"Inj. Ferric Carboxymaltose (FCM) Vs Iron Isomaltoside (IIM) In Anemia In Pregnancy (Antenatal) - A Randomized Controlled Trial"

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Dr. ANITA DALAL, MD
Professor & HOD
Department of Obstetrics
and Gynecology
J.N. Medical College Belagavi- 590010

Date: 01.01.2022
Place: Belagavi

Department of Obstetrics & Gynecology
BELAGAVI.
J.N. Medical

Dr. (Mrs.) N. S. MAHANTSHETTI, MD
Principal
J.N. Medical College
Nehru Nagar, Belagavi- 590010

Date: 01.01.2022
Place: Belagavi

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Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu principal@jnmc.edu

Ref No: MDC/PG/ Date: 29-11-2021.

ACCEPTANCE LETTER

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Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BJ0119006.
Postgraduate Student,
2019-20 Batch,
Department of Obst. & Gynecology,
J. N. Medical College, Belagavi.

LIST OF ABBREVIATIONS USED

APH	–	Antepartum Hemorrhage
B.C.	–	Before Christ
BMI	–	Body Mass Index
Cm	–	Centimeters
CARPA	–	complement activation-related pseudo allergy
DBP	–	Diastolic blood Pressure
DLHS	–	District Level Health Survey
EDD	–	Expected date of Delivery
FCM	–	Ferric carboxymaltose
Fpn	–	Ferroportin
g/dl	–	Gram per deciliter
gm	–	gram
Hb	–	Hemoglobin
IIM	–	Iron Isomaltoside
IV	–	Intravenous
ICMR	–	Indian council of Medical research
IDA	–	Iron Deficiency Anemia
IPD	–	In-Patient Department
Kg	–	Kilogram
Kg/m^2	–	Kilogram per square meter
LMP	–	Last Menstrual Period
MCH	–	Mean Corpuscular Hemoglobin
MCHC.	–	Mean Corpuscular Hemoglobin Concentration
MCV	–	Mean Corpuscular Volume

MOHFW	–	Ministry of Health and Family Welfare
mg	–	Milligram
min	–	Minutes
ml	–	Milliliter
NFHS	–	National family Health Survey
NS	–	Normal Saline
p	–	Probability
PCV	–	Packed Cell Volume
PPH	–	Post Partum Hemorrhage
RBC	–	Red Blood Cell
RES	–	Reticulo-Endothelial System
RET-He	–	Retic Hemoglobin
SBP	–	Systolic Blood Pressure
SD	–	Standard Deviation
USA	–	United States of America
Vs	–	Versus
WHO	–	World Health Organization
mcg/L	–	Microgram per liter

ABSTRACT

Background & Objectives: Despite decades of health programs, Iron Deficiency Anemia continues to be a major problem during pregnancy. Due to proven poor compliance with oral iron and multi-dosing with older parenteral iron, single dose Parental iron is preferred. In India two single dose IV iron preparations (IIM and FCM) are available. This study aims to evaluate the efficacy and safety (rise in Hemoglobin) of Inj. Iron Isomaltoside in comparison to Inj. Ferric Carboxymaltose in treating Iron deficiency anemia in pregnancy.

Methods: A Randomized controlled trial was conducted from January 2020 to November 2021 in the Department of Obstetrics & Gynaecology, KLE's Dr. Prabhakar Kore Hospital, Belagavi. 105 pregnant women with hemoglobin <11 g% between 14-22 weeks gestation attending antenatal clinic were randomized into two group, Group A (51) receiving 500mg of Inj. IIM and Group B (54) receiving Inj. FCM. Rise in hemoglobin was assessed at 28±2 weeks of gestation.

Results: In the present study, the socio demographic characteristics, obstetric history, vitals and pre-infusion hemoglobin were comparable in both the groups (p = 0.50). Mean of Hemoglobin post-infusion was significantly more in Group A (12.33 ± 0.97g%) compared to Group B post-infusion (11.7 ± 0.94g%).

Mean rise in Hemoglobin was significantly more in group A (2.44 ± 0.98 g%) compared to group B (1.93 ± 0.71g%) which is statistically significant (p = <0.001)The adverse events were comparable in Group A and B (p=0.5).

Conclusion: Both iron formulations are effective in correcting IDA, however, IIM leads to more rise in hemoglobin in comparison to FCM. 6 (11.7%) adverse events were noted in IIM group whereas 3 (5.5%) adverse events were noted with FCM.

Keywords: Iron isomaltoside, Ferric Carboxymaltose , Ferric derisomaltose, Anemia, Pregnancy

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INTRODUCTION

Anemia is one of the commonest medical disorders during pregnancy. Centres for Disease Control and Prevention (1998) defined Anemia in iron-supplemented pregnant women using a cut-off of the 5th percentile- 11g/dl in the first and third trimester and 10.5 g/dl in second trimester.

Indian council of medical research describes Hemoglobin less than 10.9 g/dl as cut-off for Anemia in pregnancy.[1,2]

In 2016, Anemia was prevalent in 40.1 percent of pregnant women all over the world (WHO), the incidence being more common in south east Asian countries.[3]

50% of Pregnant women are anemic in India, 45.7% in Karnataka and 40% in Belagavi (NFHS 5, 2019-2020).[3,4]

Due to physiological changes which occur in pregnancy, there is an uneven increase in red cell mass and plasma volume which leads to hemodilution resulting in physiological anemia.[5] Total iron requirement during pregnancy is around 1000 mg, out of which 300mg is required by the fetus and placenta, 500mg for hemoglobin mass expansion and 200mg is shed through skin, gut and urine.[5] Additionally, 150-200mg iron is lost at the time of delivery and 150-200mg during lactation.[5]

Anemia in pregnancy has an harmful impact on the mother as well as the growing fetus. It is associated with various ante-natal, intra-natal and post-natal complications like fetal growth restriction, preterm births, low birth weight, puerperal sepsis and decreases the women's ability to tolerate blood loss intra-partum and post-partum.[1,5,6] Factors like early age at childbearing, repeated pregnancies at shorter intervals and poor antenatal care further aggravate this.[5,6]

There is rising evidence on importance of adequate iron to facilitate neurodevelopment of the fetus during late gestation.[7] It has now been proven that

children born to Anemic mothers lack concentration, deficit in cognition and motor functions in comparison to those born with optimum iron stores.[8]

In order to overcome this hazard, various measures have been taken across the globe as well as by the government of India in the last five decades.

In 1970, MOHFW launched the National Nutritional Anemia Control Program, which intended to provide "100 mg elemental Iron and 500 mcg Folic acid" supplementation to all pregnant women for at least 100 days".[9]

Recently, Anemia Mukt Bharat campaign, an interministreal campaign initiated by Ministry of Health & Family welfare (2018) aims in decreasing the prevalence of anemia from 50% to 32% in pregnant women by 2022.[10]

Despite of mandatory oral iron supplementation provided to all antenatal women during routine antenatal care, compliance to them is rather poor owing to the side-effects, need for daily intake.[11,12] In this regard, treatment with Parenteral iron provides a lucrative alternative to correct iron deficiency in pregnancy.[12,13,14] It has lesser side effects and can alleviate the need for blood transfusion antenatally and postnatally.[12] Furthermore, the reactions to IV iron have been identified as complement activation-related pseudo allergy (CARPA) reactions to the infusion particles which are generally self-limiting and subside on their own.[15]

Formulations like Inj. iron sucrose, Inj. ferric gluconate, Inj. Iron-sorbitol citric acid, are available in market and have proven to be effective in management of Iron deficiency anemia in pregnancy and are not associated with major adverse events.[16,17,18,19,20] However, their limitation is that they cannot be administered in large doses and require several visits for administration or prolonged hospital stay. This limitation has been overcome by Inj. Ferric Carboxymaltose which is

administered in a single dose of 500mg or 1000mg and Inj. Iron Isomaltoside which can be given up to 20mg/kg in a single setting with minimal side effects.[21,22]

Studies comparing Inj. Ferric Carboxymaltose with Inj. Iron isomaltoside found a higher incidence of Hypophosphatemia with Inj. Ferric Carboxymaltose.[23,24]

Several studies have been carried out to assess the safety and efficacy of Inj. Iron Isomaltoside in the treatment of iron deficient anemia associated with various disorders including post-partum haemorrhage.[25,26]

Recently studies conducted have supported the effectiveness and tolerability of Iron Isomaltoside in pregnancy.[27,28] But there is a limited literature to support the evidence.

Iron Isomaltoside was launched in Europe in 2010.[29] It is composed of iron and carbohydrate complex in a matrix structure with iron tightly bound to it. This ensures that iron is released in a methodical and precise manner to its binding proteins, avoiding potential toxicity from labile iron release. This structure of the iron Isomaltoside allows high dosing (Dose of 1.5 g at once) over a bout of time. Iron Isomaltoside can be given with maximum single dose of 20mg/kg of body weight.[29]

This study aims to compare the effectiveness and tolerability between Inj. Ferric Carboxymaltose and Inj. Iron Isomaltoside.

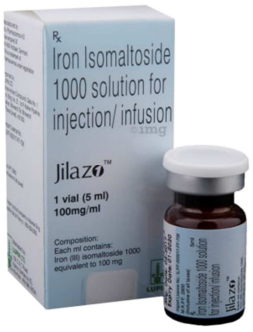


Figure 1 : Iron Isomaltoside (IIM)

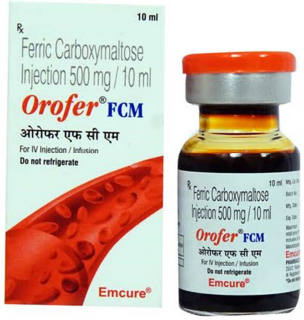


Figure 2 : Ferric Carboxymaltose (FCM)

OBJECTIVE

Primary Objective-

To evaluate the efficacy (rise in Hemoglobin) of Inj. Iron Isomaltoside compared to Inj. Ferric Carboxymaltose in treating Iron deficiency anemia in pregnancy.

Secondary Objective-

To find out safety (Prevalence of adverse drug reactions) with both IV preparations.

REVIEW OF LITERATURE

Anemia is widely prevalent and constitutes a major public health problem which affects both, emerging as well as developed nations with severe repercussions on health and socio-economic growth of the individual as well as the nation. A higher prevalence has been seen during the pregnancy due to multiple factors associated.

Pregnancy is associated with increased need for iron for fetal neurological development as well as for formation of increased iron stores to accommodate the increasing needs of pregnancy.[5,8]

Iron deficiency anemia (IDA) is associated with unfavourable consequences such as onset of preterm Labor, low-birth-weight neonates, and diminished iron stores for the neonate, these may result in compromised neuro-cognition.[5,6]

Iron deficiency is considered the commonest source of anemia in pregnancy, however there are other factors - nutritional deficiencies such as folic acid, multivitamin deficiencies and non-nutritional causes like chronic inflammation , parasitic infections , and inherited disorders which contribute to anemia.[1]

Anemia is defined as percentage of women aged 15−49 years with a hemoglobin less than 12 g/dL for non-pregnant and lactating women, and less than 11 g/dL for pregnant women, adjusted for altitude and smoking.[30]

It significantly contributes to the Maternal mortality across the world which is defined as “Total number of female deaths annually due to any cause related to or aggravated by pregnancy or its management during pregnancy and childbirth or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy excluding the incidental or accidental causes”.[31]

Despite of various health initiatives taken; it is still a chief health problem in the emerging world. Worldwide, the maternal mortality ratio in 2017 (“annual number

of deaths of women from pregnancy-related causes per 100,000 live births") is 462 in low income countries versus 11 per 1,00,000 live births in high income countries.[31]

Globally, an estimated 2,95,000 maternal deaths were reported in 2017, with an overall MMR of 211 maternal deaths per 1,00,000 live births in 185 countries . India contributed to 35,000 maternal deaths per 1,00,000 live births in 2017.

In 2017, maternal fatalities in Sub-Saharan Africa and South Asian countries accounted for almost 86 percent of all maternal deaths (254 000). Around 66 percent (1,96,000) of deaths occurred in Sub-Saharan Africa, whereas nearly 20 percent (58,000) occurred in South Asia. In addition, maternal deaths in South-Eastern Asia accounted for nearly 5% of all maternal deaths worldwide (16,000).[31]

Most maternal deaths are preventable if appropriate measures are taken to prevent the cause, or timely interventions are taken to address the cause. Therefore, it is essential that all women must receive excellent ante-natal , intra-natal and post-natal care.[32]

WHO had recommended a minimum of 8 ante-natal visits during pregnancy; first visit within 12 weeks of gestation , second contact at 20 weeks , third contact at 26 weeks , fourth contact at 30 weeks , fifth contact at 34 weeks , sixth contact at 36 weeks , seventh contact at 38 weeks , eighth contact at 40 weeks of gestation. This aimed at reducing perinatal mortality as well as to improve antenatal care.[33]

Despite all of the treatments and health programs implemented, poor women in remote locations continue to struggle to obtain adequate health care. This is particularly common in areas where skilled health personnel are scarce, such as Sub-Saharan Africa and South Asian countries.

In order to achieve Sustainable Development Goals (SDG), countries across the globe came together to decelerate maternal mortality rate by 2030. SDG 3 targets

at : "reducing the global MMR to less than 70 per 1,00,000 births, with no country having a maternal mortality rate of more than twice the global average".[34]

The Safe Motherhood movement was founded in 1987 by international institutions and officials from 45 countries with the goal of halving maternal fatalities by the year 2000.

The elimination of anemia during pregnancy is a critical component of Safe Motherhood.[35]

Historical aspect

Anemia is considered to be as ancient as the survival of human species.

Do we know if the Early man had anemia as well? Prehistoric human skeletal remains were found which showed numerous tiny dents in the outermost layers of skull condition known as Porotic Hyperostosis (PH) which is also associated with widening of diploe.

Stuart-MacAdam in 1992 studied these remains and claimed that PH is indicative of Iron deficiency anemia. This was further sustained by evolution of humans and moving of communities from hunting to agriculture as their source of food and cultivating Maize which was a poor source of dietary iron. [36]

Since Ancient times, Chalybeate water in Rome (Iron rich) were known for their remedial properties. In those times Chalybeate springs were a source of major income in many any British spa facilities.

Iron content in water is underestimated in current times but in ancient times the healing properties of this Chalybeate water may have contributed in treating

symptoms which are now linked to Iron deficiency anemia. Therefore, a miraculous treatment was recognised even before the condition itself was understood.[36]

Despite the functioning of Chalybeate springs and associated remedial nature of them, the pathology associated with Iron deficiency anemia was not understood till centuries later.

Ancient people identified blood as “life and the thing containing soul”.

In Prehistoric era there was no awareness regarding blood and its components. Iron deficiency anemia was first described in 1500 B.C. Green sickness or Chlorosis was identified as Iron deficiency anemia in European countries.

Iron salts were first recommended for treatment of anemia by Thomas Sydenham although it remained disputed until 20th century, it was then that the physiology and pathology behind iron deficiency anemia were fully comprehended .

Haematological and biochemical developments in the field of iron deficiency anemia ran together before twentieth century.

Residual particles upon burning blood were found to be attracted by Iode stone which were reported as iron by Lemery and Geoffroy (1713) and Menghini (1747).

William Harvey reached a milestone in seventeenth century and proved that the blood flows in human body. After this breakthrough, many other inventions came up related to blood and disorders of blood. Some of the significant historical inventions and developments are:

1637	"Ruddy globules" or RBC's were discovered by Jan Swammerdam
1667	Transfusion from Lamb to a man (Heterologous) by Richard Lower
1739 - 1774	Importance of RBCs and their count by William Hewson
1743 - 1794	Importance of Oxygenation (change from dark purple to red hue) by Antoine Lavoisier
1818	First ever human to human blood transfusion in PPH by James Blundell
1854 - 1915	Study of blood cell morphology by Paul Erhlich
1900	Blood grouping and importance defined by Karl Landsteiner
1937	Establishment of Blood bank in USA

The term "Anemia" was coined in the nineteenth century to describe a clinical condition characterized by pale mucous membranes and nails.

Davies and Witts published a paper in 1931 that stressed the relevance of iron in hypochromic anaemia in adults. Davies further linked iron deficiency in women to abnormalities in mucosal and epithelial structures such as the nails, tongue, and oesophagus, which improved with treatment with iron salts.

In 1933, Wintrobe and Beebe summarised the physiology and pathology behind Iron deficiency Anemia. They stated that "there is only presumptive evidence that idiopathic hypochromic anemia develops because an individual is unable to meet the demands for haemoglobin or replace the normal loss of blood on account of defective utilization of blood building materials in the diet".[36,37]

Era of modern haematology is originated from Harvard Medical School. George Richards Minot and his assistant William Murphy made excellent contributions in modern haematology.

With newer innovations, we are currently able to treat anemia with Oral iron formulations, Parenteral iron formulations, Blood transfusion and Bone marrow transplantation.

Present Scenario

Worldwide

Anemia affects 42 percent of children under the age of five and 40 percent of pregnant women worldwide, according to the World Health Organization.[30]

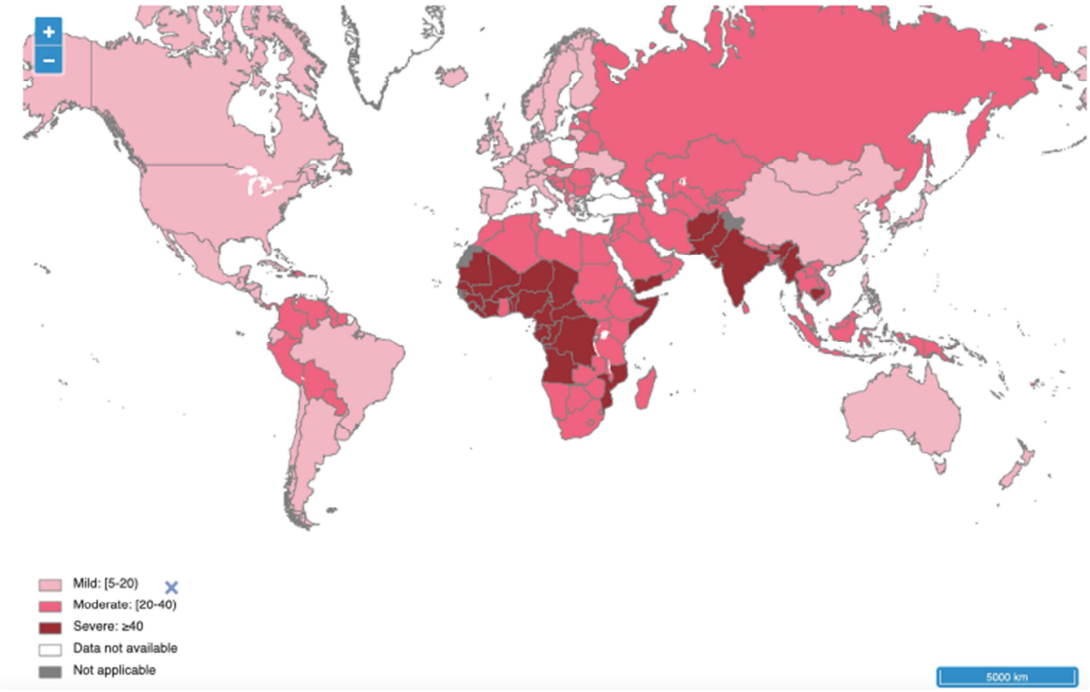


Figure 3: Anemia as a public health problem by country: Pregnant women

Indian scenario

Despite of various health programs launched by Indian government from time to time to address this problem , prevalence of anemia is still very high. According to National Family Health Survey (NFHS – 5, 2019-2020) 50.1% (44.2-54.2) Pregnant women in India are anemic.[4] Whereas , 53.4% (39.8 – 65.4%) children under 6 – 59 months are found to be anemic. Nearly 53% (43.7 – 61.6) or 1,87,325 non pregnant women are anemic in India.[30] This imposes a major challenge in ensuring a good maternal and perinatal outcome and reducing maternal mortality in India.

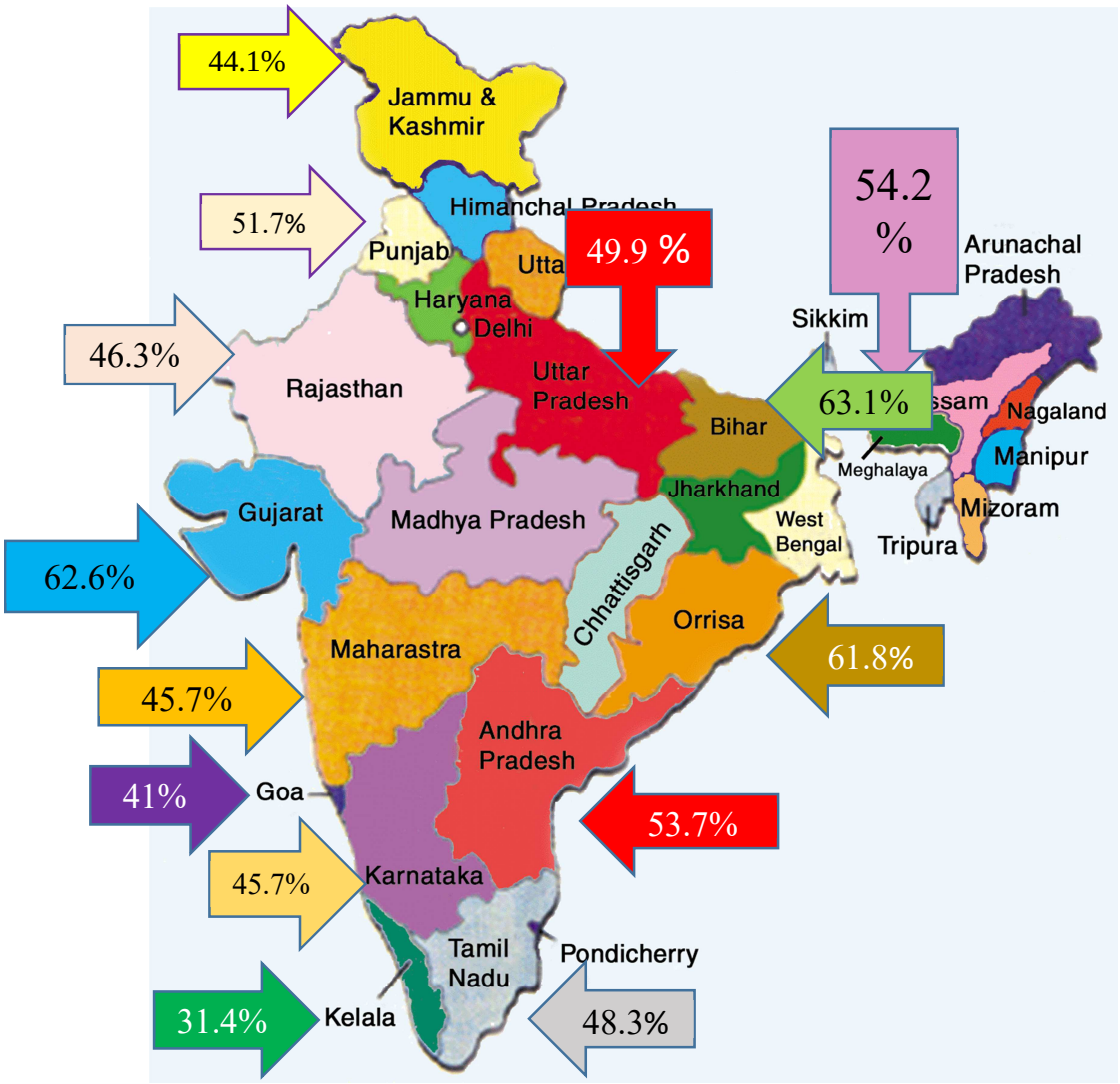


Figure 4: Prevalence of Anemia in Pregnancy (NFHS 5, 2019-2020)[4,30]

Karnataka

According to NFHS 5, 45.7% Pregnant women in Karnataka are anemic. 50.6% in rural areas and 45.7 % in urban areas.[4] This indicates an unequal distribution and operation of health services in Rural and urban areas. 60.9% children under 6 – 59 months are anemic. Nearly 44.8% or 1,87,325 non pregnant women are anemic in Karnataka.[4]

Impact of Anemia on pregnancy

In Pregnancy, disproportionate increase in volume of plasma and red cell mass leads to hemodilution which causes physiological anemia , resulting in increased demand of additional Iron throughout the pregnancy, childbirth and postpartum.

In early trimester, the diminution of iron stores results from increase need of iron by the fetus which exceeds the iron consumption by the mother with results in depletion of iron stores in a woman's body. A total of 1000mg iron is required during Pregnancy, out of which 500mg is utilised for maternal hemoglobin mass expansion, 300 mg is utilised by the fetus and placenta and the remaining 200 mg is shed through skin, gut. Nearly , 0.8 mg/day iron is required in first trimester , whereas 4-5 mg/day and 6 mg/day is required in second and third trimester respectively.[1]

According to WHO, Recommended dietary allowance of iron for a pregnant woman is 2.80mg in an average of 55 kg woman and 1.65 mg in an average of 55kg woman during lactation.

However, average iron intake from food in women is 10.5 mg/day, out of which only 10% is absorbed.[1] Therefore not enough for formation of large iron stores in a pregnant women.

Moreover, during first 6 months of pregnancy, fetus has the priority over mother's needs to ensure adequate iron stores thus rendering the mother deficient if adequate iron supplementation is not given.[8]

Classification

The WHO classifies anemia in pregnancy into:[1,5]

- Mild anemia (hemoglobin 10-10.9g/dL)
- Moderate anemia (hemoglobin 7.0-9.9g/dL)
- Severe anemia (hemoglobin < 7g/dL)

According to ICMR , Anemia in pregnancy is subdivided into:

- Mild anemia (hemoglobin 10-10.9g/dL)
- Moderate anemia (hemoglobin 7.0-9.9g/dL)
- Severe anemia (hemoglobin 4.0-6.9g/dL)
- Very Severe anemia (hemoglobin <4.0g/dL)

The prevalence of IDA is higher in women who conceive with depleted or deficient iron stores, a scenario usual in developing countries, where high parity and short intervals between children are major predisposing factors.

Literature available has suggested that iron deficiency is the leading cause of anemia followed by deficiency of folic acid and Vitamin B12.[30]

In India, the higher prevalence of anemia can be attributed to:

1. Low intake of iron and folic acid in diet
2. Presence of inhibitors of iron like phytate and fibre in Indian diet leading to poor bio-availability.
3. Malaria and hook worm infestation leading to chronic blood loss.

Various food products if consumed with iron rich products either hamper or enhance the absorption of iron depending on their properties.[1,6] Phytates, Tannins, Calcium, magnesium reduce the absorption of iron by competing with its receptors. Red meat, Proteins, Citric acid, gastric acidity, low iron stores act as enhancers for iron absorption. Low levels of iron enhancers lead to poor bioavailability of iron leading to Iron deficiency anemia. Low iron storage at birth, low iron concentration in breast milk, and low dietary iron consumption during childhood and adolescence all contribute to anemia in children.[5,6]

However, there may be isolated iron deficiency but no evidence of anemia , this may be confirmed by laboratory testing. This isolated iron deficiency is responsible for low iron stores. Low iron stores in mother are responsible for low iron stores in fetus as well.

As a result of the maternal iron shortage and anemia, the offspring are at greater risk of acquiring iron deficiency as early as the intrauterine stage.[8] It is becoming more common in Children due to the low iron content of supplemental foods and family foods ingested by young children.[38]

The prevalence and severity of anemia in adolescent girls increases with the onset of menstruation and accompanying blood loss.[30] Anemia, if present before is worsened by early marriage and adolescent pregnancy, and the offspring have low iron stores.

Iron Metabolism

Iron balance in an individual is influenced by three factors - nutritional intake, loss of iron, and demand of iron by the body. Nutritional iron intake is determined by the amount of digested iron in meals and the ability to absorb iron from the digestive

tract. The amount of iron absorbed is mostly determined by the existence or absence of gastrointestinal pathology or a comorbidity that causes increased expression of iron regulatory proteins and hepcidin, a peptide that prevents iron absorption The breakdown of erythrocytes by reticuloendothelial system (RES) macrophages, particularly those in the spleen, is the primary source of iron in humans, or, to put it another way, a recycling internal iron supply.[39]

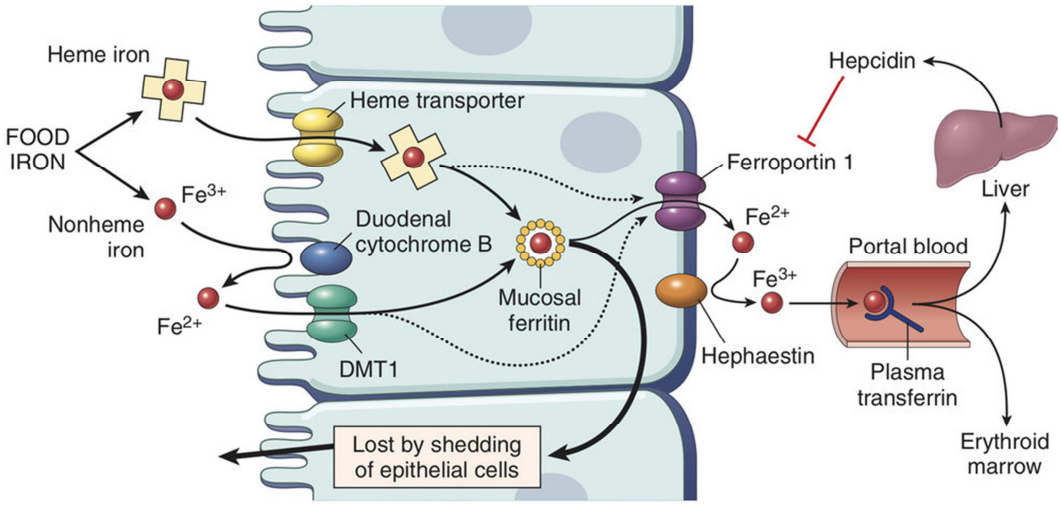


Figure 5: An intestinal villus cell absorbs iron from the intestine and transports it to the plasma.[40]

Organic complexes as well as Fe^{2+} and Fe^{3+} salts, make up nonheme dietary iron. Ferriductases in apical membrane and ascorbic acid, such as duodenal cytochrome b, reduce Fe^{3+} to Fe^{2+}. An H^{+} electrochemical potential gradient is created by the acid microenvironment at the brush-border, which favours Fe^{2+} trafficking into the enterocyte via the Divalent metal ion transporter (DMT-1). Other nutritionally important metal ions (such as Mn2+) may also get absorbed through DMT-1.

Endocytosis can take up heme, thus liberating Fe^{2+} in the endosome, although the identities of molecules of the proteins involved, including heme carrier protein 1

(HCP1), are unknown. Ferroportin, in conjunction with hephaestin, may mediate Fe^{2+} export from the basolateral membrane. HO, heme oxygenase; Fe2Tf, differentiable transferrin.[39,40]

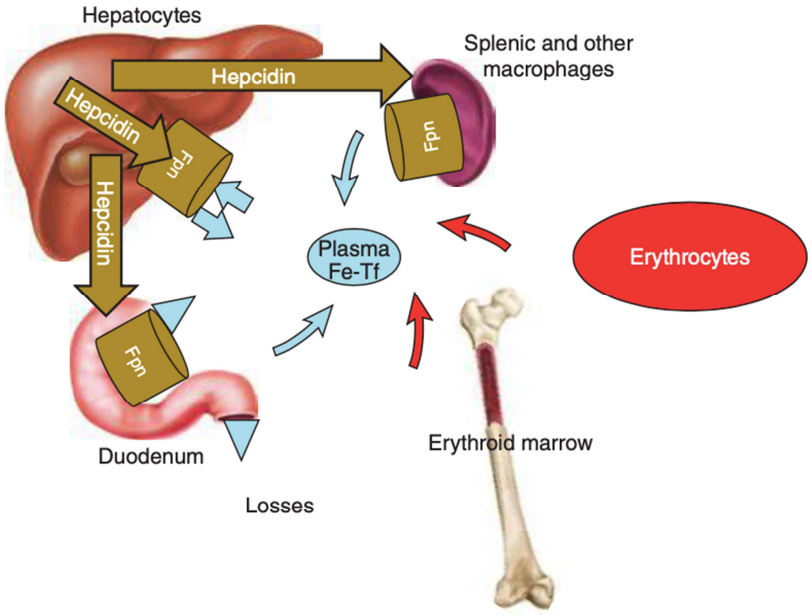


Figure 6: Hepcidin regulates the flow of iron into the plasma.

The only known transporter of iron from cells to plasma is ferroportin (and extracellular fluid). It controls the transport of iron to plasma from all of its primary sources: iron-absorbing duodenal enterocytes, iron-storing hepatocytes, and iron-recycling macrophages, via inducing ferroportin endocytosis and proteolysis.[39]

Hepcidin is the main regulator of systemic iron homeostasis.[41] Hepcidin production when disrupted, leads to a variety of iron issues.[42]

Hepcidin excess is linked to inflammatory anemia, chronic kidney disease, and iron-refractory iron deficiency anaemia. Hepcidin and ferroportin (Fpn) interact to control the flow of iron into plasma.[42] Its content is influenced by iron, erythropoietic activity, and inflammation.[43,44]

Low hepcidin conditions - Iron is exported via ferroportin into extracellular space.[43]

High hepcidin conditions- Ferroportin is degraded and hence Iron accumulates.[43]

Metabolism of Iron in Pregnancy

During pregnancy, fetal hepcidin governs the transfer of iron from maternal plasma to the fetal circulation.[45] Iron enters the bloodstream at a quicker pace when hepcidin levels are low.[44] When hepcidin levels are high, ferroportin is internalised, and iron is trapped in enterocytes, macrophages, and hepatocytes.[44] The daily requirement for outside iron remains low, ranging from 1 to 8 mg per day. More external iron, on the other hand, is needed to offset rising iron demand, especially during growth, pregnancy, and lactation. This large rise in iron need is essential in supporting mother's blood volume as well as the development of the fetus and placenta. Furthermore, iron loss occurs in pregnant women both during and after birth. The total amount of iron lost during pregnancy and lactation is around 1000 mg.[1,5,6]

Diagnosis

Various laboratory parameters are beneficial in the diagnosis of anemia due to iron deficiency. Hemoglobin estimation along with Packed cell volume should be done to look for presence of Anemia to rule out hemoconcentration in presence of other etiologies.[46] Hemoglobin is estimated with cyanmethemoglobin method, which is considered the gold standard. Iron deficiency anemia is reflected by a microcytic hypochromic picture on peripheral smear examination.[1,5,6,46] In endemic regions where sickle cell anemia, thalassemia is more common in races like sindhis and Punjabis, Hemoglobin electrophoresis should be done.

Iron deficiency anemia (IDA) is associated with decreased MCV, MCH, MCHC. Mentzer index differentiates IDA from Thalassemia as (MCV/RBC) >13 is suggestive of Iron deficiency anemia.

Ferrokinetic investigations are carried out to determine the presence of iron deficiency and anemia.

Serum ferritin <10 mcg/L , Transferrin saturation <10% , Total Iron Binding Capacity (TIBC) >400 mcg/dl , Serum iron <30mcg/L are indicative of Iron deficiency Anemia. Whereas a Serum ferritin level of <30 mcg/L is indicative of iron deficiency.

However, Serum ferritin is not a specific indicator as it may be raised in case of acute infection along with concurrent anemia. Certain newer modalities have come up in recent times which help in diagnosis of iron deficiency anemia.

1. Retic hemoglobin (RET-He) : Reticulocytes mature in the bone marrow for 1–3 days and circulate for 1–2 days before maturing into mature erythrocytes. It measures the hemoglobin content of these freshly produced reticulocytes. It provides information on the supply of iron for erythropoiesis in last 3- 4 days and provides insight into the quality of erythropoiesis.[47]

   It's notably useful for distinguishing between the two most common types of anemia, IDA and anemia of chronic disease.[47,48]

   Actual iron deficiency (low ferritin + low Ret-He) and 'functional' iron deficiency (normal/raised ferritin + low Ret-He) . Reference value: *28-30.8 pg.*[48]

2. Immature Reticulocyte fraction: ***Earliest reflector*** of erythropoietic activity of Bone marrow. It indicate the ***least mature RBC*** with high RNA ("shift" retics). It

is a ratio of young, immature to total Retic count. It has replaced total Retic count in clinical hematology practice.[49,50]

Maternal consequences of Anemia

Anemia in pregnancy can manifest in a variety of ways, ranging from diminished work capacity to heart failure, depending on the hemoglobin level. Women with mild anemia, on the other hand, can go through pregnancy and childbirth without any problems. These women find it difficult to carry out their daily chores and often complaint of easy fatiguability and generalized weakness, decreased appetite, history of Pica leading to a poor immune system. Thereby making them more susceptible to infections. Anemic women are susceptible to complications like Preterm labor, Low birth weight infants, Post-partum hemorrhage, need for blood products , Shock , sepsis , lactational failure etc. Severe anemia can show in three forms: compensated, decompensated, and circulatory failure. Hemoglobin levels below 5.0 g/dl usually indicates cardiac decompensation. Even when at rest, these compensatory adjustments cause palpitation and shortness of breath. These compensatory mechanisms are insufficient to deal with the drop in hemoglobin levels, and as a result, the presenting symptom can occur at any stage of pregnancy.[1,5,6]

Any blood loss in the third stage in severe anemic women can lead to hemorrhagic shock and death. Even today, women in India's distant rural areas reach the hospital only after they are severely decompensated, resulting in a greater mortality rate. Therefore, Severe anemia is related to high maternal mortality due to excessive blood loss, lack of care and delayed referral.

Impact of anemia on the fetus

During development, when cells' oxygen consumption rates are at their highest due to the energetic demands of growth and differentiation, iron shortage has more catastrophic implications.[8,51,52,53] A neonate's total-body oxygen demand is three to four times larger than that of an adult per kilogram of weight. Furthermore, the new-born brain consumes 60% of the oxygen consumed by the adult brain, compared to 20% in adults. Iron deficiency is more common in pregnant women and young children due to this high iron-dependent energy demand.[51-53]

A growing body of research supports the idea that appropriate fetal iron load during pregnancy affects the iron status of infant 9 months of life.[8]

The risk of postnatal iron shortage in babies is lowered if neonatal iron reserves are normal and cord clamping is delayed. Appropriate loading of the newborn via the maternal–fetal pathway may also reduce the need for excessive early iron supplementation of the infant postnatally in some iron-deficient communities.[53]

Prevention and Management of Anemia in pregnancy

Anemia poses a threat to both mother as well as the fetus and leads to adverse pregnancy outcome, therefore management of anemia is of utmost importance in obstetric practice.[1,5,6] Role of regular antenatal care and early detection of anemia by means of laboratory methods cannot be underestimated as a preventive measure.

Appropriate and timely management of anemia in form of oral iron supplementation as per Government of India (GOI), intravenous iron formulations, correction of severe anemia by blood transfusion later in pregnancy cannot be undermined.[1,5,6]

Effective management strategies and various health programs launched by GOI along with MOHFW aim to reduce incidence of maternal anemia by adapting various measures.

National Health Programs

In 1970, The National Nutritional Anemia Prophylaxis Program was established to help mothers and children avoid nutritional anemia.[9] Under this program, Pregnant women and lactating mothers were given 100 mg elementary iron, 500 mcg Folic acid daily.

The National Iron Plus Initiative aims to reach out to people of all ages to encourage them to take iron and folic acid supplements. "One pill of 100 mg elemental iron and 500mcg folic acid was recommended daily for 100 days after the first trimester and 100 days following delivery".[54] Anemia Mukt Bharat aimed to reduce the incidence of anemia to 32% by 2022.[10] Deworming, Prophylactic iron and folic acid supplements, Intensified Year – discovered a behavior change communication program (Solid body, smart mind) that included assuring delayed cord clamping, digital anemia testing, and point-of-care treatment, Compulsory inclusion of iron and folic acid fortified foods in public health programs, as well as addressing non-nutritional causes of anemia in endemic areas, with a special emphasis on malaria, hemoglobinopathies, and fluorosis.[10]

Anemia has been treated by iron in various forms since 16th century.[55] Pierre Blaud introduced ferrous sulfate in 19th century (1831) which then became the standard treatment for IDA.[55,56]

Oral iron supplements available in the market are considered to be equally efficacious and are simple to use. They are available as Ferrous and Ferric preparations. In comparison to Ferrous salts are more absorbable than Ferric salts.[57] These can be further classified into:

- Organic : Ferric polymaltose
- Inorganic : Ferrous sulphate , Ferrous fumarate , Ferric ammonium citrate
- Elemental : Carbonyl iron

- MAAC Salts : Ferrous amino acid chelate
- Technologically advanced iron salts : Ferrous ascorbate

Only 1–8% of iron is absorbed from existing oral iron preparations, depending on the type of preparation. Oral iron absorption increases with higher doses of oral iron. Gastrointestinal side effects associated with oral iron formulations limits the use of oral preparations up to 70% (especially Ferrous sulphate).

However, a study conducted in Zurich in 2015 found that giving 60–120 mg iron in single morning doses on alternate days enhances iron absorption in young women. Because of its simplicity, this regimen significantly enhanced iron absorption and may boost compliance.[58]

Oral iron therapy has been the mainstay of treatment of anemia until recently. Decreased compliance of the patients due to gastrointestinal side effects, daily administration has been a major limitation to its usage. In recent times a shift has been seen towards treatment of Anemia.[59] More and more intravenous iron formulations are now available in the market which are efficacious , easy to administer and have minimal side effects.[59,60] In older times, Intravenous iron was feared as Iron dextran was associated with major anaphylactic reactions.[61] Dextran-free parenteral iron formulations have been developed with enhanced efficacy and safety profiles and faster transportation times allows care providers to treat anemia more effectively. Various parenteral iron formulations are available in the market in present market. These dextran free intravenous iron alternatives.

Sucrosomial iron is another preparation of of ferric salt (ferric pyrophosphate) conveyed within a phospholipid. It directly engulfs into lipid bilayer of intestinal mucosa due to phospholipid structure. Due to its behavior in

gastric mucosa, it is well tolerated, highly bioavailable and is associated with less side-effects.[62,63]

In terms of hemoglobin rise and iron store replenishment, iron sucrose was found to be superior than oral iron, with minimal side effects.[64]

Iron and sucrose are separated from iron sucrose. Iron is delivered to target cells, including erythroid precursor cells, as a complex with transferrin. As the cells mature into red blood cells, the iron is absorbed into haemoglobin.[65]

Iron sucrose is given as 200 milligrams intravenously in 200 mL normal saline on alternate days for 15-20 minutes until the whole dose is reached; not to exceed the maximum dose of 1000 mg per week.[66]

Commonly seen side-effects are Dysgeusia , Hypotension , Hypertension , Nausea , Injection/ Infusion site reaction which may be attributed to its raised pH and osmolarity.[65,66]

Ferric Carboxymaltose is a colloidal solution of iron complex in ferric form. The complex provides utilizable iron for the iron transport (transferrin) and storage protein (Ferritin) in a controlled manner. It has a pH near to neutral, physiological osmolarity, and increased bioavailability, allowing a single dose of up to 1000mg to be given over 15 minutes.[67]

In terms of risk profile, efficacy, patient comfort and convenience, staff and institutional resource consumption, ferric carboxymaltose is a lucrative alternative to iron sucrose. The complex is progressively absorbed, primarily through the hepatic reticuloendothelial system (RES), with effective iron delivery to the endogenous transport system for haem production in new erythrocytes.[67]

Finally, in local tolerance testing with FCM, no sign of irritation was identified. Because of FCM's low toxicity and great efficacy, it can be given in massive doses in a single infusion or bolus injection, increasing the effective cost wise and convenience during infusion.[17,20,24] FCM possesses a number of properties that make it an effective intravenous iron preparation.[68,69]

However, in recent studies, FCM has been seen to cause higher incidence of Hypophosphatemia therefore there is a need for an alternative to combat this problem.[23,24]

In 2010, the European Union approved Iron Isomaltoside (Monofer, Denmark) or Ferric Derisomaltose. It is made up of an iron moiety and a carbohydrate moiety, with the iron securely bonded in a matrix structure. This results in a well-controlled release of iron to iron-binding proteins, reducing the risk of toxicity from labile iron release.[29] The Iron Isomaltoside formulation's structure enables for high dosing (single doses of 1.5g) in a short period of time. A maximum single dose of 20mg/kg real body weight of iron isomaltoside can be given.[29]

In a comparative trial with Inj. Iron sucrose in patients with IDA, Inj. Iron Isomaltoside resulted in mean increase in hemoglobin >2g/dl in median time of 26 days in 333 participants who were followed for 5 weeks. In the Iron Isomaltoside group, 0.6 percent of patients experienced serious adverse events (severe dyspnea and severe pruritis rash in one patient and significant syncope in another).[22]

In comparative trial with Inj. Iron sucrose, Inj. Ferric Carboxymaltose resulted in mean rise in hb of 2.96 g/dl in 12 weeks in 50 participants carried out from January 2016 to August 2017.[70] No serious adverse reactions were noted in any group, whereas another study resulted in significant increase in hemoglobin from 7.76 +/- 0.709g/dl to 13.25 +/- 0.606 g/dl in 4 weeks in 100 participants in each group with no serious adverse events reported.[71]

Inj. IIM had a much larger increase from baseline hemoglobin than Inj. FCM, with a mean difference of +0.249 g/dl, according to an indirect comparison conducted.[27]

Studies comparing the incidence of Hypophosphatemia and hypersensitivity reactions between Inj. FCM and Inj. IIM found that more patients who received Inj. FCM (45.5%)

experienced Hypophosphatemia as compared to Inj. IIM (4%) during the follow-up visits whereas more patients who received Inj. IIM experienced Hypersensitivity reactions (10.7%) in comparison to Inj. FCM (2.5%), whereas studies comparing various intravenous iron formulations to determine the risk of Hypophosphatemia resulted in higher prevalence of Hypophosphatemia (32.1%) after treatment with intravenous iron. Severe hypophosphatemia occurred exclusively after FCM (32.7%).[23,24]

In a research conducted from 2013 to 2018, 213 pregnant women were given a single IV-IIM injection. During IV-IIM administration, ten (4.7%) ADRs occurred. All of the ADRs were modest hypersensitivity reactions that went away on their own after a few minutes and did not return when the test was repeated. There was no link found between IIM dosage and ADR frequency.[28]

MATERIALS AND METHODS

KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi, to compare the efficacy and safety between Inj. Ferric Carboxymaltose and Inj. Iron Isomaltoside.

Ethical Considerations

After obtaining clearance from Institutional Ethics Committee of Jawahar Lal Nehru Medical College, Belagavi; Informed and written consent was taken from the participant. Participant was free to abandon the study, at any point during the study at her will.

Sample Size

The sample size formula is based on Average and standard deviation.

$$n = \frac{(z_\alpha + z_\beta)^2(s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Here, z_α is linked with the level of significance and z_β is linked with the power of the test.

For 5% level of the significance z_α =1.96 and z_β =0.84 for 80% power of the test.

The levels of Hb are taken in the calculations.

$\bar{X}_1$ is the mean of the first group (106) and $\bar{X}_2$ is the mean of the second group (100.1)

s_1 is the standard deviation of the first group (12.1) and s_2 is the standard deviation of the second group (7.2).

The sample size produced with these values is 62.

Considering 10% attrition, sample size obtained is 70.

There will be two groups each having 70 cases each.

Study Population

Antenatal patients admitted for iron correction in maternity ward in KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi.

Selection Criteria

Inclusion Criteria

Antenatal women in second trimester of Pregnancy from 14 to 22 weeks with Hemoglobin between 7 – 10.9 g/dl.

Exclusion criteria

Antenatal women who were not willing to participate, who had a known allergy to parenteral iron formulations, known case of Thalassemia or megaloblastic anemia, history of liver disease or any autoimmune disease, were excluded.

Methodology

After obtaining ethical clearance, all the Antenatal women admitted for parenteral iron correction were screened for baseline hemoglobin (Done by Cyanmethemoglobin method). The participants who fulfilled the inclusion criteria after considering the exclusion criteria were enrolled for the study. A detailed Informed consent form, stating the information regarding the study and drugs was given to the participant. After written consent, participant was recruited in the study and Randomization was done was done by SNOSE method (Sequentially Numbered Opaque Sealed Envelope).

The details of each participant were recorded using a self-designed, pre-tested, structured Proforma (copy enclosed).

The parameters recorded for each participant were:

- Demographic details: Age, Address, Occupation, Socio-economic status.
- Complaints: Weakness, Easy fatiguability , PICA , breathlessness , Pedal edema or any other complaints.
- Antenatal history
- Obstetric history
- Past history
- Family history

Procedure

After consent and randomization, Participants were either given inj. Iron Isomaltoside (IIM) in Group A or Inj. Ferric Carboxymaltose (FCM) in Group B. Both drugs were given as a dose of 500mg in 250ml of 0.9% Normal Saline over 20-30 minutes. No pre-medication (e.g. Anti-histaminic, steroid) was given before the administration of the drug.

Batch number and expiry date of drug to be administered was checked and noted. Participant was asked to lie in left lateral position. 20 Gauge cannula placed on the dorsum of hand.

Loading the drug: Drug to be administered was loaded in a 10ml (Inj. FCM) /5ml (Inj. IIM) syringe and immediately put in 250ml of 0.9% Normal Saline.

IV set was connected to 250ml Normal saline bottle; after filling the drip chamber, IV set was disconnected and drug was loaded directly into the bottle. IV set was reconnected to the normal saline and infusion was started.

Alternate method for loading the drug was to directly load via the syringe to the plastic bottle but it can lead to back splashing and wastage of the drug hence this method was avoided. Pulse rate, Blood Pressure, Fetal Heart rate were measured before, during and after the administration of both intravenous drugs. Starting time and ending time of the infusion was noted.

Participants were observed for complaints like headache, breathlessness, dizziness, hypertension, pain abdomen, nausea or any other complaint during the drug administration and afterwards for 30 minutes. Any minor or major complaints were documented. Participants who had such complaints; infusion was immediately stopped. They were reassured. These reactions were classified as Fish bane reactions which usually subside after stopping the infusion. Thereafter, infusion was restarted after 10-15 minutes after counselling the patient. Rise in hemoglobin was assessed at 26 - 30 weeks of gestation.

Steps for parenteral iron infusion

Figure 7: Cannula on dorsum of hand

Figure 8: Essentials for Parenteral Iron infusion

Figure 9 & 10: Loading the drug

Figure 11: Administration of drug in left lateral position

Statistical Analysis

R version 4.1.1 statistical tools and Microsoft Excel have been used to examine the data. Mean SD/Median (range) was used to represent continuous data, whereas frequency and percentage were used to represent categorical ones. The Chi-square test is used to examine the relationship between categorical variables. The Shapiro-Wilk test is used to determine whether variables are normal. A two-sample t-test is used to compare mean values between groups. The paired t-test is used to compare the mean over time points. A P-value of less than or equal to 0.05 indicates statistical significance.

RESULTS

The present study was conducted in the Department of Obstetrics and Gynaecology, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi during the period of January 2020 to November 2021. The minimum sample size was 140 divided into two groups of 70 each.

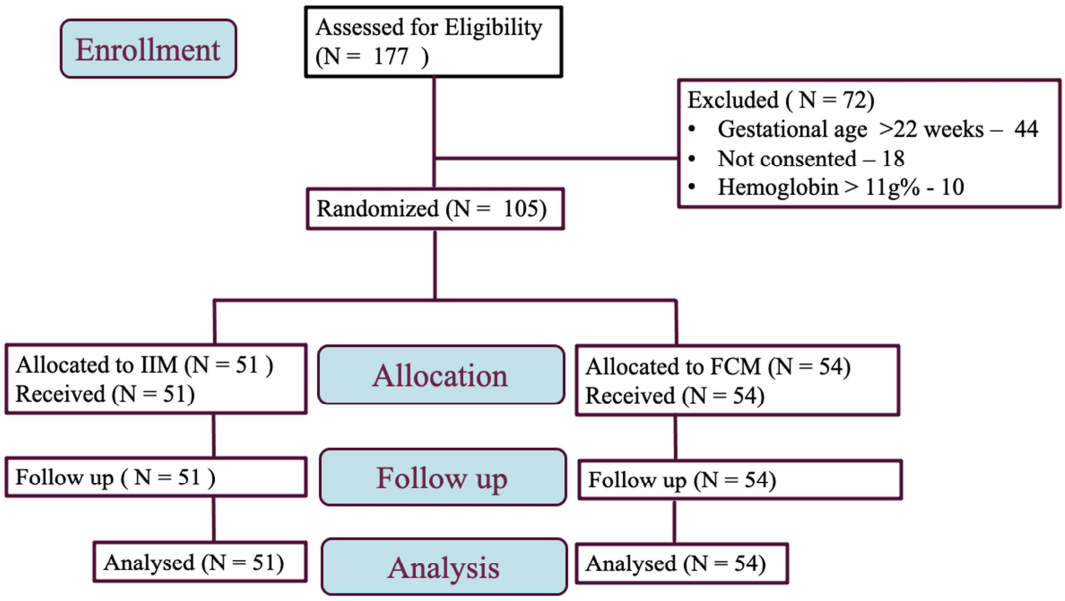
Total number of Participants screened for eligibility were 177, out of which 105 were included in the study and randomized.

The participants were randomized into two groups:

Group A (N = 51) : Received Inj. Iron Isomaltoside (IIM)

Group B (N = 54) : Received Inj. Ferric Carboxymaltose (FCM)

All 105 participants were followed at 28 ± 2 weeks to assess the rise in hemoglobin and were analyzed for the study.



CONSORT diagram (Consolidated Standards of Reporting Trials).

The data was analyzed and final results are tabulated as below:

Table 1: Comparison of demographic details between groups.

		Group A (n = 51)		Group B (n = 54)		p-value
		Number	Percentage	Number	Percentage	
Age (in years)		26.82 ± 3.66 27 (20, 38)		27.28 ± 5.14 27 (16, 38)		0.6016^{WT}
Occupation	Doctor	0	0.0%	2	3.7%	0.6612^{MC}
	Housewife	43	84.3%	45	83.3%	
	Nurse	4	7.84%	4	7.4%	
	Teacher	4	7.84%	3	5.56%	
Education	Primary	2	3.92%	3	5.56%	0.1284^{MC}
	Secondary	2	3.92%	3	5.56%	
	PUC	27	52.94%	24	44.4%	
	Diploma	19	37.25%	14	25.93%	
	Graduate	1	1.96%	7	12.96%	
	Post-graduate	0	0.0%	3	5.56%	
Socio-economic status	Class 1	0	0%	4	7.41%	0.0925^{MC}
	Class 2	24	47.06%	16	29.63%	
	Class 3	22	43.14%	27	50%	
	Class 4	5	9.8%	7	12.96%	
	Class 5	0	0%	0	0%	
Gestational Age (weeks)		18.73 ± 2.42 19 (14, 22)		17.91 ± 2.45 18 (14, 22)		0.0883^{t}
Primigravida		25	49.02%	28	51.8%	0.77^{MC}
Multigravida		26	50.9%	26	48.2%	

Abbreviations: t: two sample t-test; MC: Monte-Carlo's simulation used in Chi-square test.

By Chi-square test, there is no significant difference in the distribution of age, occupation, education, socio-economic status, gravidity between the groups.

By two-sample t-test, there is no significant difference in the mean of age between the groups and the mean of gestational age between the groups. Below plots depicts the same.

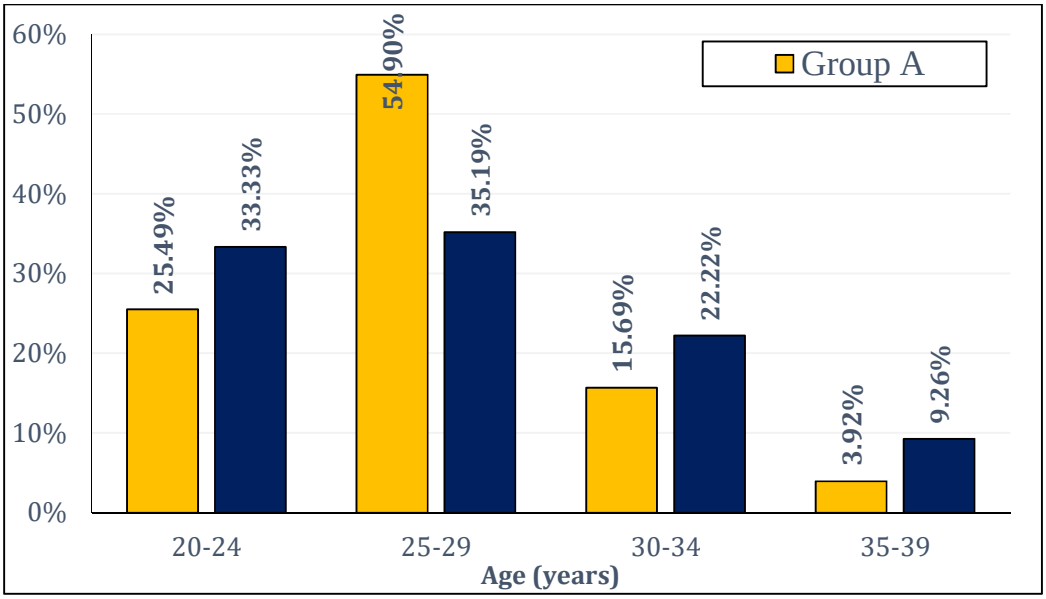


Figure 12: Age distribution over the groups

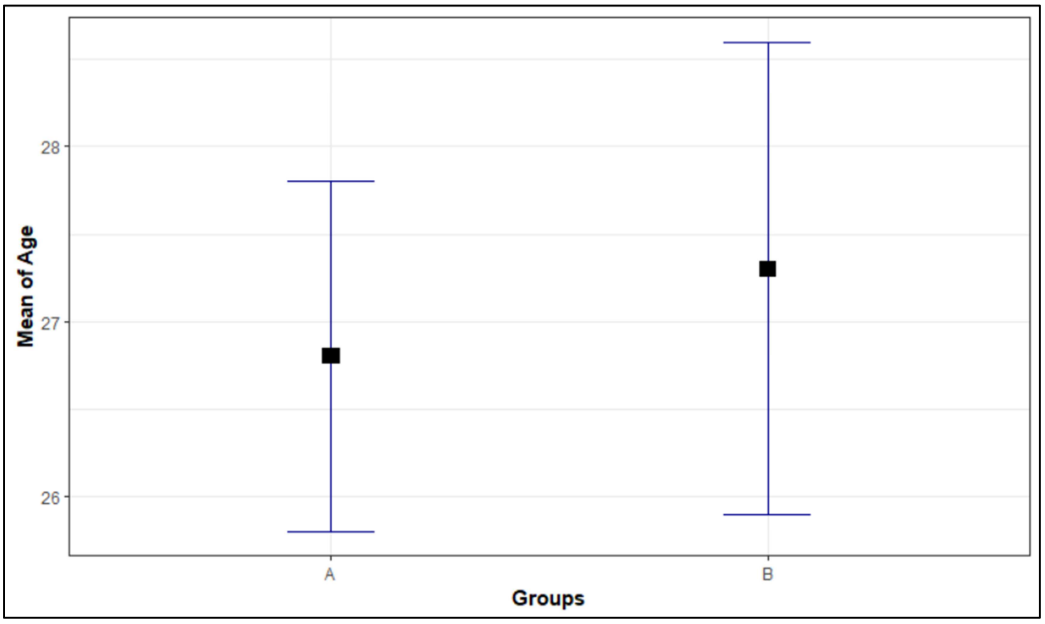


Figure 13: Mean of age between the groups.

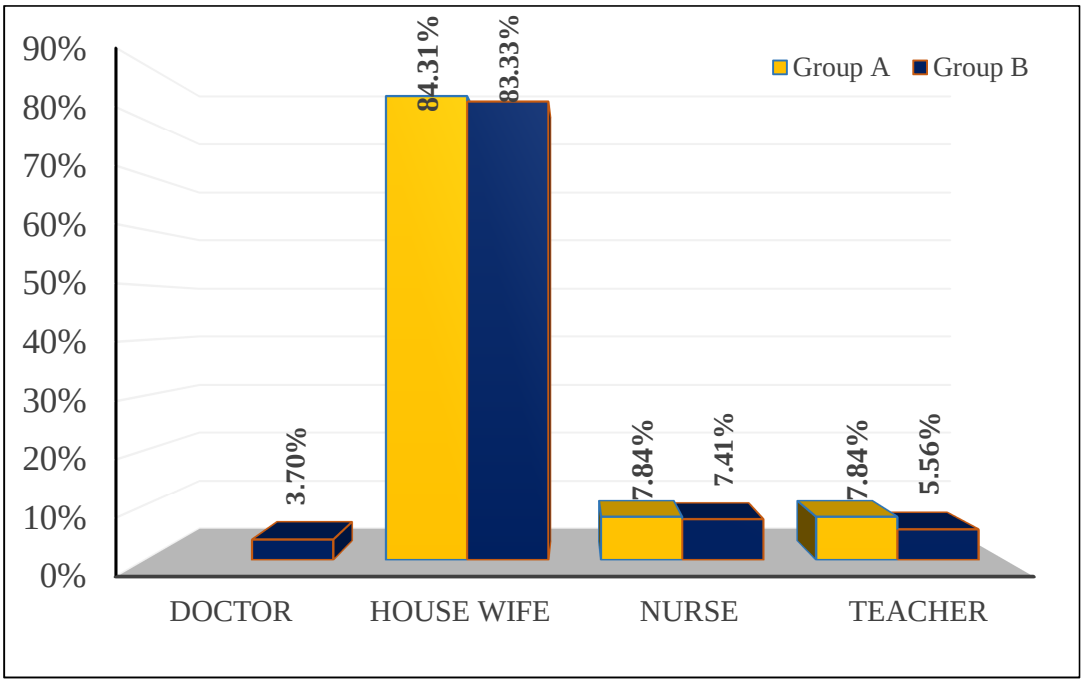


Figure 14: Distribution of occupations over groups.

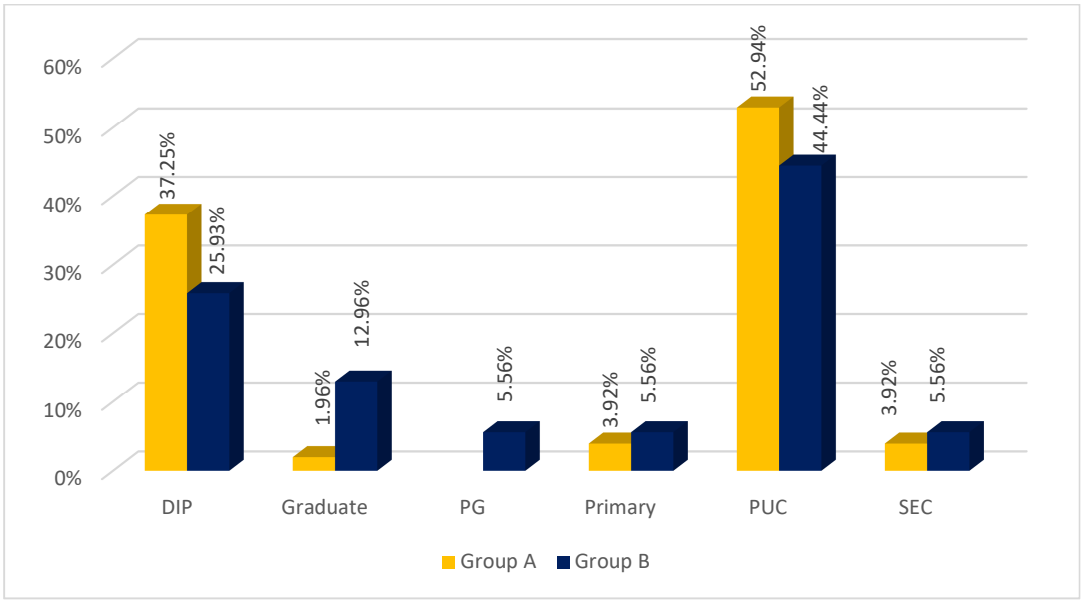


Figure 15: Distribution of education over the groups

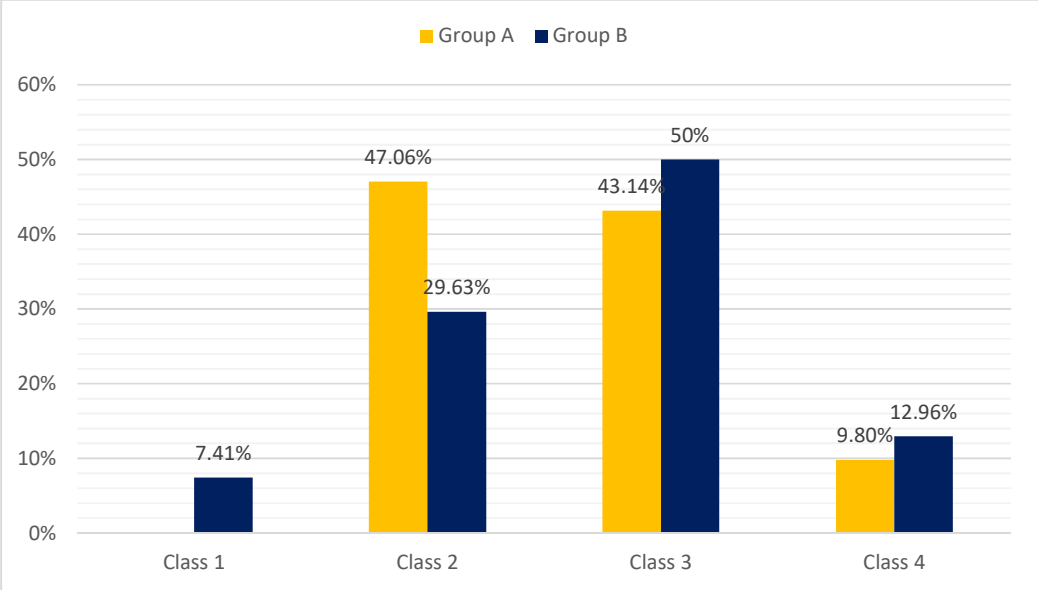


Figure 16: Distribution of Socio-economic status over the groups

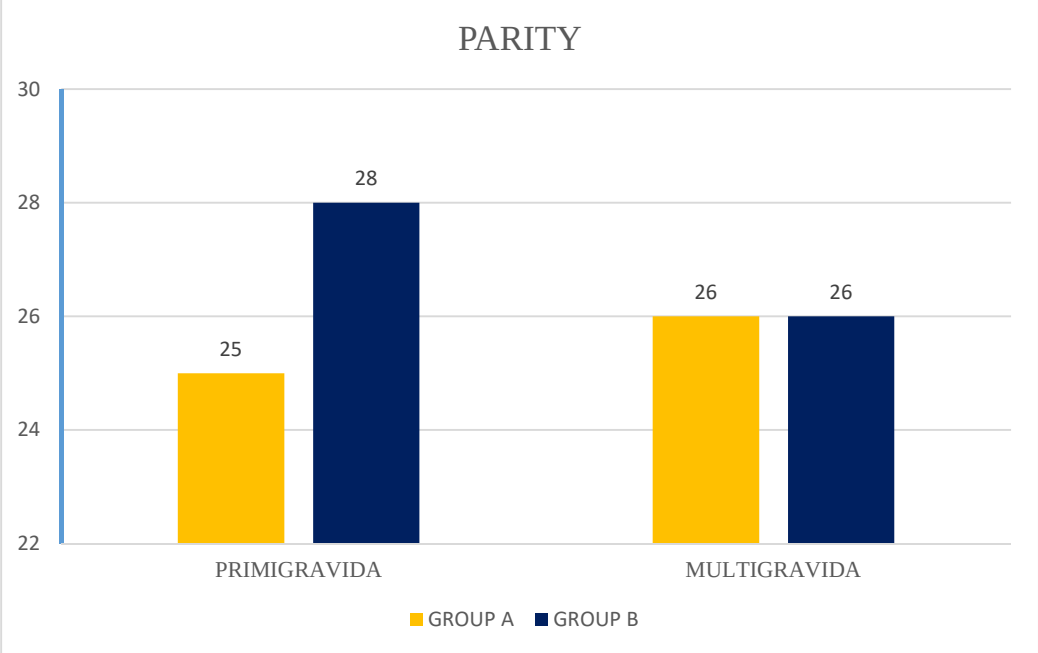


Figure 17: Distribution of Parity over the groups

Table 2: Comparison of examination details over groups.

	Group A (n = 51)	Group B (n = 54)	p-value
BMI (Kg/m^2)	23.63 ± 2.76 23.73 (16.73, 31.64)	23.12 ± 3.37 22.65 (16.63, 38.28)	0.4027[t]
Pulse rate	88.33 ± 5.94 88 (70, 100)	87.74 ± 4.96 88 (78, 100)	0.4481[MW]
Systolic Blood Pressure	112.86 ± 4.75 110 (100, 120)	112.3 ± 4.87 110 (100, 130)	0.4974[MW]
Diastolic Blood Pressure	74.12 ± 5.13 70 (62, 80)	73.07 ± 5.06 70 (60, 80)	0.2398[MW]

Abbreviations: t: t-test; MW: Mann-Whitney test.

By two sample t-test, there is no significant difference in the mean of BMI between the groups.

By Mann-Whitney test, there is no significant difference in the distribution of pulse rate, systolic blood pressure and diastolic blood pressure between the groups.

Below plot visualizes the above table.

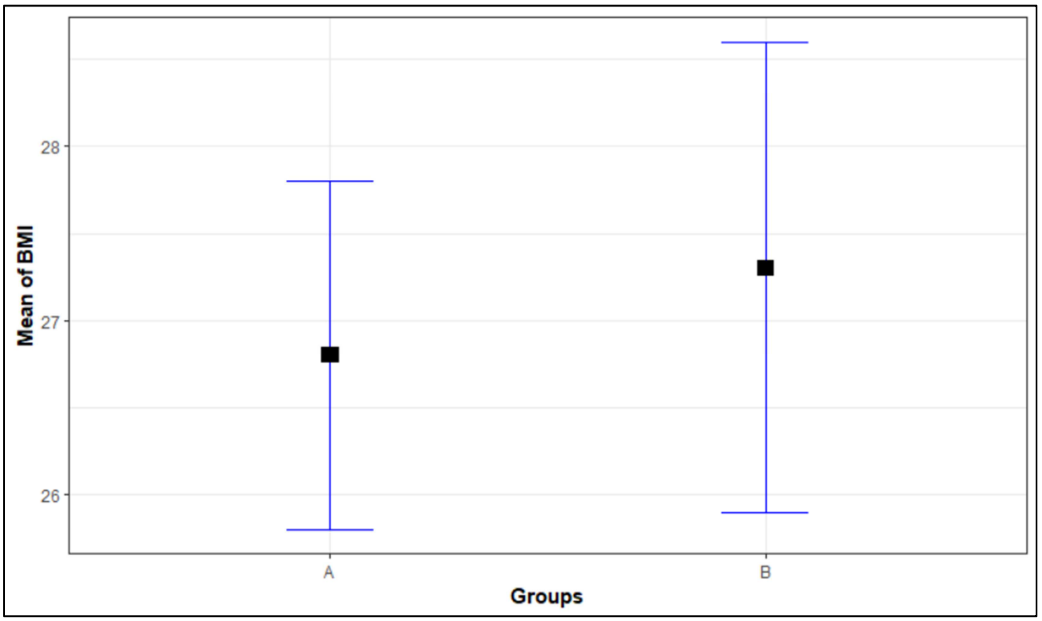


Figure 18: Mean of BMI between the groups.

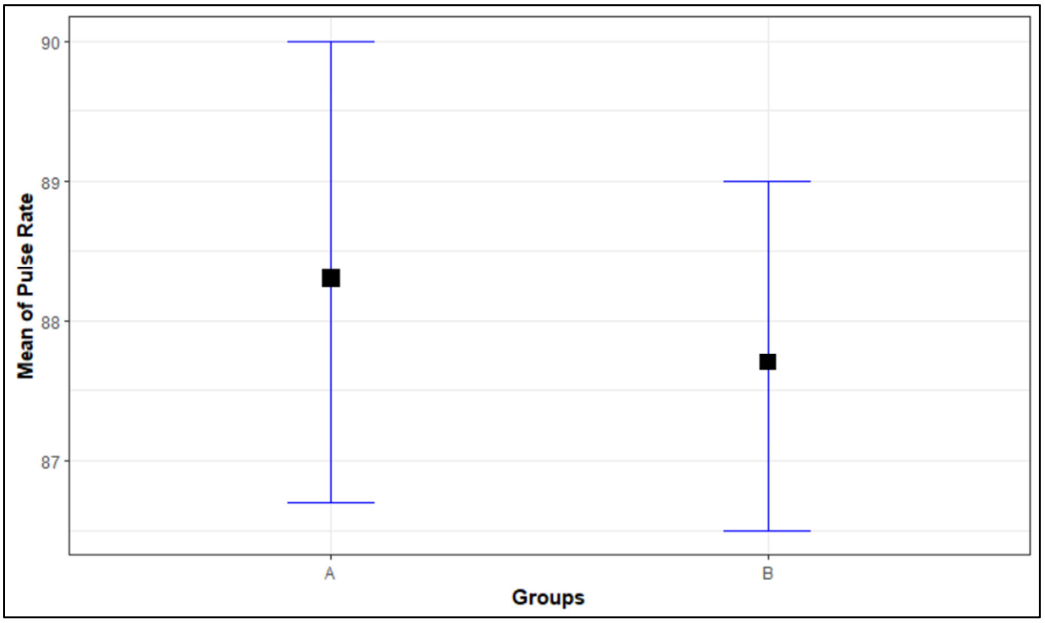


Figure 19: Mean of Pulse rate between the groups.

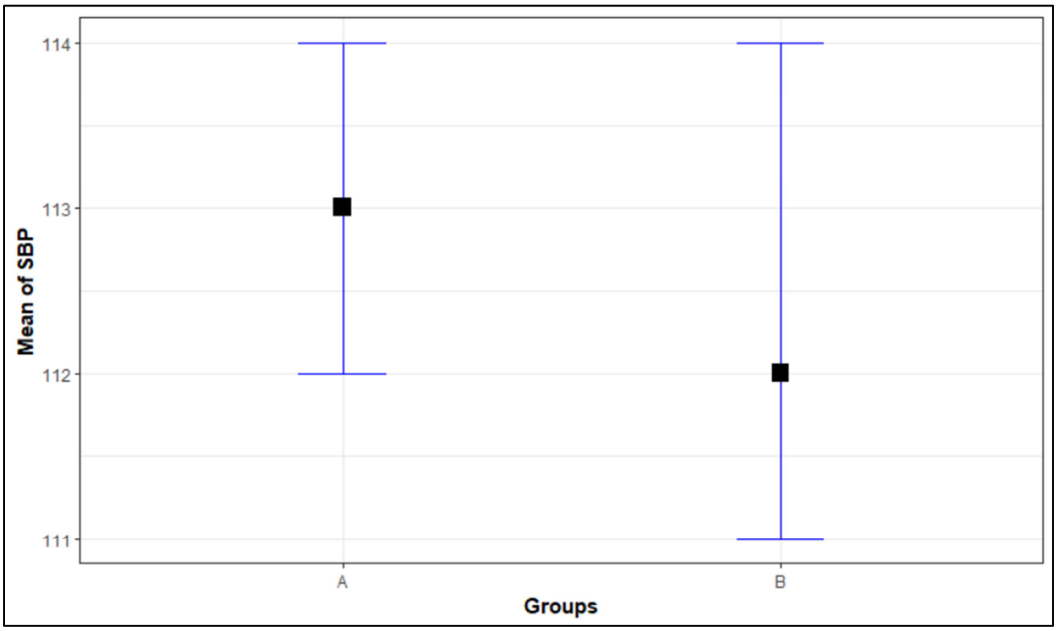


Figure 20: Mean of SBP between the groups.

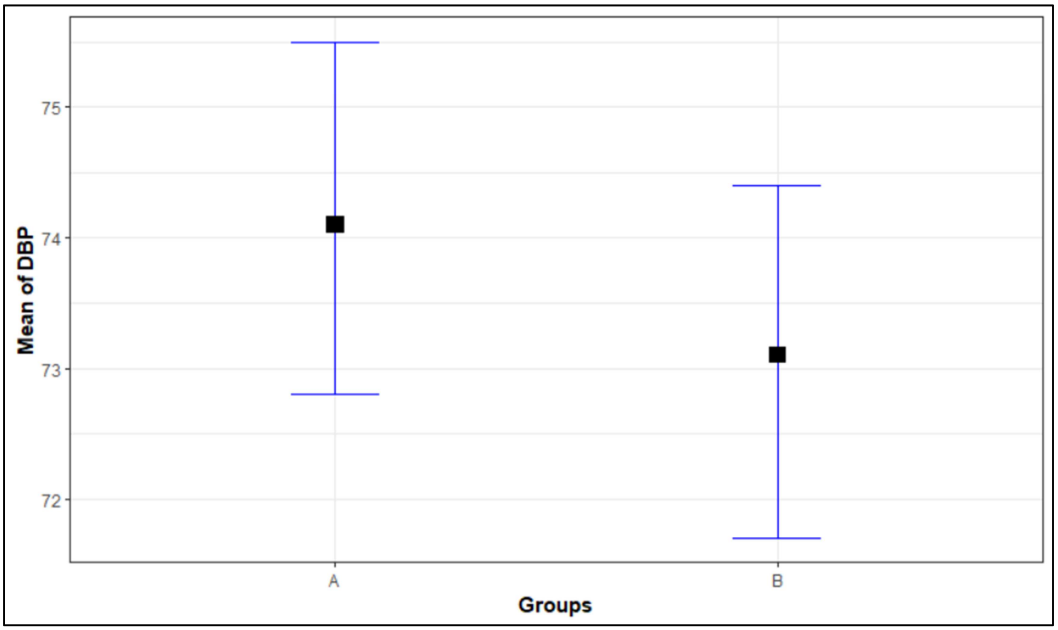


Figure 21: Mean of DBP between the groups.

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Table 3: Comparison of Severity of Anemia over groups.

Haemoglobin	Sub Category	Group A (n=51)	Group B (n = 54)	p-value
Severity of anemia	Mild (10-10.9 g%)	34 (66.67%)	26 (48.15%)	0.074^{MC}
	Moderate (7-9.9 g%)	17 (33.33%)	27 (50%)	
	Severe (<7g%)	0	1 (1.85%)	

By Chi-square test, there is no significant difference between the severity of anemia between both the groups.

Table 4: Comparison of Hemoglobin (Pre and Post infusion) over groups.

Variables	Time points	Group A (n = 51)	Group B (n = 54)	p-value
Hemoglobin (g/dl)	Pre-infusion	9.9 ± 0.91 10.2 (7.4, 10.9)	9.77 ± 1.08 9.85 (6.6, 10.9)	0.5085^{t}
	Post-infusion (at followup)	12.33 ± 0.97 12.4 (10.1, 15)	11.7 ± 0.94 11.9 (9.1, 13.6)	$< 0.001^{t}$ *
	p-value	$< 0.001^{pt}$ *	$< 0.001^{pt}$ *	-
	difference	2.44 ± 0.98 2.5 (0.7, 4.6)	1.93 ± 0.71 1.85 (0.6, 3.7)	0.0014^{t} *

Abbreviations: t: t-test; pt: paired t-test; W: Wilcoxon's test; MW: Mann-Whitney test.

By one-tailed two sample t-test, mean of Hemoglobin is significantly more in group A compared to group B post-infusion.

By paired t-test, mean of Hemoglobin is significantly less pre-infusion point compared to post-infusion within both the groups.

Mean of rise in Hemoglobin is significantly more in group A compared to group B (at follow up) by one-tailed two sample t-test.

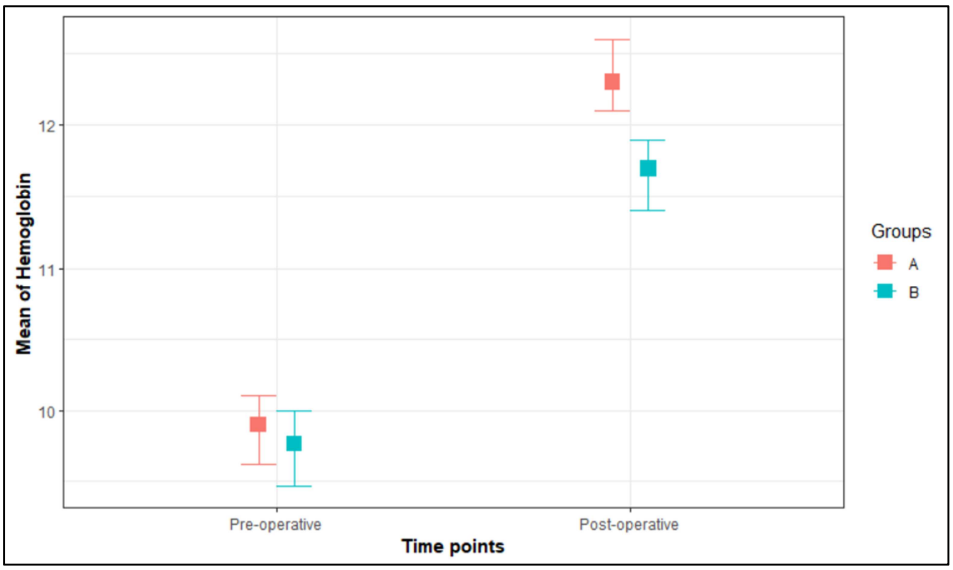

Figure 22: Mean of Hemoglobin between the groups over time

Table 5: Comparison of Adverse events between the groups.

	Group A (n=51)		Group B (n=54)		p-value
	Number	**Percentage**	**Number**	**Percentage**	
Headache	0	0.0%	0	0.0%	-
Vomiting	0	0.0%	1	1.85%	1^{MC}
Flushing	0	0.0%	0	0.0%	-
Abdominal pain	0	0.0%	0	0.0%	-
Dizziness	0	0.0%	0	0.0%	-
Paresthesia	0	0.0%	0	0.0%	-
Breathlessness	5	9.8%	0	0.0%	0.0295^{MC*}
Hypotension	0	0.0%	0	0.0%	-
Hypertension	0	0.0%	0	0.0%	-
Nausea	0	0.0%	0	0.0%	-
Chest pain	1	1.96%	0	0.0%	0.4993^{MC}
Skin discoloration	0	0.0%	2	3.7%	0.5067^{MC}
Myalgia	0	0.0%	0	0.0%	-

In the above table we can observe that, only vomiting, breathlessness, chest pain and skin discoloration is reported in study, however, these remain non-significant between the groups. Below plot depicts the same.

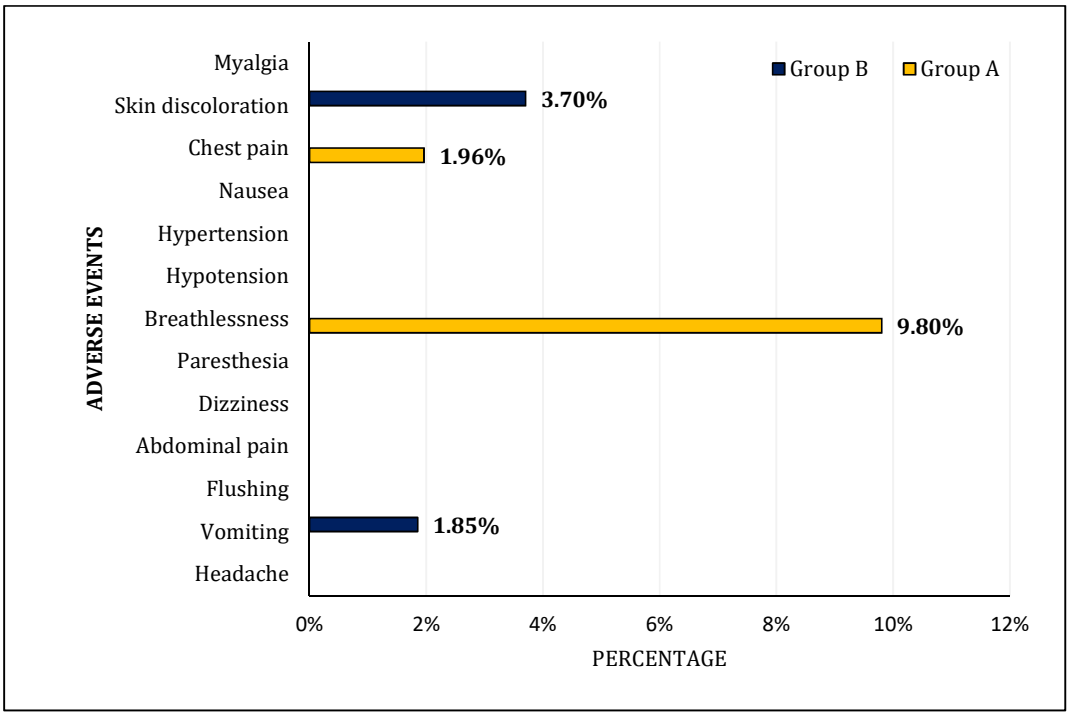

Figure 23: Distribution of reported adverse events between the groups

DISCUSSION

Anemia in pregnancy is a major cause of concern as it is associated with adverse outcomes for both, mother and the fetus. Evidence suggests that the adverse consequences of maternal anemia may not only have the detrimental effects on the neonate and infant but also leads to long term sequelae by increasing the risk of non-communicable diseases and the risk of low birth weight in the next generation.

Since decades there have been various drug formulations, local remedies, health programs which address the prevention as well as treatment of Anemia in pregnancy. Earlier, Oral iron supplementation, Blood transfusion were considered as the mainstay of treatment of iron deficiency as well as iron deficiency anemia. However, there are various other issues associated with them such as intolerance to oral iron, gastro-intestinal side-effects, non-compliance, risk of infectious diseases with blood transfusions.

With the introduction of parenteral iron therapy in treatment of anemia these problems have been addressed along with several other benefits.

Parenteral iron therapy (Intravenous) has proven to be a relatively better approach to treat iron deficiency anemia with fewer side effects, faster action and better compliance.

Iron Isomaltoside / Ferric Derisomaltose had been introduced in 2010 in Europe for the treatment of anemia in chronic kidney disease initially. It is administered intravenously in dose of 20mg/kg or 1.5 gram at a single setting with mild adverse events. It can be administered after first trimester in pregnancy however, there are very few studies available establishing its safety in pregnancy. This study aimed to compare Injection Ferric carboxymaltose with Injection Iron Isomaltoside during pregnancy regarding the efficacy, prevalence of adverse events.

This randomized controlled trial was carried out in the department of Obstetrics and Gynaecology, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

In the present study the commonest age group in Group A (54.9%) and B (35.19%) was 25years to 29 years (p=0.22). Most (84.3%) were housewives in Group A compared to 83.3% in Group B (p=0.66).

With regard to educational status most of the women in Group A and B (52.9% and 44.4% respectively) had passed PUC (p=0.12).

Higher number of women in Group A (47%) belonged to class II socio economic status (Modified BG Prasad scale) compared to Group B where 50% women belonged to Class III. but the difference observed was statistically not significant (p=0.09).

These findings suggest that the socio-demographic characteristics of the study population were comparable. With regard to obstetric history, most of the women reported Multiparity that is 50.9% in Group A whereas 48.2% women were multiparous in group B, 49% women were primiparous in Group A and 51.8% women were primiparous in Group B. However, no statistically significant difference was noted ($p=0.77^{MC}$). Gestational age is comparable in both the groups (0.02). The median of period of gestation in Group A was found to be 19 weeks and in Group B it was 18 weeks which was statistically not significant ($p = 0.08^{t}$).

In the present study based on clinical examination, the mean BMI in Group A and B was also comparable (23.63 ± 2.76 Kg/m^2) vs (23.12 ± 3.37 Kg/m^2; p=0.40).

On general examination the mean pulse rate, systolic blood pressure and diastolic blood pressure were comparable in both the groups (p = 0.44), (p = 0.49) , (p

= 0.23) respectively suggesting that the clinical characteristics of the study population in Group A and B did not differ.

In Group A, 66.6% women had mild anemia and 48.1% women had mild anemia in group B, whereas 50% women in Group B had moderate anemia in comparison to 33.3% in Group A, however, this was statistically not significant.

In this study, the mean pre-infusion hemoglobin levels were also comparable in Group A and B that is 9.9 ± 0.91 gm% in Group A and 9.77 ± 1.08 gm% in Group B (p=0.5).

In this study post-infusion, the mean hemoglobin levels in group A were 12.33 ± 0.97 gm% compared to 11.7 ± 0.9 gm% in Group B ($p=<0.001^t$), which was statistically significant.

The mean increase in hemoglobin levels post infusion was significantly high in Group A compared to Group B (2.44 ± 0.98 gm% vs 1.93 ± 0.71 gm%; $p=0.0014^t$). This was statistically significant.

These findings suggest that, treatment of anemia with intravenous Iron Isomaltoside (IIM) is superior compared to intravenous Ferric Carboxymaltose (FCM) in the treatment of iron deficiency anemia among pregnant women.

In terms of adverse events, 9.8% (n = 5) participants complaint of Breathlessness and 1.9% (n=1) complaint of chest pain in Group A whereas 1.85% (n = 1) complaint of vomiting and 3.7% (n = 2) complaint of skin discoloration in Group B, however these were statistically not significant.

In a comparative trial with Inj. Iron sucrose in patients with iron deficiency anemia, Inj. Iron Isomaltoside resulted in mean increase in haemoglobin >2g/dl in median time of 26 days in 511 participants who were followed for 5 weeks. Serious

adverse reactions (severe dyspnea and severe pruritis rash in one and moderate syncope in one) were reported by 0.6% of patients in Iron Isomaltoside group.[22]

In comparative trial with Inj. Iron sucrose, Inj. Ferric Carboxymaltose resulted in mean rise in haemoglobin of 2.96 g/dl in 12 weeks in 50 participants carried out from January 2016 to August 2017.[70] No serious adverse reactions were noted in any group, whereas another study resulted in significant increase in haemoglobin from 7.76 +/- 0.709g/dl to 13.25 +/- 0.606 g/dl in 4 weeks in 100 participants in each group with no serious adverse events reported.[71]

An indirect comparison of Inj. IIM and Inj. FCM conducted resulted in significantly larger increase from baseline haemoglobin with a mean difference of +0.249 g/dl with Inj. IIM relative with Inj. FCM.[27]

Studies comparing the incidence of Hypophosphatemia and hypersensitivity reactions between Inj. FCM and Inj. IIM found that more patients who received Inj. FCM (45.5%) experienced Hypophosphatemia as compared to Inj. IIM (4%) during the follow-up visits whereas more patients who received Inj. IIM experienced Hypersensitivity reactions (10.7%) in comparison to Inj. FCM (2.5%), whereas studies comparing various intravenous iron formulations to determine the risk of Hypophosphatemia resulted in higher prevalence of Hypophosphatemia (32.1%) after treatment with intravenous iron. Severe hypophosphatemia occurred exclusively after FCM (32.7%).[23,24]

A study conducted in 2013-2018, 213 pregnant women each received a single administration of IV-IIM. Hemoglobin levels increased significantly after IV-IIM administration with a mean rise of 2g%. Ten (4.7%) ADRs occurred during IV-IIM administration. All ADRs were mild hypersensitivity reactions, abated spontaneously

within a few minutes, and did not recur on rechallenge. No association between IIM dose and ADR frequency was noted.[28]

The results of present study are consistent with the similar studies carried out previously.

Limitations: One of the major limitations of the present study is that the sample size could not be met. Another limitation is that it is a single-centre trial.

Challenges: COVID-19 posed a major challenge in recruiting and follow-up of the participants.

Table 6: Comparison of Present study

Trials	Dose	Sample Size	Efficacy (rise in hemoglobin in g%)	Safety
Present study	500 mg	105 analyzed	2.5 g% in IIM 1.85g% in FCM	IIM = FCM (p = 0.5)
Safety of intravenous iron isomaltoside for iron deficiency and iron deficiency anemia in pregnancy.[28]	1000 or 1500 mg IV-IIM	213	2g%	10 mild adverse reactions / fish bane reactions (p = 0.2)
Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: A randomized trial.[17]	1458 ± 179 mg	1997	1.6 g% in FCM	(n = 116 [11.6%] vs. n = 167 [16.7%]) in the ferumoxytol group versus FCM
A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia.[22]	1640 ± 357 mg IIM 1127.9 ± 343 mg Iron sucrose	511	2.74 g% in IIM	137 ADR in IIM, 75 ADR in IS (p = >0.05)

Intravenous iron isomaltoside versus oral iron supplementation for treatment of iron deficiency in pregnancy: protocol for a randomised, comparative, open-label trial	1000 mg IIM	200 Pregnant women	Undergoing	Undergoing
A systematic literature review and indirect comparison of iron isomaltoside and ferric carboxymaltose in iron deficiency anemia after failure or intolerance of oral iron treatment.[27]			+0.249 g/dL in IIM than FCM (statistically not significant)	

CONCLUSION

- Both intravenous iron preparations (IIM, FCM) are well tolerated.
- From this study it is evident that, intravenous Iron Isomaltoside (IIM) is marginally more effective in comparison to FCM in the correction of iron deficiency anemia during pregnancy.
- Adverse events are comparable and actually do not need any special treatment except for temporary stoppage , counselling (Reassurance) and rarely injection Methylprednisolone 40mg or Hydrocortisone 100mg.
- No Serious adverse event was noted.
- Prior counselling along with reassurance play a very important role in successful infusion.

SUMMARY

Iron Isomaltoside/ ferric derisomaltose has been recently introduced for the treatment of anemia. The present study aimed to compare the efficacy, tolerability and safety of Injection Iron Isomaltoside with injection Ferric Carboxymaltose in the treatment of iron deficiency anemia among pregnant women.

This Randomized control trial was done from January 2020 to November 2021 in the Department of Obstetrics and Gynaecology, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi. Total number of Participants screened for eligibility were 177, out of which 105 were included in the study.

These 105 pregnant women were randomized into two groups comprising of 51 participants in Group A (IIM) and 54 in Group B (FCM) and analyzed.

In the present study, all demographic characteristics were comparable in both the groups. The mean age of the participants in group A and B was comparable (26.8 ± 3.66 vs 27.28 ± 5.14 years; p=0.6). The other socio demographic characteristics of the study population including occupation (p=0.66), educational status (p=0.12), socio economic status (p=0.0.09), parity (p=0.77), mean period of gestation (p=0.08), Body mass index (p=0.40) were also comparable. On examination, vitals including pulse rate and blood pressure did not differ in both the groups (p=0.50). The pre-infusion hemoglobin levels were between 10 to 10.9 gram% in 66.6% women in Group A compared to 48.1% in group B, whereas pre-infusion hemoglobin was 7.0 to 9.9 gram% in group A among 33.33% women compared to 50% in group B (p=0.07). The pre-infusion hemoglobin was comparable in both groups (p=0.5). The post-infusion hemoglobin (at follow-up) was higher in group A in comparison to group B (p= <0.001). Significantly higher number of women in group A had increase in

hemoglobin (2.44±0.98 gram%) in comparison to group B (1.93±0.71 gram%) (p=0.001).

Adverse events were noted in 11.7% (6) participants in group A and 5.5% (3) in group B. However, no serious adverse event was noted.

Both iron formulations are effective in correcting IDA, however, IIM leads to marginally more rise in hemoglobin in comparison to FCM. 6 (11.7%) adverse events were noted in IIM group whereas 3 (5.5%) adverse events were noted with FCM.

However, this is a single-Centre study with small group of participants. A multi-centic study with a larger sample size is required to further support the results of present study.

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ANNEXURE - I - ETHICAL CLEARANCE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 168 **Date: 24/12/2019**

To,

REG NO. B J 0 1 1 9 0 0 6

PG student in Obstetrics & Gynaecology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"INJ. FERRIC CARBOXYMALTOSE (FCM) Vs IRON ISOMALTOSIDE (IIM) IN ANEMIA IN PREGNANCY (ANTENATAL) – A RANDOMIZED CONTROLLED TRIAL "**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

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ANEXXURE II- CONSENT FORM

Informed Consent Form (ICF)

This ICF is for women attending Teaching hospital attached to KAHER, Belagavi, and who we are inviting to participate in research on evaluation of efficacy of Injection Iron isomaltoside (IIM) in comparison to Inj. Ferric CarboxyMaltose (FCM) in treating iron deficiency anemia in pregnancy.

The title of my research is **"**Inj. Ferric CarboxyMaltose (FCM) Vs Iron Isomaltoside (IIM) In Anemia In Pregnancy (Antenatal) – A Randomized Controlled Trial**"**

Principal Investigator:

Dr. _____

Professor

Department of Obstetrics & Gynaecology

J.N. Medical College, Belagavi

Co-investigator:

REG NO. BJ0119006

Post Graduate

Department of Obstetrics & Gynaecology

J.N. Medical College, Belagavi

This Informed Consent Form has two parts:

1. Information sheet (To share the information about my study)
2. Certificate of Consent

You will be given a copy of the full Informed Consent Form

Information sheet

Introduction

Good day, I am **REG NO. BJ0119006,** Post graduate (M.S. Obstetrics and Gynaecology) under the guidance of Dr. _____, Department of Obstetrics and Gynaecology, J.N. Medical College, KAHER Belagavi, we are conducting a study on correction of Anemia in Pregnant women. I am going to give you information about this research project. Before you decide to participate in this study, you can talk to anyone you feel comfortable with about the research.

There may be some terms that you do not understand. Please ask me to stop anywhere and I shall explain it to you in a better manner. If you have any questions, you can ask me anytime.

Purpose of study

Anemia is one of the most common disorder during pregnancy. It is one of the most important factors associated with maternal morbidity and mortality in India. It predisposes the mother to infections, risk of preterm labour, post-partum hemorrhage. An estimate by WHO attributes 1,15,000 maternal deaths globally to Iron deficiency anemia in pregnancy either directly or indirectly. It is associated with complications like fetal growth restriction, low birth weight, puerperal sepsis and decreases the women's ability to tolerate blood loss during the delivery and after the delivery. Oral Iron therapy is given to all pregnant women as a part of routine ante natal care but due to poor compliance and various other factors (poor dietary intake, worm infestation etc.) 50% of all pregnant women in India are anemic. Therefore, there is a need for an

efficacious drug which causes rapid elevation in haemoglobin level in a short duration with minimal side effects.

Inj. Ferric Carboxymaltose (FCM) is already used in correction of anemia in pregnancy as per the government guidelines under Anemia Mukt Bharat.

Inj. Iron Isomaltoside (IIM) is another drug with proven efficacy in correction of Iron deficiency anemia with minimal side effects.

This study will help us in evaluating the efficacy of Iron Isomaltoside in comparison to Inj. Ferric carboxymaltose in treating iron deficiency anemia in pregnancy as well as the safety in terms of local and systemic reactions.

Type of Study

This study is an interventional study. It involves administration of Injection Iron Isomaltoside (IIM) or Injection Ferric Carboxy Maltose (FCM) by intravenous route in second trimester of pregnancy (16 weeks- 20 weeks ± 2 weeks) in women with haemoglobin between 7 g/dl to 10.9 g/dl as well as follow up visit at 28 ± 2 weeks.

The participant would be subjected to iron correction with Inj. Iron Isomaltoside or Iron Ferric carboxymaltose, according to randomization. Haemoglobin estimation will be done and the iron deficit will be calculated according to Ganzoni formula:

Deficit = (12 -Haemoglobin of the patient) X 2.4 X Body Weight (Kg) + 500mg (storage)

Group A – Iron Isomaltoside

Iron Isomaltoside will be given as per the total required dose in a normal saline as follows:

IV drip infusion: Dilute in 0.9% sodium chloride Up to 1000mg : 100 ml NS over more than 15 minutes

All the doses will be given in the ward where equipment for cardiopulmonary resuscitation is available. Patients will be observed for side effects or anaphylactic reactions. Any minor or major side effects will be documented.

Group B – Ferric CarboxyMaltose

Ferric Carboxymaltose will be given as per the total required dose in normal saline as follows:

IV drip infusion: Dilute in 0.9% sodium chloride

100 to 200 mg : 50 ml NS

200 to 500 mg : 100 ml NS - 6 min duration

500 to 1000mg : 250 ml NS - 15 min duration

Not exceeding the maximum dose of 1000 mg / day/ week. All the doses will be given in the ward where equipment for cardiopulmonary resuscitation is available. Patients will be observed for side effects or anaphylactic reactions. Any minor or major side effects will be documented.

Participant selection

All the patients from the target population will be screened for baseline haemoglobin. The patients who fulfil the inclusion criteria after considering the exclusion criteria will be enrolled for the study.

Questions: Do you know why we are asking you to participate in our study? Do you understand what the study is about?

Voluntary Participation

Your participation in this research is voluntary. It is your choice whether to participate or not. Your decision whether to participate in the study or not will not change the present or future health care services offered to you and will not affect your relationship with J.N. Medical College.

If you choose not to participate in this study, you will still be offered appropriate treatment for correction iron deficiency anemia at our hospital and you will continue to receive the routine ante natal care at our hospital. If you decide to participate you are free to withdraw at any time.

Questions: Do you know what are the other options for correction of anemia in pregnancy? Do you know that you do not have to participate in this study if you do not wish to? Do you want to ask any more questions?

Information on the drug

The drugs we are comparing in this study are Inj. Iron Isomaltoside (IIM) and Inj. Ferric Carboxymaltose (FCM). Inj. Ferric Carboxymaltose is used in parenteral iron correction in iron deficiency anemia in pregnancy under Anemia Mukt Bharat campaign. It is associated with side effects like Headache, Dizziness, Hypertension, Nausea, Injection/ Infusion site reaction and Hypophosphatemia.

Inj. Iron Isomaltoside is a promising drug for correction of iron deficiency anemia of pregnancy. Studies have shown that it leads to rapid rise in haemoglobin levels as compared to other intravenous iron formulations. It has proven benefits in correction of anemia in CKD, Post-partum Haemorrhage. The drug is marketed by LUPIN ltd. in India and is originally manufactured by Pharmacosmos A/S Denmark. It leads to controlled release of iron thus avoiding potential toxicity from release of toxic iron. You should know that this drug has a few side effects like nausea, vomiting, itching, rashes. You will be monitored during the entire time while administering the drug to check for any side effects and appropriate treatment will be given for the same.

Some participants in this study will be given Inj. Iron isomaltoside and some will be given Inj. Ferric Carboxymaltose.

Procedure Involved:

If you agree to enrol yourself in my study, your detailed history will be taken to know if you are eligible for this study. If you have even one of the exclusion criteria you will not be enrolled into this study as your safety is the primary concern. If you are eligible to participate in this study, after taking your consent you will be administered a drug, either Inj. Iron Isomaltoside or Inj. Ferric Carboxymaltose via intravenous route for correction of anemia. Your blood test will be done prior to administration of these drugs, which involves withdrawing 2 ml of blood to check for level of haemoglobin. Your Blood pressure, pulse rate, Fetal heart rate will be monitored before the infusion, every five minutes during infusion and after the infusion. You will be monitored during the entire time while administering the drug to check for any side effects and appropriate treatment will be given for the same. You will be required to follow up at 28 ± 2 weeks, On your visit your blood sample will be

taken and level of Haemoglobin will be estimated.

Side effect

In this study half the participants will receive Inj. Iron Isomaltoside. As already mentioned, there could be some common adverse effects of this drug like nausea, itching, breathlessness, infusion site reaction. If you develop any of adverse effects, in such a scenario you will be given the appropriate treatment.

Half the participants will receive Inj. Ferric Carboxymaltose. It is associated with side effects like Headache, Dizziness, Hypertension, Nausea, Injection/ Infusion site reaction, breathlessness and Hypophosphatemia.

However, these side effects are mostly temporary and proper care will be given to you in occurrence of any such side-effect.

We may use some other medicines to decrease the symptoms of the side effects or reactions or we may stop the administering drug.

We will discuss together, and you will be consulted before we move to our next step.

Risks

By participating in this research, there is a possibility that you will experience adverse effect of the drug. If any of these conditions arise, you will be given the appropriate treatment for the same.

Question: Do you understand you may have some unwanted side effects from the medicine? Do you have any other questions?

Benefits

The benefits of taking part in this research is your participation will help us in

evaluating and comparing the efficacy and safety of Inj. Iron Isomaltoside and Inj. Ferric carboxymaltose in anemia in pregnancy. Even if you are given Inj. Iron Isomaltoside or Inj. Ferric Carboxymaltose, the chief concern i.e. anemia will be dealt with.

Your participation being valuable contribution to medical research to improvise treatment currently practiced i.e. parenteral iron correction in anemia in pregnancy. If Inj. Iron Isomaltoside is proven to be more effective, we aim to help other people like you.

Financial Incentives for participation

You will not be given any money or gifts to take part in this study. If any participant becomes ill during the administration of drugs, immediate treatment will be given at KAHER's Dr. Prabhakar Kore Hospital. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Privacy and Confidentiality

We will not be sharing your identity with anyone. The only people who will know that you are the research subject will be the members of the research team. The information that we collect from this study will be kept confidential. No information about you or information provided by you during the research will be disclosed to others without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law

Authorization to Publish Results

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will

remain confidential. Results of the study will be used to improve maternal outcome in Iron deficiency Anemia.

Right to refuse or withdraw from study

You do not have to participate in this research if you do not wish to. You can withdraw at any time from the study. There will be no penalty for withdrawal. Your treatment and care in this hospital will not change irrespective of whether you agree to participate or not. You can be removed from the study if necessary.

Alternative

If you do not wish to participate in this study, you do not have to. You will continue to receive the routine antenatal, intra-natal and post-natal care even if you decline to participate in the study. You will be given alternatives for Iron correction if you decline to participate in the study. You will be informed about any new information that may affect your decision to participate in the study.

Institutional/sponsor's policy

In the event of any injury related to the study, treatment will be made available through KAHER, Belagavi. There is no compensation or payment for such medical treatment by law. If you are injured you may contact **REG NO. BJ0119006**, Postgraduate student, Department of Obstetrics and Gynaecology, KAHER or by Ph. No: _____.

Contact details:

In case you have any questions related to the study, now or in future, you can contact **REG NO. BJ0119006**, Post graduate student, Department of Obstetrics and Gynaecology, KAHER, Ph.No: 8496017030 or Dr. _____, Dept. Of Obstetrics and Gynaecology, KAHER Belagavi, Ph. No: _____.

If you have any queries about your rights as a study participant, you may contact Dr. Roopa M Bellad, Prof. of Paediatrics as Chairman of J. N. Medical College Institutional Ethics Committee on Human Subjects Research, Phone No.0831 2473777 ext-1527 at J. N. Medical College, Belagavi.

Question: Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study?

Do you have any questions?

Certification Of Consent

I have read the whole information, or it has been read to me. I have asked all the questions about it and those have been answered to my satisfaction. I consent voluntarily to participate in this research.

I also agree to be contacted for follow-up.

Print Name of Participant_____

Signature of Participant_____

Date_____ (dd/mm/yyyy)

If illiterate,

A literate witness must sign (if possible, this person should be selected by the participant and should have no relation to the research team).

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given the consent freely.

Print name of witness_____

Signature of witness_____

Date_____ (dd/mm/yyyy)

Thumb Print of Participant

STATEMENT BY THE RESEARCHER

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the following will be done:

1.

2.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered to the best of my ability. I confirm that the individual has not been coerced into giving consent and it has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print name of Researcher_____

Signature of Researcher_____

Date_____ (dd/mm/yyyy)

SCREENING FORM

Screening number: IP number:

Date of screening (dd-mm-yyyy):

First name:

Middle name:

Last name:

Husband's name:

Age (years):

Address: H.no. -

Street -

Taluka -

District -

Phone number

Landline(optional):

Registered	
Unregistered	

Eligibility:

YES – 1
NO – 2

a. Women with 14 to 22 weeks period of gestation
b. Women with hemoglobin less than 11 g%
c. known cause of Thalassemia, Megaloblastic anemia
d. H/O Known allergy to parenteral iron correction
e. H/O any liver disease
f. H/O Autoimmune disorder

Is she eligible?

If eligible, consent to be taken.

Consent:

a. Does the woman assent to participate? ☐

b. Has the study consent form been signed? ☐

If Consent given,

Enrollment done:

If enrolled, Randomization done. ☐

Was the woman randomized? ☐

If not randomized indicate reason:

1. Withdrawal from study ☐
2. Other ☐

Date of Randomization: (dd-mm-yyyy) ☐☐ ☐☐ ☐☐☐☐

Time of Randomization: (hh : mm) ☐☐ ☐☐

Participant number: (see sealed envelope) ☐☐☐☐☐☐☐

Investigator's name :

Signature :

DATA COLLECTION INSTRUMENT

"Inj. Ferric Carboxymaltose (FCM) Vs Iron Isomaltoside (IIM) In Anemia In Pregnancy (Antenatal) - A Randomized Controlled Trial"

Screening Id: ☐☐☐☐ Enrollment number: ☐☐☐

Age (years): ☐☐

Date of admission (dd-mm-yyyy): ☐☐ ☐☐ ☐☐☐☐

A. Inj. Iron Isomaltoside (IIM)
B. Inj. Ferric CarboxyMaltose (FCM)

Drug given: ☐

Dose of Drug given **[**(12 – Hb) X 2.4 X Body weight] + 500mg ☐☐☐☐

Batch number: ☐☐☐☐☐☐☐☐☐☐☐☐☐

Date of expiry (dd-mm-yyyy): ☐☐ ☐☐ ☐☐☐☐

Date of Drug administration (dd-mm-yyyy): ☐☐ ☐☐ ☐☐☐☐

Time of starting Drug administration: : ☐☐ ☐☐

Time of ending Drug administration: : ☐☐ ☐☐

YES – 1

NO – 2

Any Complaints : ☐

If complaints present,

a. Weakness ☐
b. Fatigue ☐
c. Breathlessness ☐
d. Palpitations ☐
e. PV bleed ☐

Antenatal history:

a. Regular Antenatal visits ☐

b. Daily Tablet Iron and Folic acid supplementation ☐

Obstetric history:

Married Life (years) : ☐☐

Consanguinity: ☐ (YES - 1, NO - 2)

If yes,

Degree of consanguinity: ☐☐☐☐☐☐

Obstetric score:

Gravida- ☐☐ Para- ☐☐ Live- ☐☐ Abortion- ☐☐

Contraceptive use: ☐ (YES - 1, NO - 2)

If yes,

a. Combined Oral contraceptive pills ☐

b. Intrauterine device ☐

c. Implants ☐

d. Injectables ☐

e. Progesterone only pills ☐

Menstrual history:

Menarche (age in years): ☐☐

YES – 1, NO – 2

Regular Past menstrual cycles: ☐

H/O excessive menstrual bleeding: ☐

Last menstrual period (dd-mm-yyyy): ☐☐ ☐☐ ☐☐☐☐

Expected date of delivery (dd-mm-yyyy): ☐☐ ☐☐ ☐☐☐☐

USG EDD (dd-mm-yyyy): ☐☐ ☐☐ ☐☐☐☐

Period of gestation (weeks/ days): ☐☐ ☐☐

Past History :

YES – 1 , NO – 2

a. Known case of Diabetes mellitus : ☐

If yes, Duration (in years) : ☐☐

Treatment received : ☐☐☐☐☐☐☐

b. Known case of Hypertension : ☐

If yes, Duration (in years) : ☐☐

Treatment received : ☐☐☐☐☐☐☐

c. H/O recurrent blood transfusions : ☐

If yes, Duration (in years) : ☐☐

d. Known case of Cardiac disorder : ☐

If yes, Duration (in years) : ☐☐

Treatment received : ☐☐☐☐☐☐☐

e. Known case of Hypothyroidism. : ☐

If yes, Duration (in years) : ☐☐

Treatment received : ☐☐☐☐☐☐☐☐☐

f. H/O any surgery in past : ☐

g. H/O any Drug allergy : ☐

If Yes, Name of the drug: ☐☐☐☐☐☐☐☐☐

Personal History :

YES – 1 , NO – 2

Adequate diet ☐

a. Vegetarian ☐

b. Non- vegetarian ☐

Normal appetite ☐

If no, a. Increased ☐

b. decreased ☐

Adequate sleep ☐

Normal Bowel & Bladder habits ☐

H/O PICA ☐

General physical examination- at admission

Height (in centimetres) ☐☐☐

Weight (in kilogram) ☐☐☐

YES – 1, NO – 2

Pallor ☐

Icterus ☐

Pedal Oedema ☐

Blood pressure (mmHg) ☐☐☐ ☐☐

Pulse rate (beats per minute) ☐☐☐

Systemic examination :

Per Abdomen: Uterine size (in weeks) ☐☐

Relaxed ☐ (YES- 1, NO- 2)

Foetal Heart rate ☐☐☐ beats per minute

Cardiovascular: _____

Respiratory : _____

CNS : _____

Investigations-

Date (dd-mm-yyyy): ☐☐ ☐☐ ☐☐☐☐

Haemoglobin (g/dl): ☐☐ . ☐☐

Packed cell volume (%): ☐☐ . ☐

Blood Group: ☐ ☐☐☐☐☐☐☐☐

HIV: ☐ (Non- reactive – 1, Reactive – 2)

HbsAg: ☐ (Non- reactive – 1, Reactive – 2)

VDRL: ☐ (Negative – 1, Positive – 2)

YES – 1 , NO - 2

Side effects present ☐

If Yes, ☐

a. Nausea
b. Vomiting ☐
c. Anaphylactic reactions ☐
d. Headache ☐
e. Injection site erythema ☐
f. Flushing ☐
g. Hypotension ☐
h. Abdominal pain ☐
i. Chest pain ☐

FOLLOWUP AFTER AT 28 ± 2 WEEKS:

Follow up done: ☐ (YES – 1, NO – 2)

If Yes,

Symptomatic improvement present: ☐ (YES – 1, NO – 2)

Haemoglobin (g/dl): ☐☐☐☐

ANNEXURE IV – MASTERCHART

S. no.	Randomisation no.	Group	Age	Demographic data			Obstetric Score				Period of gestation (weeks)	Examination							Pre - infusion Parameters					Post - infusion Parameters					Adverse events												
				Occupation	Education	Socio-economic status	Gravida	Parity	Live	Abortion		Height (cms)	Weight (kg)	BMI (kg/m2)	Pulse rate	Systolic BP	Diastolic BP	Sytemic examination	Hemoglobin (g/dl)	Serum Iron	Serum Ferritin	Serum TIBC	T sat	Hemoglobin (g/dl)	Serum Iron	Serum Ferritin	Serum TIBC	T sat	Headache	Vomiting	Flushing	Abdomical pain	Dizziness	Parasthesia	Breathlessness	Hypotension	Hypertension	Nausea	Chestpain	Skin discoloration	Myalgia
1	1	A	28	HW	PUC	CLASS 2	3	2	1	0	19	157	78	34.66666667	100	120	70	WNL	10.6	70	9.99	409	17	11.6	100	39.04	442	23	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
2	2	A	25	HW	PUC	CLASS 2	3	2	1	0	15	160	76	29.6875	96	110	70	WNL	10.3	184	21.12	430	43	13.3	200	32	414	48	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
3	3	B	26	HW	DIP	CLASS 2	3	1	1	1	18	157	52	23.11111111	98	110	74	WNL	10.6	56	9.76	367	15	13	61	29.88	341	18	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
4	4	B	28	HW	DIP	CLASS 2	3	2	1	0	21	158	46	20.44444444	100	110	70	WNL	9.8	103	44.1	344	30	11.4	93	72.01	382	24	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
5	5	A	24	HW	PUC	CLASS 3	2	0	0	1	18	159	50	22.22222222	98	110	70	WNL	7.4	18	16.8	449	4	12	87	28.12	417	21	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
6	6	A	26	HW	PUC	CLASS 3	1	0	0	0	22	161	54	21.09375	88	110	80	WNL	9.2	26	18.2	471	6	10.8	50	13.09	447	11	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
7	7	B	32	HW	PUC	CLASS 2	2	1	1	0	21	144	56	28.57142857	86	120	80	WNL	7.9	96	10.4	306	31.3	11.6	130	305.9	675	19	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
8	8	A	28	NURSE	DIP	CLASS 3	1	0	0	0	22	158	43	18.69565217	96	110	70	WNL	10.4	36	14.3	506	7	15	89	25	409	21.7	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
9	9	A	26	HW	DIP	CLASS 2	2	0	0	1	16	164	45	18	94	110	70	WNL	7.5	336	10	630	53	12	117	39.89	384	30	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
10	10	A	20	HW	PUC	CLASS 3	1	0	0	0	20	158	43	5.217391304	92	120	80	WNL	10.6	433	28.2	637	68	13.2	100	157	429	23	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
11	11	A	26	HW	PUC	CLASS 2	5	1	0	3	15	160	67	26.171875	98	120	80	WNL	9.2	56	10.2	376	15	10.4	69	21	350	19	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
12	12	A	28	HW	PUC	CLASS 2	2	1	1	0	17	157	64	26.66666667	96	110	80	WNL	10	181	43.87	295	61	12.5	120	50	376	31.91	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
13	13	B	32	HW	PRIMARY	CLASS 3	3	0	0	2	16	160	68	26.5625	92	110	80	WNL	10.4	92	11.7	467	20	12.1	110	25	430	25.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
14	14	B	35	HW	SEC	CLASS 3	2	1	1	0	18	152	56	24.88888889	90	118	74	WNL	10.9	26	18.2	471	6	12.6	52	15	447	11.6	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
15	15	A	25	HW	SEC	CLASS 3	1	0	0	0	20	154	58	23.2	88	110	70	WNL	10.8	70	10	409	17	12.1	100	41	442	23	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
16	16	B	22	HW	PUC	CLASS 3	1	0	0	0	14	157	41	17.82608696	88	110	70	WNL	7.5	19	15.4	355	5	11	27	11.7	493	5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO
17	17	A	27	HW	GRADUATE	CLASS 2	1	0	0	0	18	153	53	22.08333333	90	114	62	WNL	9	18	17	449	4	11.5	68	207.6	320	21	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
18	18	B	22	HW	PUC	CLASS 3	1	0	0	0	17	154	58	25.77777778	88	110	70	WNL	10.7	40	14.75	411	10	13.1	76	238	351	22	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
19	19	A	23	HW	PUC	CLASS 3	1	0	0	0	20	157	60	26.08695652	70	110	80	WNL	9.6	67	30.15	377	18	11	62	35	312	19.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
20	20	B	29	HW	GRADUATE	CLASS 1	1	0	0	0	15	160	65	0.40625	88	110	70	WNL	10.8	28	39	382	7.3	11.8	45	56	350	12.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

21	21	B	23	HW	PUC	CLASS 3	2	1	1	0	19	155	50	22.22222222	78	110	80	WNL	10.8	91	39.3	390	23	12.1	131	139	463	28	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
22	22	A	28	NURSE	DIP	CLASS 3	1	0	0	0	15	158	54	23.47826087	86	114	72	WNL	9.5	33	10.3	438	8	13.7	100	48	453	22	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
23	23	A	21	HW	PUC	CLASS 3	1	0	0	0	16	157	58	25.77777778	90	110	80	WNL	10.8	60	75	261	23	12.1	181	43.7	295	61	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
24	24	A	22	HW	PUC	CLASS 3	2	1	1	0	22	160	65	25.390625	92	120	78	WNL	10.4	146	744	383	38	11.8	78	37	466	17	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
25	25	A	25	HW	PUC	CLASS 3	1	0	0	0	19	147	49	25.78947368	86	120	76	WNL	7.5	24	10.5	476	5	10.3	34	12.67	476	7	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
26	26	B	27	HW	PUC	CLASS 3	1	0	0	0	14	148	42	22.10526316	88	110	70	WNL	9.1	20	7.2	400	5	12	49	24.9	446	11	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
27	27	A	29	HW	SEC	CLASS 3	1	0	0	0	22	164	60	23.4375	84	116	72	WNL	8.3	29	6.3	585	5	12.7	76	238	351	22	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
28	28	B	34	TEACHER	DIP	CLASS 3	2	0	0	1	19	154	60	26.66666667	82	110	74	WNL	8.7	27	9.4	415	7	12.2	52	46.65	528	10	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
29	29	A	32	NURSE	DIP	CLASS 2	1	0	0	0	16	162	53	21.2	80	110	72	WNL	10.6	89	22	331	27	12.1	117	40	384	30	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
30	30	A	30	HW	DIP	CLASS 2	1	0	0	0	19	157	59	16.38888889	80	118	80	WNL	10.8	48	16.06	338	14	12.4	69	26.7	324	21.3	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
31	31	B	28	HW	PRIMARY	CLASS 3	2	1	1	0	20	150	38	16.88888889	89	120	80	WNL	7.5	32	8.9	392	8	10	44	15	360	12.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
32	32	B	26	HW	SEC	CLASS 3	1	0	0	0	20	152	40	17.77777778	90	120	80	WNL	9.5	65	65	306	21	11.4	75	67	350	21.4	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
33	33	B	33	HW	PUC	CLASS 3	4	1	1	2	19	158	63	27.39130435	88	120	80	WNL	9.1	186	5.3	624	30	11	188	15	500	27.6	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
34	34	A	28	HW	PUC	CLASS 3	2	1	1	0	19	155	67	29.77777778	90	120	80	WNL	10.8	92	111	360	26	13	94	120	355	26.4	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
35	35	B	32	HW	GRADUATE	CLASS 1	2	1	1	0	14	160	98	39.2	90	110	70	WNL	9.6	47	9.3	346	13.5	11	54	16.8	326	16.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
36	36	A	23	HW	PUC	CLASS 3	1	0	0	0	14	158	58	25.2173913	88	110	80	WNL	10.2	132	37.6	445	30	12.9	145	55	412	35.19	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
37	37	A	30	HW	DIP	CLASS 2	1	0	0	0	14	155	58	25.2173913	88	110	80	WNL	10.3	355	29	601	59	13.1	145	65	421	34.3	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
38	38	A	23	HW	PUC	CLASS 3	3	2	1	0	21	150	50	22.22222222	86	120	80	WNL	10.6	124	96	288	43	13.2	126	50	261	48.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
39	39	A	24	HW	PUC	CLASS 2	3	2	1	0	21	155	50	22.22222	88	120	80	WNL	10.6	201	21.7	500	40	13.6	175	38.6	419	41.7	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
40	40	B	26	HW	PUC	CLASS 2	1	0	0	0	15	156	52	22.60869565	88	110	70	WNL	8.6	40	17	324	12	10.2	46	25	307	14.9	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
41	41	A	25	HW	PUC	CLASS 2	6	2	2	3	20	158	56	24.88888889	90	110	80	WNL	9.5	28	18.9	381	7	11.9	44	28.9	360	12.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
42	42	B	20	HW	PUC	CLASS 3	1	0	0	0	16	152	54	24	100	120	80	WNL	6.6	85	333	306	28	9.1	89	22	331	27	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
43	43	A	28	HW	DIP	CLASS 2	2	1	1	0	16	160	60	23.4375	86	114	70	WNL	10.4	50	41.8	357	14	12.9	69	75	324	21.3	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
44	44	B	26	HW	DIP	CLASS 2	1	0	0	0	18	157	68	30.22222222	88	110	70	WNL	9.9	50	5.5	357	14	10.9	62	19.2	312	19.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
45	45	B	35	HW	PUC	CLASS 3	2	1	1	0	22	157	66	29.33333333	90	120	70	WNL	10.6	61	51.7	356	17	13	62	19.2	312	19.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
46	46	B	26	HW	PUC	CLASS 4	2	1	1	0	15	160	62	24.21875	96	110	70	WNL	9.3	98	14.7	313	31	11	100	24.1	301	33.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
47	47	A	28	HW	PUC	CLASS 3	2	1	1	0	19	160	59	23.046875	92	110	70	WNL	9.3	53	9.9	394	13	12.1	65	15.1	324	20.06	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
48	48	A	26	HW	DIP	CLASS 3	2	0	0	1	19	152	46	20.44444444	94	110	70	WNL	9.1	26	8.4	609	4	11.6	67	18.9	501	13.3	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
49	49	B	24	HW	DIP	CLASS 2	1	0	0	0	16	159	60	24	89	112	60	WNL	10.9	81	22	326	24.8	12.1	84	29	315	26.6	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

50	50	B	38	HW	PUC	CLASS 3	3	2	1	0	21	156	64	27.82608696	80	110	70	WNL	10.8	36	9.45	499	7	11.9	67	23	401	16.7	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
51	51	B	24	HW	PUC	CLASS 2	1	0	0	0	18	151	44	19.55555556	86	110	70	WNL	10.5	86	1.27	396	22	12	99	12	312	31.7	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
52	52	B	36	HW	PUC	CLASS 2	5	0	0	4	15	163	60	26.66666667	88	110	80	WNL	9.3	78	8.86	337	23	11.8	76	16.4	299	25.42	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
53	53	A	27	HW	DIP	CLASS 2	2	1	0	0	22	155	60	26.78571429	86	110	70	WNL	10.2	89	7.6	322	27	14.2	90	16.5	289	31.1	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
54	54	A	30	TEACHER	DIP	CLASS 2	2	1	0	0	22	157	62	27.55555556	86	110	70	WNL	10.2	89	7.6	322	27	13	99	18	301	32.89	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO
55	55	A	29	HW	PUC	CLASS 2	2	0	0	1	20	156	60	26.66666667	92	120	80	WNL	10.8	60	9.1	320	18	12.7	76	16.4	299	25.42	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
56	56	A	26	HW	PUC	CLASS 3	5	2	1	2	21	160	67	26.171875	98	120	80	WNL	10	86	1.27	396	22	11.6	92	10.1	304	30.26	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
57	57	A	38	HW	DIP	CLASS 3	3	2	1	0	21	156	64	28.44444444	80	110	70	WNL	10	55	3.7	329	16.7	11.1	79	18	478	17	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
58	58	A	31	TEACHER	DIP	CLASS 2	2	1	1	0	18	159	63	26.25	89	110	70	WNL	9.6	50	9	340	12.3	11.8	76	16.4	299	25.42	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
59	59	A	20	HW	PUC	CLASS 4	6	1	1	4	18	157	57	25.33333333	96	120	70	WNL	10.2	72	21	355	13	12.6	76	25	299	25.42	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
60	60	B	32	HW	DIP	CLASS 2	4	3	1	0	21	160	56	21.875	98	110	70	WNL	10.3	85	36.7	314	12.6	12.1	131	139	463	28	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
61	61	A	29	NURSE	DIP	CLASS 2	1	0	0	0	18	152	58	25.77777778	88	110	70	WNL	10	58	53	321	12.7	12.4	62	66.3	302	20.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
62	62	A	26	HW	DIP	CLASS 2	2	1	1	0	22	158	58	25.32751092	88	110	80	WNL	10.2	35	6.4	520	11.6	12.7	44	15	360	12.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
63	63	A	27	HW	DIP	CLASS 2	1	0	0	0	15	160	64	25	90	110	68	WNL	10.1	96	19.2	326	12.8	13	126	50	261	48.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
64	64	A	24	TEACHER	DIP	CLASS 2	1	0	0	0	20	162	65	25.390625	88	110	70	WNL	10	92	15	322	13.2	12.6	110	25	430	25.5	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
65	65	A	31	TEACHER	DIP	CLASS 2	1	0	0	0	18	157	64	28.4	80	100	70	WNL	10.6	61	51.7	356	17	13	62	19.2	312	19.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
66	66	A	30	HW	PUC	CLASS 2	2	1	1	0	21	159	60	26	90	110	80	WNL	10.9	80	12.7	367	21.8	12.8	86	21.3	312	27.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
67	67	B	26	HW	PUC	CLASS 2	1	0	0	0	15	158	60	26.66666667	88	110	80	WNL	9.3	98	14.7	313	31	11	100	24.1	301	33.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
68	68	B	33	DOCTOR	PG	CLASS 1	2	1	1	0	18	160	70	27.34375	90	110	80	WNL	10.9	71	18	327	21.7	11.6	79	26	298	26.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
69	69	B	29	HW	PUC	CLASS 2	3	1	1	1	18	158	60	26.20087336	88	112	68	WNL	10.6	41	3.9	321	12.7	12.1	67	11.2	289	22.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
70	70	B	21	HW	PRIMARY	CLASS 4	2	1	1	0	20	160	50	19.53125	78	110	70	WNL	8.9	61	77.2	308	20	11	69	100	267	25.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
71	71	A	26	HW	PRIMARY	CLASS 3	6	2	0	3	20	156	55	23.91304348	92	110	70	WNL	10.2	89	10	322	27	13	99	19.2	301	32.89	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
72	72	B	27	HW	PUC	CLASS 2	2	0	0	1	21	160	65	26	80	110	70	WNL	10.6	129	6.9	301	42.8	12.1	132	12.3	269	49	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
73	73	B	23	HW	DIP	CLASS 2	1	0	0	0	14	157	56	23.33333333	88	120	80	WNL	9.5	62	9.6	400	16	11.9	78	13.4	365	21.37	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO
74	74	B	29	HW	DIP	CLASS 2	2	1	1	0	18	160	59	23.6	92	130	70	WNL	9.5	64	11.3	415	15.4	11.6	89	17.1	399	22	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
75	75	B	29	HW	DIP	CLASS 2	2	1	1	0	20	159	62	24.8	86	110	70	WNL	10.5	79	9.9	319	24.7	13	87	14.2	279	31.18	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
76	76	B	21	HW	SEC	CLASS 3	1	0	0	0	16	157	50	21.73913043	88	110	70	WNL	8.6	823	95.18	881	93	10.1	676	68.9	765	88.3	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
77	77	A	36	HW	PUC	CLASS 2	4	2	2	1	18	158	60	26.08695652	90	110	70	WNL	10.3	314	64	316	99	13.2	219	69	317	69.09	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
78	78	A	28	HW	DIP	CLASS 2	3	0	0	2	18	157	60	26.08695652	78	110	70	WNL	10.8	31	6.2	345	8.9	12.9	57	14.6	269	20.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

79	79	B	28	HW	PUC	CLASS 4	1	0	0	0	18	151	50	22.22222222	80	110	70	WNL	10.7	56	21.3	366	15.3	12.1	63	30.2	280	22.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
80	80	A	23	HW	PUC	CLASS 4	2	1	1	0	20	158	60	26.08695652	86	110	70	WNL	9.3	34	13.9	566	6	11.2	58	20.1	478	12.1	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
81	81	B	20	HW	PUC	CLASS 3	1	0	0	0	20	160	56.7	22.1484375	90	120	80	WNL	10.7	56	21.3	366	15.3	12.1	63	30.2	280	22.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
82	82	B	28	HW	PUC	CLASS 3	6	1	1	4	14	158	57	25.33333333	92	118	72	WNL	9.3	34	13.9	566	6	11.2	58	20.1	478	12.1	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
83	83	B	16	NURSE	DIP	CLASS 3	3	2	2	0	16	157	58	25.77777778	88	110	70	WNL	9.2	49.3	2.6	337	14.6	11.2	58	20.1	478	12.1	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
84	84	B	29	DOCTOR	PG	CLASS 1	2	0	0	1	19	160	69	26.953125	86	110	70	WNL	9.3	27	19.3	495	5	11.2	58	20.1	478	12.1	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
85	85	A	32	HW	PUC	CLASS 4	3	2	1	0	16	159	65	28.26086957	80	110	70	WNL	8	38	2.3	332	11.4	11.8	76	16.4	299	25.42	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
86	86	A	26	HW	PUC	CLASS 4	2	1	1	0	18	158	66	28.69565217	84	120	80	WNL	10.9	102	63	403	25	11.6	89	17.1	399	22	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
87	87	B	34	HW	PG	CLASS 2	2	1	1	0	20	157	67	29.77777778	86	120	80	WNL	10	98	29	318	30.8	13	126	50	261	48.2	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
88	88	B	22	TEACHER	GRADUATE	CLASS 3	2	1	1	0	19	159	56	24.88888889	88	110	70	WNL	10.9	97	37.6	396	24	13.6	127	58	259	49	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
89	89	A	21	HW	PUC	CLASS 3	1	0	0	0	14	154	54	24	84	110	70	WNL	10.7	63	48.5	279	23	12.1	63	58	267	23.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
90	90	A	23	HW	PRIMARY	CLASS 4	2	0	0	1	19	155	55	24.44444444	86	120	70	WNL	9.2	30	10.7	393	8	10.1	42	16.8	352	12	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
91	91	B	24	HW	GRADUATE	CLASS 3	1	0	0	0	21	156	57	25.33333333	90	110	70	WNL	9.7	140	33.9	474	29.5	11.4	93	72.01	382	24	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
92	92	B	32	HW	PUC	CLASS 3	3	0	0	2	14	154	53	23.55555556	92	110	70	WNL	10.8	102	63	403	25	13	61	29.88	341	18	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
93	93	B	36	NURSE	DIP	CLASS 3	2	1	1	0	17	155	52	23.11111111	88	110	80	WNL	10.3	80	13.4	338	24	12.2	55	23	320	17	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
94	94	B	31	NURSE	DIP	CLASS 3	1	0	0	0	17	156	54	24	86	110	68	WNL	9.8	22	5.2	394	6	10.4	60	34	366	16	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
95	95	B	30	NURSE	DIP	CLASS 3	3	2	1	0	16	157	54	24	84	110	70	WNL	10.9	100	60	388	25.7	12.1	63	30.2	280	22.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
96	96	B	25	HW	GRADUATE	CLASS 3	1	0	0	0	19	154	53	23.55555556	88	100	70	WNL	9.4	20	5.1	458	4	11.9	54	16.8	326	16.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
97	97	A	29	HW	DIP	CLASS 3	3	1	1	1	21	155	55	24.44444444	80	110	80	WNL	10.3	91	21.9	336	27	13	95	32	312	30.4	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
98	98	B	23	HW	DIP	CLASS 3	1	0	0	0	17	156	52	23.11111111	86	110	80	WNL	7.9	14	5.4	411	3	9.2	27	13	378	7	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
99	99	A	28	HW	PUC	CLASS 3	4	3	3	0	21	157	56	24.34782609	88	110	80	WNL	9	63	6.3	309	20	11.8	69	16	289	24	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
100	100	B	20	HW	PUC	CLASS 3	1	0	0	0	22	156	53	23.76681614	82	112	68	WNL	10.9	42	28.3	349	12	12	63	30.2	280	22.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
101	101	B	27	HW	PUC	CLASS 4	3	2	1	0	20	153	51	22.66666667	84	110	70	WNL	10.6	74	14.6	400	18.5	12.1	63	30.2	280	22.5	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
102	102	B	24	HW	PUC	CLASS 4	1	0	0	0	22	152	52	22.66666667	88	110	80	WNL	9.8	82	15.4	434	19	12	49	24.9	446	11	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
103	103	B	22	TEACHER	GRADUATE	CLASS 3	3	2	1	0	16	155	51	22.66666667	82	110	80	WNL	10.9	77	15.5	406	19	12.1	84	29	315	26.6	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
104	104	B	31	HW	GRADUATE	CLASS 4	3	2	2	0	21	151	52	23.11111111	80	112	68	WNL	7.6	19	9.3	621	3	11	69	100	267	25.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
105	105	B	17	HW	PUC	CLASS 4	2	0	0	1	17	152	50	22.22222222	82	110	70	WNL	10.7	77	8.7	403	19	13	62	19.2	312	19.8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO