

## A study on the aspects of pharmacoepidemiology and pharmacohaemovigilance of ferrous ascorbate, ferrous fumarate, ferrous sulphate and ferric ammonium citrate, among the rural anaemic women, in the Indian spectrum

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**Received:** 27 August 2019

**Revised:** 16 November 2019

**Accepted:** 18 November 2019

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### ABSTRACT

**Background:** Anaemia is a global health concern, associated with increased maternal and perinatal mortality, preterm delivery, low birth weight, extreme fatigue and impaired immune system; and controlled by oral haematinics; with a rise in haemoglobin concentration. The objective was to examine the various aspects of pharmacoepidemiology and pharmacohaemovigilance of oral haematinics, among the anaemic women population, in rural India.

**Methods:** This was a multi-centre, retrospective, observational and analytical study of the hospital medical records of 250 anaemic patients, who were allocated into group A of 125 patients within 15-21 years and group B of 125 patients within 22-35 years. The patients were prescribed oral haematinics, containing 60 mg of elemental iron, thrice daily, with meals. The various aspects of pharmacoepidemiology and pharmacohaemovigilance of ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate, including patients' demographic characteristics, anaemic symptoms assessment, prescription patterns, and safety assessment, on 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> months and follow-up visits, were recorded and thoroughly analysed.

**Results:** In groups A and B, the demographic characteristics of the patients were comparable; ferrous ascorbate was the most commonly prescribed oral haematinic, followed by ferrous sulphate, ferrous fumarate and ferric ammonium citrate, which controlled mild to moderate iron deficiency anaemia, with a gradual significant rise in haemoglobin concentration, in the successive 3 months; and adverse effects were observed to be statistically non-significant in either group.

**Conclusions:** The different aspects of pharmacoepidemiology and pharmacohaemovigilance in the study established that the oral haematinics were reasonably beneficial and safe among the anaemic women population, in rural India.

**Keywords:** Pharmacoepidemiology, Pharmacohaemovigilance, Ferrous ascorbate, Ferrous fumarate, Ferrous sulphate, Ferric ammonium citrate

### INTRODUCTION

The modern concept of iron metabolism began in 1937, with the work of McCance et al on iron absorption and excretion; and the measurement of iron in plasma by Heilmeyer et al.<sup>1</sup>

According to the World Health Organization, more than 30% of the world's population is anaemic, majority suffering from iron deficiency anaemia; mostly found in

the economically underprivileged countries within Asia and Africa.<sup>2</sup> In the Western countries, iron deficiency anaemia is quite common among the infants, children, women with menorrhagia, pregnant women, and women after childbirth. A large epidemiological study from France showed that approximately 93% of women have insufficient dietary iron intake and 23% of women of child bearing age lack iron, among which 4% are anaemic. A survey of data showed that one out of 6 adult women is iron deficient.<sup>3-5</sup>

Iron deficiency is the most common nutritional cause of microcytic, hypochromic anaemia. Iron is an essential component of myoglobin; haeme enzymes such as the cytochromes, catalase, and peroxidase; and the metallo-flavoprotein enzymes, including xanthine oxidase and the mitochondrial enzyme  $\alpha$ -glycerophosphate oxidase. Iron deficiency has been associated with behavioural and learning problems in children, abnormalities in the metabolism in muscle, catecholamine metabolism and impaired heat production. The ubiquitous role of iron has led to widespread studies on early and accurate detection of iron deficiency and its prevention.<sup>1</sup>

The average daily iron requirement for an infant is 67 mg/kg, for a child is 22 mg/kg, for a male adolescent is 21 mg/kg, for a female adolescent is 20 mg/kg, for a male adult is 13 mg/kg, for a female adult is 21 mg/kg and for a mid-to-late pregnancy is 80 mg/kg.<sup>1</sup>

In developed countries, the normal adult diet contains ~6 mg of iron per 1000 calories, providing an average daily intake for adult men of between 12 and 20 mg and for adult women of between 8 and 15 mg. The average dose for the treatment of iron-deficiency anaemia is ~200 mg of iron per day (2-3 mg/kg), given in three equal doses of 60-65 mg; half the average adult dose for children weighing 15-30 kg; small children and infants can tolerate relatively large doses of iron, like 5 mg/kg. These doses are a compromise between the desired therapeutic action and the toxic effects. Prophylaxis and nutritional iron deficiency may be managed with modest doses. For prevention of iron deficiency in pregnant women, doses of 15 to 30 mg of iron per day are adequate to meet the 3 to 6 mg daily requirement of the last two trimesters. To treat iron-deficiency anaemia, where the circumstances do not demand haste, a total dose of ~100 mg (35 mg three times daily) may be used. For patients who require maximal therapy to encourage a rapid response or to counteract continued bleeding, as much as 120 mg of iron may be administered 4 times a day. Sustained high rates of red-cell production require an uninterrupted supply of iron, and oral doses should be spaced equally to maintain a continuous high concentration of iron in plasma. The duration of treatment depends upon the rate of recovery of haemoglobin (Hb) (which depends on the severity of anaemia) and the desire to create iron stores. An anaemic patient treated with 25 mg of iron per day would respond with a rise of 1% of Hb (0.15 g Hb/100 ml) per day; and the reticulocyte response would occur between 4 and 12 days. An increase in the Hb of at least 2 g/dl after 3 weeks of therapy is a reasonable criterion of an adequate response. Thus, an individual with Hb of 50 g/l may achieve a normal complement of 150g/l in ~50 days, whereas an individual with Hb of 100 g/l may take only half that time. The creation of stores of iron requires many months of oral iron administration. The rate of absorption decreases rapidly after recovery from anaemia, and after 3-4 months of treatment, stores may increase at a rate of not much more than 100 mg/month. Much of the strategy of continued therapy depends on the estimated

future iron balance. Patients with an inadequate diet may require continued therapy with low doses of iron. If the bleeding has stopped, no further therapy is required after the Hb has returned to normal. With continued bleeding, long-term, high dose therapy is indicated.<sup>1,6</sup>

Intolerance to oral preparations of iron primarily is a function of the amount of soluble iron in the upper gastrointestinal tract. Adverse effects of oral haematinics include heartburn, nausea, upper gastric discomfort, and diarrhea or constipation. The best way of treatment is to initiate therapy at a small dosage, to demonstrate freedom from symptoms at that level, and then gradually to increase the dosage to that desired. Nausea and upper abdominal pain are very common at high dosage. Constipation and diarrhoea, perhaps related to iron-induced changes in the intestinal bacterial flora are not more prevalent at higher dosage, nor is heartburn. For liquid iron therapy, the iron solution must be placed on the back of the tongue with a dropper to prevent transient staining of teeth. The normal individual is able to control absorption of iron despite high intake, and it is only individuals with underlying disorders that augment the absorption of iron who run the hazard of developing iron overload in haemochromatosis.<sup>1</sup>

Parenteral iron therapy should be used only when clearly indicated because acute hypersensitivity, including anaphylactoid reactions, can occur in 0.2-3% of patients. Other reactions to intravenous iron include headache, malaise, fever, generalized lymphadenopathy, arthralgias, urticaria, and in some patients with rheumatoid arthritis, exacerbation of the disease.<sup>1</sup>

The main causes of iron deficiency are inadequate iron absorption, increased iron requirements, inadequate iron intake or increased iron losses. Iron enhances immune defense, has anti-carcinogenic properties, as well as, improves cognitive activities. The prophylactic use of oral iron should be reserved for patients at high risk, including pregnant women, women with excessive menstrual blood loss, and rapidly growing infants and for adults with chronic blood loss. The goal of iron therapy is to repair the Hb deficit and replenish storage iron.<sup>1,7-9</sup>

Conventional oral iron preparations include ferrous sulphate, ferrous fumarate and ferric ammonium citrate, while newer preparations include ferrous ascorbate.<sup>10</sup>

Ferrous ascorbate has the advantage of providing both ferrous iron and ascorbate in the same compound. It has excellent absorption as ascorbic acid enhances absorption of iron. When administered as ferrous ascorbate, ferrous salt delivers maximum amount of ferrous iron to the duodenal brush border and at the same time produces minimum gastrointestinal tract adverse effects. Ascorbate forms complexes with and/or reduces ferric to ferrous iron. Ferrous salts are absorbed about three times as well as ferric salts, and the discrepancy becomes even greater at high dosages. It has been demonstrated that ferrous

ascorbate is less easily oxidized than ferrous in ferrous sulphate.<sup>1,11-13</sup>

### **Aim**

The aim of this study was to examine the different aspects of pharmaco-epidemiology, (including patients' demographic characteristics, anaemic symptoms assessment, prescription patterns), and pharmacohaemovigilance (safety assessment), of oral haematinics, like ferrous ascorbate, ferrous fumarate, ferrous sulphate and ferric ammonium citrate, among the rural anaemic women of 15-35 years, who are suffering from mild to moderate iron deficiency anaemia, in the Indian spectrum.

## **METHODS**

### **Study type**

It was a multi-centre, retrospective, observational and analytical study of the hospital medical records.

### **Study population**

250 patients, who had earlier attended the out-patients departments, of the hospitals, and were treated for mild to moderate iron deficiency anaemia, and who were allocated into group A (consisting of 125 patients, within 15-21 years) and group B (consisting of 125 patients, within 22-35 years).

### **Study place**

The departments of Pharmacology, Obstetrics and Gynaecology and Internal Medicine of Gouri Devi Institute of Medical Sciences and Hospital, and Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Durgapur, West Bengal, India and J. J. M. Medical College, Bapuji Hospital and Chigateri General Hospital, Davangere, Karnataka, India, and the departments of Clinical Pharmacology, Obstetrics and Gynaecology and Internal Medicine of Hazra Polyclinic and Diagnostic Centre, Hazra Nursing Home, Domjur, Howrah, Kolkata, West Bengal, India.

### **Study period**

5 months (the research study was conducted and the compilation of the study literature was done, within the months of November 2012-January 2013, March 2017-April 2017 and July 2019).

### **Selection criteria of the patients**

The patients were selected based on the inclusion and the exclusion criteria given below, and the patients fulfilling those criteria, were included in the study.

### **Inclusion criteria**

The inclusion criteria were patients with mild or moderate iron-deficiency anaemia, women patients aged 15-35 years of age, patients with haemoglobin concentration more than or equal to 7 gm/dl, patients not using any previous iron supplements, and World Health Organisation definitions and criteria for anaemia.

### **Exclusion criteria**

The exclusion criteria were patients less than 15 years and more than 35 years, patients presenting with severe anaemia, patients with a history of hypersensitivity to the iron supplements, high-risk pregnancies, cardiac, renal or any other associated complications, any chronic disease intervening with the study data, patients suffering from gastrointestinal diseases, like peptic ulcer, regional enteritis and ulcerative colitis, haemosiderosis, bacterial infections, haemochromatosis, haemolytic anaemia and repeated blood transfusions..

### **Ethical approval**

At first, the clearance and the approval from the institutional ethics committee were obtained. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6), and in compliance with the regulatory requirements. Written permissions to access the relevant medical records were obtained from the hospitals, outlining the aims of the study. The study involved almost negligible risk, of any type, to the patients. The design provided an equal opportunity to all the eligible women to be included in the study. The patients who were included in the study were assured confidentiality, and an informed consent was obtained from each individual.

The hospital medical records of the patients prescribed with oral ferrous ascorbate, ferrous fumarate, ferrous sulphate or ferric ammonium citrate, containing 60 mg of elemental iron, thrice daily, with meals, were obtained. The detailed case history was obtained, from the records, with the proforma. The patients' present and past history, obstetric and gynaecological history for female patients, family history, personal history, socio-economic and reproductive history, and medication history, were recorded. The details of complete general physical examination and systemic examination, including obstetric and gynaecological examination, were recorded. Then, the values from the haematological evaluation reports were recorded. The details of patients' demographic characteristics, (duration of symptoms, pulse rate, respiratory rate and severity of anaemia, mild or moderate), anaemic symptoms (extreme fatigue, weakness, pale skin, shortness of breath, dizziness, soreness of tongue, brittle nails, pica, poor appetite,

irritability) assessment, prescription patterns of oral ferrous ascorbate, ferrous fumarate, ferrous sulphate or ferric ammonium citrate, efficacy assessment (by Hb concentration improvement), safety assessment (by recording the occurrence of any epigastric pain, heartburn, nausea, vomiting, staining of teeth, metallic taste, bloating, colic, diarrhoea and constipation on appropriate Adverse Event Case Report Form), the follow-up details, and their Hb concentration improvement, on 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> months and follow-up visits, were recorded and thoroughly analysed. The patients' participation assessment and adherence to treatment (including patients who completed the study thoroughly, number of drop-out patients to adverse effects, patients who were lost to follow-up and patients who withdrew voluntarily) were done from the records.<sup>14</sup>

### Statistical analysis

The study data was statistically analysed with mean±standard deviation values, probability values and different percentages.

## RESULTS

In this study, in both groups A and B, the demographic characteristics of the patients, like duration of symptoms, pulse rate, respiratory rate and severity of anaemia (mild or moderate), were comparable, as depicted in Table 1.

The predominant symptom in both group A and group B patients was extreme fatigue (A=44%, B=44.8%), as depicted in Table 2.

**Table 1: Demographic characteristics of group A and group B patients.**

Patients' characteristics	Group A (15-21 years) (n=125)	Group B (22-35 years) (n=125)
Duration of symptoms (years, mean/SD)	4.4/0.2	5.1/0.3
Pulse rate/min (mean/SD)	98.8/06	99.1/0.6
Respiratory rate/min (mean/SD)	21.3/1.7	21.4/1.8
Severity of anaemia (baseline haemoglobin g/dl) (mean/SD)		
Mild	9.2/0.2	9.1/0.3
Moderate	8.1/0.3	8.2/0.1

**Table 2: Assessment of symptoms in iron deficiency anaemia.**

Symptoms of anaemia	Group A (%) (15-21 years)	Group B (%) (22-35 years)
Extreme fatigue	44	44.8
Weakness	18.4	17.6
Pale skin	4.8	4.8
Shortness of breath	2.4	3.2
Dizziness	12.8	13.6
Soreness of tongue	4.8	4
Brittle nails	3.2	2.4
Pica	4.8	4
Poor appetite	4	4
Irritability	0.8	1.6

**Table 3: Prescription rates of different iron supplements.**

Iron supplements	No. of prescriptions	%
Ferrous sulphate	34	13.6
Ferrous ascorbate	173	69.2
Ferric ammonium citrate	19	7.6
Ferrous fumarate	24	9.6

As depicted in Table 3, ferrous ascorbate was most commonly prescribed (173 prescriptions, 69.2%), followed by ferrous sulphate (34 prescriptions, 13.6%), ferrous fumarate (24 prescriptions, 9.6%) and ferric ammonium citrate (19 prescriptions, 7.6%). In the successive 3 months, a gradual significant increase in Hb

concentration was observed, with each oral haematinic, mostly with ferrous ascorbate.

As depicted in Table 4, adverse effects were negligible in either group. Tolerability was good for the oral haematinics in both the groups. The observations were not statistically significant in either group.

250 patients participated in the study. All the patients completed the study thoroughly. There were no drop-out patients due to adverse effects, none was lost to follow-up

and none of the patients withdrew voluntarily. The patients' adherence to treatment was very high.

**Table 4: Adverse effects and their frequency.**

Adverse effects	Group A	P value	Group B	P value
	(15-21 years) N (%)		(22-35 years) N (%)	
Epigastric pain	0	NS	0	NS
Heartburn	0	NS	1	NS
Nausea	0	NS	0	NS
Vomiting	0	NS	0	NS
Staining of teeth	0	NS	0	NS
Metallic taste	0	NS	0	NS
Bloating	0	NS	0	NS
Colic	0	NS	0	NS
Diarrhoea	0	NS	0	NS
Constipation	0	NS	0	NS

\*NS: non-significant.

## DISCUSSION

Anaemia is a global health problem, among adolescence, pregnancy and lactation.<sup>4,15</sup> The adverse health outcomes of anaemia include increased maternal and perinatal mortality, preterm delivery, low birth weight, extreme fatigue and impaired immune system.<sup>16-22</sup>

Anaemia can be defined as the “fall of Hb concentration below a statistically defined threshold laying at two standard deviations below the median of a healthy population of the same age, sex, and stages of pregnancy”.<sup>23</sup>

Anaemia is a common problem in obstetrics and perinatal care. Reasons for anaemia in pregnancy are mainly nutritional deficiencies, parasitic and bacterial diseases, and inborn red blood cell disorders such as thalassemia's. The main cause of anaemia in obstetrics is iron deficiency, which has a worldwide prevalence between estimated 20–80% and consists of a primarily female population. Stages of iron deficiency are depletion of iron stores, iron-deficient erythropoiesis without anemia, and iron deficiency anemia, the most pronounced form of iron deficiency. Pregnancy anemia can be aggravated by various conditions such as uterine or placental bleedings, gastrointestinal bleedings, and peripartum blood loss. Anaemia has specific risks during pregnancy for the mother and the fetus, such as, intrauterine growth retardation, prematurity, foeto-placental miss ratio, and higher risk for peripartum blood transfusion. Besides the importance of prophylaxis of iron deficiency, the main therapy options for the treatment of pregnancy anemia are oral iron and intravenous iron preparations.<sup>24</sup>

The average iron requirements for pregnancy includes 170 mg for external iron loss, 450 mg for expansion of red cell mass, 270 mg of foetal iron, 90 mg of iron in placenta and cord, and 150 mg for blood loss at delivery.<sup>1</sup>

Subjects with normal iron stores absorb 10-35% of iron dose. Those who are iron deficit may absorb upto 95% of an iron dose. Poor bioavailability has been reported as the major cause of iron deficiency in a population whose diet is predominantly cereal-based. The effectiveness of iron therapy is best evaluated by tracking the reticulocyte response, and the rise in the haematocrit. An increase of  $\geq 20$  g/l in the concentration of Hb by 3-4 weeks shows a significant improvement in the iron therapy. Once a response to oral iron is demonstrated, therapy should be continued until the Hb returns to normal. Treatment may be extended if it is desirable to replenish iron stores. Gastrointestinal upset is minimal if the daily dose does not exceed 180 mg elemental iron and if iron is given with food.<sup>1,25</sup>

Ferumoxitol is a semisynthetic carbohydrate-coated superparamagnetic iron oxide nanoparticle that is approved for treatment of iron deficiency in patients with chronic kidney disease.<sup>1</sup>

A variety of substances designed to enhance the absorption of iron include surface acting agents, carbohydrates, inorganic salts, amino acids, and vitamins. When present in an amount of  $\geq 200$  mg, ascorbic acid increase the absorption of medicinal iron by at least 30%.<sup>1</sup>

The response of iron-deficiency anaemia to iron therapy is influenced by several factors, including the severity of anaemia, the ability of the patient to tolerate and absorb medicinal iron, and the presence of other complicating illnesses. Therapeutic effectiveness is best measured by the resulting increase in the rate of production of red cells. The magnitude of the marrow response to iron therapy is proportional to the severity of the anaemia (level of erythropoietin stimulation) and the amount of iron delivered to marrow precursors. In adults, depletion of iron stores may be recognized by a plasma ferritin  $< 12$



µg/l and the absence of reticuloendothelial haemosiderin in the marrow aspirate. Iron-deficient erythropoiesis is identified by a decreased saturation of transferrin to <16% and/or by an increase above normal in red cell protoporphyrin. Iron-deficiency anaemia is associated with a significant decrease in the concentration of Hb in the blood. However, the physiological variation in Hb levels is so great that only about half the individuals with iron-deficient erythropoiesis are identified from their anaemia. Moreover, normal Hb and iron values in infancy and childhood are lower because of the more restricted supply of iron in young children. The patient's ability to tolerate and absorb medicinal iron is a key factor in determining the rate of response to therapy.<sup>1</sup>

The efficiency of absorption depends on the salt form, the amount administered, the dosing regimen and the size of iron stores. Tolerability is influenced by several factors e.g., age, body mass, socioeconomic status (genetic variants).

Agarwal et al conducted a comparative study to compare the efficacy of ferrous ascorbate and carbonyl iron and showed that ferrous ascorbate resulted in significantly higher increase in hemoglobin as compared to carbonyl iron.<sup>26</sup>

Sarkate et al conducted a study comparing efficacy of sodium feredetate with ferrous fumarate in pregnant anemic women and showed that hemoglobin rise was more with sodium feredetate than ferrous fumarate as in the present study.<sup>27</sup>

Szarfarc et al in their study concluded that ferrous bisglycinate was significantly more effective than ferrous sulphate even in lower doses as in our study.

Study conducted by Patil et al showed comparable rise in Hb with ferrous bisglycinate, ferrous fumarate and carbonyl iron.

Pineda et al showed significant rise in serum ferritin with 60 mg and 120 mg of iron from ferrous bisglycinate and with 120 mg of iron from ferrous sulphate and not with ferrous bisglycinate containing 30 mg of iron.<sup>28</sup>

Melamed et al conducted a study to assess the use, side effects and discontinuation rates of iron preparations in pregnancy. They found that maximum side effects were with ferrous fumarate and minimum with ferrous bisglycinate.<sup>28</sup>

Another study, conducted in the North-Western pharmacoepidemiological region of the Indian spectrum, had shown that ferrous sulfate and iron peptone and ferrous ascorbate were most commonly used iron preparations. The results showed no significant differences in the efficacy in between the treatment groups for treating iron-deficiency anaemia. Various adverse drug effects were seen like nausea, vomiting and

heart burn. Iron peptone and ferrous ascorbate had more adverse drug reactions than patients receiving ferrous sulfate.<sup>29</sup>

Yet another study, conducted in the North-Central pharmacoepidemiological region of the Indian spectrum, had shown that on intergroup comparison it was found that maximum rise in Hb on day 60 was with ferrous ascorbate and minimum rise was with ferrous sulphate. Ferrous ascorbate and ferrous bisglycinate showed significantly more rise in Hb as compared to ferrous sulphate. Sodium feredetate and ferrous fumarate also showed more rise as compared to ferrous sulphate but the difference was not significant. Maximum side effects were with ferrous fumarate followed by ferrous sulphate. Minimum side effects were with sodium feredetate. The side effects reported by women were tolerable and not to the extent of leading to discontinuation of iron salts.<sup>28</sup>

In this study, conducted in the South-Eastern pharmacoepidemiological region of the Indian spectrum, in both groups A and B, the different demographic characteristics of the patients, like duration of symptoms, pulse rate, respiratory rate and severity of anaemia (mild or moderate), were comparable. The predominant symptom in both group A and group B was extreme fatigue (A=44%, B=44.8%). Ferrous ascorbate was most commonly prescribed (173 prescriptions, 69.2%), followed by ferrous sulphate (34 prescriptions, 13.6%), ferrous fumarate (24 prescriptions, 9.6%) and ferric ammonium citrate (19 prescriptions, 7.6%). In the successive 3 months, a gradual significant increase in Hb concentration was observed, with each oral haematinic, mostly with ferrous ascorbate. Adverse effects were negligible in either group. Tolerability was good for the oral haematinics in both groups. The observations were not statistically significant, in either group. These aspects of pharmacoepidemiology and pharmacohaemovigilance sufficiently established that the oral haematinics were reasonably beneficial and safe among the anaemic women population, in rural India.

## CONCLUSION

The different aspects of pharmacoepidemiology and pharmacohaemovigilance in the study established that the oral haematinics were reasonably beneficial and safe among the anaemic women population, in rural India.

## ACKNOWLEDGEMENTS

My sincere acknowledgements to the departments of Pharmacology, Obstetrics and Gynaecology and Internal Medicine, Gouri Devi Institute of Medical Sciences and Hospital, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Durgapur, West Bengal, India, and J. J. M. Medical College, Bapuji Hospital and Chigateri General Hospital, Davangere, Karnataka, India, and departments of Clinical Pharmacology, Obstetrics and Gynaecology and Internal Medicine, Hazra Polyclinic

and Diagnostic Centre and Hazra Nursing Home, Domjur, Howrah, Kolkata, West Bengal, India, for the successful completion of this research project.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Hazra M. A study on the aspects of pharmacoepidemiology and pharmacohaemovigilance of ferrous ascorbate, ferrous fumarate, ferrous sulphate and ferric ammonium citrate, among the rural anaemic women, in the Indian spectrum. *Int J Basic Clin Pharmacol* 2019;8:2751-8.