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**ORIGINAL ARTICLE**

# Frequency of Adverse Reaction in Antenatal Booked Patients of a Tertiary Care Centre Receiving Intravenous Iron Isomaltoside

SIDRA KHALIID[1], FARAH DEEBA NASRULLAH[2], RIFFAT JALEEL[3], FARAH SHABIH-UL-HASNAIN[4]
[1]*Postgraduate Gyn unit 2 DUHS/CHK*
[2]*Associate Professor Gyn Unit II DUHS/CHK*
[3]*HOD Gyn unit 2 DUHS/CHK*
[4]*Assistant Professor Gyn Unit 2 DUHS/CHK*
*Corresponding author: Farah Deeba Nasrullah, Email: farah.deeba@duhs.edu.pk, Cell: 0334-327782*

## ABSTRACT

**Aim:** To determine the frequency of adverse reaction in antenatal patients of Civil Hospital Karachi receiving intravenous iron isomaltoside for the treatment of iron deficiency anaemia.

**Methodology:** A six months cross sectional study was undertaken at the department of Obstetrics & Gynaecology Civil Hospital Karachi. In this study women who weighted < 75 kg at the time of presentation to the antenatal clinic received 1000 mg parenteral iron isomaltoside infusion. Women with body weight ≥ 75 kg on the same occasion received 1500 mg parenteral iron during a minimum infusion of 30 min, diluted in 100–500 ml of saline. The patients who received parenteral iron were kept under observation in a secluded quiet room and directed to lie on her back on a comfortable bed. The researcher monitored the patient during and thirty minutes after the end of infusion to assess the adverse reactions.

**Results:** The mean age of the women was 27.2 + 4 years, mean gestational age was 36 + 4 weeks. Out of 276 women, 17 (6%) experienced the adverse reactions. Majority (>94%) developed mild reaction which did not require any treatment. The adverse effects were significantly associated with younger age <30 years (p value .03), gestational age < 36 weeks (p value .001), use of tobacco (p value .001), hypertension (p value .001) and diabetes (p value .001)

**Conclusion:** Findings of the study concludes that the use of a single high-dose infusion (up to 1500 mg) of paranteral iron (isomaltoside) during pregnancy is effective and safe for treating IDA in this population.

**Keywords:** Adverse reaction, antenatal booked patients, Intravenous iron isomaltoside.

## INTRODUCTION

Iron deficiency anaemia is one of the important Health issues in the women of reproductive age group in most of the developing countries [(1).] In low resource countries like Pakistan iron deficiency anaemia is very common in women because of repeated childbirths or heavy menstrual bleeding. Iron requirement is increased in pregnancy to meet the demands of growing fetus and placenta. Additional iron is required for women to increase the physiological rise in red blood cell volume and replace iron lost due to bleeding at the time of delivery [(2).] The reported prevalence of iron deficiency anaemia in pregnancy during the first, second, and third trimesters of pregnancy is 7%, 14%, and 30%, respectively [(3).]

In a systematic review and meta-analysis of 26 studies it was observed that anaemia in pregnant women (mostly due to iron deficiency) was associated with a higher risk of low birth weight, preterm birth, perinatal mortality and neonatal mortality [(4).] Routine iron supplementation during pregnancy is recommended by the World Health Organization (WHO) for the developing world [(5)] .

Intravenous iron therapy is reserved for a small number of patients who cannot tolerate oral iron therapy, are unable to adequately absorb oral iron or as is the case of majority of our population they are non-compliant [(6)].

Nausea and hyperemesis in early months of pregnancy and heart burns in late pregnancy makes oral iron therapy difficult to tolerate in many women. In such cases treatment with intravenous iron is relatively superior to oral iron with respect to a faster increase in hemoglobin and faster replenishment of body iron stores. Intravenous iron definitely reduces the need for blood transfusions and constitutes an alternative to transfusion in moderate IDA [(7)].

Despite its profound use, IV iron has some adverse effects as well. Common Side effects of IV iron are Palpitation, Shivering, Heat intolerance and Small joint stiffness [(7)].Hypersensitivity reactions to parenteral iron therapy are rare, but if occurs they can be life-threatening [(8)]. A study conducted in United States stated that 75 (22.5%) out of 342 patients report adverse drug reactions [(9)]. Occurrence of hypersensitivity reactions is associated with history of previous reaction to an iron, rapid intravenous iron infusion, previous drug allergies, severe atopy, and any chronic illness. Management of iron infusions depend upon the severity and requires vigilant monitoring, and early recognition and severity- related management of adverse reaction by a multidisciplinary team [(10)]. A study conducted by Wesström et al found the frequency of adverse reaction to be 4.7% [(11).]

**Rationale:** Iron deficiency anaemia (IDA) during pregnancy and after child birth leads to increased risk of low birth weight, preterm birth causing high perinatal morbidity, lactation problems and may result in early-childhood iron deficiency .Treatment with oral iron may be ineffective due to poor compliance or intolerance leading to poor absorption. Treatment dose may also be insufficient when the required iron need is very high. Therefore, in these women parenteral (mostly IV) iron is considered more effective and better tolerated and significantly improves their symptoms and hence avoids the need of blood transfusion and associated complications. However, there is risk of allergic reaction with parenteral iron. There is limited literature documenting the frequency of the adverse reaction following parenteral iron. Hence, most of obstetricians are very reluctant to use parenteral iron therapy in pregnancy even if it is required. This study was planned to determine the frequency of adverse iron reaction in pregnant women to understand and improve the knowledge of clinicians involved in their care. This will help in future for better management of iron deficiency anaemia in pregnancy

## MATERIALS & METHODS

This was a Cross-sectional study conducted at the department of Obstetrics and Gynaecology Civil Hospital Karachi which is a tertiary care Centre, from March 2021 to September 2022.

Sample Size was calculated by taking the prevalence of adverse reaction, P= 4.7%11 using margin of error = 2.5%. The total calculated sample size was 276 patients with the help of WHO software for sample size calculation taking 95% confidence level. Booked pregnant women of any parity, gestational age ≥10 weeks and age between 20-35 years presenting with shortness of breath, weakness and lethargy for more than one week diagnosed as having iron deficiency anaemia(IDA) were included in the study. Iron deficiency anaemia was diagnosed by Hb >7gm/dl and <10.5gm/dl MCV <76fl, MCH <28pg, MCHC <32pg and Ferritin <20ng/ml (44.9 pmol/l). Patients with severe anaemia or signs of anemic failure, previous history of allergic reaction with parenteral iron isomaltoside, history of blood transfusion in last 2 months or

any hemolytic disease/ haemoglobinopathy were excluded from the study.

**Data Collection:** This study was conducted after approval of synopsis from Institutional ethical review committee and College of Physician and Surgeons Pakistan. Consenting patients fulfilling the inclusion criteria booked in the Department of Obstetrics and Gynaecology at Civil Hospital Karachi were enrolled in the study. Brief history was taken about the duration of shortness of breath and demographic data was taken from each patient. Women weighing < 75 kg at the time of presentation to the antenatal clinic received 1000 mg parenteral iron during a minimum of 15 min, whereas those with body weight ≥ 75 kg received 1500 mg parenteral iron during a minimum infusion of 30 min. Iron was diluted in 100–500 ml of saline. Infusion was administered by the researcher. The pregnant woman was placed in a separate, quiet room and directed to lie on her back on a comfortable bed for 30 minutes. She was informed about the possibility of a mild, quickly reversible reaction. The researcher monitored the patient during and thirty minutes after the end of infusion for any adverse reaction. Patients were assessed for developing chest pain, flushing, itching, urticaria, hypotension, tachypnea, tachycardia, wheeze, periorbital edema to label adverse reaction to intravenous iron isomaltoside as per operational definition. The patients were treated for the adverse reaction as per hospital protocol. All the findings including outcome variable were reported on a predesigned proforma.

**Data Analysis:** Patient's data was entered and analyzed by using statistical package for Social Sciences (SPSS) Version 21. Frequency and percentage were calculated for qualitative variables like residence status, parity, diabetes mellitus, hypertension, smokeless tobacco use, family monthly income status, and adverse reaction. Mean ± SD was calculated for quantitative variable including age, gestational age and duration of shortness of breath. The stratification was done on age, residence status, parity, gestational age, diabetes mellitus type II, hypertension and smokeless tobacco use to see the effect of these modifiers on outcome using chi square test/ Fischer's test. P value ≤0.05 was considered as significant.

## RESULTS

In this study a total 276 antenatal booked women receiving intravenous iron isomaltoside were included. The mean age of the women was 27.2 + 4 years, mean gestational age was 36 + 4 weeks and mean duration of shortness of breath was 6.2 + 4 weeks. Out of 276 women, 179 (65%) were primipara and 97 (35%) were multiparous. In these women 74 (26.8%) belonged to urban and 202 (73.1%) to rural area .Majority were from low income group with 239 (76.8%) had monthly income < Rs. 50,000 and 37 (13.4%) had > Rs. 50,000.descriptive stats are shown in table 1.

Table 1: Descriptive statistics showing patient characteristics n = 276

| Key feature | frequency | percentage |
|---|---|---|
| Age 20-30 years<br>>30 years | 231<br>45 | 83.6%<br>16.4% |
| Parity Primi<br>Multi | 179<br>97 | 65%<br>35% |
| Gestational age<br><36 weeks<br>>36 weeks | <br>191<br>85 | <br>69.2%<br>30.8% |
| Occupational Status<br>Un-Employed<br>Employed | <br>201<br>75 | <br>72.8%<br>27.2% |
| Shortness of breath<br>< 3 weeks<br>>3 weeks | <br>227<br>49 | <br>82.2%<br>17.7% |

Among these patients 3 (1%) were diabetic, 4 (1%) were hypertensive and 2 (0.7%) used smokeless tobacco. Out of 276 women, 17 (6%) experienced the adverse reactions, as shown in table 2. Majority (>90%) developed only mild reaction causing nausea, flushing, anxiety and rash and were managed by re assurance and monitoring. Only one patient developed hypotension and dyspnea and required oxygen, stopping infusion, hydration, steroid injection and monitoring in high dependency unit for observation. None of the patient developed severe reaction requiring extensive monitoring and treatment. There was significant association of adverse reaction with age, gestational age, DM, HTN and use of smokeless tobacco as illustrated in table 3

Table 2: Frequency of Adverse Reactions N= 276

| Adverse Reaction | Frequency | Percentage |
|---|---|---|
| Yes | 17 | 6% |
| No | 259 | 94% |

Table 3: Association of adverse reaction with various factors

| Associated factor | Adverse reaction<br>N= number of patients | P value |
|---|---|---|
| Age Groups<br>20-30<br>>30 | <br>03<br>14 | <br>003 |
| Primipara n=179<br>Multiparan=97 | 07<br>10 | <br>712 |
| Diabetes status<br>Diabetic n= 3<br>Non diabetic n=273 | <br>02<br>15 | <br>0.002 |
| Blood Pressure<br>Hypertension n= 4<br>Normotensive n= 272 | <br>04<br>13 | <br>0.001 |
| Tobacco<br>Smokeless tobacco n=2<br>No tobacco n= 274 | <br>02<br>15 | <br>0.001 |
| Gestational age<br><36 weeks n=191<br>>36 weeks n= 85 | <br>01<br>16 | <br>001 |

## DISCUSSION

Iron deficiency anaemia is very common among pregnant women in low resource countries. They frequently need parenteral iron supplementation to improve their reserves. Different iron preperations are available in market. Parenteral iron is usually given in divided doses due to risk of anaphylactic reactions. Iron isomaltoside is a new intravenous iron supplement composed of iron and chemically modified isomaltooligosaccharides with molecular weight of 1000Da ,consisting predominantly 3-5 glucose units. In contrast to dextran present in iron dextran, this iron preparation is a linear and unbranched less potential of anaphylactic reactions .Strong binding of iron in this preparation enables a controlled and slow release of bioavailable iron to theiron-binding proteins resulting in low risk of iron toxicity. This gives the opportunity of single high dose iron administration. Studies have shown better toleration of this variant of iron [(12)].

Wesstrom in their study observed that single high dose (up to 1500mg) iron (isomaltoside) is safe and convinient in pregnancy[(11)].

The results of this study support the conclusion that a single high-dose infusion (up to 1500 mg) of parenteral iron(isomaltoside) during pregnancy is effective and safe for treating IDA in thepregnancy. This has been reported by previous studies as well [(13)]. There is a fear among obstetricians of giving high dose parenteral iron to the pregnant women leading to insufficient replacement and consequences of iron deficiency on maternal and fetal health. Severe and life threatening hypersensitivity reactions to iron are very rare and are acute medical emergency requiring multidisciplinary team involvement.

A meta-analysis from 2018 reported the prevalence of treatment-related mild ADRs in pregnancy with three different types of intravenous iron treatments with median prevalence from 2.2 to 6.7% [(14).] In 2017 a study from England described 4 cases (3.3%) of mild, quickly reversible ARDs during parenteral iron administration among 121 women[(15)].In their report, there was no difference in the incidence of ADRs between patients receiving

less than or more than 1000 mg of iron. Other studies also concluded that parenteral iron therapy is safe in pregnancy with very low risk of hypersensitivity reactions [16,17] .Similar to these previous findings, it was observed in this study that only ten patients (6%) experienced mild symptoms which all were managed conservatively without any significant morbidity or mortality. The symptoms included rash, nausea and sometimes anxiety. Symptoms disappeared within minutes and did not re occurred. Only one patient developed moderate reaction for which infusion was stopped and patient was treated by hydration and steroid injection.in this study age more than 30,gestational age > 36 weeks, diabetes ,hypertension and tobacco were significantly associated with occurrence of adverse reactions. Our data, and those of others, support the call for large prospective studies of IV iron for the treatment of maternal IDA.

## CONCLUSION

Findings of our study concludes that the use of parenteral iron for iron deficiency anaemia is safe in pregnancy. However, further prospective studies with better study designs and larger sample size should be carried out in order to draw a concrete conclusion.

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