Evaluation of the Impact of Iron Deficiency Anemia during Pregnancy on Hospital Admission and Utilization of Hospital Resources in Latifa Women and Children Hospital, Dubai, UAE

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Keywords
Maternal-fetal outcomes · Anti-anemic · Oral liposomal iron

Abstract
\textbf{Introduction:} Iron deficiency anemia (IDA) is endemic among pregnant females worldwide. Liposomal iron preparation is a novel therapy for treating IDA in pregnant females. There is a lack of research on cost-effect and comparison between various new iron preparations as liposomal and intravenous (IV) iron supplements in the international literature.

\textbf{Objective:} The objective of this study was to evaluate the cost-effect and maternal-fetal outcome of IDA during pregnancy in Latifa Women and Children Hospital, Dubai, UAE.

\textbf{Design:} The study was a quasi-experimental study.

\textbf{Settings:} Settings include tertiary-care hospital settings affiliated with academic center in UAE.

\textbf{Patients and Methods:} A total of 226 pregnant women were inducted in the study who were controlled in terms of age, BMI, baseline hemoglobin (Hb), severity of anemia, and ferritin levels. There were 116 patients who received oral liposomal iron pyrophosphate and 110 patients received IV iron saccharate complex for 4 weeks.

The overall cost-effect and maternal-fetal outcomes were compared in 2 groups. \textbf{Main Outcomes Measured:} The main outcomes measured the cost-effect of liposomal and IV iron therapy, and the 2 treatments were compared in terms of maternal and fetal outcomes.

\textbf{Result:} The subjects were matched for age and body mass index and showed that the patients in the IV group were more symptomatic than those in the oral group (18.1 vs. 31.9\% \(p\) value <0.01). There was no statistically significant difference among women from different nationalities living in UAE (\(p\) value 0.079). There were 98 (84.4\%) patients in the oral group and 99 (90\%) patients in the IV group who achieved the desired Hb levels after 1 month of treatment (\(p\) value = 0.878). Moreover, the side effects were also comparable in both groups (1.72 vs. 1.82\% \(p\) value = 0.56). The incremental cost-effect ratio for IV iron was USD 108,633/rise to desired Hb.

\textbf{Conclusion:} Liposomal iron preparations may be cost-effective and have fewer side effects than IV iron. In terms of outcome, the maternal and fetal variables are comparable in liposomal and IV groups.
Introduction

Iron deficiency anemia (IDA) is the most prevalent nutritional deficiency disease during pregnancy all over the world. It is endemic in developing countries where approximately 50% of women have iron deficiency during childbearing age where there can be many causes like nutritional deficiency, worm infestation, malaria, and thalassemia [1]. Whereas in the western world, the disease is less common with 24% of women having anemia during pregnancy and in UAE its prevalence is 28% [2]. The stark difference can be due to better surveillance and diet. There is a lot of debate regarding the cut off limit of hemoglobin (Hb) in order to declare a person anemic especially during pregnancy. The World Health Organization considers a pregnant female anemic with Hb <11 g/dL in the first trimester or <10.5 g/dL in the second trimester or <10 g/dL in the third trimester [3]. It is further classified as mild (Hb 10–10.9 g/dL), moderate (Hb 7–9.9 g/dL), severe (Hb 4–6.9 g/dL), and very severe (Hb <4 g/dL) disease [4].

Pregnancy is a high metabolic state wherein the body requires extra nutrients, vitamins, and elemental iron. It is estimated that 1,000 mg of iron is lost from mother during pregnancy and lactation [3]. Since most of the Asian women in child bearing age start pregnancy with depleted stores of iron, the outcome is manifested in the form of anemia, which can have adverse implications for both mother and child [5]. Maternal anemia is associated with high risks of abortion, infection, postpartum hemorrhage, depression, and even death [3, 6]. Likewise, mothers with low Hb levels have higher odds of preterm labor, low birth weight, and perinatal death [7]. Children born to anemic mothers are shown to have poor cognitive functions and mental impairment [8].

The antenatal management of IDA is crucial and involves 3 basic steps. This includes dietary modification of iron-rich nutrients, iron supplementation therapy, and general awareness [2]. Oral iron is the preferred method of replenishing reserves because of low cost and safety. However, they are shown to be associated with adverse effects and slow rise in Hb levels. However, a new liposomal formulation containing iron pyrophosphate has been shown to mitigate the adverse effects while simultaneously increasing iron absorption [9]. Intravenous (IV) iron is administered in cases who do not tolerate oral preparations, and iron sucrose is considered to be safest and reliable. Both oral and IV iron supplements may reduce the risk of peripartum blood transfusions [10]. There is a lack of comparison between the novel liposomal iron supple-ments and IV iron preparations [9, 11]. The aim of this study was to evaluate the effectiveness of various iron replacement therapies during pregnancy in a multicultural and multiethnic society in terms of cost and utilization of resources. The secondary objective was to evaluate the overall maternal-fetal outcome with the use of iron therapy.

Materials and Methods

This was a prospective observational study conducted at Latifa Hospital, Dubai Health Authority (Dubai, UAE). Prior approval of the Ethical Committee was obtained, and all interventions were in accordance with set guidelines. Informed written consent was taken for all the cases. A total of 226 pregnant women were inducted in this study. The sampling was done in a consecutive nonrandom manner. All the booked and non-booked pregnant patients between the age of 18 and 46 years diagnosed with mild to moderate anemia and delivered from 1 January 2016 to 31 December 2016 having Hb <11.0 g/dL in the first trimester or <10.5 g/dL in the second trimester or <10 g/dL in the third trimester and ferritin <30 μg/L were included in the study. The patients who had previously been taking iron supplements, having hemoglobinopathies as thalassemia trait, severe anemia or anemia due to other causes, history of severe allergic reactions to iron, asthma, and malignancy were excluded. Moreover, patients who had some active infection, renal, or hepatic dysfunctions were also excluded.

All the patients who reported in obstetric OPD of Latifa Hospital, Dubai, were screened for anemia by Hb levels. If found to be anemic, the patients were counseled about the disease in detail, and written consent was obtained and then further tests were conducted, namely, serum ferritin and Hb electrophoresis. The patients were allotted groups in a consecutive manner based on their personal preference after they were briefed about both drugs and the administration pattern. The oral group was required to take lipo-
Iron tablets were administered with a dose of 30 mg elemental iron twice daily for 4 weeks. The IV group received iron (III) hydroxide saccharate complex, with the dose calculated by the formula: weight in kg × (desired Hb − patient Hb) × 0.24 + 500 mg. The desired dose was rounded off to the nearest multiple of 100. It was then administered as an infusion through peripheral cannula with a maximum dose of 200 mg at any time diluted in 200 mL of 0.9% NaCl and given over 30 min. There were a total of 6–8 doses given over 4 weeks (twice a week). The first dose was given as inpatient or outpatient. All the precautions for possible allergic reactions and gastrointestinal upset were taken during administration. Patients were closely monitored for 12 h for hypersensitivity and then rest were given at a peripheral health center.

The demographic data collected in data sheet were age, nationality, body mass index, gestational age at diagnosis, maternal Hb at the time of diagnosis, severity of anemia based on WHO classification, parity, and patient education. The primary maternal outcome measured was Hb at 4 weeks, development of preeclampsia, preterm delivery, mode of delivery, postpartum hemorrhage, infection, hospital admission days, and blood transfusions. The primary fetal outcomes were birth weight, APGAR score at delivery, NICU admissions, and still births. The data were analyzed using Statistical Package for the Social Sciences version 21. The mean and standard deviation were calculated for age, Hb, BMI, and serum ferritin levels. These quantitative variables were compared by independent t test. Qualitative variables were representative in the form of percentages. The χ² test was applied to calculate the p value taking the value <0.05 as significant. Logistic and multinomial regression models were used to ascertain any association. To determine the cost-effect relation, the incremental cost-effect ratio (ICER) was calculated by the formula (total cost IV − total cost oral)/(proportion of cases reaching desired Hb IV − proportion of cases reaching desired Hb Oral).

**Results**

A total of 226 females were part of the study. The patients were divided into 2 groups based on the treatment they were taking. There were 116 (51.33%) participants in the group taking oral liposomal iron and 110 (48.67%) patients in the group taking IV iron supplements. As Dubai is a multicultural and multiethnic society, we had representation of nearly all ethnic groups. Figure 1 shows the general distribution of different nationalities and the severity of anemia in them. There was no statistical difference seen among the races in terms of presence of IDA (p value = 0.08). The

| Variable | Oral group (N = 116) | IV group (N = 110) | p value |
|----------|----------------------|--------------------|---------|
| Age (SD) | 32.34±5.73           | 31.62±5.938        | 0.35    |
| BMI (SD) | 29.7±4.9             | 29.8±5.5           | 0.86    |
| Nationality, n (%) | Arabian 81 (69.8) | Asian 12 (10.3) | 0.08    |
| | African 17 (14.7)  | European 6 (5.2)   |         |
| Parity, n (%) | Nulliparous 4 (3.4) | Nulliparous 5 (4.5) | 0.51    |
| | Having 2–4 children 91 (78.4) | Having 2–4 children 91 (82.7) |         |
| | ≥5 children 21 (18.1) | ≥5 children 14 (12.7) |         |
| Gestational age at diagnosis, n (%) | First trimester 12 (10.3) | First trimester 17 (15.5) | 0.389   |
| | Second trimester 55 (47.4) | Second trimester 54 (49.1) |         |
| | Third trimester 49 (42.2) | Third trimester 39 (35.4) |         |
| Symptomatic, n (%) | Symptomatic 21 (18.1) | Symptomatic 37 (31.9) | 0.008   |
| Severity of anemia at time of diagnosis, n (%) | Mild 76 (65.5) | Moderate 40 (34.5) | 0.079 |
| | Mild 61 (55.5) | Moderate 49 (44.5) |         |
| Baseline Hb | 9.85±0.77 | 9.68±0.71 | 0.070   |
| Serum ferritin | 16.08±8.1 | 14.21±8.1 | 0.085   |

Hb, hemoglobin.
Impact of IDA on Maternal-Fetal Outcome

Demographic characteristics of both groups are shown in Table 1. The mean (SD) age and BMI of all participants were 31.9 ± 5.8 years and 29.8 ± 5.3, respectively. The baseline characteristics of mothers in oral and IV groups are shown in Table 1. Patients in the IV group were more symptomatic than those in the oral group ($p$ value = 0.008).

After 4 weeks of treatment, the groups were observed closely during pregnancy, peripartum, and 1 week postpartum period. In the oral group, 2 (1.72%) patients reported having side effects of the therapy, mainly mild gastrointestinal upsets, but they were able to tolerate the treatment. In the IV group, 2 (1.8%) patients had palpita-
comparable in both groups. The severity of anemia, baseline Hb, and ferritin were
visits during the second and third trimester of pregnancy. It. Most of our target population had their first antenatal
ue 0.079). Mild to moderate anemia is often well tolerated
during pregnancy and diagnosed at the first antenatal vis-
tue = 0.56). The ma-
differences between the 2 groups (p value = 0.56). The ma-
ternal and fetal outcomes between both groups are shown
in Table 2. Ninety-eight (84.4%) patients in the oral group
and 99 (90%) patients in the IV group achieved the de-
sired Hb levels after 1 month of treatment (p value = 0.878). In terms of the cost-effect analysis shown in Ta-
ble 3, IV treatment has an incremental cost of USD 6,083
per case and the ICER of USD 108,625/rise in Hb.

Discussion

This observational study compared oral liposomal
iron pyrophosphatate with IV ferrous (III) saccharate in
terms of cost-effectiveness and maternal-fetal outcome
among pregnant women. IDA is rampant among preg-
nant females, and various strategies have been devised to
diminish the problem [12]. It was also noted that symp-
tomatic patients chose IV treatment over oral therapy
(18.1 vs. 31.9% p value <0.01). It is worth mentioning that
there was no statistically significant difference among
women from different nationalities living in UAE (p val-
ue = 0.079). Mild to moderate anemia is often well tolerated
during pregnancy and diagnosed at the first antenatal vis-
it. Most of our target population had their first antenatal
visits during the second and third trimester of pregnancy.
The severity of anemia, baseline Hb, and ferritin were
comparable in both groups.

There is a lack of published literature on comparison
of liposomal iron and IV preparations. Our study dem-
strated that oral liposomal iron which contains mi-
cronized ferrous pyrophosphate in liposomal microen-
capsulation has efficacy comparable to IV ferrous sac-
charate complex after 4 weeks of treatment with 84.4%
of patients achieving desired Hb in said time. Moreover,
the side effects were also comparable in both groups
(1.72 vs. 1.82% p value = 0.56). The lipid bilayer prevents
the interaction between the iron particles and mucosal
membrane of gut as well as digestive enzymes [13].
Hence, they are better tolerated than the conventional
iron preparations. Moreover, the liposomal iron has bet-
ter bioavailability than conventional iron regimens. It
also does not require any protein carrier in the gut for
transport [14]. None of the oral group patients had to be
left out owing to side effects of iron supplements. Simi-
larly, a study on palatability of iron preparations showed
that liposomal iron had a significant visual analog score
when compared with other oral iron supplements (7.6
vs. 2.9 p value <0.01) [15], whereas a study by Fouelifack
et al. [16] showed that only 16.4% of pregnant women
were fully compliant to conventional iron sulfate and
the main reason for noncompliance was GI side effects
in 20% of cases. Parisi et al. [17] showed that liposomal
oral iron containing elemental iron of 28 mg achieved
the greatest increase in the mean Hb as compared to
other groups.

It was observed that maternal and fetal outcomes were
comparable in both groups. The oral iron group had few-
er cases of preterm delivery (8.6 vs. 17.3% p value = 0.056),
emergency C-sections (19.8 vs. 29.1% p value = 0.137),
low birth weight (10.3 vs. 14.5% p value = 0.340), and
NICU admission (4.3 vs. 7.2% p value = 0.34), but the re-

results were statistically insignificant. Parisi et al. [18]
showed that the newborns born to mothers taking oral
liposomal iron had more mean birth weight than others
(3,479 ± 587 vs. 3,092 ± 469 g, p < 0.05). The exact mech-
anism of having more weight in newborns in the oral
group is not known, but it can be due to better availability
of iron to the fetus for hemopoiesis.

It is estimated that around 20% of patients with mild
to moderate anemia require transfusion during delivery
and afterward [19]. The total number of patients who
were transfused blood in our study was 3%. So, oral and
IV supplements may prevent the requirement of transfu-
sion, thus providing overall cost benefit.

The liposomal iron is cost-effective when compared
with IV iron. The ICER for IV iron was USD 108,633/rise
to desired Hb. This means that as compared to oral iron,
an additional cost of USD 108,633 has to be spent for de-
sired rise in Hb. There is a lack of data comparing oral and
IV iron in pregnancy. This is high as in the USA, and the
threshold for ICER is USD 75,000–100,000 [20].

There are few limitations in our study. Although the
study encompassed nearly all nationalities, it was con-
ducted in a single center. Although both the groups were
matched in terms of age, BMI, Hb, and serum ferritin,
there were still biases. The authors recommend a multi-
centric randomized control trial to assess the overall ef-
fectiveness of liposomal iron preparations.

Conclusion

Liposomal iron preparations may be cost-effective in
terms of increase in Hb levels at 4 weeks and have fewer
side effects than IV iron. The number of transfusions re-
quired was also comparable with the IV group. In terms
of outcome, the maternal and fetal variables are compa-
rable in liposomal and IV groups.
Impact of IDA on Maternal-Fetal Outcome

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Statement of Ethics

All procedures followed were in accordance with the ethical standards of the Responsible Committee and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. Subjects (or their parents or guardians) gave their written informed consent and the study protocol was approved by the Dubai Scientific Research Ethics Committee (DSREC), Dubai Health Authority, DSREC-08/2018_04 dated 8 September 2018.

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Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

N.A. conceived and designed the research. S.F., K.H., and T.E. did data analysis and manuscript writing. N.A.S. supervised the whole study and editing of the manuscript. A.F., A.Q., S.N., L.P., and W.A. did data collection and compiling international research.