignored because we did not observe the efficacy of the treatment.

Conclusion

Maternal anemia is one of the chronic hypoxic conditions affecting the development of the fetus. It induces a vascular response as a fetal adaptation, which is shown by changes in UA and MCA. Our results suggested that MCA PI, UA PI, UA RI, and MCA/UA PI were altered in the presence of iron deficiency anemia in the third trimester of pregnancy.

Ethics

Ethics Committee Approval: This was a prospective study approved by the Marmara University Faculty of Medicine (decision no: 09.2020.1144/date: 06.11.2020), and conducted at Marmara University, in accordance with the Declaration of Helsinki.

Informed Consent: An informed consent form was obtained from the participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.M.K., M.Ç., O.S.S., D.Ü., Concept: M.M.K., M.E.Ş., Design: M.M.K., Data Collection or Processing: M.M.K., M.Ç., O.S.S., D.Ü., Analysis or Interpretation: M.Ç., O.S.S., Literature Search: D.Ü., Writing: M.M.K., M.E.Ş.

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