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MATERNAL ANEMIA AND FETAL CEREBRAL HEMODYNAMIC RESPONSE – DOPPLER ASSESSMENT

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Summary. *The aim of this study was to evaluate the fetal vascular adaptation to moderate and severe maternal anemia. Biometry, amniotic fluid index, uterine, cerebral and umbilical Doppler, and maternal hemoglobin level were measured at admission and 10 days after treatment. Results: Group 1 consisted of 18 pregnancies (maternal hemoglobin level > 60 g/L); Group 2 consisted of 14 pregnancies (maternal hemoglobin level < 60 g/L). At admission the cerebral and cerebral/umbilical Doppler index, amniotic fluid index, and biometry were lower in Group 2. The uterine index was normal in both groups. An abnormal fetal heart rate was found only in Group 2 (57.14%). At day 10, maternal hemoglobin level and amniotic fluid index was higher in Group 2 than in Group 1. The cerebral index and the cerebral-to-umbilical resistance ratio increased only in Group 2. The abnormal fetal heart rate disappeared in Group 2. Conclusion: Only severe maternal anemia (maternal hemoglobin level < 60 g/L) triggered fetal cerebral vasodilatation and reduced amniotic volume.*

Key words: *Maternal anemia, fetus, amniotic fluid volume, Doppler*

Introduction

Distribution of fetal blood flow (between the placental and cerebral regions) is determined with C/U resistance ratio, which is the ratio between the cerebral (CRI) and umbilical (URI) resistance index (1,2-4). This parameter is always >1.1 during normal pregnancy, but decreases in the case of hypoxia because of the URI increase (increase in placental resistance) and CRI decrease (cerebral vasodilatation) (3,5). In severe intrauterine growth restriction associated with hypoxemia, there is increased impendence to blood flow in the umbilical and the fetal renal arteries (6). At the same time, vasodilatation of the fetal middle cerebral artery occurs resulting in the so-called "brain sparing effect" (compensatory flow or adaptation changes). These physiological adaptations have been demonstrated by changes in Doppler indices of the middle cerebral artery (7). Alteration of the placental vascular bed as induced by pregnancy-induced hypertension triggers a redistribution of the fetal cardiac output in favor of the brain because of vasodilatation at this level (1). Such cerebral vasodilatation has been related to a fetal PO2 decrease (8,9). The maternal anemia, which sometimes reaches very low levels (maternal hemoglobin level, 40-50 g/L) is frequently associated with pre-maturity, reduced neonatal weight, and infant iron deficiency (10-13). Maternal anemia is also suspected to markedly reduce the oxygen supply to the fetus, which may be responsible for fetal blood flow redistribution, despite there being no evidence of placental insufficiency. The objective of our study was to evaluate the fetal vascular adaptation to moderate or severe maternal anemia and to quantify the fetal vascular response to maternal treatment: red blood cell transfusion or oral iron intake.

Material and Methods

The study, designed as a retrospective one, was carried out in the Obstetric Department of the Clinical Center Nis. The population consisted of 18 pregnancies with moderate anemia (maternal hemoglobin level > 60 g/L [group 1]) and 14 pregnancies that were complicated by severe anemia (maternal hemoglobin level < 60 g/L [group 2]).

Both groups of patients were hospitalized for at least 10 days. All pregnant women and fetuses were investigated on the day of admission and treated on the same day. Group 1 received oral iron daily; Group 2 received two red blood cell units on the day of admission. The same maternal and fetal investigations were performed 10 days after admission.

Informed consent had been obtained from each patient before the investigations were undertaken. The admission of the cases and monitoring of the growth and fetal circulation by ultrasound and Doppler scanning were carried out according to a well-defined protocol: Doppler investigation consisted of uterine, umbilical, and cerebral artery recording at admission and 10 days later. Echography for fetal biometry (biparietal and abdominal diameters, femur length) was performed at admission only. Maternal hemoglobin content and amniotic index (Pheelan index: sum of the maximum liquid deepness in the four amniotic cavities [in millimeters])

were measured at admission. FHR recording (cardiotocography) was performed at admission, 10 days later, and at delivery.

All patients returned to the hospital for delivery.

Doppler and echographic examination was performed by two obstetricians in charge of the pregnancies, with a Shimazu SDU 2200 donation of the Government of Japan. The B mode was used to collect fetal images for fetal biometry, placenta, and amniotic fluid volume evaluation. The pulsed Doppler mode was used for recording blood flow velocity spectrums on the uterine, umbilical, and fetal middle cerebral arteries. Distribution of the fetal blood flow was evaluated with the C/U resistance ratio. This parameter is not dependent on the FHR and has a cutoff limit between the normal and pathologic zones, which is constant throughout gestation (25-40 weeks) and equal to 1.1. The CRI was used to evaluate the cerebral vasodilatation or vasoconstriction that was induced by maternal anemia or maternal treatment (oral iron intake or red blood cell transfusion).

The FHR was considered to be abnormal in the case of low (< 120 beats/min) or high (> 160 beats/min) heart rate, low modulation, or variable decelerations. The Apgar score at 5 minutes was considered to be pathologic when the score was than < 7. Normal delivery was defined as at-term delivery, without any signs of perinatal aphyxia or maternal complication.

The Doppler and amniotic indexes and maternal hemoglobin level at admission and after 10 days were compared with the use of a Wilcoxon Signed Rank Test and McNemar Test. General maternal and fetal parameters between the group with moderate anemia and group with severe anemia were compared using Mann-Whitney U - Wilcoxon Rank Sum W Test and Student T-test. Prevalence of abnormal findings between the groups were compared with Fisher's Exact Test.

Results

The population consisted of a group of 18 pregnancies with moderate maternal anemia (Group 1: mean hemoglobin level ± SD, 70 ± 5.66 g/L [range, 60-79 g/L]) and 14 pregnancies that were complicated by severe maternal anemia (Group 2: maternal hemoglobin level 48.43 ± 3.88 g/L [range, 40-59 g/L]).

The maternal and perinatal data at admission are presented in Table 1.

The pregnant women were admitted between 29 and 39 weeks of gestation; parity and maternal age were similar in the two groups. Fetuses were delivered earlier in Group 2, but only two of the deliveries (14.3%) took place before 37 weeks of gestation. The fetal weight was significantly lower in Group 2; two fetuses (14.3%) in this group were growth-restricted (< 10 percentile). There was no growth restriction in Group 1. Abnormal FHR was detected at delivery in two cases with growth retardation, and was the reason of cesarean delivery in those cases; all other Apgar scores were normal (>7 at 5 min).

Perinatal data at admission and after 10 days are presented in Table 2.

Table 1. General maternal and fetal parameters

Parameter	Group 1 (moderate anemia)	Group 2 (severe anemia)	P value
Age (y)*	26.06 ± 4.40	24.21 ± 4.12	NS
Parity*	1.78 ± 0.81	1.71 ± 0.73	NS
Gestational age at admission (wk)*	33.22 ± 2 60	33.04 ± 2.45	NS
Fetal biometry at admission (percentile)*	59.39 ± 16.94	33.93 ± 13.73	< 0.001
Delivery (wk)*	38.99 ± 1.21	38.13 ± 1.77	NS
Fetal weight (g)*	3391.67 ± 354.90	2939.29 ± 361.72	< 0.01
Intrauterine growth restriction (< 10^{th} percentile) (%)	0	2 (14.3%)	NS
Premature (%)	0	2 (14.3%)	NS
Abnormal FHR at delivery (%)	0	2 (14.3%)	NS
Abnormal Apgar score at 5 minutes (%)	0	2 (14.3%)	NS

NS=Not significant.
* Data are given as mean ± SD

Table 2. Perinatal data at admission and after 10 days

Parameter	Group 1 (moderate anemia)	Group 2 (severe anemia)	P value
Abnormal FHR at admission (%)	0	8 (57.14%)	< 0.001
Abnormal FHR at day 10 (%)	0	0	NS
Hemoglobin content at admission (g/L)*	70.06 ± 5.66	48.43 ± 3.88	< 0.00001
Hemoglobin content at day 10 (g/L)*	70.83 ± 6.14	69.79 ± 4.77	NS
Amniotic index at admission (mm)*	116.22 ± 19.76	66.14 ± 15.32	< 0.000001
Amniotic index at day 10 (mm)*	109.83 ± 17.01	98.64 ± 9.90	NS
UtRI at admission	Normal	Normal	NS
UtRI at day 10	Normal	Normal	NS
URI at admission*	0.63 ± 0.07	0.62 ± 0.07	NS
URI at day 10*	0.62 ± 0.07	0.61 ± 0.05	NS
CRI at admission*	0.84 ± 0.04	0.66 ± 0.03	< 0.00001
CRI at day 10*	0.83 ± 0.04	0.76 ± 0.03	< 0.0001
C/U ratio at admission*	1.35 ± 0.13	1.07 ± 0.12	< 0.0001
C/U ratio at day 10*	1.36 ± 0.15	1.25 ± 0.12	< 0.05

NS=Not significant
* Data are given as mean ± SD

At admission abnormal FHR was found in 8 (57.14%) of the fetuses only in Group 2, the result that

is statistically significant. After the therapy there were no abnormal FHR in either group.

Hemoglobin levels at admission were significantly lower in Group 2, and that was the reason for a different approach to therapy. After 10 days hemoglobin level increased significantly in Group 2 but remained lower than in Group 1.

Amniotic fluid index was significantly lower in severe anemia group at admission and after the therapy.

Uterine and umbilical RI was normal at admission and 10 days after in both groups.

Middle cerebral artery RI was significantly lower in Group 2 both at admission and after the treatment, but the difference was less significant.

At admission C/U ratio was below the cut-off value in Group 2. Therapy increased this ratio above the cut-off value, but remained significantly lower than in Group 1.

Table 3. Changes in perinatal and maternal parameters after 10 days

Parameter	Group 1 (moderate anemia)	Group 2 (severe anemia)	p
Abnormal FHR (%)	0	–57.14	< 0.001
Hemoglobin content (g/L)*	0.77 ± 3.25	21.36 ± 7.03	< 0.000001
Amniotic index *	–6.39 ± 4.10	32.50 ±11.61	<0.000001
URI*	–0.01 ± 0.01	–0.02 ± 0.03	NS
CRI*	–0.01 ± 0.01	0.10 ± 0.03	< 0.000001
C/U*	0.01 ± 0.03	0.19 ± 0.06	< 0.000001

NS=Not significant
* Data are given as mean ± SD

Table 3 summarizes the changes in maternal hemoglobin level, amniotic fluid, URI, CRI and fetal blood flow redistribution ratio (C/U) between the admission day and 10 days after treatment with red cell transfusion or oral iron administration. In Group 2, transfusion of red blood cells had a much stronger effect on the Doppler evaluation or on the amniotic fluid index.

Comment

The fetal Doppler examination that was performed at admission showed that severe maternal anemia (Group 2) induced significant hemodynamic changes at the cerebral, but neither at the uterine nor at the umbilical level. The cerebral vasodilatation in Group 2, as confirmed by the cerebral resistance level that was lower than normal, resulted in an increased cerebral blood flow, which probably maintained the fetal oxygen supply. Nevertheless, for quantifying the fetal hemodynamic response, we used the C/U ratio cut-off value, which is usually quite constant (C/U = 1.1) during pregnancy and allows for the quantification of the blood flow redistribution (5). Moreover, this ratio was found to be more powerful for the prediction of fetal growth retardation, hypoxia, and behavior than any isolated resistance index, at least for the fetuses at < 34 weeks of gestation (for behavior) and in pathologic pregnancies with fetal hypoxia (2, 4, 5, 8). In the current case, there was no sign of placental alteration, as in the pathologic pregnancies mentioned earlier, so the blood flow redistribution probably was related to maternal anemia and subsequent reduction in fetal PO2.

In Group 2 the C/U values were below the normal range (< 1.1), which confirms that the fetus had to adapt by increasing its blood flow redistribution towards the brain. Such adaptation was confirmed by the increase of both the cerebral index and the C/U ratio after maternal red blood cell transfusion. The increase in cerebral resistance after the transfusion without significant change in umbilical or uterine resistance confirms that maternal anemia does not create placental dysfunction and that the situation can be restored quickly by two units of red blood transfusion to the patient. In Group 1, the C/U values were within the normal range, which means that the blood flow distribution between the brain and placenta was normal, despite the maternal hemoglobin content being significantly lower compared to normal. After maternal transfusion (Group 2), the C/U ratio restored normal values, but the fetal weight at delivery, even though it was in the normal range, remained significantly lower than in Group 1.

The amniotic index was reduced in Group 2 compared to Group 1 at admission and recovered after transfusion, even though it remained lower in Group 2. This could be connected with abnormal FHR pattern present in 57.14% in Group 2 at admission. After transfusion in Group 2 the average amniotic fluid index rose from about 66 to about 98 and there was no abnormal FHR in either groups. Besides the amniotic index, abnormal FHR is related to fetal hypoxia as well, which may suggest that, below a certain level of hemoglobin content, there could be a direct relationship between the maternal hemoglobin content and fetal pO2 (14,15).

In the present study, we did not have access to the duration of maternal anemic period. On the other hand, it was demonstrated that the fetal cerebral vasodilatation during a period of several weeks under hypoxia does not protect against cerebral organic damage (16,17). Thus, because the severe maternal anemia triggers a marked fetal cerebral vasodilatation, the hemoglobin content (if < 60 g/L) has to be restored as soon as possible to suppress the cerebral vasodilatation. In Group 2, the transfusion restored the maternal hemoglobin content up to the level of Group 1 at admission and suppressed the fetal blood flow redistribution by cerebral vasodilatation and abnormal FHR patterns.

The absence of fetal blood flow redistribution for maternal hemoglobin levels of > 60 g/L suggest that the oxygenation of the fetus was still satisfactory. The placenta is a huge reservoir of maternal blood; therefore, even if the maternal blood oxygen content is lower than normal, there is enough oxygen passing through the placenta (18).

Anemia affected primiparous and multiparous women to a similar extent, and there was no correlation with age, gestational age at admission, or delivery date. Finally, it seems that maternal anemia is for the fetus an acute but

reversible aggression that can be prevented as soon as it is detected by means of maternal blood assay.

Conclusion

Close monitoring of the fetal umbilical and cerebral circulation by Doppler examination in anemic pregnancies allows the measurement of the amplitude of the fetal vascular response and the fetal recovery as well. Hemoglobin content of < 60 g/L is strongly associated with marked fetal hemodynamic adaptation and must be treated with acute red cells transfusion. Moderate anemia (maternal hemoglobin > 60 g/L) is not sufficient to trigger fetal blood flow redistribution and can be treated with oral iron intake.

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MATERNALNA ANEMIJA I FETALNI CEREBRALNI HEMODINAMSKI ODGOVOR – DOPLER MERENJA

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Kratak sadržaj: *Svrha ove studije je ispitavanje vaskularne adaptacije fetusa na umerenu i tešku anemiju majke. Nivo maternalnog hemoglobina, biometrija, količina plodove vode, uterini, cerebralni i protok kroz pupčanik ispitan je Dopler ultrazvučnom pretragom na prijemu i 10 dana nakon terapije. Rezultati: Grupu 1 čini 18 trudnica (nivo maternalnog hemoglobina > 60 g/L); grupu 2 čini 14 trudnica (nivo maternalnog hemoglobina < 60 g/L). Na prijemu su cerebralni, cerebralni/umbilikalni Dopler indeksi, indeks količine plodove vode, i biometrija bili niži u grupi 2. Uterini Dopler indeksi bili su normalni u obe grupe. Patološki CTG zapis ustanovljen je samo u grupi 2 (57,14%). Nakon 10 dana, nivo maternalnog hemoglobina i indeks količine plodove vode porasli su više u grupi 2. Cerebralni indeks i cerebralni/umbilikalni odnos indeksa otpora raste samo u grupi 2. Patološki CTG zapis više nije prisutan u grupi 2. Zaključak: Samo je teška maternalna anemija (nivo maternalnog hemoglobina < 60 g/L) pokretač fetalne cerebralne vazodilatacije i uzrok smanjenja količine plodove vode.*

Ključne reči: *Maternalna anemija, fetus, plodova voda, Dopler*