Evaluation of Anemia in Obese Pregnant Mothers Using Transferrin Receptor Index (TRI) and Hepcidin and Finding its Relation to Iron Stores of the Newborn

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Abstract

Aim: The study aimed to analyze the cause of anemia associated with pre-pregnancy maternal obesity and to clarify relationship between obesity, inflammation and anemia and identify their effect on newborns iron stores.

Patients and Methods: The study was conducted on (39) full term pregnant women, randomly selected from Al-Zahraa hospital. Categorized to; Group 1 (17) obese anemic and Group 2 (13) lean non anemic. Corresponding newborns of group 1 and 2 only where studied for their iron stores and Group 3 (9) obese non anemic pregnant.

Results: Comparing group 1, 2 revealed significant differences in median values of Hepcidin ($p<0.001$), serum iron ($p<0.001$). No significant differences in Iron stores among newborns. Comparing group 1, 3 revealed no significant differences in Hepcidin ($p=0.092$).

Using TRI (transferrin receptor index) cutoff=2.2 group 1 participants were categorized to; Group 1A and Group 1B. Their comparison revealed that there were significant differences in median values of, maternal TRI ($p=0.001$), maternal TSI ($p=0.001$). No significant differences in Hepcidin, nor Iron stores of infants.

There was significant correlations seen between BMI and Hepcidin ($r=0.051$, $p=0.002$), and Hb ($r=-0.350$, $p=0.029$). Hepcidin was correlated to CRP ($r=0.489$, $p=0.002$), SF ($r=0.391$, $p=0.018$), S.iron ($r=-0.392$, $p=0.018$). Fetal ferritin was correlated to maternal CRP ($r=-0.376$, $p=0.041$).

Conclusion: Study showed that TRI cutoffs showed powerful potential in estimating prevalence and differentiating ID, IDA and AI in pregnant obese mothers. Adiposity was associated with significant elevation of inflammatory marker Hepcidin. Fetal iron stores did not correlate to maternal anemia. Fetal ferritin correlated to maternal CRP.

Key Words: Hepcidin – Transferrin Receptor Index (TRI) – TSI.

Introduction

IRON Deficiency Anemia (IDA) is a common disease affecting human health. Pregnant women and infants belong to the population of those at high risk for IDA [1].

Adipose tissue contributes to inflammatory process by secreting pro-inflammatory adipokines [2]. So determining iron status in obese individuals is complicated because low-grade chronic inflammation affects several markers of iron status [3]. Body Mass Index (BMI) defines (18.50-24.99 kg/m$^2$) as normal, while (30.00-39.99kg/m$^2$) as obese [4].

Hepcidin represents the main regulator of intestinal iron absorption and macrophage iron release. Hepcidin increases in humans in inflammatory disorders, causing anemia of infection [2]. However there was a question of whether the alterations in iron are due to inflammation mediated deficiency or true iron deficiency [5].

Confirmation of a true iron deficiency associated to inflammation is of clinical importance to prevent useless treatment. In addition, iron therapy for patients with Anemia of Inflammation (AI) (previously called anemia of chronic disease) is controversial since iron is an essential nutriment for proliferation of microorganisms that could increase infectious risk [6].

Common methods of IDA detection have disadvantages; poor stability of serum iron (S.iron) and transferrin level is decreased in infection or impaired liver function. Serum Ferritin (SF) is acute phase protein susceptible to inflammation, pregnancy, lactation, and infant growth period [1].
The role of the transferrin receptor is to insert iron into cell center. Soluble Transferrin Receptor (sTfR) is formed in result of proteolytic disintegration the whole cellular receptor. It has been documented that an intensification of erythropoiesis and iron status had the biggest influence on soluble transferrin receptor levels [7].

The sTfR is considered not to be affected by the acute-phase response. However, in addition to reflecting erythroblast transferrin receptor expression (sTfR is indicative of functional tissue Iron Deficiency (ID), sTfR in plasma is also a general marker of erythropoiesis. Therefore, assessment of iron status using sTfR may be confounded by factors other than iron that affect erythropoiesis, such as age, pregnancy, and hemolytic diseases [8].

The sTfR was used in distinguishing between AI and IDA, because serum sTfR concentration was expected to rise in IDA, but not in AI [9]. But recently it was proposed that sTfR expression on cells could be also affected by inflammation, which negatively affects the sensitivity of sTfR levels to indicate true ID in inflammatory diseases [6].

A calculated ratio of sTfR/log ferritin index (transferrin receptor index: TRI) was developed as an accurate indicator of true iron deficiency in patients with inflammation [10]. The use of TRI, takes advantage of the reciprocal relationship between two variables influenced by iron depletion (T sTfR and ^ferritin concentrations) [11].

During pregnancy, substantial amounts of iron are trafficked across the placenta to endow the neonate with ~300mg of iron at birth. Neonatal body iron content at term (75mg/kg) is nearly twice that of an adult female. Because there are no physiologically regulatable routes of iron loss from the fetus body, iron transport across the enterocyte is limited even in the face of high iron demands [12]. Studies proved the importance of neonatal iron status at birth on subsequent cognitive and behavioral outcomes of the child [3].

In pregnancy, IDA can not only affect the health of the pregnant woman, but can cause a lack of iron storage in the fetal liver, resulting in a greatly increased possibility of Subclinical Iron Deficiency (SID) and IDA occurrence in infants [1].

The aim of this study was to differentiate maternal anemia associated with obesity using TRI [sTfR/log F] and hepcidin and also finding out its implications on fetal iron stores.

Patients and Methods

A comparative case control study, pre-pregnancy BMI [weight (kg)/height (m)^2], was based on self-reported pre-pregnancy weight and height.

The study was conducted on randomly selected (39) full term pregnant women who gave birth from March – August 2015 in the Al-Zahraa Hospital.

All qualifiers age was between 25-35 and were taking iron supplementation during pregnancy.

Pregnant women were divided into 3 groups according to BMI and presence of anemia:

Group 1: (17) case group of pregnant obese anemic with pre-pregnancy BMI mean=31.96 kg/m^2 and Hemoglobin (Hb) mean=9.453 gm/dL.

Group 2: (13) control group of pregnant lean non anemic women with pre-pregnancy BMI mean=23.24kg/m^2 and Hb mean= 11.5 6 gm/dL.

The 30 newborns delivered by women in each group were included in corresponding offspring case and control groups, respectively.

Group 3: (9) Pregnant obese non anemic women with pre-pregnancy BMI=32.967kg/m^2, and Hb mean= 11.69gm/dl and. But their newborns were not included in the study.

Exclusion criteria:

Chronic illness, preterm labor and morbid obesity BMI >40kg/m^2 to exclude their co morbidities.

All the included (39) mothers were subjected to:
I- Complete history taking.
II- Systemic examination.
III- Lab examinations:

All Mothers were examined for (I) CBC (II) sTfR, (III) Serum ferritin. (IV) S.iron (V) TIBC (VI) hepcidin (VII) Latex CRP.

Only apparently healthy, CRP (–ve) with Hb >10.5 were included in the control Group (2).

All 30 neonates of mothers in Group (1) and (2) cord blood was examined for serum (I) sTR (II) ferritin and TSI and TRI were calculated.

An informed consent was obtained before enrollment in the study.

Instruments and biochemical analysis:

The CBC was done using (Sysmex, KX-2 1N, hematological analyzer). Serum ferritin detection
was performed using chemoluminesces. SF kit (Cobas.E411 Roche); Both S.iron and Total Iron Binding Capacity (TIBC) by chemoluminesces (Cobas.C 311, Roche). Transferrin Saturation Index (TSI) was calculated as [serum iron/TIBC X100]. Enzyme-Linked Immunoassay (ELISA) was done for sTfR (R & D Systems, USA). The TRI was calculated by [sTfR/log ferritin]. Hepcidin was measured by ELISA.

Reference ranges used were >10.5g/dl for Hb; 33-193ug/dl for S.iron; 240-440ug/dl for TIBC; and 13-307ug/l for SF; 5-32.4ng/ml for Hepcidin; 0.74-2.39mg/l for sTfR.

In our study TRI was used to identify participants with ID (TRI 1.80-2.20), IDA (TRI >2.20) by ELISA. The TRI was calculated by [sTfR/log ferritin]. Hepcidin was measured by ELISA.

Statistical methods:
Data were statistically described in terms of mean ± standard deviation (± SD), median. Comparison of numerical variables was done using Mann Whitney U test. Correlation between various variables was done using Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. \( p \)-values <0.05 considered statistically significant. Statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results
Study was conducted on (39) full term pregnant women, divided to 3 groups: Group 1 (17) obese anemic and Group 2 (13) lean non anemic. Corresponding newborns of Group 1 and 2 only where studied for their iron stores and Group 3 (9) of obese not anemic pregnant.

Comparison between maternal Groups (1) and (2) revealed significant increases within median values of BMI (\( p < 0.001 \)), Hepcidin (\( p < 0.001 \)) in Group 1 while there was significant decrease in mean of Hb (\( p < 0.001 \)) and S.iron (\( p < 0.001 \)). There were no significant differences as regard maternal iron stores indicators; TRI (\( p = 0.786 \)), sTR (\( p = 0.194 \)), SF (\( p = 0.675 \)). There were no significant differences as regard TSI (\( p = 0.137 \)), fetal ferritin (\( p = 0.155 \)), Fetal sTfR (\( p = 0.174 \)), Fetal TRI (\( p = 0.167 \)).

Comparison between maternal Groups (1) and (3) revealed significant difference in maternal sTfR (\( p = 0.019 \)), serum iron (\( p < 0.001 \)) and hemoglobin (\( p < 0.001 \)) but there was no significant differences seen in BMI (\( p = 0.291 \)), Hepcidin (\( p = 0.092 \)), maternal ferritin (\( p = 0.647 \)), maternal TRI (\( p = 0.319 \)), and maternal TSI (\( p = 0.186 \)).

In our study we used a high cutoff for TRI to categorize the anemic participants in Group 1, this was proposed by Cheng et al., who stated that TRI was used to identify anemic participants with IDA (TRI >2.20), AI + IDA (TRI 1-2.2) and AI (TRI <1.00) [5]. According to TRI cutoff=2.2, anemic participants of Group 1 were categorized to Group 1A (8) with TRI >2.2 and Group 1B (9) with TRI <2.2.

Comparison between maternal Groups (1A) and (1B) revealed significant differences in median levels of maternal TRI (\( p = 0.001 \)), maternal SF (\( p = 0.00 1 \)), maternal sTFR (\( p = 0.001 \)) and maternal TSI (\( p = 0.001 \)). There were no significant differences seen in BMI (\( p = 0.334 \)), hepcidin (\( p = 0.149 \)), serum iron (\( p = 0.147 \)), fetal ferritin (\( p -value 0.068 \)), fetal sTFR (\( p = 0.336 \)) and fetal TRI (\( p = 0.268 \)).

As control Group 2 was apparently non anemic, in our study TRI was used to identify participants with subclinical ID using TRI cut off=1.8, so ID participants had (TRI 1.80-2.20), and while true non anemic participants had (TRI 1-1.8). So (Group 2) was categorized according to TRI into; 2A (6 patients) with TRI >1.8 and 2B (7 patients) with TRI <1.8.

Comparison of Group 2A and 2B revealed significant differences in median values of hepcidin (\( p = 0.019 \)), maternal SF (\( p = 0.003 \)), serum iron (\( p = 0.007 \)), maternal TSI (\( p = 0.004 \)) and maternal TRI (\( p = 0.003 \)). There was no significant differences in; BMI (\( p = 0.367 \)), fetal ferritin (\( p = 0.886 \)), fetal sTFR (\( p = 0.830 \)) and fetal TRI (\( p = 1.000 \)).

Correlation studies of whole participants (n=39) revealed that maternal BMI showed significant positive correlation with maternal hepcidin (\( r = 0.05 1 \), \( p = 0.002 \)), and significant negative correlation with maternal Hb (\( r = -0.3 50 \), \( p = 0.029 \)).

There was significant positive correlation between maternal hepcidin and maternal CRP (\( r = 0.489 \), \( p = 0.002 \)), and between maternal hepcidin and maternal SF (\( r = 0.3 91 \), \( p = 0.18 \), but there was significant negative correlation between hepcidin and S.iron (\( r = 0.3 92 \), \( p = 0.018 \)).

There was significant negative correlation between fetal ferritin and maternal CRP (\( r = -0.3 76 \), \( p = 0.041 \)).
There was significant positive correlation between fetal sTR and fetal TRI \( (r=0.970, p=0.000) \), but no significant correlation was seen between sTR and Fetal ferrtin \( (r=-0.290, p=0.119) \). There was significant negative correlation between fetal TRI and fetal ferrtin \( (r=-0.462, p=0.010) \), while positive significant correlation was seen between fetal TRI and fetal sTR \( (r=0.970, p=0.000) \).

There was significant positive correlation between fetal sTR and fetal TRI \( (r=0.970, p=0.000) \), but no significant correlation was seen between sTR and Fetal ferrtin \( (r=-0.290, p=0.119) \). There was significant negative correlation between fetal TRI and fetal ferrtin \( (r=-0.462, p=0.010) \), while positive significant correlation was seen between fetal TRI and fetal sTR \( (r=0.970, p=0.000) \).

Fig. (1): Incidence of IDA was 52.9% using TRI >2.2 criterion while the incidence of IDA using traditionally used ferritin < 13 criterion was 29.4% in Group 1 of anemic obese mother.

Fig. (2): Comparison between Group 1A and 1B revealed significant differences in median values of TRI, SF, TSI and non significant differences in median values of hepcidin.

Fig. (3): Comparison between Group 2A and 2B revealed significant differences in median values of hepcidin, TRI, SF, TSI.

**Discussion**

Comparison between maternal Groups (1) and (2) revealed significant increase in median values of BMI \( (p<0.001) \), Hepcidin \( (p<0.001) \) in Group 1 as median values of Hepcidin were 18.400ng/ml, 5.000ng/ml in Group 1, 2 respectively while there was significant decrease in median values of Hb \( (p<0.001) \) and S.iron means \((p<0.001) \) in Group 1 with median value of iron=26.00ug/dl in Group 1 while in Group 2=61.00ug/dl. Being less than reference ranges in Group 1.

This data was in agreement with reported data that Hepcidin being significantly elevated in obese compared to lean women and that in obesity chronic inflammation leads to iron deficiency as a result of long-term decreased iron absorption and unregulated iron loss. This is similar to what is seen with the AI [13].

Also our data was in line with Garcia-Valdes et al study which stated that obese pregnant women have a greater risk of iron deficiency and that Hepcidin may be the factor as Hepcidin levels were higher in obese than normal women at the end of the pregnancy [14].

It was said that the association between obesity and low iron status was independent of iron intake or other dietary factors and that adiposity in young women predicted not only lower iron intake but also reduced response to iron supplementation, possibly due to increased Hepcidin production [3,15].
There were no significant differences between Group (1) and (2) in iron stores indicators; TRI ($p=0.786$), sTfR ($p=0.194$), SF ($p=0.675$), TSI ($p=0.137$), but still our data was in line with Cheng et al., [8] who observed lower hepcidin concentrations in females with lower iron stores. As the median values of iron stores indicators in Group (1) who had higher hepcidin levels were; [TRI median=1.320, Maternal sTfR median=2.07mg/l, maternal SF median=27.00mg/L], was higher than indicators in Group 2 with the lower hepcidin levels; [TRI median=1.070, maternal SF median=21.55ug/L, maternal sTfR median=1.91 mg/l].

Hepcidin elevation in obese participants could be explained by Challier et al., who stated that obesity and pregnancy are associated with inflammatory changes and that the placenta develops exaggerated inflammation in response to obesity with accumulation of macrophages and increased expression of interleukin-1 (IL-1), tumor necrotizing factor (TNF), IL-6 [16]. Those pro-inflammatory cytokines are known with their stimulatory effect on hepcidin. Also SF expression in hepatocytes, macrophages, and adipocytes is induced by IL-1β and TNF-α, known to be upregulated in obesity [17].

There were no significant differences in fetal ferritin ($p=0.155$), fetal sTfR ($p=0.174$), fetal TRI ($p=0.167$). This data was in agreement with Liu et al., study which revealed no significant difference in newborns of anemic and control mothers, however, as they followed-up the infants they found significant differences in sTfR levels of the 6-month-old infants compared with controls ($p<0.001$) even if the mother had mild IDA during pregnancy [1].

McArdle et al., claimed that in case of maternal iron deficiency, the placenta can protect the fetus significantly [18]. This is corresponding to data given by a study done by Garcia-Valdes et al., which proved that the placenta responds to decreased maternal iron status by increasing expression of placental transferrin receptor (pTFR1) and that maternal iron deficiency is minimized in the fetus by the resulting increase of iron transfer at the expense of maternal iron stores [14].

Corresponding to our data Cao et al., found that placental LDL receptor-related protein 1 (LRP1) the receptor for heme and its plasma-binding protein hemopexin (Hx) was upregulated in maternal/neonatal Fe insufficiency and was associated with placental heme exporter Feline Leukemia Virus C Receptor 1 (FLVCR1) which was proven to have a role in placental heme Fe utilization in supporting fetal Fe demands [19].

As we wanted to study differences between obese and non-anaemic we compared maternal Groups (1) and (3) and the comparison revealed significant differences seen in maternal sTfR ($p=0.019$), serum iron ($p<0.001$) and Hb ($p<0.001$) but no significant difference seen in hepcidin ($p=0.092$) but still higher median. Levels of 18.40ng/ml were found in Group 1 of anemic while Group 3 was associated with lower median=13.00ng/ml which may indicate that increased hepcidin may play a role in presence of anemia. There was no significant difference in maternal ferritin ($p=0.647$), maternal TRI ($p=0.319$), maternal TSI ($p=0.186$). There was no significant difference in BMI ($p=0.291$) between Group (1) and (3).

Rimon et al., performed a prospective controlled study in 49 patients with chronic disease. BM confirmed iron deficiency in all patients. Only 8 patients could be diagnosed by ferritin test. In contrast, the TRI disclosed ID in 43 of 49 patients, thus increasing the sensitivity from 16% to 88% [21]. Similar results were shown in a population of anemic patients with rheumatoid arthritis in whom iron deficiency diagnosis was confirmed by iron staining in the bone marrow. According to the authors, a single value of TIR-F index helps to elucidate differential diagnosis between true iron deficiency anemia and anemia of chronic disease with functional iron deficiency [22].

With the given potential effects of pregnancy on accuracy of results of sTfR as iron indicators [8]. We used TRI for ranking of obese mothers using cutoffs to indicate depletion and deficiency. It was proposed previously that TRI >1.4 had a high discriminating power (sensitivity 91.1%, specificity 92%) in the diagnosis of IDA [23]. A higher cutoff for TR >2 was afterward recommended by Abitbol et al., for IDA diagnosis in inflammatory chronic disease [6].

In our study a higher cutoff was chosen as proposed by Cheng et al., in which TRI was used to identify anemic participants with IDA (TRI>2.20) and AI (TRI <1.00) with concurrent haemoglobin <10.5g/l) [8].

Anemic obese participants of Group 1 were categorized to Group (1A) with TRI >2.2 and Group 1B with TRI <2.2. Comparison between
both groups revealed significant increase in Group 

in median levels of maternal TRI \( p=0.001 \), with median TRI=4.1 and 0.64 in Groups (1A) & (1B) respectively; Maternal SF \( p=0.001 \) with median values of SF=8.5mg/l, 125mg/l in Group (1A), (1B) respectively; maternal sTFR \( p=0.001 \) with median value=4.01mg/L, and 1.52mg/L in Group (1A), (1B) respectively. There was significant decrease in Group (1A) in median value of maternal TSI \( p=0.001 \) with median value in Group (1A)=4.375 while in Group (1B)=16.50 and it was claimed that TSI below 16% to be the best ID indicator. There was no significant difference seen in serum iron \( p=0.147 \) but both median values lies below normal being 20.00ug/dl, 30.00ug/dl in Group (1A) and (1B). There was no significant difference seen in Hepcidin \( p=0.149 \).

This categorization of patients using TRI showed that median levels of iron profile of Group (1A) shows IDA profile with \(^{7}\)S.iron, \(^{7}\)SF, and TSI <16%. while Group (1 B) was in line with AI profile with \(^{7}\)S.iron, normal SF, and TSI >16%. This was in agreement with studies who claimed that TRI was an accurate indicator of true iron deficiency in patients with inflammation \([6]\) and with Cheng et al., who stated that TRI >2.2 is indicative to IDA while TRI <0.8 is indicative to AI \([6]\).

Our data was in agreement with Infusino et al., that serum sTFR concentrations are expected to rise in IDA, but not in AI \([9]\).

There was no significant differences in Hepcidin \( p\text{-value } 0.149 \), Still Group (1 B) showed Hepcidin median value=21.300ng/ml than Group (1A)=15.250ng/ml.

This given data was in agreement with that of Cao and O’Brien who stated that Hepcidin levels increases in conditions of inflammation \([24]\). This could be explained by the presence of obesity that may play a role in secreting proinflammatory cytokines which contributes in \(^{7}\)Hepcidin levels in blood and may be secreted by adipose tissue as was suggested by Nazif et al., \([2]\). There were no significant differences between both groups in BMI \( p=0.334 \). Also there was no significant difference in fetal ferritin \( p=0.068 \), Fetal sTFR \( p=0.336 \), Fetal TRI \( p=0.268 \) which may indicate that level of fetal iron stores is not affected by the type of mothers anemia whether due to AI or IDA.

In order to study the effect of isolated maternal IDA on newborn iron stores another comparison was done between iron stores of newborn of obese mothers with IDA in Group (1 A) \( (N=8) \) with control Group 2 \( (N=13) \) but also revealed no significant difference in fetal ferritin \( p=0.717 \), Fetal sTFR \( p=0.538 \) and Fetal TRI \( p=0.800 \). In another study they concluded that infants of iron-depleted mothers with maternal SF <13.6mg/L had lower cord-blood SF than controls \([28]\). Previous studies indicated that the compromise to fetal iron status occurs only if maternal SF is <10mg/L \([26]\) or <12 mg/L \([27]\).

In order to study the effect of isolated maternal obesity creating AI state on newborn iron stores we made a comparison between iron stores of newborn of obese mothers with AI in Group (1 B) \( (N=9) \) with control Group 2 \( (N= 13) \) which revealed significant difference in Fetal ferritin \( p=0.009 \) with median=134ug/ml and 177ug/ml in 1B & 2 respectively; Fetal TRI \( p=0.049 \) with median=2.1 and 0.8 in 1B and 2 respectively while no significant difference was seen in Fetal sTFR \( p=0.109 \).

As control Group 2 was non anemic TRI cutoff=1.8, as it was stated that TRI (1.8-2.2) is indicative to subclinical Iron Depletion (ID). So it was categorized according to TRI into; 2A (6 pts) with TRI >1.8 and 2B (7pts) with TRI <1.8. Comparison of Group 2A and 2B revealed that significant increases were seen in Group 2B of Hepcidin \( p=0.019 \) with median=4.5ng/ml and 6.6ng/ml in Group (2A) and (2B) respectively; Maternal SF \( p=0.003 \) with median in Group (2A) & (2B) was =1 3.00mg/l and 36mg/l being on low reference range in Group (2A); Serum iron \( p=0.007 \) with median=42.50 ug/dl and 78.00ug/dl in Group 2A & 2B respectively; Maternal TSI \( p=0.004 \) with median=9.55 & 17 in Group (2A) & (2B) respectively. While significant decrease was seen in Group 2B in median values of maternal TRI \( p=0.003 \) with median values=2.759 and 0.86 in Group 2A and 2B respectively.

The profile of 2A was in line with IDA with \( \mu \) mean of sTfr=3.0800mg/l but normal Hb mean 11.15mg/dl can be explained by that IDA includes 3 periods: Iron Depletion (ID), Iron Deficient Erythropoiesis (IDE), and IDA. During the ID and IDE periods, iron storage is depleted, but the Hb remains normal. This is called Subclinical Iron Deficiency (SID).

Our findings stated that Hepcidin decreased in early stages of ID even when Hb and iron stores were normal. Also Cao and O’Brien stated levels of Hepcidin decreases in conditions leading to or resulting from iron deficiency \([25]\). Others stated
lower Hepcidin concentrations are found in those with lower iron stores due to normal suppression of hepatic Hepcidin secretion in the iron depleted state to allow for greater iron absorption and mobilization [28]. There was no significant differences in; BMI \((p=0.367)\).

Comparison between newborn iron stores from ID mothers in Group 2A \((N=6)\) with Group 2B \((N=7)\) revealed no significant difference in Fetal ferritin \((p\text{-value}=0.886)\), Fetal sTFR \((p=0.830)\) and Fetal TRI \((p=1.000)\).

Correlation studies revealed:

There was significant positive correlation between maternal BMI and maternal Hepcidin \((r=0.051, p=0.002)\), on the other hand there was significant negative correlation between maternal BMI and maternal Hb \((r=-0.350, p=0.029)\). Another review also reported elevated BMI to be associated with increase in SF and decrease in transferrin saturation but they claimed that critical level of adiposity BMI \([>35.0kg/m^2]\) may be required for significant Hepcidin elevation and iron disturbances [8].

Hepcidin was significantly positively correlated to CRP \((r=0.489, p=0.002)\) and SF \((r=0.391, p=0.018)\), in addition to BMI \((r=0.051, p=0.002)\), while significant inverse correlation seen with hepcidin and maternal S.iron \((r=-0.392, p=0.018)\). No correlation was seen between hepcidin and indicators neonatal iron stores.

Our data was in agreement with Garcia-Valdes et al., who showed that maternal hepcidin levels were correlated with maternal iron status but not with neonatal iron store [14].

Another study stated that Hepcidin is important modulator of anemia in obese patients and that obesity can be considered as a low grade inflammatory state, that stimulates the production of inflammatory markers such as CRP which can up-regulate hepcidin synthesis [2].

There was significant positive correlation between TRI and sTR \((r=0.911, p<0.001)\), while there was significant negative correlation between TRI and SF \((r=-0.845, p<0.001)\), serum iron \((r=-0.333, p=0.039)\), TSI \((r=-0.753, p<0.001)\). No significant correlation seen with TRI and Hepcidin \((r=-0.291, p=0.085)\). There was significant negative correlation between sTR and SF \((r=-0.664, p<0.001)\), TSI \((r=0.761, p<0.001)\) and serum iron \((r=0.537, p=0.039)\), the correlation analysis showed statistically significant relationships among both TRI, and sTR with other biochemical iron indices; S.iron, SF, and TSI value and with each other indicating the usefulness of sTR, TRI in estimation of the true iron state and anemia type differentiation.

The maternal SF showed significant negative correlation with TRI \((r=-0.845, p<0.001)\), and sTR \((r=-0.664, p<0.001)\). While there was significant positive correlation between maternal SF and TSI value \((r=0.627, p<0.001)\) only but no significant correlation was seen with S. iron \((r=0.138, p=0.401)\). Showing the upper hand of TRI iron indicator over S. ferritin.

Our study showed significant negative correlation between fetal ferritin and maternal CRP \((r=-0.376, p=0.041)\) which may explain why newborns of obese mothers with AI had significant difference in SF and TRI with control group, as obesity is associated with chronic inflammation markers, specifically CRP [3]. Significant negative correlation was seen with Fetal ferritin to fetal TRI \((r=-0.462, p=0.010)\). There was no significant correlation seen to fetal sTR \((r=0.290, p=0.119)\).

There was significant negative correlation between fetal ferritin with Fetal TRI \((r=-0.462, p=0.010)\), but no correlation was seen between Fetal ferritin and fetal sTR \((r=-0.290, p=0.119)\).

One of methods proposed to help interpret iron status measured by ferritin during inflammation is to increase the ferritin cutoff indicative of deficiency in settings where inflammation or infection is common. The WHO has followed this approach, recommending a ferritin cutoff of <30mg/L rather than <12mg/L for children <5y old in areas where infection is prevalent [8].

Guidelines in other disease associated with inflammation as Inflammatory Bowel Diseases (IBD) consider ferritin level between 30 and 100 ng/mL associated with inflammation as diagnostic criteria for iron deficiency. However, if increased ferritin cutoff improves its sensitivity, it is at the cost of loss in specificity [6].

There was significant positive correlation between Fetal sTR and fetal TRI \((r=0.970, p<0.001)\), but no significant correlation was seen between sTR and Fetal ferritin \((r=-0.290, p=0.119)\). There was significant negative correlation between Fetal TRI and Fetal ferritin \((r=-0.462, p=0.10)\), while positive significant correlation was seen between fetal TRI and fetal sTR \((r=0.970, p<0.001)\) the given data showed usefulness of TRI in estimation of true iron state in neonates over ferritin and sTR.
Another study made by Kamer et al., showed statistically significant relationships among sTfR and S.iron, and TSI only in children with IDA only [7]. Other authors have not shown any statistically significant correlations between sTfR and biochemical iron indices in infants and children [29]. The discrepancy could be related to age and maternal condition differences.

Conclusion:

1- TRI cutoffs showed powerful potential in estimating prevalence and differentiating ID, IDA and AI in pregnant obese mothers.

2- The stated correlation between TRI and the examined parameters of iron balance suggests that TRI can be treated as a proper iron deficiency indicator in both obese pregnant mothers and their neonates.

3- The relatively low examination costs and small blood sample amounts needed to perform sTfR assay makes its TRI useful in the differential diagnosis of anemia, especially in obese pregnant mothers and their neonates.

4- Adiposity was associated with significant elevation of Hepcidin which is considered an inflammatory marker.

5- Fetal TRI did not correlate to maternal anemia nor BMI. Fetal ferritin correlated to maternal CRP.

Our results may be population specific, depending on the prevalence of inflammation and other micronutrient deficiencies that affect iron status and/or anemia prevalence. Further studies on larger scales and other populations are needed to explore these relationships.

References


