Effect of Maternal Iron Deficiency Anemia on Fetal Hemodynamics

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Abstract

Background: Iron deficiency anemia is a worldwide complication. So far, it is the most common medical complication in pregnancy with several complications. It is also suspected to reduce the oxygen supply to the fetus, which may be responsible for fetal blood redistribution, despite there being no evidence of placental insufficiency.

Objective: To evaluate the effect of maternal iron deficiency anemia on the vascular adaptive potentials of the fetus to withstand it by Doppler parameters. Also to evaluate the effect of iron therapy or blood transfusion during pregnancy.

Study Design: Prospective comparative study included ninety pregnant women (>32 weeks) diagnosed with iron deficiency anemia who were subjected to Doppler examination of umbilical artery, middle cerebral artery and fetal renal artery at time of admission, 10 days after receiving iron therapy or blood transfusion according to Hb level and again at time of delivery to show the impact of treatment.

Results: Vasodilatation of the fetal middle cerebral artery occurred (brain sparing effect), this demonstrated by changes in Doppler indices of the middle cerebral artery, umbilical artery and renal artery. Treatment of anemia resulted in correction of these Doppler changes and decreased fetal complications which were attributed to anemia.

Conclusion: Prevention of iron deficiency anemia is better than treatment. Prevention is simply by oral iron supplements, but treatment might need oral, parenteral iron or even blood transfusion.

Key Words: Iron deficiency anemia – Pregnant female – Doppler examination – Iron therapy.

Introduction

HEMOGLOBIN concentration is used to determine the diagnosis and severity of anemia in low resource settings, an indicator that is routinely screened using WHO-defined hemoglobin cutoffs. These thresholds are lower for pregnant women (females ≥ 15 years of age) than non-pregnant women (11.0g/dl versus 12.0g/dl). Severity of anemia is determined using additional cutoffs, with severe anemia defined as a hemoglobin level of less than 7.0g/dl [1].

Iron deficiency is defined as a condition in which there are no mobilizable iron stores, resulting from a long-term negative iron balance and leading to a compromised supply of iron to the tissues. Finally, the most significant negative consequence of ID is anemia, usually microcytic hypochromic in nature [2].

IDA has been linked to unfavorable outcomes of pregnancy. It is the most common nutritional disorder in the world affecting two billion people worldwide with pregnant women particularly at risk. According to WHO report, 2001 indicates that IDA is a significant problem throughout the world ranging from 35-75% in developing countries (average 56%) whereas in industrialized countries the average prevalence is 14% [3].

Distribution of blood flow (between the placental and cerebral regions) is determined with Middle cerebral artery RI/Umbilical artery RI (C/U resistance ratio); this parameter is always >1.1 during normal pregnancy, but decreases in the case of hypoxia because of umbilical artery resistance index increase (increase in placental resistance) and cerebral resistance index decrease (cerebral vasodilation) [4].

Perinatal morbidity and mortality of IUGR infants is 3-20 times greater than normal infants. These cases may be followed with outpatient monitoring and they often deliver at term. However process is not severe enough to stop fetal growth completely or to deteriorate. The umbilical artery and the middle cerebral artery waveforms may be abnormal, without effect is seen on Doppler and growth until 26-32 weeks gestation. Mild uteroplacental insufficiency [13].
Iron deficiency and iron deficiency anemia during pregnancy are risk factors for preterm delivery, prematurity and small for gestational age birth weight. Iron deficiency has a negative effect on intelligence and behavioral development in the infant. It is essential to prevent iron deficiency in the fetus by preventing iron deficiency in the pregnant woman [8].

Prevention and control is typically achieved through iron fortification of food staples like flour and rice and/or through administration of iron supplements most often in iron pill. Although iron supplements are widely available and fortified foods constitute a major component of the diet in the developed world, access is limited in the developing world [2].

Aim of work: The present study was conducted to show the effect of different degrees of maternal iron deficiency anemia on fetal hemodynamics and to evaluate the effect of treatment.

Patients and Methods

This prospective comparative study included 90 pregnant women out of 300 suitable candidates who attended Kasr El-Aini Hospital Obstetric Outpatient Clinic and Casualty Department in the period between June 2015 and June 2016. This study was ethically approved by the Ethical Committee, Faculty of Medicine, Cairo University.

Patients aged 20-35 years with singleton living fetus of >32 weeks gestation at time of first visit with no history of chronic illness or medical disorder other than iron deficiency anemia such as chronic hypertension, D.M. or chronic blood loss e.g.: peptic ulcer and no history of recurrent perinatal deaths, recent blood transfusion or other vitamin deficiency anemia. And patients with pregnancy associated disorders as: Preeclampsia, gestational diabetes or placenta previa (recurrent vaginal bleeding) were excluded from the study.

The pregnant women were divided into three groups:

- Group A (30 patients): Patients with mild anemia (Hb concentration: 9.0-10.9g/dl).
- Group B (30 patients): Patients with moderate anemia (Hb concentration: 7.0-8.9g/dl).
- Group C (30 patients): Patients with severe anemia (Hb concentration: >7.0g/dl).

All patients were subjected to:

- Oral informed consent.
- Complete history taking: Symptoms of anemia as headache, weakness and palpitations, date of 1st day of last menses, obstetric code, previous mode of deliveries and any prior complication during pregnancy or labor.
- Physical examination: General examination for pallor, tachycardia, local obstetric examination for fundal height, rupture membranes, cervical dilatation and effacement.
- Laboratory investigations:
  - Venous samples: Hemoglobin concentration, MCV, MCH, MCHC, random blood sugar, serum ferritin (as measurement of ferritin levels has the highest sensitivity and specificity for diagnosing iron deficiency in anemic patients).
  - Urine analysis: For glucose and albumin.

Maternal hemoglobin levels were repeated after ten days and repeated every follow-up visit and at expected date of delivery.

- Ultrasonography: For fetal heart activity, location of the placenta, fetal biometry (biparietal diameter, femur length and abdominal circumference), presentation and position and amniotic fluid volume by AFI and screening for congenital anomalies, Ultrasound examinations were done using 3.75MHz curvilinear transducer with color Doppler ultrasound on Samsung-Medison ultrasound machine.

- Doppler flowmetry: For umbilical artery, middle cerebral artery and fetal renal artery. Distribution of blood flow in the fetus was measured by C/U (C=middle cerebral artery resistance index, U=umbilical artery resistance index) which is more than 1.1 through out the normal pregnancy.

Ultrasonography and Doppler were done at time of first visit and repeated 10 days later after initiation of treatment and then followed-up regularly until expected date of delivery (every 2 weeks till 36 week then every week till delivery).

The three groups were managed accordingly:

- Group A: Received oral iron before meals in the form of ferrous fumerate therapeutic dose: 100-200mg/d, with the possible side effects of gastritis, constipation and diarrhea. In case of failure to respond or intolerance to oral iron; shift to parenteral iron. After Hb returned normal, iron therapy was continued for 3 months to replenish iron stores, adequate iron replacement when ferritin reaches 50ng/ml, the rationale is that treatment maintains
maternal iron stores and may be beneficial for neonatal iron stores.

- **Group B**: Were admitted to receive parenteral iron infusion: In the form of iron sucrose (to be repeated if still Hb level is below 9g/dl during follow-up visits).

The dose was calculated according to the following formula according to product literature:

\[ \text{IV iron dose (mg)} = \text{blood volume (dl)} \times \text{Hb deficit (g/dl)} \times 3.3. \]

- Blood volume (ml) = 65ml X weight in kg (blood volume/kg=65ml/kg).
- Blood volume (dl) = blood volume (ml)/ 100 (each dl contains 100ml).
- Hb deficit = difference between observed and desired Hb. (Desired hemoglobin 11g%).
- 3.3 = reflects the amount of iron (in milligrams) in each gram of Hb.

Each 200mg iron sucrose will raise Hb by 1g/dl, possibly if allergic reaction may happen in some patients manifested by dyspnea, chest pain, flushing, rash and back pain; antiallergic measures were undertaken by stopping infusion, intravenous antihistaminic and steroid, cardiopulmonary resuscitation was available if needed.

- **Group C**: Received blood transfusion in the form of packed RBC, each unit packed RBCs increases Hb by 1g/dl (similar to 200mg iron sucrose); each unit packed RBCs (300ml) contains 200ml RBCs, which contain 200mg iron.

Transfusion was repeated if Hb level was found less than 7g/dl at follow-up visits.

Side effects include allergic reaction, pyrogenic reaction, and risk of infection transmission.

The patients coming back for delivery were subjected to: Physical examination, laboratory investigations, ultrasonography and Doppler (for the same criteria mentioned before).

**Statistical analysis:**

Data were statistically described in terms of range, mean ± standard deviation (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test with posthoc multiple 2-group comparisons. Within group comparison of numerical variables was done using paired t-test in comparing 2 groups.

For comparing categorical data, Chi square (\( \chi^2 \)) test was performed.

Exact test was used instead when the expected frequency is less than 5. \( p \)-values less than 0.05 was considered statistically significant.

**Results**

The clinical criteria of the study population are presented in Table (1).

<table>
<thead>
<tr>
<th>Group (A)</th>
<th>Group (B)</th>
<th>Group (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years).</td>
<td>29±2SD</td>
<td>29.8±0.5 SD</td>
</tr>
<tr>
<td>Mean parity.</td>
<td>1.5±2.5 SD</td>
<td>2.04±3.5 SD</td>
</tr>
<tr>
<td>Mean gestational age</td>
<td>32.8±2SD</td>
<td>34.4±2.8 SD</td>
</tr>
<tr>
<td>by dates on admission (weeks).</td>
<td></td>
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<tr>
<td>Mean gestational age</td>
<td>32.8±0.6SD</td>
<td>32.5±2.2SD</td>
</tr>
<tr>
<td>by ultrasound on admission (weeks).</td>
<td></td>
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</tr>
<tr>
<td>Mean gestational age</td>
<td>39.2±0.5SD</td>
<td>37.8±0.3 SD</td>
</tr>
<tr>
<td>by dates at delivery (weeks).</td>
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</tbody>
</table>

There was a statistically significant difference among Hb levels on admission. After 10 days of treatment, Hb level was elevated in the 3 groups but the difference was statistically non-significant. At the time of delivery, the Hb level was further elevated and the difference between groups (A) and (B) was statistically significant (Table 2).

<table>
<thead>
<tr>
<th>Group (A)</th>
<th>Group (B)</th>
<th>Group (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hb (g%) on admission.</td>
<td>9.9±0.6 SD</td>
<td>8.47±0.4 SD</td>
</tr>
<tr>
<td>Mean Hb (g%) 10 days later.</td>
<td>10.56±0.2 SD</td>
<td>10±0.5 SD</td>
</tr>
<tr>
<td>Mean Hb (g%) at delivery.</td>
<td>10.5±0.8 SD</td>
<td>10.06±1.1 SD</td>
</tr>
</tbody>
</table>

\( p \)-value is significant if <0.05.

There was a statistically significant difference among serum ferritin levels on admission. After 10 days of treatment, serum ferritin level was elevated in the 3 groups but the difference was statistically non-significant. At the time of delivery, the serum ferritin level was further elevated and the difference between Groups (A) and (B) was statistically significant (Table 3).
There was no statistically significant difference between the umbilical arteries RI among the three groups on admission. After 10 days of treatment, there was a decrease in the umbilical artery RI in the 3 groups with a statistically significant difference between Group (A) and the other 2 groups. At delivery, there was further decrease in the umbilical artery RI in the 3 groups with a statistically significant difference between the 3 groups as shown in Table (4).

<table>
<thead>
<tr>
<th>Table (4): Mean umbilical artery RI between the three groups.</th>
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<tbody>
<tr>
<td>Group (A)</td>
</tr>
<tr>
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</tr>
<tr>
<td>Mean umbilical artery RI on admission (SD)</td>
</tr>
<tr>
<td>Mean umbilical artery RI 10 days later (SD)</td>
</tr>
<tr>
<td>Mean umbilical artery RI at delivery (SD)</td>
</tr>
</tbody>
</table>

p-value is significant if <0.05.

There was a statistically significant difference between Group (B) and the other 2 groups as regards the AFI on admission. After 10 days of treatment, the mean AFI was reduced in the 3 groups and the difference was statistically significant as shown in Table (5).

<table>
<thead>
<tr>
<th>Table (5): Mean AFI between the three groups.</th>
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<tbody>
<tr>
<td>Group (A)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Mean AFI on admission (cm)</td>
</tr>
<tr>
<td>Mean AFI 10 days later (cm)</td>
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<tr>
<td>Mean AFI at delivery (cm)</td>
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</tbody>
</table>

p-value is significant if <0.05.

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 normal pregnancy and allows for the quantification of the blood flow redistribution.

The mean C/U ratio on admission was less than 1.1 in Group (B) and Group (C) while Group (A) showed a normal C/U ratio and this difference was statistically significant between all groups.

After 10 days of treatment, the mean C/U ratio improved in the 3 groups and was highest in Group (C). This showed a statistically non significant difference between the three groups.

At the time of delivery, the mean C/U ratio was slightly decreased in the 3 groups but still >1.1. However, no statistically significant difference was found between the three groups (Table 6).

<table>
<thead>
<tr>
<th>Table (6): MCA/Umbilical artery ratio between the three groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (A)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Mean MCA/ Umbilical artery ratio on admission. (SD)</td>
</tr>
<tr>
<td>Mean MCA/ Umbilical artery ratio 10 days later. (SD)</td>
</tr>
<tr>
<td>Mean MCA/ Umbilical artery ratio at delivery. (SD)</td>
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</tbody>
</table>

p-value is significant if <0.05.

There was statistically significant difference between the renal arteries RI between Group (C) the other 2 groups on admission. After 10 days of treatment, there was a decrease in the renal artery RI in the 3 groups with a statistically significant difference between Group (A) and the other 2 groups. At delivery, there was further decrease in the renal artery RI in the 3 groups with a statistically significant difference between Group (C) the other 2 groups as shown in Table (7).

<table>
<thead>
<tr>
<th>Table (7): Mean renal artery RI between the three groups.</th>
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<tbody>
<tr>
<td>Group (A)</td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>Mean renal artery RI on admission. (SD)</td>
</tr>
<tr>
<td>Mean renal artery RI 10 days later. (SD)</td>
</tr>
<tr>
<td>Mean renal artery RI at delivery. (SD)</td>
</tr>
</tbody>
</table>

p-value is significant if <0.05.
Discussion

Anemia during pregnancy is defined according to WHO guidelines to be hemoglobin level below 11 g/dl. Mild anemia is defined as a hemoglobin value between 10-10.9 g/dl, hemoglobin concentration between 7-9.9 g/dl indicates moderate anemia and severe anemia is defined as a hemoglobin concentration <7 g/dl [6].

While the causes of anemia are variable, it is estimated that half of cases are due to iron deficiency. In some settings, considerable reductions in the prevalence of anemia have been achieved; however, overall, progress has been insufficient. Further actions are required to reach the World Health Assembly target of a 50% reduction of anemia in women of reproductive age [7].

Pregnant and lactating women should be given the (UNICEF)/WHO micronutrient supplements providing one RNI (recommended nutrient intake) of micronutrients daily (including 27 mg iron), whether or not they receive fortified rations. Iron and folic acid supplements, when already provided, should be continued [8].

The present study was conducted to show the effect of different degrees of maternal iron deficiency anemia on fetal hemodynamics and to evaluate the effect of treatment.

In this study, there was no statistical significant difference in the mean age and parity in between mild, moderate and severe iron deficiency anemic pregnant females.

This agrees with result of Judith Angelitta who suggests that maternal age and parity were independently associated with maternal anemia [12].

Regarding the hemoglobin levels and serum ferritin levels, it was found that the major impact of treatment was on the patients in Group (C) (severe anemia) as the hemoglobin concentration was elevated by about 3.5 g% from admission to time of labor. This shows the impact of blood transfusion on improving the blood hemoglobin status. Yet, the hemoglobin levels in moderate anemia were also elevated by about 2.0 g%, meanwhile in mild anemia group an elevation by about 1 g%.

Ten days after treatment, as we compared the effect of oral iron to parenteral iron; a more rapid response may be attributed to parenteral iron than oral iron.

At time of labor, a statistically significant difference was found between Group (A) (mild anemia) and Group (B) (moderate anemia). This result spotlights the fact that both oral iron supplementation and parenteral iron transfusion had almost a similar impact on hemoglobin level and serum ferritin level on the long run.

This result agrees with that reported by Khalfallah et al., who found that the intravenous plus oral iron was superior to the oral iron only as measured by the increase in hemoglobin level and the increase in mean serum ferritin level [9].

As for the AFI, in this study there is no significant effect was noticed in the 3 groups but a potential benefit might be the prevention of development of oligohydramnios as pregnancy advances especially in Group (C) [severe anemia].

And this is similar to what has been reported by Milan Stefanovic and colleagues that there was no statistically significant increase in AFI after treatment [11].

Also noted in this study that there was an increase in AFI in Group (B), (C) after 10 days of treatment and which correlated with umbilical artery resistance index which decreased after 10 days of treatment; showing that increased perfusion in the umbilical artery may be the cause for increased AFI.

In this study, data regarding the umbilical artery RI showed a statistically significant difference between Group (A) (mild anemia) and the other 2 groups after 10 days of treatment with a higher RI in Group (A); this might be attributed to the non-effectiveness of oral iron supplementation on short-term therapy. On the other hand, at the time of delivery the 3 groups showed improvement in the umbilical RI but still Group (C) (severe anemia) had the best chance of improved RI. This result also points out to the effectiveness of blood transfusion on the long-term outcome.

As regards renal artery RI in this study, there was a statistically significant difference between the renal arteries RI between Group (C) the other 2 groups on admission and this may be attributed to the higher percentage of cases with fetal growth restriction in Group (C) in whom FGR is associated with decreased kidney size and nephron number and hence decreased urine production so decreased AFI which is similar to what has been stated by Stigter et al., as regards renal artery RI in cases of growth restriction [15].
After 10 days of treatment, there was a decrease in the renal artery RI in the 3 groups with a statistically significant difference between Group (A) and the other 2 groups. At delivery, there was further decrease in the renal artery RI in the 3 groups with a statistically significant difference between Group (C) the other 2 groups. This result also points out to the effectiveness of blood transfusion on the long-term outcome.

This comes in accordance with that stated by another study: In severe intrauterine growth restriction associated with hypoxemia, there is increased impedance to blood flow in the umbilical and the fetal renal arteries [14].

In this study, as for the C\(\text{AU}\) ratio, in Group B & C (mild and severe anemia), 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 and parenteral iron transfusion. The increase in cerebral resistance after the transfusion without significant change in umbilical 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 or intravenous iron. In Group (A) (mild anemia), 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.

This result agrees with:

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. This parameter is always >1.1 during normal pregnancy, but decreases in the case of hypoxia because the URI increase (increase in placental resistance) while the CRI decreases (cerebral vasodilatation) [10].

Also this result agrees with Milan Stefanović and colleagues study in 2005 that showed similar impact of blood transfusion and parenteral iron on Doppler indices [11].

In Conclusion: Prevention of iron deficiency anemia is better than treatment. Prevention is simply by oral iron supplements, but treatment might need oral, parenteral iron or even blood transfusion.

Acknowledgement:

We would like to thank Prof. Dr. Salah Ali Sanad, Professor of Obstetrics and Gynecology for his support and advice during this work.

References


تأثیر آنئیمیا نقص الحديد لدى الأم الحامل
على الدورة الدموية للجنین

مقدمة: تعتبر الامدنیا مشکلة عالمیة البیان وتعترف بأنها نقص ترکیز مادة الهیومجلوبین وكذلك نقص ترکیز خلايا الدم الحمراء إلى مستوى أقل من المستوى الطبيعي الكافی لحمل الأکسیجین لسد حاجات نسیة الجسم.

لقد عرفت منظمة الصحیة العالمية الامدنیا بأنها إنخفاض نسبة الهیومجلوبین عن 11 جم/ل في السیادات الحوامل في أي فترة من فترات الحمل بغض النظر عن التغییرات الفسيولوجیة التي تحدث أثناء الحمل، بشیر إلى وجود امدنیا تستریع الإنتباه.

ویعد قیاس نسبة الهیومجلوبین أو الهماتوتركیب هو أهم الطرق وأكثرها شهرة لکشف الامدنیا. وترجع أسباب زيادة نسبة امدنیا نقص الحديد بين السیادات الحوامل لنقص مستوی مخزون الحديد في الجسم لدى السیادات من قبیل بداية الحمل هذا بالإضافة إلى الزيادة في كثافة كرات الدم الحمراء عند الأم وأیضا الإحتیاج المتزايد للجنین من عنصر الحديد أثناء الحمل.

إن الهدف من هذه الدراسة هو تحديد ما إذا كانت هناك علاقة سبیبیة بين نسبة امدنیا نقص الحديد سوءا كانت طفیقة أو متوسطة أو شدیدة أثناء الثلث الأخر من الحمل على حالة الجنین وما إذا كان علاج الامدنیا مفيدا في تخفیف الآثار الفسیولوجیة والمرضیة أم لا.

ويتبارі تتراکم الحديد عن طريق الفم وبسیطة فعالة. المدة واحدة تکلفة منخفضة كما يتم تنظیمها بطریقة طبعیة. أما الحديد عن طريق الحقن فیستخدم في المرضى الذين لا يستطيعون تتراکم الحديد عن طريق الفم أو يحتاجون لجرعات عالية من الحديد، كما أن المرضى الذين يعانون من متلازمة سوء الامتصاص مع نقص شدید في الحديد فربما يستفدو هؤلاء من الحديد عن طريق الحقن. أما المرضى الذين يعانون من امدنیا شدیدة فیجب إعطائهم نقل دم.