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A Study of Adverse Drug Reactions to Iron among Pregnant Women of a Teaching Hospital

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Abstract

Objective: To study the incidence of Adverse Drug Reactions (ADRs) to common iron preparations among the women attending the antenatal care clinic of a teaching hospital and associations with clinical, pharmacological and lifestyle factors.

Methods: This cross sectional study was conducted from May to July 2021 after obtaining approval from the institutional ethical committee and enrolled pregnant women with pre-assessed laboratory parameters. Case report form entailed details about demographic, lifestyle-related and clinical data and details of iron supplement-related information. ADRs were documented using a checklist from KD. Tripathi, WHO-UMC assessment for causality, Hartwig assessment for severity and modified Schumock and Thorton assessment for preventability of ADRs.

Results: Among 156 participants who fulfilled the inclusion criteria, 46 were reported to have at least 1 ADR which were more for oral iron therapy compared to parenteral preparations (94.2% vs 5.8% P= 0.077), the most common adverse reaction among oral iron users was heartburn. 84.8% of these ADRs were probable in causality, mild in severity and probably preventable. ADRs were documented more for women who consumed iron and calcium supplements together (40.8% vs 59.2% P=0.007) and among the upper and upper middle classes compared to middle, lower middle and lower classes (91.7% vs 8.3% P=0.036).

Conclusion: ADRs to common drugs like iron are often unreported. They were found to be more incident among oral iron users but it is the preferred mode of therapy due to its ease of use and price. Better therapeutic advice and vigilance can be minimize ADR occurrence.

Keywords: ADR, iron, supplement, safety.

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1. Introduction

Anaemia in pregnancy, particularly due to dietary deficiencies is common and deserves special attention due to its potential complications. According to the National Family Health Survey III (2005–2006), the prevalence of anaemia in India is 57.9% [1]. A study conducted by the Federation of Obstetric and Gynaecological Societies of India/World Health Organization (FOGSI-WHO) study (1997) on maternal mortality revealed that 64.4% of women who died had a haemoglobin of 8 g/dL [2]. In view of these findings, women have been supplemented with iron, folic acid and vitamin B12 during pregnancy, in the antenatal period as a part of both central and state government initiatives to prevent maternal mortality and unwanted fetal outcomes. With administration of any pharmaco-therapeutic agent, the risk of adverse reactions exists. ADRs cause frequent hospital admission and can prove to be potentially

fatal if untreated or ignored [3,4]. For this precise reason, effective documentation of these ADRs is mandatory to allow post marketing surveillance of the drug and for clinicians to ascertain a preferable form or fixed dose combination of the drug which can reduce the chances of eliciting an adverse reaction [5]. Females have also been proven to have a higher risk for development of ADRs [6]. The maximum numbers of ADRs were found to be those related to iron supplements (42%), among women visiting the obstetrics and gynaecology department of a tertiary hospital [7].

Among iron preparations, differential severity and causality has been documented for different iron preparations and different modes of delivery. A randomized clinical trial conducted about the preferred mode of delivery, revealed intravenous preparations, particularly iron sucrose to alleviate the erythropoietic response better and at a faster rate compared to oral preparations [8].

A systematic review and meta-analysis of 47 studies conducted to assess the efficacy of intravenous preparations of iron to alleviate haematological parameters and cause fewer adverse effects revealed the mean prevalence of adverse reactions to be higher for oral iron therapy as obtained from the 9 studies comparing oral and intravenous iron therapy for adverse reactions. Adverse reactions were recorded higher for intramuscular iron supplements when compared to the intravenous mode of administration. The prevalence of adverse reactions to different iron preparations were least for Iron Polymaltose, the highest for Ferrous Sulphate [9].

Aims and objectives:

(i) To obtain the incidence of ADRs to iron supplementation (both oral and parenteral) among the participant pregnant women, (ii) to systematically report the various adverse reactions and the characteristics of these ADRs (severity, causality and preventability), (iii) to find a possible correlation of these ADRs to dietary and lifestyle parameters and laboratory and radiological evaluates.

2. Material and Methods

2.1 Study duration and Ethical approval

The study was conducted from May 2021 to July 2021 after approval from the Institutional Ethics Committee (IEC) numbered: SKNMC/Ethics/App/2021/803, with a duration dependent sampling technique based on detailed interviews of pregnant women receiving iron supplementation.

2.2 Inclusion criteria

All pregnant women receiving iron supplementation in the antenatal clinic of this institute who consented to participate and with pre-assessed laboratory and obstetric parameters were included. Females with Diabetes Mellitus, Hypertension, Thyroid disorders, Pre-eclampsia and Eclampsia and any other allied health disorder during or prior to pregnancy were excluded.

2.3 Case Report Form

The interview was conducted after obtaining informed consent from the participating women and was based on a detailed case report form, which had different sections.

2.3.1 Demographic details:

Age in years, Height in centimeters, Weight in kilograms, Body Mass Index, Annual income of the family, Socio-economic status (using Modified B.G. Prasad Classification for 2021) [10], Blood Pressure at the time of interview in millimeters of mercury and history of allergies if any.

2.3.2 Laboratory and Obstetric profile:

Random Blood Glucose (RBG), S. TSH, Hemoglobin count at the time of interview was collected. It was assessed using an aseptic technique and the machine used was a fully automated batch analyzer used routinely in the laboratory of our institute. The trimester of pregnancy, gestational age of fetus, Effective Fetal Weight (EFW) were determined using ultrasound guided sonography, gravidity, parity, number of live births, abortions and post-delivery deaths were recorded as a part of obstetric profile.

2.3.3 Details about iron intake:

Dosage form, frequency, other dietary supplements if taken with iron, time of day when iron is taken, relation with meals.

2.3.4 Lifestyle factors:

Type of food eaten (by a seven-day recall method), eating speed (using a visual analogue scale), frequency of meals (in hours), interval between each meal in a day (in hours) frequency per day of the week, duration and type of exercise done (Aerobic, Weight Lifting or Yoga), history of substance abuse and or other non-dietary medications consumed with iron)

2.3.5 ADR reporting:

The ADR checklist was cited from KD Tripathi [11], severity was assessed using Hartwig's scale [12] and WHO-UMC scale was used for determining the causality of ADRs [13] while the modified Schumock Thornton assessment was used to ascertain the preventability of ADRs [14].

2.4 Statistical analysis

Statistical analysis was carried out with the help of SPSS (version 20) for Windows package (SPSS Science, Chicago, IL, USA). The description of the data was done in form of arithmetic mean ±SD for quantitative data while in the form of frequencies (%) for qualitative (categorical) data. P-values of < 0.05 was considered significant. For quantitative data, Unpaired Student's t-test was used to test

statistical significance of difference between means of variables among two independent groups. Significance of the differences between means for more than 2 group was tested using ANOVA. For comparison of categorical variables (to examine the associations between qualitative/quantitative variables), chi-square test was used if the number of elements in each cell are 5 or higher and Fisher's exact test, otherwise.

3. Results

In the given duration of this study 156 females were interviewed, who fulfilled the inclusion criteria with the average age 24.67±3.9 (Mean ± Standard Deviation) with an average Body Mass Index (BMI) of 25.16±4.58 kg/m^2. 74.4% women belonged to Social Class I. Adverse Drug Reactions (ADRs) were seen predominantly in women belonging to upper and upper middle classes compared to middle, lower middle and lower class (91.7% vs 8.3% P=0.036) with the most common Adverse Reaction being that of Heartburn which had a probable causality and mild severity. **Figure 1.**

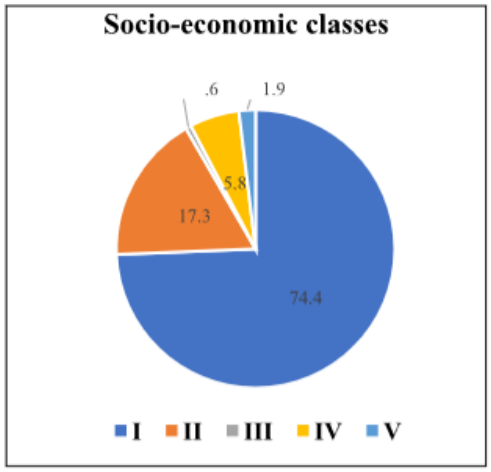

Figure 1: Pie-chart of Socio-economic classes according to modified BG Prasad classification

A majority of women interviewed, were in the third trimester of pregnancy (73.1%) with equal distribution of obstetric and laboratory parameters among the groups. **Table 1**.

Table 1: Demography and Clinical Profile

Parameter	No ADRs (n=110)	With ADRs (n=46)	Total (n=156)	p value
Age (yr) #	24.55 ± 3.85	24.96 ± 4.35	24.67 ± 3.99	0.559
BMI (kg/m^2) #	25.37 ± 4.69	24.67 ± 4.34	25.16 ± 4.59	0.383
Socio-economic class $				
I	87(79.1)	29(63)	116(74.4)	**0.036***
II	18(16.4)	9(19.6)	27(17.3)	
III	0(0)	1(2.2)	1(0.6)	
IV	4(3.6)	5(10.9)	9(5.8)	
V	1(0.9)	2(4.3)	3(1.9)	
Area of residence $				
Rural	3 (2.7)	2 (4.3)	5 (3.2)	0.6
Urban	107 (97.3)	44 (95.7)	151 (96.8)	
Obstetric details $				
Trimester				
2	30 (27.3)	12 (26.1)	42(26.3)	0.879
3	80 (72.7)	34 (74.0)	114(73.1)	
Gravidity				
Primigravida	44(40)	21(45.7)	65(41.7)	0.514
Multigravida	66(60)	25(54.3)	91(58.3)	
Parity				
Primipara	59(53.6)	23(50)	82(52.6)	0.678
Multipara	51(46.4)	23(50)	74(47.4)	
H/O abortions in the past $				
Yes	26(23.6)	10(21.7)	36(23.1)	0.798
No	84(76.4)	36(78.3)	120(76.9)	
Effective fetal weight(gm) #	28.07 ± 5.88	28.17 ± 5.96	28.1 ± 5.87	0.922
Gestational age of fetus(weeks) #	1421.41 ± 862.74	1590.45 ± 1236.1	1471.26 ± 986.41	0.331
Clinical profile #				
Random Blood Glucose(mg/dl)	87.35 ± 16.92	89.26 ± 11.9	87.91 ± 15.59	0.486
Sr. TSH(microIU/ml)	1.66 ± 0.92	1.61 ± 0.83	1.65 ± 0.89	0.779
Hemoglobin (gm%)	11.16 ± 1.25	11.01 ± 1.41	11.12 ± 1.29	0.508
Systolic blood pressure(mmHg)	111.45 ± 8.28	109.67 ± 7.14	110.92 ± 7.98	0.207
Diastolic Blood Pressure(mmHg)	72.48 ± 6.91	71.52 ± 7.4	72.2 ± 7.05	0.44
# : M±SD : p values using either t-test or ANOVA				
$: n(%) : p values using Chi-square				

All of the women were given iron supplementation, predominantly by the oral route (94.2%) with the most common preparation used being Ferrous Ascorbate (80.8% of oral iron users). About 75% of them consumed their iron preparation once a day with 97.3% doing so after meals. Among these women 40.8% consumed iron and calcium preparations together and had significantly higher ADRs (40.8% vs 59.2% P=0.007) **Table 2**.

Table 2 : Details of Iron Supplement intake #

Parameter	No ADRs (n=110)	With ADRs (n=46)	Total (n=156)	p value
Route				
Oral	106(96.4)	41(89.1)	147(94.2)	**0.077**
Parenteral	4(3.6)	5(10.9)	9(5.8)	
Dosing Frequency for oral iron users				
once daily	82(77.4)	35(85.4)	117(79.6)	0.28
twice daily	24(22.6)	6(14.6)	30(20.4)	
Time of day when Iron is consumed (Oral Iron Users)				
Morning	30(36.6)	12(34.3)	42(35.9)	0.838
Afternoon	17(20.7)	9(25.7)	26(22.2)	
Evening	35(42.7)	14(40)	49(41.9)	
whether iron is taken with calcium or not				
Yes	70(66)	17(41.5)	87(59.2)	**0.007***
No	36(34)	24(58.5)	60(40.8)	
Other dietary supplements taken with Iron				
containing Zinc	15(13.6)	3(6.5)	18(11.5)	0.205
Without Zinc	95(86.4)	43(93.5)	138(88.5)	
# All values are n(%) & p values using Chi-square				

Upon being enquired about lifestyle and daily habits, 84% women preferred to brisk walk daily one or more times a day for an average of 27.6±23.5 minutes. 78.8% women consumed a mixed diet (a mixture of vegetarian and non-vegetarian food) and 47.4% of the interviewed women were slow eaters (0 on Visual Analogue Scale). The average duration of sleep reported was 8.62±1.82 hours through 24 hours. Among the women interviewed, none had history of substance abuse anytime during or prior to pregnancy **Table 3.**

Table 3 : Lifestyle Habits

Parameter	No ADRs (n=110)	With ADRs (n=46)	Total (n=156)	p value
Physical Activity $				
Never	16(64)	9(36)	25(100)	0.403
Once daily	82(74.5)	32(25.5)	114(100)	
Twice daily	12(70.6)	5(29.4)	17(100)	
Type of Diet followed $				
Vegetarian	24(80)	6(20)	30(100)	0.182
Non-vegetarian	1(33.3)	2(66.7)	3(100)	
Mixed	24(80)	6(20)	30(100)	
Eating speed $				
Fast	17(15.5)	5(10.9)	22(14.1)	0.621
Medium	40(36.4)	20(43.5)	60(38.5)	
Slow	17(15.5)	5(10.9)	22(14.1)	
Sleep in hours #	8.71 ± 1.72	8.44 ± 2.07	8.63 ± 1.83	0.402
# : M±SD : p values using either t-test or ANOVA				
$: n(%) : p values using Chi-square				

46 out of 156 women (29.5%) reported at least 1 ADR to either oral or parenteral iron preparations with 41 women taking oral iron therapy. 84.8% of these ADRs were probable in causality and 15.2% possible. Severity assessment revealed 84.8% to be mild and 15.2% to be severe in nature with 63% having grade 1 severity **Figure 2**.

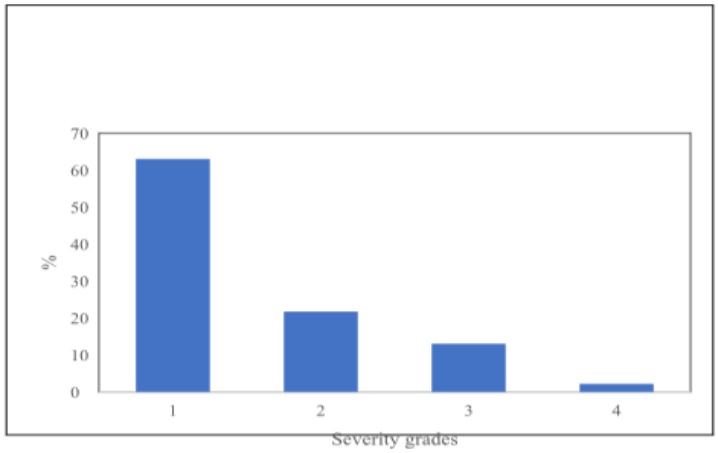

Figure 2: Severity Grades according to Hartwig's Assessment

Among these ADRs, 13% were definitely preventable, 2.2% not preventable while 84.8% were probably preventable when assessed for preventability. ADRs documented were more for oral iron users than parenteral therapy users and showed marginal significance (94.2% vs 5.8% P= 0.077), with the most common ADR reported being Heartburn and 64.1% women reporting the same, the symptom had a probable causality and mild (Grade 1 Hartwig's assessment) severity among 69.2% women. Among, 66.7% women reporting ADRs, this problem could have been definitely prevented. **Figure 3**.

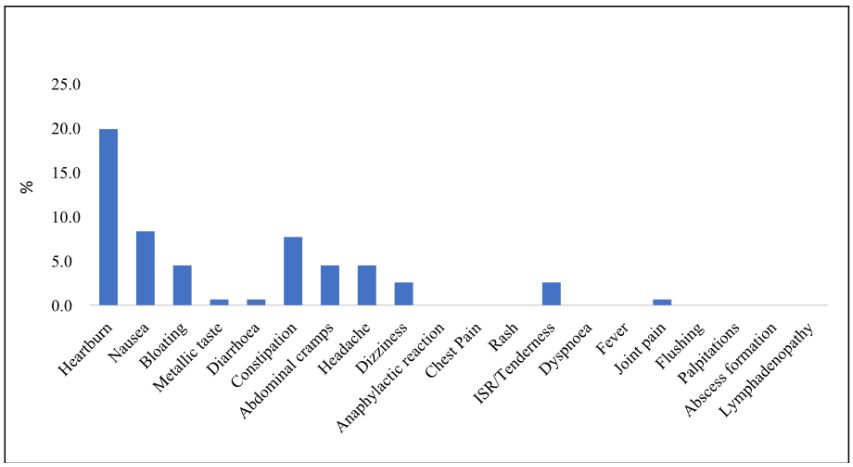

Figure 3: Distribution of the Adverse Reactions among the Participant Women

4. Discussion

The observational analysis of the data was done with the purpose of finding a relation between adverse reactions to iron preparations and other influential factors such as diet and lifestyle, clinical profile demography and methods of drug administration and intake. The analysis performed on the data obtained by interviewing 156 women in the antenatal clinic revealed, a majority of women to be in their third trimester followed by many in the second trimester. This is the time when usually iron supplementation is initiated. Incidence of adverse reactions increases proportionately with age [15], adverse reactions among study participants, were reported more among the age group 21-25 years (P>0.05). Obesity and high body mass index (more than 25kg/m^2) is associated with an increased occurrence of adverse reactions [16]. The adverse reactions, however, reported in our study had no significant association with anthropometric parameter like weight or Body Mass Index. When compared among Socio-economic classes, adverse reactions were found to be more among the upper class and upper middle class compared to the middle class, lower middle class and lower class population. Although the latter groups due to possible financial and social constraints may have a reduced access to health care facilities and report fewer ADRs, an increase documentation of ADRs in the former group could be postulated to be a result of better health education practices prevalent in the former classes and awareness to report their problems, as and when they arose throughout the course of pregnancy.

The laboratory profile and obstetric profile of women reporting adverse reactions and those not reporting any was found to be comparable. Adverse reactions were found to be more among multigravidas, primiparous women and women with no history of abortions in the past (P>0.05).

Intravenous iron therapy has been documented to be more effective in terms of providing rapid improvement of serum iron levels and ferritin along with being safer and better tolerated in pregnancy but has limited role among unwilling patients and those with limited venous access [17-20]. Oral iron therapy, on the other hand, although poses increased side effects in addition to the symptoms of pregnancy and can influence patient compliance to therapy. Oral preparations are however, preferred by patients due to its ease of administration and pharmacoeconomic factors like price of the medication which is lower in case of oral preparations when compared to parenteral iron therapy. Adverse reactions were observed more among the group receiving oral iron supplements with the most common among the reported adverse effects being that of heartburn followed by other symptoms of gastric irritation such as bloating and constipation. Iron supplements are known to affect the gastric mucosa to cause erosions and influence gastric motility and hence gastric irritation [21, 22]. Adverse reactions to oral supplements are often missed or go unreported due to lack of proper counselling of women with regards to information about the various adverse effects which may be missed under the many symptoms of pregnancy. Adverse reactions were reported more for women consuming oral iron preparations once a day compared to those on a twice-a-day regimen (P>0.05). Increased dosing frequency elevates levels of a particular medication in the body fluids and tissues increasing the chances of adverse reactions. Sometimes, errors of commission on the physician's part can also account for this discrepancy in dosing and hence adverse reactions [23]. In our study, we attempted to study the association of dosing time of the day (that is morning, evening or afternoon) for the oral iron users, which was found to be not associated with occurrence of adverse reactions and has not been ascertained in the literature available on the topic. Furthermore, the lifestyle factors studied, were not significantly associated with occurrence of ADRs during pregnancy and factors like sleep and physical activity were comparable between the group of women who reported adverse reactions and among those who didn't.

A highly significant association among intake of iron and calcium supplements together and increased occurrence of ADRs was found in our study. Concomitant nutrients administered with iron often affect its absorption and hence bioavailability. Supplements like calcium are associated with dose related reduction in non-haeme iron absorption from the intestines [24] especially when taken after a meal [25] a majority of the study participants, here, consumed iron preparations after a meal thereby, prolonging the action of the iron preparation in the gastrointestinal tract and hence accentuating occurrence of ADRs. Additionally, protein digestion products such as those of milk (casein) due to the presence of bovine serum albumin have also been known to inhibit iron absorption [26]. Among the participants of our study, the number of women consuming iron supplements with milk was too small to compare with. Concomitant administration of zinc along with iron can only inhibit iron absorption if consumed with a higher ratio of zinc in the combination (5:1 zinc to iron) [27]. This was not the case observed, among our study participants when the combined commercial preparations were checked for the same. Adverse reactions however, were recorded more for those who consumed non zinc containing dietary supplements along with iron preparations (P>0.05)

5. Conclusion

Adverse reactions to commonly used drugs like iron (particularly the oral preparations) often go unreported as they are non-specific in nature and may occur without active iron therapy as well. Although adverse reactions were reported more for oral iron therapy, it is the preferred mode of therapy among pregnant women. This study not only reports ADRs to iron therapy and their characteristics but also shows how ADRs are affected by parameters like demography, anthropometry, clinical parameters, lifestyle habits, dosing and concomitant nutrient supplements. Adverse reactions, although inevitable, can negatively influence patient safety and compliance to therapy. They can be reduced in frequency of occurrence and severity through proper medication dosing regimens and active reporting of problems being encountered. This requires active vigilance on the part of doctors and patients alike. The former must try and avert as many errors in prescriptions along with provision of adequate advice and explain the variety of effects that can be expected after taking the medication and also the ones that require reporting along with other non-pharmacological means to reduce adverse reactions and augment the prescribed therapy. The latter, must actively report the problems they face while taking medications for it ultimately allows better post marketing surveillance of these common drugs so as to permit designing of a safer therapy and consumer-friendly guidelines which can help address all such problems arising in healthcare.

Limitations

The sample size of our study, although sufficient enough to analyze was small compared to other cross sectional studies due to the limited patient exposure because of the second wave of COVID-19 during the study duration.

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Conflict of Interests

The authors have no conflicting interests to declare.

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