INTRODUCTION

Anemia during pregnancy, a well-known and considerable risk factor for both mother and fetus, is associated with an increased incidence of both maternal and fetal morbidity and mortality.1,2 Fetal consequences of anemia are increased susceptibility to infection and premature delivery, intrauterine growth restriction, increased peri-natal morbidity and mortality.3 Maternal consequences of anemia are also well-known and include cardiovascular symptoms, impaired physical and mental performance, reduced immune function, tiredness and reduced peripartal blood reserves.1 The effects of iron deficiency anemia are exaggerated in pregnant women, because of the ability of the fetus to extract its iron requirement in an obligatory one-way direction even from iron deficient mothers.4

Anemia leads to an increased risk of blood transfusion during the peripartum period.1,5 There is no clear evidence from randomized controlled trials to show modification of available treatments in women with iron deficiency anemia during pregnancy to achieve increase in hemoglobin.

In Pakistan, like rest of the world, microcytic hypochromic anemia during pregnancy is well-documented.7-9 The first-choice treatment in iron deficiency anemia for almost all patients is oral iron replacement because of its effectiveness, safety, and low-cost.5 Parenteral iron therapy is reserved for patients in whom oral therapy fails or is not possible due to intolerance or non-compliance. Especially, candidates are pregnant women who present too close to term, and those who have severe anemia and their hemoglobin level is required to be restored quickly.2,10-12 Intravenous iron sucrose complex has been used in pregnancy with success.4,5,13 Compared to various
available parenteral iron preparations, low molecular weight iron dextran has the advantage that in addition to intravenous and intramuscular route, it can also be used as total dose infusion with the entire iron deficit calculated by the available formula and the required dose given in one setting. The use of high molecular weight preparations have been restricted in pregnant women because of their side effects.\textsuperscript{12,15}

Though iron dextran has been in use for almost 30 years and its efficacy is well-established,\textsuperscript{14} with the introduction of low molecular weight iron dextran in 1992, a better safety profile has been achieved.\textsuperscript{12,16}

The aim of this study was to determine the safety and efficacy of total dose infusion of low molecular weight iron dextran in the treatment of iron deficiency anemia in pregnant females, who were intolerant to oral iron supplementation.

**PATIENTS AND METHODS**

The study was an experimental open-label, non-randomized control trial carried out at Shifa International Hospital, Islamabad and Shifa Foundation Community Health Centre between January 2005 to January 2006. Approval was obtained from the institutional review board. One-hundred consecutive iron-deficient pregnant females (gestation age > 12 weeks) who were either intolerant or non-compliant with oral iron supplementation were recruited from antenatal clinics of Shifa International Hospital and Shifa Foundation Community Health Centre. Patients with multiple pregnancies, history of hematological disease, known allergy to iron, cancer, bleeding, bronchial asthma and other allergic conditions were excluded. After signing informed consent, thorough history and physical examination was performed. Complete blood count with peripheral smear and absolute indices were performed on both groups, while serum ferritin was obtained only for intervention patients. Iron-deficiency anemia was defined with Hb <10.5 g/dl, MCV < 76 fl, serum ferritin <12 ug/l and microcytic hypochromic picture on peripheral smear. Baseline characteristics in both groups included age, socioeconomic status, parity and duration of pregnancy.

Patients selected for parenteral iron were admitted as day cases. The dose for total iron dextran was calculated from the formula: weight in kg x hemoglobin deficit (target hemoglobin-actual hemoglobin) x 0.24 + 500 mg. After the test dose (0.1 ml diluted in 20 cc of normal saline intravenously over a period of 20 minutes), patients were observed for any side effects for one hour and subsequently the entire dose diluted in normal saline was infused over a period of 6 hours. Adverse events after infusion were identified by observation, direct inquiry and physical examination of each patient. Blood pressure was measured before, during, and after each infusion. Patients were seen after a week and enquired for any delayed side effects like myalgias, arthralgias and gastric problems. Additional oral iron was not administered to these patients till the delivery though folic acid supplementation was continued.

Pregnant women matched for age, parity, gestational age and baseline hemoglobin, who were compliant and tolerant to oral iron supplementation, attending the same antenatal clinics during the same period, served as comparison group.

The primary outcome measure was comparison of hemoglobin concentration between 3\textsuperscript{rd} and 4\textsuperscript{th} week in both groups.

All data collected through questionnaire were fed in SPSS (Statistical package for Social Sciences) version 10.0. Chi-square statistics were obtained and p-value < 0.05 was regarded as significant.

**RESULTS**

Out of 100 women of interventional group, mean age 26.0 ± 4.8 years, 29 were primigravida, 41 were gravida 2-3, 20 were gravida 4-5 and 10 were above 5 gravida. Fifty percent were registered in antenatal follow-up and 50% were registered from OPD. Mean pre-infusion hemoglobin levels in intervention and comparison groups were 8.57±0.9 gm/dl (range 5-10.5) and 9.5 ± 0.9 gm/dl (range 7-10.5) respectively. In intervention group, 70% had serum ferritin levels less than 6ug/l. Mean post-infusion Hb in intervention group was 11.0 ± 1.1 gm/dl (range 8.4-14.3) and post-oral iron intake in control groups was 10.2 ± 1.2 gm/dl (range 6.4-12.8). Mean increase of Hb in intervention group was 2.43 gm/dl (95% CI 2.4-3.8) and controls was 0.7 gm/dl (95% CI 0.6-2.3) from baseline.

Thirty-one percent of women in intervention group had pre-infusion hemoglobin of less than 8.4 g/dl, while 69% of women had hemoglobin level greater than 8.5 g/dl. Post-infusion 16 (51.6%) women showed correction of anemia (Hb>10.5 g/dl), while 51 (73.9%) women with baseline hemoglobin > 8.5 g/dl had their anemia corrected.

Comparison group consisted of 50 age matched pregnant females who had similar parity and gestational age. They were also divided into two groups on the basis of pre-oral intake hemoglobin. Ten (20%) patients had hemoglobin less than 8.5 gm/dl and 40 (80%) greater than 8.5 gm/dl. After oral therapy for 4 weeks, 28 (56%) patients had hemoglobin of <10.5 and 22 (44%) had values of >10.5 gm/dl.

**Table I: Anemia correction in interventional and control group.**

<table>
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<tr>
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<th>Interventional group</th>
<th>Control group</th>
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<tr>
<td>Hb &gt; 10.5 g/dl n (%)</td>
<td>67 (67%)</td>
<td>33 (33%)</td>
</tr>
<tr>
<td>Hb&lt;10.5 g/dl n (%)</td>
<td>33 (33%)</td>
<td>67 (67%)</td>
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\( ^{*}p < 0.01 \)
In interventional group, side effects were seen only in 4 patients, 2 had flushing and the other 2 developed palpitations.

**DISCUSSION**

A mean increase in Hb of 2.43 gm/dl from baseline compared to 7 gm/dl for the control group shows an improvement equivalent to 2 packed red cell concentrates transfused, at the same time avoiding all the infective, allergic adverse effects and achieving correction of anemia.

The study illustrates that total dose infusion of low molecular weight iron dextran increases hemoglobin faster than oral iron (ferrous sulphate) in the treatment of iron deficiency anemia during pregnancy. It is also quite safe as mild side effects of palpitations and flushing was observed in only 4% of patients.

According to World Health Organization (WHO), oral iron programs have often failed to reduce frequency of iron-deficiency anemia. High levels of iron-deficiency anemia exist in pregnancy despite routine use of iron prophylaxis adopted by many centres in the developing world.8,16 The WHO technical working group on the prevention and the treatment of severe anemia has documented that parenteral iron therapy produces a rapid and complete correction of iron deficiency, including replacement of iron stores producing a more rapid erythropoietic response than oral iron replacement.10 However, its use should be limited to a selected group of patients who are unable to tolerate oral iron, in whom oral iron therapy fails due to non-compliance and where the hemoglobin level is required to be restored rapidly in those pregnant women who present too close to term, and those who have severe anemia.2,10-12

In this study, the mean age of patients was 26 years, which is similar to other studies.8,10,13 This shows the high prevalence of iron-deficiency anemia in young pregnant women. Most of the women throughout the world enter pregnancy with less than desirable iron reserves and many with depleted iron stores.7,12 High incidence of iron-deficiency anemia has been repeatedly reported by various Pakistani studies.9,13 In a study conducted in Karachi, the prevalence of iron-deficiency anemia was found to be 50% despite routine oral and or intramuscular iron therapy.9,13 Studies from other developing nations mainly India and Africa report a similarly high incidence of iron-deficiency anemia among pregnant women.8,17 Interestingly, iron-deficiency anemia is also an issue even in developed countries where high proportions of women develop anemia during pregnancy.5

In this study, iron-deficiency anemia was diagnosed on the basis of hemoglobin levels, blood indices, peripheral film and serum ferritin. The inclusion criteria of baseline hemoglobin was less than 10.5 gm/dl in those patients and this is similar to other Pakistani13,16 and international studies. In this cohort, 70% women had serum ferritin levels of less than 6 µg/dl and 30% had ferritin levels between 6 and 15 µg/dl. According to the National Academy of Sciences panel on nutrition and pregnancy, iron-deficiency in pregnancy has been defined as ferritin levels lower than 12 µg/dl and it is considered the gold standard for the diagnosis of iron-deficiency anemia in pregnancy.3,12

The data on the efficacy of oral and parenteral iron supplementation is mixed. In a study conducted by Mahale *et al.*,18 it was concluded at 36 weeks of gestation that intramuscular iron replacement was more effective in raising hemoglobin and serum ferritin concentration than the oral group,18 whereas, Sharma *et al.*19 concluded that hemoglobin and iron indicators improved significantly with both treatments.19 In this study, maternal hemoglobin was restored more rapidly with intravenously administered iron dextran than orally administered iron. All the cases showed improvement in their hemoglobin levels. Though some of them have not apparently reached the target Hb of 10.5 gm/dl but those were the women who started with very poor iron stores and extremely low Hb levels. These findings regarding the efficacy of parenteral iron have also been reported in earlier studies.12,16 Maimoonâ *et al.* reported findings similar to those in this study that intravenous iron treatment is rapid and highly effective.16

Most of the available studies on pregnant women have used intramuscular route of administration for iron dextran. Side effects related to intramuscular administration were mostly pain at the site of injection, staining and abscess formation, which have restricted its use in clinical practice.3,12,19

No significant adverse drug effects was recorded in the study. It was observed that side effects were more when the test dose volume was upto 25 mg or 0.5 ml diluted in 10 ml of normal saline as recommended by the manufacturer. When the amount of test dose was reduced to 0.1 ml of low molecular iron dextran, diluted in 20 ml of normal saline, and infused slowly, over a period of 30 minutes, the side effects were minimized.

A major advantage of total dose iron, given as a single dose, is the relative ease and confirmed patient compliance and does not require repeated visits to clinic. There were a few limitations of this study. It was not a randomized control trial. The small number of patients in this study may have limited the applicability of findings regarding the efficacy, safety and ease of iron replacement in iron-deficient pregnant females.

**CONCLUSION**

Intravenous iron dextran is a safe and effective alternative to oral iron in the treatment of iron-deficiency
anemia in oral iron-intolerant or non-compliant patients. Intravenous iron restores body iron stores more rapidly, and a prompt increase in hemoglobin is more likely to be achieved. Major inconvenience of intravenous treatment is the need for short hospitalization or at least an outpatient setting for close monitoring.

REFERENCES