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Comparative Studies of the Effect of Different Types of Iron Tonics on Umbilical and Middle Cerebral Blood Flow in Cases of Moderate Iron Deficiency Anemia in Late Second Trimester of Pregnant Women

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Authors' contributions

This work was carried out in collaboration among all authors. Author BME designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors RAEl-D and MFD managed the analyses of the study. Author MME managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Maternal anemia is frequently associated with premature delivery, reduced neonatal weight, infant iron deficiency, neonatal death, and low Apgar scores at 1 min. It is also suspected to reduce the oxygen supply to the growing fetus, leading to the redistribution of fetal blood flow. This study aims to evaluate the effect of the different types of iron medications given to anemic patients on fetal Doppler indices namely umbilical artery and middle cerebral artery in the late second trimester of pregnancy.
Materials and Methods: This cohort prospective study. This study conducted at department of obstetrics and gynecology at Tanta university hospital. Participants consisted of 90 pregnant

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women during their gestational age (20-28 weeks) they were attended or admitted to obstetric unit.divided into 3 groups. Lactoferrin group included 30 cases received 250 mg lactoferrin capsules once daily for 4 weeks. Iron amino acid chelated group included 30 cases received ferrous bis – glycine chelate (FeBC) 15 mg/day for 4 weeks. Ferrous fumarate group included 30 cases received 350 mg dried ferrous fumarate capsules once daily for 4 weeks. Pre-and post-treatment Doppler measurement of umbilical artery and middle cerebral artery parameter compared 4 weeks after the start of treatment for patients whose anemia successfully treated.

Results: Post hoc analysis of maternal serum hemoglobin of the studied groups show insignificant different between the groups. Pre- and Post-treatment follow-up of resistance index (RI) of the studied groups, Pre- and Post-treatment follow-up of pulsatility index (PI) of the studied groups, Post hoc analysis of pulsatility index (PI) of the studied groups and Post hoc analysis of resistance index (RI) of the studied groups show insignificant different between groups.

Conclusion: Based on our results, it can be concluded that cerebral vasodilatation due to severe maternal anemia is a reversible condition that can be corrected through the prompt treatment of anemia. Additionally, the three therapeutics tested in the current study showed a comparable effect in treating maternal anemia, with subsequent improvement of doppler indices.

Keywords: Iron tonics; middle cerebral blood flow; iron deficiency anemia; umbilical artery.

1. INTRODUCTION

Maternal anemia is frequently associated with premature delivery, reduced neonatal weight, infant iron deficiency, neonatal death, and low Apgar scores at 1 min. It is also suspected to reduce the oxygen supply to the growing fetus, leading to the redistribution of fetal blood flow [1]. In the presence of fetal hypoxemia, fetal blood flow becomes centrally distributed to preserve cerebral oxygenation, known as the brain-sparing reflex; this plays a major role in fetal adaptations to oxygen deprivation. Maternal anemia is a hypoxic condition that could be responsible for the redistribution of fetal blood flow; however, no evidence of placental insufficiency has been documented currently [2]. The combination of increased placental resistance and decreased cerebral resistance, measured using Doppler ultrasonography, is quantified by calculating the cerebral-to-umbilical artery resistance ratio [1].

Anemia in general is characterized by a decrease in number of red blood cells or less than the normal quantity of hemoglobin [2,3].

Iron deficiency anemia (IDA) is the condition in which there is anemia due to a lack of iron. IDA develops when available iron is insufficient to support normal red cell production and is the most common type of anemia [4]. The oral route is the first choice to replace iron stores as this allows the normal mechanism of absorption to be used, in addition to being an inexpensive and effective treatment [5]. Lactoferrin (formerly known as lacto-transferrin) is a glycoprotein, and a member of a transferrin family, thus belonging to those proteins capable of binding and transferring iron [6].This study will be conducted to evaluate the effectiveness, safety and acceptability of lactoferrin in comparison to Iron amino acid chelate and ferrous fumarate for the treatment of IDA during pregnancy& evaluate the effect of maternal anemia on fetal Doppler indices namely umbilical artery and middle cerebral artery in the second trimester of pregnancy [2]. This study aims to evaluate the effect of the different types of iron medications given to anemic patients on fetal Doppler indices namely umbilical artery and middle cerebral artery in the late second trimester of pregnancy.

2. SUBJECTS AND METHODS

This cohort prospective study. This study conducted at department of obstetrics and gynecology at Tanta university hospital during the period from January 1, 2019 till August 2020.The study participants consisted of 90 pregnant women during their gestational age (20-28 weeks) they were attended or admitted to obstetric unit. Patients were selected according to inclusion and exclusion criteria: Inclusion criteria Pregnant Women aged between 18-35 years. BMI (18-25) kg/m2 (not overweight or underweight), Fetus is alive and Diagnosed iron deficiency anemia [Hb (10.5-8 g/dl), Serum ferritin < 25ng/dl].

2.1 Exclusion Criteria

- Pregnant women aged < 18 years or > 35 years.
- BMI < 18kg/m2 or > 25 kg/m2.

- Multiple pregnancies.
- Preterm labor.
- Intra uterine fetal growth restriction, oligohydramnios or polyhydramnios.
- Intra uterine fetal death.
- Any major congenital fetal anomalies.
- Maternal diseases like diabetes, pre-eclampsia, bronchial asthma, etc.
- Antepartum hemorrhage
- Any hemoglobinopathies,
- Other types of anemia.
- Anemia need blood trans fusion HB< 7 g/dl.
- Anemic heart failure, anemic murmur
- Serum ferritin alone is highly sensitive test of IDA, iron study (serum iron, iron binding capacity and serum transferritin should not be done indicated if iron overload is suspected or other comorbidities are known or suspected if serum iron level more than 100 microgram/L. Patients were subjected to the following:

- Detailed history taking.
- General examination for measurement of vital sign (temperature blood pressure pulse and respiratory rate) and calculated BMI.
- Obstetric examination.
- Ultrasound for estimation gestational age. amniotic fluid, fetal growth, and Doppler indices. (resistance index, pulsating index and systolic / diastolic ratio of umbilical artery will measure and the resistance index, pulsating index systolic / diastolic ratio and peak systolic velocity of middle cerebral artery was measured and peak variable, the mean of three measurement will record.
- Routine laboratory investigation including complete blood count (CBC), complete urine analysis, random blood sugar (RBS), serum ferritin level. The study included a total 90 pregnant women in late second trimester with Iron deficiency anemia who were enrolled and randomly divided into 3 group.

- Lactoferrin group included 30 cases received 250 mg lactoferrin capsules once daily for 4 weeks.
- Iron amino acid chelated group included 30 cases received ferrous bis – glycine chelate (FeBC) 15 mg/day for 4 weeks.
- Ferrous fumarate group included 30 cases received 350 mg dried ferrous fumarate capsules once daily for 4 weeks.Patients assigned to take the medication orally once daily after lunch patients advised to avoid the intake of tea, coffee, milk product, antacids and calcium preparation within 2 hours Before or after iron capsules. Pre-and post-treatment Doppler measurement of umbilical artery and middle cerebral artery parameter compared 4 weeks after the start of treatment for patients whose anemia successfully treated.

2.2 Statistical Analysis

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002.The criteria used for sample size calculation (n>33) were 95% confidence limit, 80%power of the study.

Analysis of data were performed by SPSS v25 (SPSS Inc., Chicago, IL, USA).Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). Pearson's rho coefficient of correlation (r) was used to calculate the degree of correlation between 2 variables. P value < 0.05 was considered significant.

3. RESULTS

As regards demographic data,mean 26.13 with (SD) (4.36) years of age of the current study population. The mean BMI was 30.09 with (SD) (2.10). Most cases were housewives (62.5%) and from rural areas (72.5%) Table 1.

According to the operative details of the studied sample, Post hoc analysis of maternal serum hemoglobin of the studied groups show insignificant different between the groups Table 2. Pre- and Post-treatment follow-up of resistance index (RI) of the studied groups in significant as shown in Fig. 1, according to Pre- and Post-treatment follow-up of pulsatility index (PI) of the studied groups was in significant also as shown in Table 3.

According to Post hoc analysis of pulsatility index (PI) of the studied groups was in significant difference between groups as in Fig. 2.

According to Post hoc analysis of resistance index (RI) of the studied groups show insignificant different between groups Table 4.

Table 1. Demographic characteristics of the studied groups

		Lactoferrin group (n= 30)	Iron amino acid group (n= 30)	Ferrous fumarate group (n= 30)	p
Age		24.80 ± 4.180	25.07 ± 3.600	25.80 ± 4.483	0.622
BMI		23.45 ± 0.996	23.16 ± 1.013	23.45 ± 0.996	0.439
Occupation	Housewife	56.7% (17)	63.3% (19)	56.7% (17)	0.832
	Worker	43.3% (13)	36.7% (11)	43.3% (13)	
Residency	Urban	26.7% (8)	33.3% (10)	26.7% (8)	0.805
	Rural	73.3% (22)	66.7% (20)	73.3% (22)	

Data is expressed as mean and standard deviation or as percentage and frequency. P is significant when < 0.05

Table 2. Post hoc analysis of demographic characteristics of the studied groups

	Lactoferrin group and Iron amino acid group	Lactoferrin group and Ferrous fumarate group	Iron amino acid group and Ferrous fumarate group
Age	0.966	0.614	0.769
BMI	0.506	1	0.506
Occupation	> 0.05	> 0.05	> 0.05
Residency	> 0.05	> 0.05	> 0.05

P is significant when < 0.05

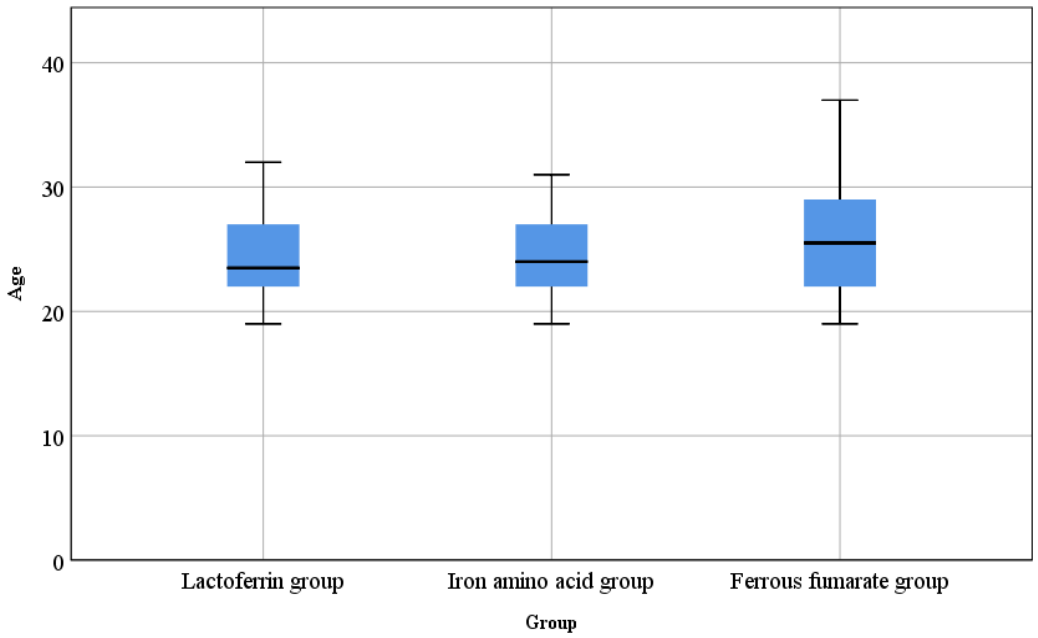

Fig. 1. Age distribution in the studied groups

Table 3. Obstetric history of the studied groups

	Lactoferrin group (n= 30)	Iron amino acid group (n= 30)	Ferrous fumarate group (n= 30)	p
Number of Gestations	2.53 ± 0.973	2.47 ± 0.900	2.07 ± 0.740	0.089
Gestational age	26.17 ± 1.510	25.50 ± 1.503	26.17 ± 1.487	0.145

Data is expressed as mean and standard deviation. P is significant when < 0.05

Table 4. Basal, post-treatment and change in maternal serum hemoglobin of the studied groups

Maternal hemoglobin	Lactoferrin group (n= 30)	Iron amino acid group (n= 30)	Ferrous fumarate group (n= 30)	p
Basal	9.16 ± 0.487	9.10 ± 0.597	8.86 ± 0.489	0.074
After treatment	10.29 ± 0.280	10.21 ± 0.318	10.11 ± 0.298	0.064
Change	1.13 ± 0.259	1.12 ± 0.320	1.25 ± 0.249	0.143

Data is expressed as mean and standard deviation. P is significant when < 0.05

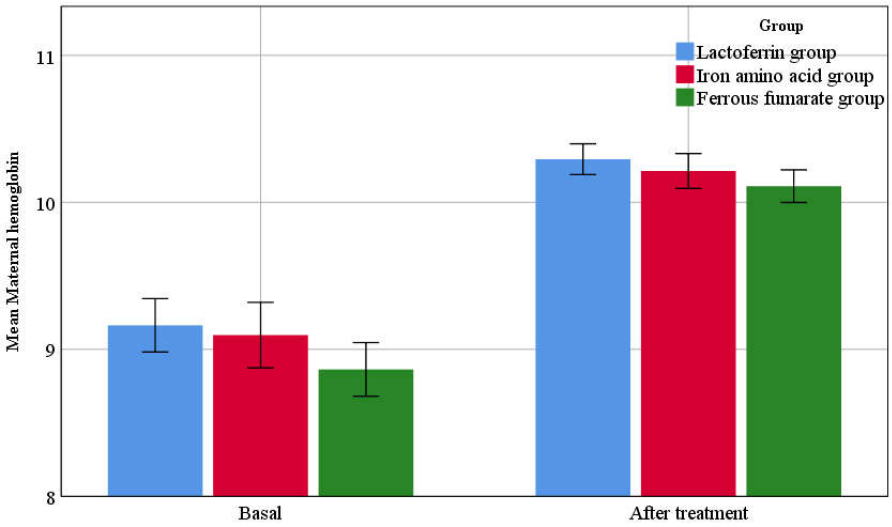

Fig. 2. Basal, post-treatment maternal serum hemoglobin of the studied groups

4. DISCUSSION

The overwhelming majority of anemia in reproductive-age women is due to low or absent iron stores, making iron deficiency anemia the world's most common anemia due to a micronutrient deficiency [7] Iron deficiency is defined as a condition in which there are no mobilizable iron sores, resulting from a long-term negative iron balance and leading to a compromised supply of iron to the tissues. Finally, the non-significant negative consequence of ID is anemia, usually microcytic hypochromic in nature [8].

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 [9].

IDA should be treated by replenishing body iron deficits either by oral or parenteral administration of iron. The high absorption capacity that develops in pregnancy, especially for those with iron deficiency, favors for treatment of IDA with the oral iron forms [10].

This study was conducted at Tanta university Hospitals aiming to evaluate the effect of the different types of iron medications (ferrous fumarate, iron amino acid chelate, and lactoferrin) given to anemic patients on fetal Doppler indices namely umbilical artery and middle cerebral artery in the second trimester of pregnancy. To the best of our knowledge, there is a paucity of studies comparing the same three regimens regarding their effect on anemia and doppler indices, and this is one of the strengths of the current study .

We included a total of 90 cases who were randomly divided into three groups; lactoferrin, amino acid chelate, and ferrous fumarate. The mean age of the included cases was 24.8, 25.07, and 25.8 in the three groups respectively (p = 0.622).

Another study confirmed our findings regarding age as the age of pregnant participants with anemia ranged between 26.12 and 26.55 years

[11], which is near to our findings. Also, a previous meta-analysis reported that about 91.3% of females presented with anemia had age between 14 and 34 years [12].

In the current study, housewives represented 56.7, 63.3, and 56.7% of cases in the three groups respectively. This is in agreement with the previously mentioned meta-analysis which reported that 61.1% of pregnant females presenting with anemia were housewives (unemployed) [13]. This should raise concern about the risk of iron deficiency anemia in this population.

In our study, most of the included cases had rural residence, as these ladies formed 73.3, 66.7, and 73.3% of cases in the three groups respectively, without any significant difference between the two groups (p = 0.805).

Previous studies have shown that women having poor living standards and low income of is associated with anemia during pregnancy [14]. Poor income leads to limited access to nutritious diets and is associated with poor eating habits that might lead to anemia. A study in Ethiopia showed that women with low income were more anemic than women with higher income [15,16] Furthermore, the education level between rural and urban areas could explain that finding. Educated pregnant women have better income and eat nutritious food and hence do not get nutritional anemia [17]. A study in Ethiopia also reported higher prevalence of anemia among pregnant women who had no education [18]. Based on these data, further health programs should be conducted to target pregnant ladies in the Egyptian rural areas.

Overall, our study revealed no significant difference between the three groups as regard demographics, baseline laboratory and radiological parameters. This should nullify bias that might have skewed the results in favor of one group over another one.

In the current study, no significant difference was detected between the three groups as regard pre- or post-treatment hemoglobin level. Also, hemoglobin levels increased in the three study groups. Another study that handled the same drugs tested by us reported that there was no statistically significant difference between the three groups regarding hemoglobin levels before treatment (mean values = 11.25, 11.18, and 11.26 in ferrous sulphate, amino acid chelated iron, and lactoferrin groups respectively – p = 0.448). After 4 weeks of therapy heamoglobin level increased in the three groups however the difference between them was statistically insignificant (12.45, 12.6, and 12.9 in the same groups respectively - p=0.6) [19]. This is in accordance with our findings.

In our study, Iron amino acid was successful in increasing maternal hemoglobin from 9.1 up to 10.21 gm/dl after treatment. In agreement with our findings, Makled and his associates reported that hemoglobin increased from 9.2 up to 11.6 gm/dl after treatment [20]. Furthermore, another study reported that iron amino acid therapy was led to an increase of 1.6 gm/dl after 12 weeks of treatment (from 10.14 up to 10.98 gm/dl) [21].

In the current study, oral lactoferrin therapy resulted in a significant increase in hemoglobin levels from 9.16 up to 10.29 gm/dl after treatment. Similarly, Nappi et al. reported that lactoferrin therapy resulted in an increase in hemoglobin levels from 10.1 up to 11.2 gm/dl after treatment [22]. Besides, other authors reported that oral lactoferrin therapy increased hemoglobin levels from 8.15 up to 10.41 gm/dl after treatment [23].

In our study, treatment with ferrous fumarate increased hemoglobin levels from 8.86 up to 10.11 gm/dl after treatment. Likewise, another study reported that ferrous fumarate therapy was associated with a significant rise in hemoglobin levels from 9.3 up to 11.3 gm/dl after treatment (124). Nasr et al. also reported that ferrous salt administration led to an increase in hemoglobin levels from 11.25 up to 12.45 gm/dl after therapy [24].

On post-hoc analysis of our groups, there was no significant difference between lactoferrin and amino acid groups regarding the same parameters either before or after treatment (p = 0.876 and 0.556 respectively). Before treatment, Hb had mean levels of 9.16 and 9.10 gm/dl, which increased up to 10.29 and 10.21 after treatment in both groups respectively .

Our results were concordant with another previously performed research, found that Hb level showed significant improvement after 30 days in comparison to that before treatment (11.5 vs. 12.6, p < 0.05) among the group of patients who received bovine lactoferrin [25]. Additionally, Ghada et al. examined the effect of different oral iron therapies in an experimental study

performed on rats. The authors reported that due to its high bioavailability, lower doses of ferrous IAAC were required in IDA treatment when compared to inorganic iron salts [26]. Both of the previous studies support our findings regarding the efficacy of thee two therapeutics. Unluckily, the existing literature is poor in studies comparing these two drugs in the management of such health problem.

In the current study, there was no significant difference between lactoferrin and ferrous fumarate as regard both pre- and post-treatment levels ($p = 0.076$ and 0.051 respectively). It increased from 9.16 up to 10.29 gm/dl in the lactoferrin group versus 8.86 and 10.11 gm/dl in the ferrous fumarate group respectively.

Another study reported that oral ferrous fumarate led to an increase in Hb levels from 9.42 gm/dl at admission up to 9.79 after 10 days, and 11.72 gm/dl at delivery. This denotes that oral ferrous fumarate is an effective management plan for maternal anemia during pregnancy which supports our findings [27].

Moreover, the results of our study is in accordance to Nappi et al who compared the efficacy and tolerability of oral bovine lactoferrin and ferrous salts in pregnant women with iron deficiency anemia on 100 pregnant women they found that for both types of oral iron, Hb level was significantly increased compared to pretreatment levels but with no significant difference between both types of iron [28].

Conversely, Hemeda et al. reported that lactoferrin was more efficient compared to ferrous fumarate in improving hemoglobin levels during pregnancy ($p < 0.05$) despite the non-significance before treatment ($p = 0.8$). It had mean values of 10.44 and 10.1 after 1 month, and 11.6 and 11 gm/dl after 2 months in the lactoferrin and ferrous fumarate groups respectively [6].

Additionally, Fawzy et al. reported that lactoferrin was associated with a more significant rise in hemoglobin levels compared to ferrous salts in spite of the non-significant difference prior to treatment. After treatment, hemoglobin levels had mean values of 11.4 and 10.2 in both groups respectively after being 8.9 and 9.2 gm/dl before treatment [29].

In the current study, when iron amino acid chelate was compared to the ferrous fumarate group, there was no significant difference between the two groups regarding either of basal or post-treatment hemoglobin levels ($p = 0.205$ and 0.378 respectively) .

Likewise, Fouad et al. in 2013 reported that there was no significant differences in any of the hematological outcomes for women receiving iron chelate, ferrous sulfate or placebo [30]. Moety et al. reported that both iron amino acid chelate and ferrous fumarate were effective in the correction of hemoglobin in pregnant cases associated with anemia, as hemoglobin levels increased up to 10.98 and 10.84 after 3 months of treatment, with no significant difference between the two groups ($p = 0.052$). Of note, there was no significant difference between the two groups before treatment [31]. This supports our findings.

On the contrary, Abdel-Lah et al. reported the superiority of iron amino acid chelate over ferrous sulfate and ferrous gluconate in terms of rapid improvement of hemoglobin level in pregnant women with IDA [32].

When it comes to serum ferritin levels in our study, it showed no significant difference when comparing the three groups neither before or after treatment ($p = 0.091$ and 0.234 respectively). On post-hoc analysis, there was no significant difference between lactoferrin, and iron chelate, as pretreatment mean values were 9.4 and 11.5 while post-treatment values were 15.59 and 17.62 ng/dl in both groups respectively.

Szarfarc et al., reported that ferrous chelate therapy led to a significant rise in serum ferritin [33]. In addition, another study reported that lactoferrin led to a significant increase in ferritin level from 12 up to 29 ng/ml [34]. Both of the previous studies confirm our findings.
In the current study, no significant difference was noted between the lactoferrin and ferrous fumarate groups regarding basal and post-treatment ferritin levels ($p = 0.921$ and 0.997 respectively). It had mean values of 9.4 and 8.93 before treatment, versus 15.95 and 15.49 ng/dl in both groups respectively .

On the contrary, in the study conducted by Hemeda et al., lactoferrin was more efficient in improving ferritin levels in anemic pregnant ladies ($p < 0.001$). After 1 month, it increased up to 20.12 and 18.5, while it increased up to 31.39 and 27.37 after 3 months in the lactoferrin and ferrous fumarate respectively [6].

Fawzy and his associates also reported that lactoferrin was also superior to ferrous sulphate in the correction of ferritin levels ($p < 0.001$). It increased from 9.4 up to 12.9 in the lactoferrin group, whereas it increased from 10 up to 15.5 ng/dl in the ferrous salt group [35].

However, the efficacy of ferrous salt reported in our study was confirmed by another research group study conducting similar methodology, found that serum ferritin level showed significant increase after 30 days in comparison to that before treatment (27 vs. 12, $p < 0.05$) among the group of patients who received ferrous sulphate [36].

In the current study, both iron chelate and iron fumarate had comparable results when comparing both pre- and post-treatment ferritin levels ($p = 0.098$ and 0.285 respectively). Pre-treatment mean values were 11.5 and 8.93 ng/dl which increased up to 17.62 and 15.49 ng/dl in both groups respectively.

Likewise, other authors reported no significant difference between iron amino acid chelate and ferrous fumarate regarding 4-month serum ferritin levels, which increased up to 40.3 and 38.47 ng/ml in both groups respectively ($p = 0.69$) [37].

Contrarily, Kamdi and Palkar reported that iron amino acid chelate resulted in a significantly higher rise in hemoglobin and ferritin levels on day 14 and 28 ng/dl when compared to ferrous salts [38]. The discrepancies in post-treatment ferritin levels could be explained by the different follow up periods and treatment durations between these studies.

When it comes to UA and MCA Indies, no significant difference was detected between the three groups neither before or after medical treatment ($p > 0.05$). Both PI and RI showed improvement with the resolution of anemia. As there was no significant difference between the three study groups in the degree of anemia improvement, it was expected to detect no significant difference between doppler findings. This may support the significant correlation between the degrees of hemoglobin improvement with DI normalization. Nevertheless, this concept needs further evaluation.

In the presence of fetal hypoxemia secondary to maternal anemia, fetal blood flow becomes centrally distributed to preserve cerebral oxygenation, known as the brain-sparing reflex; this plays a major role in fetal adaptations to oxygen deprivation [39].

In our study, MCA RI decreased in the three groups after treatment when compared to their pre-treatment values. It decreased from 0.7, 0.72, and 0.73 before treatment down to 0.56, 0.57, and 0.57 after treatment in the three groups respectively. In line with our findings, Another study reported that MCA RI decrease from 0.87 at admission down to 0.78 after treatment [40].

On the other hand, Ali et al. reported that MCA RI showed a significant increase after the treatment of anemia ($p = 0.001$), as it increased from 0.67 up to 0.72 after treatment [41] In another study, when the middle cerebral artery resistance index of the anemia group at admission was compared with the same group after 4 weeks of treatment, a significant increase was observed. This change could be the result of severe anemia-induced fetal cerebral vasodilatation being corrected following treatment [2].

Additionally, Janjgir and his associates reported that MCA RI showed a significant increase compared to baseline after management of anemia ($p = 0.001$). It increased from 0.82 before treatment up to 0.87 twenty days after treatment [42].

In our study, MCA PI decreased in the three groups from 1.42, 1.47, and 1.35 down to 1.38, 1.4, and 1.3 after treatment. Ali and his associates reported that there was no significant difference between MCA pulsatility indices measured before and after anemia treatment ($p = 0.573$). It had mean values of 1.42 and 1.4 in these time intervals respectively [43].

In the current study, MCA S/D ratio decreased after treatment in the three groups, as their mean values decreased from 3.18, 3.28, and 3.12 before treatment down to 306, 3.13, and 2.95 after treatment.

Another study reported that MCA systolic/diastolic ratio was significantly decreased after treatment of anemia ($p = 0.002$), as it decreased from 3.73 before treatment down to 3.29 after treatment [44]. Also, Amin and his associates reported that MCA S/D ratio showed a significant decrease after anemia treatment (4.5 vs. 3.59 respectively) [45]. Both of the

previous studies are in accordance with our results.

In our study, UA RI expressed lower values after the correction of anemia compared to their pre-treatment levels. It decreased from 0.67, 0.69, and 0.69 before treatment in the three groups respectively down to 0.57 in the three groups after treatment.

In 2016, other authors reported that UA RI showed a significant decrease after treatment of anemia ($p = 0.001$). It decreased from 0.63 before treatment down to 0.57 after treatment [46]. Another study also reported that the treatment of anemia was associated with a significant decrease in UA RI, which decreased from 0.63 at admission down to 0.57 after treatment s [47].

In addition, Janjgir et al. also reported that UA RI decreased from 0.68 before treatment down to 0.57 twenty days after treatment of anemia ($p < 0.001$) (138). Ali and his colleagues denied any significant difference regarding UA PI before and after treatment of anemia ($p = 0.059$). It had mean values of 0.99 and 0.94 before and after treatment respectively [48].

In our study, UA PI decreased from 1.01, 1.08, and 0.96 before treatment down to 0.96, 0.99, and 0.91 after treatment in the three groups respectively. Ali et al. confirmed our findings as the same parameter as it decreased from 0.99 at admission down to 0.94 after treatment [49]. However, that change was statistically insignificant ($p = 0.059$) .

In the current study, UA S/D ratio decreased from 2.51, 2.65, and 2.47 before treatment down to 2.38, 2.42, and 2.31 after treatment in the three groups respectively .

In agreement with our findings, Ali et al. reported a significant reduction of UA systolic/diastolic ratio after treatment of anemia ($p = 0.002$). It had mean values of 2.68 and 2.4 before and after treatment respectively [50]. Amin et al. also reported that UA S/D ratio showed a significant decrease after anemia treatment compered to admission values (2.59 vs. 2.24 respectively) [51].

Our study has several limitations, first of all, the relatively small sample size. Also, it was a single center study. The correlation between hemoglobin levels, ferritin levels, along with doppler indices should have been performed. In addition, more cases with severe anemia and parenteral iron therapy should have been included as well to evaluate doppler changes between these two different administration methods. These drawbacks should be covered in the upcoming studies.

5. CONCLUSION

Based on our results, it can be concluded that cerebral vasodilatation due to severe maternal anemia is a reversible condition that can be corrected through the prompt treatment of anemia. The present study also demonstrated that, in cases with severe maternal anemia, the fetus is in a compromised state and that close monitoring of the fetal umbilical and cerebral circulations using doppler US allows fetal vascular responses and recovery to be measured. Additionally, the three therapeutics tested in the current study showed a comparable effect in treating maternal anemia, with subsequent improvement of doppler indices.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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