Management of GESTATIONAL ANEMIA

Fresh Thinking and New Frontiers

John Lawson, in his classic annual report in 1954, concluded that it was hoped that maternal (and fetal) loss from anemia would show a steady decline in the future. In his view, the declining level of Hb, in some patients, meant that they reached a point of no return and would die; however, they were treated. Fifty years later, maternal and fetal losses are still unacceptably high, although today we have better ways of preventing women from reaching that point of no return.

The book takes you through the ground realities in the Indian context, right from the rising prevalence of iron-deficiency anemia through the perils of failure of programs to control this and the fresh thinking and new frontiers of the use of parenteral iron to combat this problem.

The original research work by the authors in the Indian context and a comparative study in the West is placed before you in a comprehensive manner with practical suggestions for implementation. The cutting-edge information, summary points, recommendations, and additional algorithms provide the practitioners and postgraduates with an authoritative coverage on Gestational Anemia. This book demonstrates the great commitment on the part of the authors to research, education, and translating knowledge to the bedside.

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Preface

Iron-deficiency anemia (IDA) is the most common form of anemia the world over, and also the most common nutritional disorder in the world. It is probably true, and not unfair, to state that most obstetricians view iron deficiency (ID) and IDA in pregnancy from the perspective of its impact on increased risk of intrauterine growth restriction, preterm labor, and postpartum hemorrhage, and therefore, increased maternal and perinatal mortality and morbidity. Their focus is on detection and treatment during pregnancy, and sometimes after pregnancy, they then consider their job as done and dusted. In reality, ID and IDA have other major negative consequences on the mother, fetus, newborn, neonate, and child, and the adult in the long term.

Those who care for rural women are encountering a significant number of cases of moderate-to-severe gestational anemia, and anemia is implicated as a direct cause in 20% of these cases. It is self-evident that effective treatment of anemia would make a major contribution to a reduction in this high maternal mortality rate. The IFA (iron–folic acid) programs were initiated in India some 30 years ago, yet all evaluations of their impact indicate that the prevalence of anemia in pregnancy either has remained the same or has risen.

Progress can now only be made by an acceptance that the IFA programs have failed, and a determined effort to explore alternatives. Clearly, no single intervention will succeed, but a combination of factors that include the general economic development that hopefully will herald better diets, improved general health of the population, and improved education at a population level which will allow those most in need, especially the rural populations, to embrace the strategies made available to them. The range of treatment options to be considered in this book includes oral iron supplements, intramuscular- and, intravenous iron preparations, and blood transfusion.

In the immediate future, an intervention that might just have a positive impact, might be the introduction of intravenous iron to the mass population. This will immediately circumvent many of the problems associated with oral iron supplementation including compliance, but there will be the challenges of acceptance by the populace, cost, and delivery issues. Unfortunately, newer forms of management are unfamiliar to many clinicians, and the care may be compromised by the lack of up-to-date information.

This book presents critical discussions on the current scenario and ways forward in the management of gestational anemia. It is the intention of the authors that this book continues to be authoritative and a useful contribution to an expanding field. We hope that it will serve practitioners, residents, and other healthcare providers in the day-to-day care of patients and inspire them to devote their services to achieve the goal of safe motherhood.

Hema Divakar

Isaac T Manyonda

Acknowledgments

We would like to express our gratitude to our research team from Asian Research and Training Institute for Skill Transfer (ARTIST) who helped us to make a preliminary assessment of the current situation and execute the operational research work in the Indian context.

We are deeply grateful to Dr Sikandar, Dr Chaitra, Dr Richa, Deepti Jain, Pratima Hosmani, Nitin, Lalitha, and Rincy who worked hard with little reward to provide assistance in recruiting patients and data documentation, and administering the drugs and completion of laboratory work. We would have been unable to put all our ideas into action but for the ARTIST team who worked with us to plan and implement the action that we identified as being both necessary and feasible.

Dr Sudarshan, who allowed us the access to the health centers, and his staff collectively deserve much praise for their co-operation.

We would like to thank Dr Nandakumar, Dr Pritvish, and Ravishankar Vishwanath who invested many hours for the statistical analysis and technical support.

Our lives have been greatly touched as we interacted with many practitioners and healthcare providers who participated in the "Knowledge Cafe" discussions and shared experiences which inspired us to remain determined to translate this into the text form—to all of them we remain deeply grateful.

Finally, we remain indebted to Dr Anupam Ghose and his team from Macmillan Medical Communications, whose patience and forbearance allowed us to complete this book in good spirits and on friendly terms.

Hema Divakar

Isaac T Manyonda

Foreword

I take this opportunity to congratulate Dr (Mrs) Hema Divakar and Dr Isaac T Manyonda for the publication entitled *Management of Gestational Anemia*. Their effort for a meaningful investigation into the problem of anemia and offering us well-reasoned out and convincing practical therapeutic alternative to correct anemia in good time is laudable. Timely correction of gestational anemia helps to improve obstetric outcome and prevent long-term adverse consequences in the future life of the newborn.

Anemia is widely prevalent in India and the developing countries of the Indian subcontinent. Its incidence during pregnancy exceeds 60%. Anemia is a major contributor towards maternal and perinatal morbidity and mortality, and is implicated directly or indirectly in about 40% of cases.

The major causes of anemia during pregnancy are malnutrition, poverty, lack of education, faulty diet habits and food taboos, teenage pregnancies, multiparity, poor birth spacing, poor sanitation and hygiene, and the subservient status of women in society. Intercurrent infections, parasitic (malaria) and helminthic infestations (hookworms) are prevalent in rural and farming communities. Lastly, hemoglobinopathies have been observed in certain tribal belts and communities living in India.

Although widespread attempts to treat pregnant women with oral iron and folic acid supplements have had some impact. However, the results have fallen short of expectations. Noncompliance, due to side effects, malabsorption, and ignorance, has led to persistence of the problem, mandating the need for seeking more effective alternative modes of therapy.

A newer promising drug delivery system has been evolved, which has shown the way to tackle this widespread problem more effectively. Evaluation of parenteral iron sucrose compound by these authors points to the direction for future therapy.

Shirish N Daftary MD FICOG
Prof Emeritus and Former Dean – Nowrosjee Wadia Maternity Hospital
Past President – Federation of Obstetric & Gynecological Societies of India

About the Authors

Hema Divakar obtained her DGO (1986) and MD degrees from Mumbai University in 1989. Having served at the Wadia Maternity Hospital (Mumbai), she furthered her academic qualifications and went on to obtain FICMCH 1999 (Kolkata), FICOG 2000 (Mumbai), Postgraduate Diploma in Medical Law and Ethics from National Law School, Bengaluru; Diploma from All India Institute of Management; Masters Degree in Alternative Medicine; PG Diploma in Preventive and Promotive Health Care. She is a practicing OBGYN consultant and head of Divakar's Hospital, Bengaluru. In her over 25 years of contribution to the OBGYN field in India, she has and continues to be an outstanding clinician, a keen researcher, and a great trainer. Besides being a visiting faculty to Devaraj Urs and Kuppam Medical Colleges, her academic and teaching interests are sustained at the Divakar's Hospital itself, being the only recognized FOGSI USG Training Center in Karnataka for the last 10 years, and one of the few ICOG-recognized centers in the country, for 6-month certification courses in USG and High Risk Pregnancy.

Being an active member of FOGSI for the past 20 years, she has held various administrative and research positions. Having held the posts of Chairperson, Perinatology Committee FOGSI and Senior Vice President FOGSI, she has represented FOGSI in Knowledge-Sharing Platform for Solution Exchange and Indian Confederation for Health Accreditation. Her present positions are Hon. Secretary of ICOG and President of Karnataka Societies of OBGYN; Hon. Fellow of Sri Lankan Perinatology Society; Governing Council Member of South Asian Society for Menopause; National Technical Expert for Emergency Obstetric Care Program and a member of the Technical Advisory Group of FOGSI; Core group member for the formation of Good Clinical Practice Recommendations (GCPRs); Task Force for Policy Making in FOGSI; Technical Advisor for the Institute of Public Health and IIMB; Principal Investigator for FOGSI—PSI Research Project on Post Placental IUCD Insertion and FOGSI Research Project on the Study of GDM Prevalence.

She is passionate about making contributions for improving women's healthcare in India and has worked with the Government of India on the Emergency Obstetric Care Program, contributed in the capacity of National Technical Expert Director for standards and quality control monitoring and evaluation training and supportive supervision for medical officers in rural India, and worked:

- as Technical Expert on the Hospital Accreditation Committee for improving standards of healthcare delivery systems,

- as Technical and Training In-charge for skilled birth attendants training program for the Southern State of Karnataka,
- in public–private partnership with the Government for managing primary health centers and an FRU (First Referral Unit) for maternal healthcare in Karnataka, and
- for strengthening PPTTC Program and training private healthcare providers for HIV management in pregnancy.

She has authored several publications and contributed chapters to several textbooks and journals and is on the Advisory Board of Elsevier Publications and one of the National Editors for FOGSI Journal Committee. She is also the Editor of FOGSI Bulletin on Perinatology in the Journal of Perinatal and Neonatal Care and has edited an FOGSI Publication, The First Trimester.

Isaac T Manyonda is a leading London Consultant Obstetrician and Gynecologist and member of the Royal College of Obstetricians and Gynecologists. Isaac T Manyonda works as a Consultant in the Department of Obstetrics & Gynecology, St George's Hospital NHS Trust and also in private practice from several hospitals across London. He is a Reader in the Department of Obstetrics & Gynecology, St George's Hospital Medical School, London.

He has an extensive range of publications of original research in high-impact factor journals, including Nature, New England of Medicine, The Lancet, BMJ, and BJOG.

He is the Author/Editor of several books such as Immunology of Human Reproduction, Fibroids, and Hysterectomy, and also the author of first case report of the use of recombinant erythropoietin in pregnancy. Dr Manyonda has to his credit a track record of securing funding from the major charities, including the UK MRC, The Welcome Trust, and Sir Jules Thorne Trust, and current research funding from the British Heart Foundation (£120,000 over 2 years), Department of Health's NIHR (£1.2m).

His research interests revolve around areas, such as Anemia in pregnancy, Fibroid disease, Pre-eclampsia, Diabetes in Pregnancy, Recurrent Miscarriage, and Outcomes of Hysterectomy.

His research collaborations include:

- In India: Scientific Director for ARTIST: research on anemia in pregnancy and diabetes in pregnancy
- With Universities of Reading & Sussex
- National Projects on Fibroid Disease in the UK

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Chapter - 1

Prevalence of Gestational Anemia

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Prevalence of Gestational Anemia

Introduction

Anemia is said to be present when the measured hemoglobin (Hb) falls below a defined level or range. However, there are differences in Hb concentrations between men and women, and between pregnant and nonpregnant women, and there are also well-recognized physiological changes in the Hb concentration during the course of a normal nonanemic pregnancy. It is, therefore, not surprising that there is no universally accepted or used definition of anemia in pregnancy. Here we will consider definitions from three sources: the World Health Organization (WHO), the US Centers of Disease Control (US CDC), and the Indian Council of Medical Research (ICMR).

WHO (1972): Regardless of its etiology, the WHO defines anemia as the presence of a Hb level of less than 11 g/dL during pregnancy and less than 10 g/dL in the puerperium.[1]

US CDC (1989): Taking into consideration the physiological trough in Hb concentration during pregnancy, CDC defines anemia as the presence of a hemoglobin level of less than 11 g/dL during the first and third trimesters (weeks 1–12, and 29–40 of pregnancy) and less than 10.5 g/dL during the second trimester (weeks 13–28 of pregnancy).[2]

ICMR (1989): Anemia is defined by an Hb of less than 11.0 g/dL, and the severity of the anemia categorized as follows:[3]

<4 g/dL	=	very severe
4–6.9 g/dL	=	severe
7–9.9 g/dL	=	moderate
10–10.9 g/dL	=	mild

Types of Anemia Based on Cause

Anemia is most commonly caused by a deficiency of iron, but it may also be caused by a deficiency of the vitamins B12 and folic acid. Chronic renal disease and chronic infestations, or other chronic inflammatory conditions, may also be associated with anemia.

Iron Deficiency and Iron-Deficiency Anemia

Although the distinction is not always made, in fact it is important to recognize that a state of iron deficiency precedes iron-deficiency anemia, and for clarity, it is important to define various possible states.

- *Absolute iron deficiency* is when serum ferritin is less than 15 μg/L, regardless of whether anemia is present.
- *Iron-deficiency anemia* is when serum ferritin is less than 15 μg/L and Hb level fulfils the definition of anemia as above (i.e. either WHO, CDC or ICMR).

Other categories encountered in the literature include the following:

- *Latent iron deficiency*, when serum ferritin is less than 15 μg/L, but Hb levels are within the non-anemic range.
- *Functional iron deficiency*, when serum ferritin is normal or even elevated, but transferrin saturation is reduced or the hypochromic erythrocyte fraction is greater than 10%, or Chris less than 29 pg.

Iron-deficiency anemia is the most common form of anemia the world over, and also the most common nutritional disorder in the world.

Prevalence of Gestational Anemia

Iron-deficiency anemia is the most common form of anemia the world over, and also the most common nutritional disorder in the world. Iron deficiency and the subsequent anemia occur in a progressive sequence:

- Depletion of the iron stores
- Iron-deficiency erythropoiesis – the stage when iron levels are low, but the indices defining anemia have not been reached.
- Iron-deficiency anemia – the stage when the iron stores are depleted, and the indices that define anemia have been attained.

Global Context

There is a wide geographical variation in the incidence of iron deficiency and iron-deficiency anemia in pregnancy. There are no figures for iron deficiency

only from the developing world, but in Europe, the figures range from about 25% in the UK to about 50% in Switzerland, while the corresponding figures for iron-deficiency anemia in the same countries are approximately 6% and 18%. Thus, in the industrialized western countries, iron deficiency is relatively common, while the anemia itself is relatively uncommon, at least in comparison to sharply contrasting situation in the developing world. For what its worth, mean quoted figures for the global prevalence of gestational anemia are as follows:

- Africa: 35–60%
- Asia: 37–75%
- Europe (and other industrialized countries): 6–18%
- Latin America: 35–50%

In practice, however, these figures are largely meaningless since the ranges are so high, even in the industrialized countries. They do, however, underline the gravity of the situation. The overall mean global figure for the incidence of gestational anemia is 25%:[4] an average 56% in the developing world and 18% in industrialized countries.[5,6] Pregnant women are particularly at high risk for iron deficiency and iron-deficiency anemia because of increased iron needs during pregnancy.

Postpartum hemorrhage is a major contributor to the high maternal mortality, estimated as contributing up to 25–30% to the figure of 401 per 100,000 live births in India. Anemia is implicated as the direct contributor in 20% of cases.

Indian Context

With a rapidly growing economy and having established herself as a leader in information technology, it is curious and surprising that India continues to report one of the highest maternal mortality figures in the world, lagging behind Sri Lanka and Botswana. The explanations are not immediately apparent, although the wide gap between rich and poor may be a major contributor. Other factors will be explored in a separate chapter in this book. What is clear is that postpartum hemorrhage (PPH) is a major contributor to the high maternal mortality, estimated as contributing up to 25–30% to the figure of 401 per 100,000 live births in India. Anemia is implicated as the direct contributor in 20% of cases.[7]

In response to the high levels of anemia in pregnancy, the National Nutritional Anemia Control Program (NNACP) was initiated in India in 1970 to provide free iron–folic acid tablet supplementation to pregnant women from second trimester onwards right up until 3 months of lactation—this was the now

famous Iron–Folic Acid (IFA) Program which even today operates across the country. This program has been taken up by the Maternal and Child Health (MCH) Division of the Ministry of Health and Family Welfare (MOHWF). It is also now part of the Reproductive and Child Health (RCH) Program. There have since been a series of surveys, studies, or audits to assess the prevalence of anemia in women in India, and thereby also to assess the impact of the IFA Program. The key ones are as follows:

1. The National Family Health Surveys (NFHS)-I, -II, and -III are among the most comprehensive surveys of their kind ever conducted in India. Survey responses provide information on fertility, mortality, family planning, and important aspects of nutrition, health, and health care. Surveys were coordinated by the International Institute for Population Sciences (IIPS) in Mumbai under the auspices of the MOHWF. The East-published West Center and ORC Macro provided technical assistance, and the United States Agency for International Development gave financial support.

   The prevalence figures from the various sources can be summarized as follows:

   i. NFHS-I (1995) was conducted in 1992-93. The survey collected extensive information on population, health, and nutrition, with an emphasis on women and young children. Reports indicated that 40% of rural women receive care from a doctor during at least one antenatal visit and 45% of these receive the iron–folic acid tablets.[8]

   ii. NFHS-II (2002) was conducted in 1998-99, using the hemocue technique to measure Hb, and reported anemia prevalence of 49.7% in pregnant women, 56.4% in breast-feeding women, and 50.4% among nonpregnant and non–breast-feeding women.[9]

   iii. NFHS-III (2008) was carried in 2005-06 and reported anemia prevalence of 57.9% in pregnant women, 54.6% in urban and 59% in rural. Of these, 35% were mildly anemic, 15% moderately anemic, and 2% severely anemic.[10]

2. The Indian Council of Medical Research (ICMR) has conducted a series of studies as follows:

   i. ICMR (1998) – A study of the prevalence of anemia in 4181 pregnant rural women in 11 States – 87.6% women had Hb < 10.9 g/dL.

   ii. ICMR (1999-2000) – District nutrition survey of micronutrient profile of Indian population. Toteja and Singh (2001) reported a prevalence of anemia of 84.2% with 13.1% with severe anemia in pregnancy.[11]

iii. ICMR (2004) – Study on a sample of 1937 healthy adolescent girls aged 11–19 years from three districts of Orissa, India. This study revealed that the prevalence of anemia in nonschool going adolescent girls was 96.5% (Hb < 12 g/dL), of which, 45.2%, 46.9%, and 4.4% had mild, moderate, and severe anemia, respectively.[12]

Other Surveys/Studies

National Nutrition Monitoring Bureau

National Nutrition Monitoring Bureau Micronutrient survey conducted by Hyderabad: National Institute of Nutrition in 2000-01 in the States of Andhra Pradesh, Gujarat, Karnataka, Kerala, Madhya Pradesh, Orissa, Tamil Nadu, Maharashtra, Uttar Pradesh, and West Bengal assessed the levels of Hb in the rural communities by covering statistically adequate sample. The technical report published in 2003 revealed the following.[13]

- Preschool children – 67%
- Adolescent girls (12–17 years) – 69–71%
- Pregnant women – 75% (moderate anemia 46%; severe anemia 4%)
- Lactating women – 78%

District Level Household Survey

District Level Household Survey 2002-04 is one of the largest ever demographic and health surveys carried out in India, with a sample size of about 700,000 households covering 563 districts of the country. DLHS-RCH undertook direct measurement of Hb levels by collecting blood samples in the field using the filter paper technique. This assessment showed that over 70% of pregnant women and adolescent girls in the country were anemic. The prevalence of moderate and severe anemia was high even among educated and higher income groups.[14]

Hemoglobin Estimations in Rural Pregnant Women

In this study conducted in Varanasi (1986-91) Hb estimations in rural pregnant women showed 94.5%, 95.3%, and 95.9% prevalence of anemia in the first, second, and third trimesters, respectively.[15]

Prevalence of Gestational Anemia in Rural and Urban Setting

As a prelude to further studies on gestational anemia in the State of Karnataka, the authors have also conducted their own study of the prevalence of gestational anemia in both, a rural and an urban setting. They

studied 10,000 pregnant women in a rural setting and 1985 women in an urban setting. Estimation of Hb was done by Sahli's Hemoglobinometer. Using the ICMR categorization of anemia, they found an overall prevalence rate of anemia of 69.4% in the rural and 61.4% in the urban setting. This difference in prevalence of anemia among rural and urban pregnant women was found to be statistically significant ($P < 0.001$) [Divakar and Manyonda, 2009, unpublished figures]. Among the rural women, the vast majority (43.5%) had a moderate degree of anemia, while the majority (35.7%) among the urban women had a mild degree of anemia. No woman in the urban setting had very severe anemia, while the prevalence in this category in the rural setting was 0.6%. The full data are shown in Figures 1.1 and 1.2, and Table 1.1.

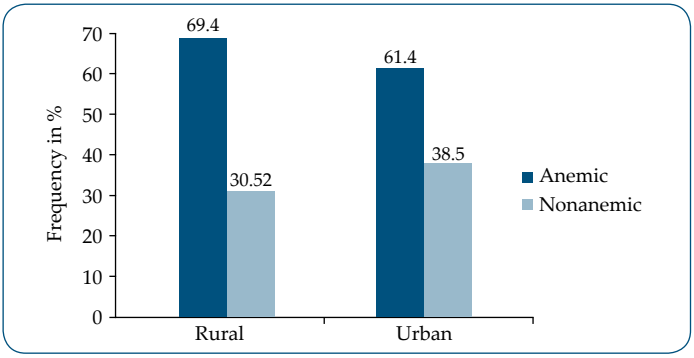

Fig. 1.1. Distribution of anemia among rural and urban pregnant women (Divakar and Manyonda, 2009).

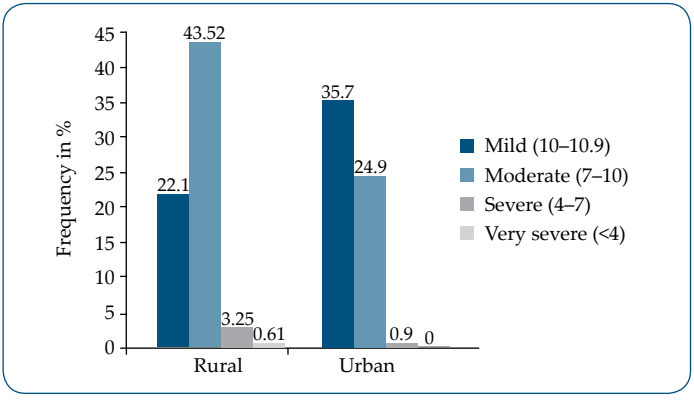

Fig. 1.2. Severity of anemia among rural and urban pregnant women (Divakar and Manyonda, 2009).

Table 1.1. Prevalence of iron-deficiency anemia among rural and urban pregnant women in the State of Karnataka (Divakar and Manyonda, 2009).

Status	Rural *n* = 10,000		Urban *n* = 1985	
	(n)	(%)	*(n)*	(%)
Anemic	6948	69.40	1247	61.40
Nonanemic	3052	30.52	738	38.50
Total	10,000	100	1985	100

Conclusion

The prevalence of IDA in both rural and urban India is, at best, static, although there are indications that it might be rising. Studies in India have shown that as compared to classical cyanmet Hb method using colorimetry, the hemocue overestimates Hb levels.[16,17] The use of hemocue method for Hb estimation in the NFHS-II and -III studies may be responsible for reporting a lower prevalence (57.9%), whereas all the other groups, using the cyanmethemoglobin method, have reported a higher prevalence of anemia (70–85%).

Whatever the cause, these women enter pregnancy with frank anemia and/or deficient iron stores. This puts these women at risk of hemorrhage and all the other attendant risks of IDA, and this increases mortality and morbidity in these women. Although not overtly anemic, the newborns of anemic women are at significant risk of the nonhematological consequences. Iron-deficiency anemia remains a major challenge in India, and there is a need for fresh thinking in tackling this problem.

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Chapter - 2

Gestational Anemia: Hematological/ Nonhematological Consequences

- Introduction
- Regulation of Iron Transfer to the Fetus
- Intrauterine Iron Metabolism and the Consequences of IDA
- Maternal and Perinatal Morbidity and Mortality
- Impact on Cognitive Function and Behavior in Childhood
- Impact on the Immune System
- Impact on the Endocrine and Nervous Systems
- Iron-Deficiency Anemia increases Risks of Heavy Metal Poisoning
- Economic and Societal Consequences of IDA
- Conclusion

Gestational Anemia: Hematological/ Nonhematological Consequences

Introduction

It is probably true, and not unfair, to state that most obstetricians view iron deficiency (ID) and iron-deficiency anemia (IDA) in pregnancy from the perspective of its impact on increased risk of intrauterine growth restriction, preterm labor and postpartum hemorrhage, and therefore, increased maternal and perinatal mortality, and morbidity. Their focus is on detection and treatment during pregnancy, and sometimes, after pregnancy, they then consider their job as done and dusted. In reality, ID and IDA have other major negative consequences on the mother, fetus, newborn, neonate, and child, and on the adult in the long term. Knowledge of the impact of intrauterine nutrition, including ID, on later life cardiovascular and other disorders is increasing. Pediatricians, if not their obstetrician counterparts, are well aware of the negative consequences of neonatal ID and IDA on cognitive and motor development, on the immune, endocrine, and nervous systems, and on increasing risks from heavy metal poisoning. Even less appreciated by obstetricians is the economic impact of IDA. Some of the sequelae of IDA in the neonate, such as impaired cognitive development, may not be reversed by subsequent iron supplementation and correction of the IDA, thus having a major impact on the life prospects of that child. By far, the commonest cause of IDA in the neonate is maternal IDA during pregnancy; thus, the obstetrician needs to be fully aware of the full spectrum of the consequences of ID and IDA, since simple interventions of prevention, detection, and treatment of pregestational and gestational IDA will impact so profoundly on the offspring.

Some of the sequelae of IDA in the neonate, such as impaired cognitive development, may not be reversed by subsequent iron supplementation and correction of the IDA, thus having a major impact on the life prospects of that child.

Regulation of Iron Transfer to the Fetus

Transfer of iron from the maternal to the fetal compartment increases 3–4 fold during the weeks 20–37 of gestation, and effective transport mechanisms exist that function even across a positive gradient in favor of the fetus. During pregnancy, there is a substantial increase in maternal iron absorption. Serum ferritin, usually, falls markedly between 12 and 25 weeks of gestation, probably, as a result of iron utilization for expansion of the maternal red blood cell mass. Most iron transfer to the fetus occurs after week 30 of gestation, which corresponds to the time of peak efficiency of maternal iron absorption. Serum transferrin carries iron from the maternal circulation to transferrin receptors located on the apical surface of the placental syncytiotrophoblast, holotransferrin is endocytosed, iron is released, and apotransferrin is returned to the maternal circulation. In the fetal compartment, the free iron binds to ferritin in placental cells where it is transferred to apotransferrin, which enters from the fetal side of the placenta and exits as holotransferrin into the fetal circulation. When maternal iron status is poor, the number of placental transferrin receptors increases so that more iron is taken up by the placenta.

Based on research from countries as diverse as Ireland, Niger, China, Japan, and India, it is generally assumed that the iron status of the fetus, and by inference, the neonate is independent of the maternal iron status during pregnancy, with the exception perhaps of fetuses/neonates of severely anemic mothers. This research shows that there is no significant association between maternal hemoglobin (Hb) concentrations at or near term and cord blood Hb concentrations. This lack of association was also reported in research carried out in France and Denmark, even when half of the women were provided with iron supplements. However, although studies from the UK also found no correlation between low Hb concentrations in unsupplemented women in the third trimester and Hb concentrations in 3- to 5-day-old infants, those infants born to nonanemic mothers had distinctly higher blood volumes, red cell volumes, and circulating hemoglobin mass than those born to anemic mothers. There is also a well-documented high prevalence of ID in infants after 6 months of age in developing countries. Thus, there is a need for more rigorous studies that assess the relation between the iron status of pregnant women and the iron status of their fetuses *in utero* and infants postpartum. The situation *in utero* is likely to prove difficult to define, since the anemic or iron-deficient pregnant woman is at higher risk of preterm labor, and the fetus may be born before adequate iron stores are laid down in the fetus.

Despite the limited knowledge, and sometimes conflicting data from research, the general consensus appears to be that the commonest cause of neonatal ID and IDA is maternal ID and IDA during pregnancy. Though nutritional factors are relevant, it seems evident that ID in infancy and early childhood is largely secondary to maternal ID during pregnancy. In the first year of life, when the iron intake is poor, newborn infants of iron-deficient mothers have significantly decreased ferritin levels[1] and an increased incidence of iron deficiency. There is also evidence that infants born to women taking iron have more than double the iron reserves at 2 months of age and beyond when compared with the offspring of unsupplemented mothers. Thus, to address the problem of ID in infancy and early childhood is to close the proverbial stable door after the horse has bolted. A significant part of the solution lies in preventing ID during pregnancy.

Intrauterine Iron Metabolism and the Consequences of IDA

Until around a decade ago, the intrauterine milieu, in which a fetus developed, was largely viewed in terms of potential poor nutrition in conditions, such as pre-eclampsia, or excess nutrient supply in diabetes. Though the undernutrition might result in intrauterine growth restriction, and fetuses were closely monitored to balance between continued intrauterine existence to allow for fetal lung maturation and the risks of intrauterine death, it was always considered that the malnourished fetus would "catch-up" in growth once born and exposed to adequate nutrition. What has become clearer, however, is that intrauterine malnutrition has profound influences that transcend simple birth weight. Many studies have demonstrated a link between fetal nutrition, low birth weight and coronary heart disease, hypertension and impaired glucose tolerance in adults. It has been proposed that the adaptation made by the fetus to cope with inappropriate nutrition may lead to morphological and physiological changes that persist into postnatal life. These changes, though ensuring fetal survival, may have detrimental effects in later life. Where iron metabolism is concerned, anemia and ID in pregnancy are associated with large placental weight and a high ratio of placental weight to birth weight (placental ratio),[2] both of which are predictors of adult hypertension.[3] Much has now been written on the intrauterine origins of adult disease, and is beyond the scope of this chapter, which is limited to a brief expose on the issue of ID and IDA.

A basic principle of fetal/neonatal iron biology is that iron is prioritized to red cells at the expense of other tissues, even including the brain. Thus, when iron supply does not meet iron demand, the fetal brain may be at risk

even if the fetus/infant is not anemic. As stated above, the most common etiology of reduced fetal iron supply is maternal ID. A number of studies have shown that IDA during pregnancy, especially if severe, constitutes a significant threat to fetal iron stores and thus, may place both the fetal and neonatal brain at risk. The degree of reduction in brain iron concentrations in infants born to IDA mothers is not known, since brain iron can only be determined at autopsy. Serum markers, such as ferritin concentration, have to be used to infer the risk to the brain. Neonates born to mothers with IDA have lower ferritin concentrations and may even have IDA if the mother is severely anemic. The sequelae of ID and IDA such as impaired cognitive function in the neonate presumably have their origins in the deprivation of iron of the fetal brain *in utero*.

Maternal and Perinatal Morbidity and Mortality

In the developing world, anemia remains the commonest medical disorder during pregnancy, and a major direct and indirect cause of maternal mortality.[4–7] For the mother, morbidity in severe pregnancy anemia can include breathlessness, edema, congestive heart failure, and even cerebral anoxia. Nonanemic, but iron-deficient women with otherwise unexplained fatigue, may benefit from iron supplementation.[8] Tissue enzyme dysfunction is thought to occur in iron deficiency, since treatment with oral or parenteral iron results in improved well-being before a significant rise in hemoglobin is noted, suggesting a central nervous system effect.[9] The effect of ID on neuromuscular transmission[10] may be responsible for reports of increased blood loss at delivery in anemic women. Forty percent of all maternal perinatal deaths are linked to anemia, and India makes a major contribution to the overall global maternal mortality rates, completely out of synchrony with the recent economic and technological advances seen in the country. There are profound consequences for the fetus/neonate: the odds for low birth weight are tripled, while those for preterm delivery more than doubled in association with iron-deficiency anemia.[11] Data from studies in India suggests that maternal anemia results in considerable fetal loss (12–28%), perinatal deaths (30%) and neonatal deaths (7–12%). In addition to the sequelae described in more detail below, studies have shown that poor iron status at birth correlated with higher levels of negative emotionality and lower levels of alertness

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and soothability. Infants of mothers with IDA in the peripartum period have been shown to have lower scores for hand–eye movement at 10 weeks and locomotion at 9 months. A longitudinal study found that lower cord ferritin levels predicted poorer behavior/development at 5 years, specifically poorer auditory comprehension of language, fine motor skills, and self-regulation. This is additional evidence, linking maternal prenatal iron status to ID and IDA in neonates and infants.

Impact on Cognitive Function and Behavior in Childhood

In the face of high levels of maternal morbidity and mortality due to IDA in the developing world, the adverse impact of ID with or without anemia on the offspring is often overlooked, yet it is profound. Iron-deficiency anemia is associated with poor performance in the Bayley Mental Development Index.[12] A recent academic meeting at the Royal Society of Medicine in the UK highlighted the adverse effect of ID on childhood mental development.[13] Poor mental and motor performance improves with iron therapy in iron-deficient infants at 12–18 months of age.[14]

There is overwhelming and irrefutable evidence that IDA delays psychomotor development and impairs cognitive performance in infants and children, and a majorly worrying aspect of this is that subsequent iron supplementation may not correct the effects of the earlier deficiency.

There is overwhelming and irrefutable evidence that IDA delays psychomotor development and impairs cognitive performance in infants and children, and a majorly worrying aspect of this is that subsequent iron supplementation may not correct the effects of the earlier deficiency. Though evidence has come from a diversity of studies in a variety of countries,[15–25] it has also been supported by animal experimentation where iron has been shown to play a key role in brain function. Several areas of the brain contain iron, sometimes, in large quantities, and iron-deficient animals show alterations both in neurotransmitters and behavior that do not usually respond to iron replenishment. Electrophysiological measurements have shown that ID is associated with neurological malfunction in young children, adolescents, and adults.[26]

Just to give examples of research findings: in a study in Costa Rica, children who had moderate anemia as infants achieved lower scores on intelligence quotient (IQ) tests and other cognitive performance upon entry in school than did children who were nonanemic during infancy. This finding emerged even when the tests were controlled for a comprehensive set

of socioeconomic factors.[19] Other studies corroborated this report, and research from Thailand showed that the poor performance in Thai language and mathematics tests of children with low Hb levels was not reversed by iron supplementation.[23] On a somewhat more positive note, adolescent girls, whose diet was supplemented with iron, felt less fatigued and their ability to concentrate in school increased and their mood improved,[27] the point here being that although some of the major consequences of ID in childhood may not be reversible, the anemia should always be corrected when diagnosed.

In summary, ID can impair cognitive performance at all stages of life, and these effects of ID in infancy and early childhood are not likely to be corrected by subsequent iron therapy. It is estimated that 10–20% of preschool children in developed countries, and 30–80% in developing countries, are anemic at 1 year of age.[28] These children will have delayed psychomotor development, and when they reach school age they will have impaired performance in tests of language skills, motor skills, and coordination, equivalent to a 5- to 10-point deficit in IQ.[29] It is a sobering thought to imagine the extent to which the whole-life outlook for a child can be so negatively impacted upon for want of a simple, cheap, and potentially readily available intervention.

Impact on the Immune System

There is now strong evidence that iron is important in the development of the immune system as well as the immune response itself. Thus, it is well documented that in situations of iron deficiency, cell-mediated immune (CMI) responses are compromised, as evidenced by a lower concentration of cells involved in CMI, and depressed skin-test responses to common antigens, such as seen in the Mantoux test. *In-vitro* lymphocytes show decreased responses to mitogen stimulation, and the capacity of macrophages and other leukocytes to kill ingested micro-organisms is diminished. Thus, morbidity from infectious disease is increased in iron-deficient populations. The positive side to this is that iron supplementation and milk, or cereal fortification among deficient children, has been reported to correct the deficiency in the immune system and reduce the associated morbidity from infectious disease.

Impact on the Endocrine and Nervous Systems

Iron is also important in other metabolic pathways in the body including those involving the endocrine and nervous systems. Thus, ID alters the production of tri-iodothyronine (T3) and thyroid function in general, and the production and metabolism of catecholamines and other neurotransmitters. This results in impaired temperature response to a cold environment. Both, under

experimental conditions in animals and in nonexperimental conditions in humans, iron-deficient subjects become hypothermic and have a depressed thyroid function more readily than nonanemic subjects.[30–34] This is likely the explanation for why poorly nourished individuals feel discomfort from cold at temperatures at which well-nourished persons tend not to.

Iron-Deficiency Anemia increases Risks of Heavy Metal Poisoning

Iron-deficiency anemia results in an increased capacity for iron absorption—this is a physiological response aimed at correcting the iron deficiency. Unfortunately, this increased absorption capacity is not confined to iron but includes increased absorption capacity for other divalent metals that include toxic metals. Thus, an important consequence of ID is an apparent increased risk of heavy metal poisoning in children, including lead poisoning. Unfortunately, areas of the world (especially developing countries), where ID in children is prevalent, are also the same areas where there is high exposure to the risk of heavy metal poisoning, pollution from automobile fumes, chipped lead paints, uncontrolled mining activity, and general poor regulation that might not be seen in the more affluent countries. The challenge is to recognize that though massive economic interventions are required to reduce the levels of risk from pollution, simple prevention of ID would significantly reduce the number of children susceptible to lead poisoning—a simple measure not always immediately evident to the public health authorities, and where the obstetrician can start the ball rolling by preventing anemia during pregnancy.

Economic and Societal Consequences of IDA

Although it may not be evident to the obstetrician, and indeed s/he might not consider that this issue has anything to do with him/her, yet it is a fact that ID and IDA impair national socioeconomic development. A simplistic way of looking at the issues is that a significantly anemic woman cannot perform her economic role or societal duties to her optimal capacity, and this direct reduces performance impact on productivity. Dealing with the consequences of IDA in women, who enter pregnancy anemia (the maternal and perinatal mortality and morbidity), poses a huge economic burden. The long-term consequences of retarded cognitive development, consequent on childhood anemia, can only be imagined: a child that could have been destined to be a captain of industry ends up as a supermarket checkout person, depriving the nation of people with a potential to help develop the economy.

There are the health care costs of treating children who readily succumb to infections due to the compromised immune systems associated with IDA, and increased risk of heavy metal poisoning, or the endocrine and neurological compromise consequent upon IDA. Where there the government is proactive, there are the costs of interventions specifically directed at nutrition and health education, dietary diversification, and other public health interventions aimed at improvements in iron nutrition. The societal consequences of increased maternal mortality and resultant restraints on productivity are difficult to quantify. Indeed any estimates of the economic and/or societal impact of ID and IDA can only be gross understatements of the true negative impact on the economy and society.

No pretence is made here that it is in the hands of the obstetrician to solve the economic and societal consequences of ID and IDA, but by meticulous attention to dealing with this, the commonest metabolic disorder of pregnancy, the obstetrician will have played a major direct and indirect role. The challenge is perhaps for the health economists to better define the problem, the public health specialists to develop effective policies, and for government to fund the policies. Without these prerequisites, even when armed with all types of iron preparations, the obstetrician would not overcome this major problem.

The consequences of ID and IDA include increased maternal and perinatal morbidity and mortality including intrauterine growth restriction, preterm birth and postpartum hemorrhage, and their attended sequelae.

Conclusion

Though there may be major gaps in our knowledge regarding ID, IDA, and their consequences on the mother, fetus, neonate, child, adolescent, and future adult, there is sufficient data to reach the following conclusions:

- Although accelerated transplacental transport systems may protect the fetus from the ID and IDA in an anemic mother, nevertheless there will be many instances where this is inadequate, and the fetus suffers ID and IDA which impact negatively on brain development. The impact of intrauterine and other nutritional deficiencies on adult disease are now well documented.
- The consequences of ID and IDA include increased maternal and perinatal morbidity and mortality including intrauterine growth restriction, preterm birth and postpartum hemorrhage, and their attended sequelae.
- Iron deficiency and IDA in the newborn and infant are most likely secondary to maternal ID and IDA. Some of the consequences of ID

and IDA, such as cognitive development, may be irreversible even if the ID and IDA are later corrected. Children with IDA have increased morbidity from increased infections, impaired endocrine and nervous system function, and are at increased risk of heavy metal poisoning.

- It is self-evident that ID and IDA have major negative socioeconomic implications, although it is difficult to quantify these with any degree of accuracy.

The obstetric profession cannot alone solve the problems of ID and IDA, but they have the potential to make a major difference to outcomes:

- by the simple measures of advocating and helping to implement the eradication of ID and IDA in the adolescent girl (the future mother), and
- by advocating and implementing anemia surveillance throughout pregnancy, leading to accurate diagnosis, treatment with effective regimens that include intravenous iron where indicated, and appropriate follow-up to ensure optimal and sustained response to therapy.

In these endeavors, the partner players include pediatricians, public health policy makers, pharmaceutical industry and the government.

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Chapter - 3

The Iron–Folic Acid Supplementation Program in India: Profound Failure of an Idyll

- Introduction
- Historical Perspectives
- Evaluation of the Impact of the IFA Program on Anemia Prevalence
- IFA Programs: Reasons for Failure and its Solution
- Acceptance that the IFA Program has Failed to Eradicate IDA in India

The Iron–Folic Acid Supplementation Program in India: Profound Failure of an Idyll

Introduction

Iron-deficiency anemia (IDA) is the most common medical disorder of pregnancy in the developing world. In India, iron–folic acid (IFA) supplementation programs were launched in 1970 to provide free IFA supplementation to pregnant women commencing from the second trimester until 3 months of lactation. In 1970, the prevalence of IDA in pregnancy was estimated at approximately 50%. In 2010, it is estimated that the prevalence is well in excess of 50%. Thus, the IFA programs have effectively failed to achieve the stated goals, and the issues surrounding the profound failure of an idyll are explored in this chapter.

Historical Perspectives

The Unmet Need

In the 1970s, maternal mortality in India was estimated at 450/100,000 pregnancies, a figure not dissimilar to that reported in Europe 200 years ago. Anemia was implicated as a direct cause in 20% of these cases. It was self-evident that effective treatment of anemia would make a major contribution to a reduction in this high maternal mortality rate. Several national and international studies had repeatedly reported a high prevalence of anemia, especially that due to iron deficiency, in pregnancy in India. This was especially true for women in the rural areas, and even current reports indicate that the prevalence of IDA remains high. The Government of India was galvanized into action, and the Ministry of Health and Family Welfare initiated the National Nutritional Anemia Control Program (NNACP) in 1970 to provide free IFA supplementation to all pregnant women commencing from the second trimester until 3 months of lactation.

The Rationale Behind the IFA Program

The fundamental aim was simple enough—to decrease the prevalence and incidence of anemia in women of reproductive age. It was expected that this strategy of giving free supplements of iron would work for the following reasons:

- Oral iron therapy has been shown to be effective in correcting IDA in most cases.
- It is a common understanding that almost all women can be treated effectively with oral preparations, and in routine practice, prescribing oral supplementation is considered the treatment of choice due to its low cost and high effectiveness.
- Supplementation programs, especially for pregnant women, operate in developed as well as in developing countries. For example, Sweden has been implementing iron supplementation and fortification of many foods for many years. This practice may explain a relatively low prevalence of IDA in that country, and it was suggested that a similar program would meet with the same success in India.

The Program Components

- Pregnant women were recommended to have one adult tablet per day (containing 100 mg iron and 5000 μg folic acid) for 100 days from after the first trimester of pregnancy through till 3 months into lactation.
- For treatment of severe anemia, women in the reproductive age group were recommended to take three adult tablets per day for a minimum of 100 days.
- Preschool children (aged 1–5 years) were recommended to take one small tablet (pediatric tablet contains 20 mg iron and 100 μg folic acid) per day for 100 days every year.[1]

Implementation Strategies

- The IFA program was to form an integral part of the safe motherhood services, offered as part of the Reproductive and Child Health care (RCH) program.
- The IFA program was to be implemented through the Primary Health Centers (PHC's) and its sub-centers.
- The program was to solicit the support of various departments in implementing the dietary modification and supplementary measures. For example, drinking tea was to be discouraged, as components of tea can chelate iron and impair absorption.

Evaluation of the Impact of the IFA Program on Anemia Prevalence

It makes sense to periodically evaluate an interventional program, such as the IFA program, and this has indeed been undertaken, not just by the NNACP, but also by a variety of other agencies and organizations. The results are as follows:

- In 1970, at the time of implementation of the IFA program, the prevalence of IDA in pregnancy, as assessed by the National Family Planning Survey (NHFS, 1970) was 82%.
- To monitor the impact of the IFA program, the NHFS launched another survey in the year 1998/1999 (NHFS-II), following which they reported a prevalence of IDA of 49.7%.
- In a (September 2001–April 2003) study, conducted by the Healthcare and Research Association for Adolescents, Noida, and the Nutrition Foundation of India, New Delhi, women in the same districts and villages studied in NFHS-II were evaluated. The study concluded that the prevalence and severity of anemia in rural pregnant women was much higher than that reflected in NFHS-II: 84% prevalence, of which 9.2% fell into the severe anemia category.[2]

The study concluded that the prevalence and severity of anemia in rural pregnant women was much higher than that reflected in NFHS-II: 84% prevalence, of which 9.2% fell into the severe anemia category.

The most recent survey by the NFHS itself (NFHS-III, 2005-06) has reported a rise in prevalence from 49.7% to 57.9%, indicating a rising trend.[3]

The authors' data (Divakar and Manyonda, 2008) show that the prevalence of IDA in pregnancy has continued to rise (69%) over the past 2 decades, despite the IFA program, and the economic revolution that India is witnessing. As expected, the more severe forms of anemia are seen in rural populations, but the urban populations do not fare that much better.

IFA Programs: Reasons for Failure and its Solution

There can be no doubt the observations from a variety of sources that the IFA programs have not been the anticipated success they could or should have been. A number of problems have been identified which have contributed to the apparent failure of these programs, including problems with the delivery system, problems of poor compliance, and failure to deworm women prior

to taking supplements.

Failure of Delivery Systems

It is envisaged within the IFA programs that tablets will be distributed through PHC's and Community Health Centers (CHC's) where women are expected to present themselves for antenatal check-ups. Thus, unless a woman seeks antenatal care, she does not avail herself of the opportunity to receive the tablets. The practical reality is that less than 50% of women visit the PHC's and CHC's for the following reasons:

- Lack of awareness of the existence of such centers
- Hesitation in approaching a health facility without an escort (lack of transport and constraints of accessibility)
- Time constraints (owing to burden of housework and taking care of young children)
- Economic constraints (cost involved in transit, cost of services and loss of wages)

Potential solutions to the failure of delivery systems

When IFA tablets were being provided through the NGO working in the slums in the Urban Health Resource Center (UHRC) program, the supply would reach the women at their doorstep. Similar system of distribution, involving other human resources in the community, should be seriously considered. These include the school system, women's clubs, religious organizations, and nongovernmental organizations, together with formal and informal community leaders who could distribute the tablets. Involvement and participation of the private health system might also help to achieve maximum coverage.

Poor Compliance, Even when Provision is Ensured

There is strong evidence that even when women do receive the IFA tablets, actual consumption is not ensured:

- Findings from NFHS-II (1998-99), for urban slum dwellers of Madhya Pradesh, suggested that only 61.1% pregnant women consumed the required number of IFA tablets.
- The RCH report from the Government of India indicated that even in areas where the coverage was as high as 86.2%, only 11.5% of mothers who received IFA tablets, actually consumed them for more than 3 months during their pregnancy.

In some areas, instead of giving 100 IFA tablets to antenatal women at one visit, the healthcare providers would give 30 tablets at first visit. On

the second visit, those women who reported that they had not consumed or would not like to consume the tablets, the provider chose not to give them the next set of 30 tablets. This indicated that the healthcare providers did not counsel on the importance of adherence to schedule and accepted noncompliance.

The Nutrition Foundation India Survey in 2003 reported that in Assam, 32% of pregnant women received IFA tablets but only 4.9% consumed them. The equivalent figures in Madhya Pradesh were 74% and 6.3%, respectively.[4] Studies, conducted by the Indian Council for Medical Research (ICMR), corroborated these reports.[5] Research has also been conducted on why women would accept the IFA tablets but fail to consume the required numbers (ICMR 1985, 1989).[6,7]

The responses were varied, but the main themes were as follows:

- Some women did not like the taste of the tablets.
- Other women found the IFA tablets foul-smelling.
- Some said they forgot to consume the tablet due to household workload.
- There was a belief among some women that consumption of the full course of tablets would result in the baby growing too large, and eventually causing difficulties with delivery of a large baby.
- Some women were advised against tablet consumption by the elders of the village.
- Multiparous, women who had experienced no problems in previous pregnancies when they had received no supplements, often saw no need to take supplements in this pregnancy.

Potential solutions to the problems of poor compliance

The side effects of oral iron supplements generally increase with higher dosages, and approaches to minimizing poor compliance due to side effects include:

- prescribing one daily tablet instead of two: justified on the argument that one tablet taken consistently is preferable to the risk of total rejection or nonacceptance of supplements, and
- the single tablet supplementation being best ingested at bedtime.

Motivating the target group to take iron tablets according to the prescribed schedule is of utmost importance, but there are no clearly established/tested strategies that can improve IFA tablet consumption. Possible program options or solution could be:

- sustained, persuasive counseling, including peer counseling through early adopters,
- identification of someone progressive in the family to take the responsibility of ensuring that the pregnant woman consumes her daily dose of IFA tablets at a fixed time,[8] and
- a comprehensive education and information program, organized through the health and other community infrastructures. Such a program should emphasize the benefits of iron supplementation and provide advice concerning possible side effects.

Poor Responders (Assuming Adequate Supplies and Consumption, Hemoglobin Fails to show an Adequate Rise)

There are a significant proportion of women who have access to the supplements, consume them as directed, yet fail to show a rise in hemoglobin. Contributory factors to the poor response in these circumstances include:

- Failure to deworm the women prior to taking the supplements: hookworm infestation is a common cause of failure to respond to iron supplementation.
- Malaria is prevalent in many parts of India, and the inflammatory response associated will interfere with the efficacy of iron supplementation by hampering absorption.
- Poor iron absorption due to the nature of the Indian diet: the Indian diet is predominantly vegetarian and contains large amounts of inhibitory ligands such as phytates, phosphates, and polyphenols that are known to inhibit iron absorption by oxidizing ferrous iron to ferric form. In the alkaline pH of the small intestine, ferric iron gets converted to insoluble ferric hydroxide which is not absorbed in the body.[9]

Potential solutions to the problems of nonresponders

- The provision of deworming tablets with two tablets of Mebex Plus, a combination of Pyrantel Paomate and Mebendazole (Cipla India Pvt Ltd) concurrently with the iron–folic acid tablets.
- Malaria prophylaxis programs
- Advise on appropriate meal timing and pattern:
  - a breakfast of a low-iron cereal (bread or corn tortilla) is the lowest in iron content, and consumption of these with inhibitors, such as tea or milk products, should be avoided.
  - the consumption of milk, cheese, and other dairy products as "between-meal snacks", rather than at mealtime.

- advice on appropriate iron–folate tablet consumption to minimize the negative impact of dietary components, e.g. separate tea drinking from mealtime—one or two hours later, the tea will not inhibit iron absorption because most of the food will have left the stomach.
- encourage the consumption of the iron–folate tablet with vitamin C, which will aid iron absorption, either by way of fruit juices (simple orange juice will do), or inclusion in the diet of alternative sources of vitamin C, such as tubers, cabbage, carrots, or cauliflower.

Acceptance that the IFA Program has Failed to Eradicate IDA in India

The IFA programs were initiated in India some 30 years ago, yet all evaluations of their impact indicate that the prevalence of anemia in pregnancy has either remained the same or has risen. A variety of assessments has identified a range of reasons why the programs have not been effective in eradicating IDA, but the measures implemented to circumvent the causes of failure have not succeeded in overcoming the difficulties.

In the immediate future, an intervention that might just have a positive impact might be the introduction of intravenous iron to the mass population. This will immediately circumvent many of the problems associated with oral iron supplementation, including compliance, but there will be the challenges of acceptance by the populace, cost, and delivery issues.

Progress can now only be made by an acceptance that the IFA programs have failed, and a determined effort to explore alternatives. Clearly no single intervention will succeed, but a combination of factors that include the general economic development that hopefully will herald better diets, improved general health of the population, and improved education at a population level which will allow those most in need, especially the rural populations, to embrace the strategies made available to them. In the immediate future, an intervention that might just have a positive impact might be the introduction of intravenous (IV) iron to the mass population. This will immediately circumvent many of the problems associated with oral iron supplementation, including compliance, but there will be the challenges of acceptance by the populace, cost, and delivery issues.

However, there would appear to be no immediate options if a dent is to be made in the persistently high maternal mortality rates linked to iron

deficiency in pregnancy in India. The issue of cost of IV iron and its delivery is a challenge to be addressed by government and the pharmaceutical industry. The economic boom, being witnessed in India, may mean that adequate resources may finally be diverted to health programs, and with good governance, and good will on the part of the pharmaceutical industry and a recognition that adequate profit margins can be made on the volumes of IV iron required, the cost issue may be overcome. It will be a challenge for the health care professionals to demonstrate safety and efficacy, and educate the masses to improve acceptance of this treatment.

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Chapter - 4

Management of Iron-Deficiency Anemia: Novel Approaches

- Introduction
- Use of IV Iron Sucrose: Western Experience
- Use of IV Iron Sucrose: Indian Experience
- Response to Iron Supplementation: Intensive Oral Iron Supplementation *versus* a Two-Dose (400 mg) IV Iron Sucrose Regimen
- Conclusion

Management of Iron-Deficiency Anemia: Novel Approaches

Introduction

Among the medical profession, obstetricians are probably some of the most conservative when it comes to trying out new medicines. So, they are still using what hypertension physicians would regard as stone-age drugs when they treat hypertensive disorders of pregnancy. Pharmaceutical companies are also noncommittal, seeking always to protect themselves by often refusing to sanction the use of a wide variety of medicines in pregnancy. In reality, this is quite right the right approach—the Western experience with thalidomide given to pregnant women in the 1960s continues to cast a large shadow, with its consequences still very evident in the community at large, and the German manufacturers of thalidomide still paying out compensation to affected people.

Here was a simple, cheap, and effective drug for the treatment of nausea and vomiting in pregnancy, with no apparent immediate negative sequelae, only to emerge years later as the cause of quite major upper-limb physical deformities in the offspring of the mothers who took the drug. Caution is, therefore, rightly exercised before any new drug is utilized, especially during the first 12 weeks when organogenesis is taking place. Even beyond organogenesis, drugs may have negative sequelae. Thus, warfarin was once-upon-a-time considered safe to use after the first trimester, and indeed some practitioners do still use it, but it crosses the placenta and can cause intracranial hemorrhage in the fetus: with the emergence of safe, effective, easy-to-use low molecular weight heparins which do not cross the placenta. Many would say there is no justification for the continued use of warfarin at any stage during pregnancy. The bottom line has to be: if it is not imperative that a drug should be used during pregnancy, it should not be used.

In the case of iron deficiency and iron-deficiency anemia (IDA) in pregnancy, the impact on maternal and perinatal mortality and morbidity, and

long-term sequelae on offspring, has been argued cogently discussed elsewhere. There can be no doubt that the problem of IDA has to be tackled, both within and without pregnancy. While there is no evidence that iron, given orally or by any other route, causes teratogenesis, there is also no requirement to administer it during the organogenesis phase. Thus, iron can be safely given immediately after 12 weeks gestation, in the puerperium and during the nonpregnancy state.

During 50 years of worldwide clinical experience, iron sucrose has been approved for use in 54 countries as hematinic therapy for a variety of disorders, ranging from the iron-deficiency anemia of chronic kidney disease to anemias associated with pregnancy, and during the postsurgical period. In the USA, the Food and Drug Administration (FDA) approved the use of iron sucrose for the treatment of iron-deficiency anemia in chronic hemodialysis patients in November 2000. The Indian FDA gave their approval for the use of iron sucrose in pregnancy and the postpartum period in 2005. All studies of the use of iron sucrose during pregnancy and the puerperium, both in the West and in India, have demonstrated a high level of efficacy and safety. Examples of studies are presented here to further reassure the Indian Obstetricians on the use of iron sucrose in their routine practice.

During 50 years of worldwide clinical experience, iron sucrose has been approved for use in 54 countries as hematinic therapy for a variety of disorders, ranging from the iron-deficiency anemia of chronic kidney disease to anemias associated with pregnancy, and during the postsurgical period.

Use of IV Iron Sucrose: Western Experience

Zurich University Hospital Experience

Arguably, the world's greatest experience with iron sucrose has been reported from the Zurich University Hospital. Since the early 1990s, iron sucrose has been the only parenteral iron product used during pregnancy and the puerperium at the Zurich University Hospital Obstetrics Clinic. Here the authors present examples of their experience.

Over an 8-year period (1992-2000), 500 patients received a total of 2500 ampoules, each containing the equivalent of 100 mg elemental iron.[1,2] Prerequisites for the use of parenteral iron included extensive diagnostic investigations to exclude hemoglobinopathy, liver disease, acute or chronic bacterial infection, and unknown iron overload (e.g. hemochromatosis).

The inclusion criteria for the administration of iron were as follows:

- Anemia, Hb < 10.0 g/dL
- Iron deficiency confirmed (ferritin <15 μg/dL)
- Completion of the first trimester
- Failure of a 14-day course of oral iron therapy (160 mg/day)

At gestational age 31.5 weeks (range 20–38 weeks), pretreatment mean Hb was 9.2 g/dL (7.9–9.9 g/dL) and both ferritin and transferrin saturations were clearly pathological at a baseline (7.0 mg/L and 6.2%, respectively). Hypochromic red cell levels were markedly elevated at 18.5%.

Administration and dosage

Iron sucrose was administered as either a bolus (undiluted) over 5–10 min or short infusion over 30 min [in 200 mL NaCl (9 g/L)]. Maximum cumulative doses were 1600 mg in pregnancy (200 mg twice per week to a target Hb of 11 g/dL or for a maximum of 4 weeks). The mean treatment duration was 21 days (8–29 d).

Safety profile

Side effects (mainly flushing or a rash), all occurred on the first day of treatment, and rates were 1.5% relative to the total number of patients and 0.36% relative to the number of ampoules. No serious side effects or anaphylactoid reactions were observed. In no case, was treatment discontinued due to safety issues, or blood transfused due to nonresponse to treatment.

Efficacy

Anemia was corrected in all patients. All parameters improved significantly after 2 weeks, with a mean increase in Hb of 1.9 g/dL (significant from day 7). By the end of treatment, transferrin saturation and ferritin were normal and significant increases in mean corpuscular volume and mean corpuscular Hb were observed. Hypochromic red cells fell by a mean value of 4.2%.

Prospective, Open-Label Controlled Trial of IV Iron *Versus* Oral Iron

In this study, 111 pregnant women with severe iron-deficiency anemia [Hb < 9 g/dL, serum ferritin (SF < 20 g/L)] were sequentially assigned to receive either IV iron sucrose (n = 52) or oral ferrous sulfate (n = 59). Intravenous iron dosage was calculated to correct the Hb deficit according the published

formula, and administered as divided single 200-mg infusions in normal saline every 1–3 days. The control group received ferrous sulfate 300 mg (60 mg elemental iron) 3 times a day until the target Hb was reached, then once daily.[3]

Adverse reactions

No serious adverse events were noted with iron sucrose while 6% of patients could not tolerate oral ferrous sulfate and were excluded from the study; 30% of patients in the control group presented with disturbing gastrointestinal symptoms and 32% were noncompliant.

Efficacy

The IV iron therapy resulted in higher levels of both Hb and SF, with the time to achieve maximal Hb concentration also significantly shorter in this group compared with the control group (mean 6.9 *vs*. 14.9 weeks).

The Nancy Regional Maternity Hospital Experience

This random, prospective, open study with individual benefit aimed at comparing IV iron sucrose *versus* oral iron sulfate in the treatment of anemia at 6 months of pregnancy, and took place over a period of 15 months. The study population consisted of 50 women aged at least 18 years with a hemoglobin (Hb) level of 8–10 g/dL at 6 months of pregnancy. Intravenous iron was administered at a maximum dose of 200 mg (2 ampules) over 5 minutes per ampule, using a small catheter, into a vein of sufficient caliber. For the first injection, 25 mg was injected very slowly and the patient was monitored during 15 minutes for signs of intolerance, such as an anaphylactoid reaction or hypotension, phenomena previously observed with iron dextran administration. If the dose exceeded 200 mg per injection, iron was administered by slow infusion, with each 100 mg diluted in 100 mL of an isotonic sodium chloride solution, over a minimum period of 1.5 hours for 300 mg. Treatment was stopped either after administration of the calculated dose or once the hemoglobin level had reached 12 g/dL. Treatment often lasted for 21 days with 6 slow IV injections (on days 1, 4, 8, 12, 15, and 21). Oral iron was excluded from the IV iron group during the 4 weeks of study.[4]

The group receiving oral treatment received three 80-mg iron sulfate tablets (i.e. a total of 240 mg of elemental iron per day for 4 weeks). Patients were required to carefully note treatment compliance on a calendar provided for that purpose. Both groups received 15 mg of folic acid per day to prevent an eventual folic acid deficiency and to eliminate the influence of such a deficiency on the results.

Adverse reactions

In the oral iron group, only one patient interrupted treatment because of diarrhea. This patient required a blood transfusion. In the other patients compliance, controlled by investigators, was excellent—a rare achievement. In the IV iron group, the only adverse reaction reported by the patients was the experience of a not-unpleasant taste during injection.

Efficacy

On day 30, there was a highly significant difference in serum ferritin levels between the two groups, with iron reserves restored only in the IV iron group ($P < 0.0001$). This difference, although it became less significant ($P = 0.01$) over time, was observed up until delivery. An increase in Hb was observed, rising from 9.6 ± 0.79 g/dL to 11.11 ± 1.3 g/dL on day 30 in the IV group, compared to from 9.7 ± 0.5 g/dL to 11 ± 1.25 g/dL on day 30 in the oral iron group (not significant). There could have been a faster rise in Hb documented in the IV iron group, if the permissible dose of 600 mg was given over 1 week (200 mg on alternate days) instead of prolonging the treatment for 21 days as per the protocol. Iron sucrose appears to be a treatment without serious side effects indicated in correction of pregnancy anemia or iron stores depletion (*Am J Obstet Gynecol* 2002;**186**:518–22).

Experience with IV Iron Treatment in Pregnancy in Turkey

This was an open-label, randomized controlled clinical trial comparing the efficacy of IV iron to oral iron in the treatment of anemia in pregnancy, and was conducted between May 2004 and July 2004. Eligible participants (pregnant women, 26th–34th weeks of gestation, with established iron-deficiency anemia who had Hb levels of 8–10.5 g/dL and ferritin levels less than 13 g/L): 90 such women were randomly assigned to receive either oral iron ($n = 45$) or IV iron ($n = 45$).[5]

In each infusion, the maximum total dose administered was 200 mg elemental iron in 100 mL 0.9% NaCl, infused over 20–30 minutes at an outpatient setting. All women were observed for 1 hour after the infusions. In the iron sucrose group, most women received their infusions at the rate of 200 mg every other day. Treatment was completed after administration of the calculated dose. Total dose was administered over 5 days and maximum daily dose administered was 400 mg elemental iron. No test dose was given. Additional oral iron was not administered

during the study. In the oral iron group, three 100-mg iron tablets per day were given (i.e. a total of 300 mg of elemental iron per day) over the study period. Adherence to oral treatment was assessed by the number of returned tablets. Both groups were supplemented with 0.5 mg folic acid per day.

Adverse reactions

There were no serious adverse drug reactions, patient withdrawals, or drug discontinuation due to adverse events. Minor adverse events included a metallic taste (n = 11), hot flush (n = 12), arthralgia (n = 1), dizziness (n = 8), nausea (n = 5), and vomiting (n = 1). During antenatal visits, 14 patients (31.1%) in the oral group experienced gastrointestinal symptoms.

Efficacy

Hemoglobin and ferritin were measured on the 14th and 28th days and at delivery, and Hb only on the first postpartum day. In the IV iron group, the rise in Hb was significantly faster than that observed with orally administered iron, and a significantly higher number of patients achieved the targeted Hb at the 4th week and at delivery. At 4 weeks, 9 patients (20%) reached the Hb target of 11 g/dL in the oral iron group compared to 28 (62.2%) in the IV iron group ($P < 0.001$). At birth, 28 patients (62.2%) had reached the Hb target of 11 g/dL in the oral iron group compared to 43 (95.6%) in the IV iron group ($P < 0.0001$). Serum ferritin levels remained higher in the IV iron group at each measurement.

Prompted by the obvious failure of the iron–folic acid supplementation program and the apparent increasing prevalence of IDA in pregnancy, the authors embarked on a drive to research alternative approaches to the eradication of this common problem.

Use of IV Iron Sucrose: Indian Experience

Prompted by the obvious failure of the iron–folic acid (IFA) supplementation program and the apparent increasing prevalence of IDA in pregnancy, the authors embarked on a drive to research alternative approaches to the eradication of this common problem. They initially sought to prospectively assess the response to oral iron in a highly motivated and closely monitored cohort of pregnant women, more to gather data on the response to oral iron in an ideal setting rather than to address the inadequacies of the IFA program. They then followed this up by prospectively studying the response to IV iron and compared the two. The authors' preliminary experience with IV iron sucrose corroborated reports from other countries on efficacy, safety,

and acceptability. The challenge is whether the costs and logistic difficulties posed by the use of iron sucrose on a population scale can be overcome.

Optimizing the Response to Oral IFA Supplementation

With the aim of independently assessing the efficacy of oral iron supplementation in a highly motivated and compliant urban population of antenatal women, the authors prospectively studied the Hb response to oral IFA supplementation in 354 consecutive, unselected anemic (Hb < 11 g/dL) women recruited at booking (14–20 weeks gestation) in one urban center. A complete hemogram and peripheral smear were taken, and women with anemia due to causes other than iron deficiency were excluded. Women already receiving iron supplements, or those destined to receive a blood transfusion, as well as women not willing to participate, were also excluded from the trial. Women were recruited on the basis that they were willing and motivated to adhere to a daily course of 200 mg iron–folic acid supplementation for a minimum period of 10 weeks. Measures to ascertain compliance were by verbal enquiry on every visit and checking the entries in the daily intake diary provided. Prior to commencing iron therapy, all women were dewormed with two tablets of Mebex Plus, a combination of Pyrantel Paomate and Mebendazole. Hemoglobin was estimated prior to commencing supplements and at 10 weeks post-treatment. Individuals with a minimum raise of 0.5 g% of Hb were considered as responders and those below and unchanged Hb% were considered as nonresponders.

Efficacy

The results must be interpreted bearing in mind that this was a closely monitored, highly motivated group of women. Ninety-seven women (30.69%) responded to the iron–folate supplementation by showing a rise in Hb, the majority (40.21%) showing a rise of up to 0.5 g/dL. A 1–2 g% rise was observed in 29% of the women in 10 weeks, while only 3% of women showed an Hb rise greater than 2 g%. The data are presented in Tables 4.1 and 4.2.

Intravenous Iron Therapy for IDA in Pregnancy: Preliminary Experience in India

The authors conducted a preliminary study of the efficacy, safety, and feasibility of the use of IV iron sucrose in pregnancy IDA in a cohort of 96 women from a rural center. These women had been administered IFA tablets from the time of booking and for a minimum duration of 4 weeks.

Table 4.1. Response to oral IFA		
Response to oral IFA	**Frequency**	**Percentage**
Responders	97	30.69
Nonresponders	219	69.31
Total	316	100

Table 4.2. Degree of response to oral IFA		
Responders (Hb% increased)	**Frequency**	**Percentage**
Up to 0.5 g/dL	39	40.21
0.6–0.9 g/dL	26	29.90
1.0–2.0 g/dL	29	29.90
>2.0 g/dL	3	3.09
Total	97	100

They had been declared as "failed to oral therapy" as their Hb had remained below 11 g/dL. They were recruited into the study, if they were willing to receive IV iron sucrose. Women were excluded, if they had a known allergy to parenteral iron, or had received a blood transfusion during this pregnancy. The mean gestational age was 23.5 weeks (range 20–34 weeks gestation) and the mean Hb was 9.2 g/dL (range 6.8–10.8 g/dL). All participants were dewormed with two tablets of Mebex Plus, a combination of Pyrantel Paomate and Mebendazole, prior to IV iron therapy. The women received two doses of IV iron sucrose of 200 mg per sitting, 3–5 days apart, on an outpatient basis and their Hb was estimated before and 4 weeks after therapy. The iron was administered neat as a bolus push over 5 minutes or as an infusion over 30 minutes after dilution with 100 mL isotonic saline solution. No test dose was given, and any adverse reactions were monitored over an hour following the first injection. The optimal dose of iron sucrose required by each woman based on her pretreatment Hb was not calculated: the authors sought to study the response to a uniform dose of IV iron sucrose over a range of pretreatment Hb's.

Adverse reactions

Minor adverse reactions occurred in 18.89% of the women. These included nausea, vomiting, burning at the infusion site, and itching, none lasting beyond 30 minutes. No major adverse reactions occurred (Fig. 4.1).

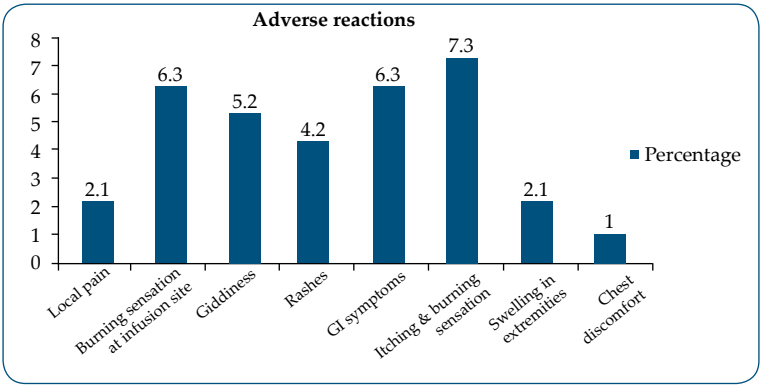

Fig. 4.1. Adverse reactions were of a minor nature and none needed extramedication or hospitalization

Efficacy

In the 69 women available to follow-up 92.75% registered a rise in Hb across all ranges of anemia. Eleven women (17.2%) showed an increase of Hb% over 2.0 g%. A majority of 34 (53.10%) showed an improvement of 0.6–0.9 g% (Tables 4.3–4.5).

Response to Iron Supplementation: Intensive Oral Iron Supplementation *versus* a Two-Dose (400 mg) IV Iron Sucrose Regimen

A comparison of the outcomes of treatment with oral iron *versus* IV iron sucrose is depicted in Figure 4.2. It is evident that 40% of women who took oral iron showed an increase in Hb of up to 0.5 g%, whereas 53% in the IV iron sucrose group showed a greater improvement of 0.6–0.9 g%. In the IV iron sucrose group, 17% of the pregnant women showed an increase in Hb of greater than 2.0 g%, whereas such a rise was seen in only 3% of the oral iron group. The differences in the responses were highly significant ($P < 0.001$). The superiority of IV iron sucrose, even when given at suboptimal doses (no calculations were conducted to determine dosage based on pretreatment Hb) over oral iron is unquestionable.

Conclusion

In the western world, it has long been documented that IV iron supplementation is highly effective in treating IDA in a variety of settings, including pregnancy. There is irrefutable evidence that compared to oral iron,

Table 4.3. Response to IV iron sucrose 400 mg		
Response to IV iron sucrose	**Frequency**	**Percentage**
Responders	64	92.75
Nonresponders	5	07.25
Total	69	100

Table 4.4. Comparison of change in Hb% status after therapy by paired sample statistics				
	Paired sample statistics			
	Mean	**N**	**Std. deviation**	***P* value**
Hb%-I (in grams)	9.213	69	0.7787	<0.001
Hb%-II (in grams)	10.39	69	0.661	

Hb-I = Hb before treatment, Hb-II = Hb 4 weeks after treatment

Table 4.5. Degree of response to IV iron sucrose 200 mg (two doses) in the group of 64 responders available for follow up		
Responders (Hb% increased)	**Frequency**	**Percentage**
Up to 0.5 g/dL	9	14.1
0.6–0.9 g/dL	34	53.1
1.0–2.0 g/dL	10	15.6
>2.0 g/dL	11	17.2
Total	64	100

IV iron sucrose results in a much more rapid resolution of IDA, has minimal side effects, and because it is administered intravenously, it circumvents many of the problems that bedeviled the IFA program, including problems of compliance. Unlike IV dextran iron, anaphylactic reactions are very rare with iron sucrose. Preliminary experience in India corroborates the western experience with regards to safety, efficacy, and acceptability. The challenge lies in the cost and logistics of delivering such treatment to the wider, largely rural, and largely impoverished populations of the developing world. Intravenous iron sucrose could yet be the Holy Grail in the eradication of IDA in pregnancy in low-resource settings.

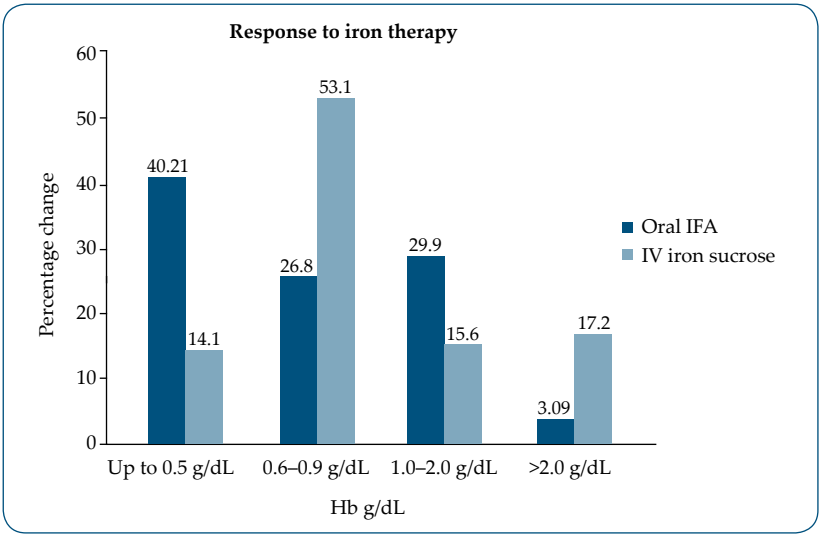

Fig. 4.2. A comparison of the outcomes of treatment with oral iron *versus* IV iron sucrose—degree of rise in Hb g/dL

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Chapter - 5

Management of Gestational Anemia: Safety Issues

- Introduction
- Oral Iron
- Parenteral Iron
- Blood Transfusion
- Blood Transfusion: Safety Issues

Management of Gestational Anemia: Safety Issues

Introduction

Virtually all treatments known to man either have side effects of varying severity and/or have the potential to cause harm. This is true of all the treatments available for the treatment of anemia in pregnancy, and an in-depth understanding of these issues is paramount in order to minimize side effects and risks in the management of this common disorder of pregnancy. The range of treatment options to be considered in this section includes oral iron supplements, intramuscular iron, intravenous (IV) iron preparations, and blood transfusion.

Oral Iron

Problems with Oral Iron

Among other factors, poor compliance due to side effects is undoubtedly a major contributor to the failure of the iron–folic acid supplementation program in India.

The vast majority of women with anemia in association with pregnancy will respond to oral iron supplementation. Indeed with rare exceptions, oral iron should be the first line of treatment. Safety issues with oral iron relate mainly to side effects, whose prevalence increase with increasing dose of iron. It is estimated that 10–40% of pregnant women taking iron supplements will experience side effects. The principal adverse effects are of gastrointestinal nature,[1] the most common being constipation, diarrhea, epigastric discomfort, nausea, severe abdominal pain, and vomiting. These side effects are a significant disadvantage, since they affect compliance rates. It is estimated that only 35–40% of pregnant women regularly take iron supplements, even when they are aware of the importance of so doing. Among other factors, poor compliance due to side effects is undoubtedly a major contributor to the failure of the iron–folic acid (IFA) supplementation program in India.

Circumventing the Side Effect Problems of Oral Iron

The most commonly prescribed oral iron preparation is ferrous sulfate. The mistake often made by many prescribers is the assumption that the higher the dose, the better. In reality, 200 mg twice daily is probably the highest dose with maximal efficacy, whereas giving the 200 mg 3 times daily increases side effects prevalence without increasing efficacy with regards to the treatment of anemia. Absorption is of course increased by the concomitant administration of vitamin C (simple orange juice will do) and the avoidance of foods and other substances that contain iron chelators, e.g. avoidance of dairy products at the time iron supplements are taken.

There is also a misconception that liquid iron preparations are better than the tablet form. It is certainly true that in intestinal achlorhydria (e.g. following gastrointestinal surgery), the absorption of liquid iron is superior whereas tablets show poor solubility. However, in normal routine usage, liquid preparations are neither more effective nor do they have a more favorable side effect profile. There are, of course, women who have difficulty swallowing tablets, and liquid preparations come in handy. What needs to be recognized is that, often for no apparent good reason, some women will better tolerate one form of iron preparation than another, be it another tablet or a liquid preparation. The good news is that there is a wide selection, and therefore an opportunity to try different types before resorting to more expensive parenteral approaches to the treatment of iron-deficiency anemia.

The dextran component is thought to be the cause of the severe allergic reactions occasionally seen with type 1 complexes.

Parenteral Iron

The place and efficacy of parenteral iron in the treatment of anemia of pregnancy has been dealt with in a preceding chapter, and here the authors address mainly the safety issues involved. Intramuscular iron is rarely prescribed because of the pain and skin discoloration associated with its use. The focus here will, therefore, be on IV iron preparations. As indicated in previous chapters, there are three main groups of IV iron preparations distinguished on the basis of pharmacokinetics, complex stability, molecular mass, toxicity, and side effects.

Type I Complexes (Iron Dextrin and Iron Dextran)

These have high molecular weight (>100,000 dalton) and high stability, and a commonly used example is Imferon. The dextran component is thought to be the cause of the severe allergic reactions occasionally seen with type 1

complexes. The exact mechanism involved is unknown, but they have all the hallmarks of an anaphylactic (type 1 hypersensitivity) reaction, which involves mast cell degranulation with the release of anaphylatoxins Recipients, who have allergic reactions to drugs, appear to be at higher risk of developing allergic reactions to iron dextran. It is also possible that dextran forms complexes with antibodies, and/or cross-links the antibodies (IgE) on mast cell surfaces, thereby triggering the mast degranulation. The fact that dextran chains form biological polymers of varying size adds credence to this hypothesis.[2] Dextrins seem to be much safer with regards to anaphylactic reactions. A significant advantage of type I complexes is that they can be given as total dose infusions.

Type II Complexes (Iron Hydroxide–Sucrose Complex)

These are complexes of a lower molecular weight (30–60,000 dalton) and are exemplified by iron hydroxide–sucrose complex. When used at standard doses, no biological polymers are formed, and therefore anaphylactic reactions are extremely rare. However, that is not to say that they are without side effects, which include nausea, a sensation of heat, a metallic taste, local irritation, and dizziness. A not- insignificant disadvantage is that iron hydroxide–sucrose complex can only be given at a maximum dose of 200 mg on alternate days. However, a newer type II complex preparation, ferric carboxy maltose is available, which can be given in large (up to 1000 mg) doses by rapid (15 minutes) IV infusions. Ferric carboxy maltose is not yet available in India.

Type III Complexes (Iron Gluconate, Iron Ammonium Citrate, and Iron Hydroxide Sorbitol Complex)

It has molecular weights of less than 50,000 dalton and is unstable, labile complexes. Though the iron gluconates, in particular, are comparable to the iron sucroses with regards to allergic or anaphylactic reactions, and therefore, have a better side effect profile than the iron dextrans, the problem is that they show less binding to transport proteins. This results in greater quantities of free iron being released in the short term, much of it being deposited in the parenchyma of various organs where it effectively acts as a free radical, leading to lipid peroxidation and tissue toxicity.

Making Safe Choices in Parenteral Iron Therapy

Intramuscular iron dextran

The main drawbacks of intramuscular injection are the pain and staining of the skin, the inconvenience of repeated injections, and the possibility of

abscess formation at the injection site. This route of therapy has also been associated with the development of myalgia, arthralgia, and malignancy.[3,4] In contemporary practice, this approach is rarely used in both developed and developing countries.[3,4]

Intravenous iron dextran

In practice, the use of iron dextran is not generally recommended due to the unpredictable risk of life-threatening or serious acute reactions in 0.6–2.3% of patients.[2]

Intravenous iron dextran has been withdrawn from use in many countries from the time that the newer and safer agents became available, but it will continue to be used in some countries because of the fact that it is often much cheaper than the newer preparations. The key approaches to safety include the careful selection of recipients (great caution should be exercised in patients with a history of anaphylaxis or who have allergies to other drugs—avoidance being the wise approach); use of a test dose in all patients, and the availability of appropriate resuscitation facilities whenever iron dextran is given.

Intravenous iron sucrose

Knowledge of safety aspects is now based on experience from 5 decades of use. The relative safety and efficacy of iron sucrose have been proven and are based on the following:

Iron sucrose is bound in a polynuclear nonionic iron (III) hydroxide: This lack of iron ions accounts for the low toxicity; furthermore, no biological polymers are formed, so that anaphylactic reactions are extremely rare.

Low molecular mass: Iron sucrose belongs to the iron complexes of the half robust and medium strong type (molecular weight 30–60,000 dalton). High molecular mass substances produce more allergic reactions than similar low molecular mass substances. For example, the high molecular mass of iron dextran (over 100,000 dalton) can be a potential cause of its adverse effects. This mechanism of dextran anaphylaxis, which is based on dextran antibodies, is not seen in IV iron sucrose preparations due to their low molecular mass.

Readily available for erythropoiesis: Iron sucrose is more readily bioavailable for erythropoiesis than iron dextran preparations. After IV administration, iron sucrose delivers the complexed iron from the serum to endogenous iron-binding proteins with a half-life of 90 minutes. It is taken up mainly by the reticuloendothelial system of the liver as well as by

transferrin and apoferritin, the spleen and the bone marrow. Subsequently, it is rapidly metabolized and readily available for erythropoiesis.

In addition, iron sucrose complex has a little renal excretion (5%) and low tissue accumulation and toxicity. In contrast, parenteral preparations, such as ferric gluconate and ferric citrate, deliver their complexed iron to all types of proteins instead of specifically to iron-binding proteins. The main part of the iron is deposited in the parenchyma and not in the reticuloendothelial system. This is a distinct disadvantage, as it leads to severe and extended liver necrosis, proved by histological examination.[5]

No oversaturation: After the IV administration of iron sucrose, there is rapid distribution into plasma-binding proteins, primarily into apotransferrin and, to a lesser extent, ferritin. The rapid disappearance of iron sucrose from plasma is associated with its distribution within minutes, as assessed by positron emission tomographic scanning, into iron depots, including the liver and bone marrow.[6] This is why iron sucrose does not oversaturate, an important attribute since oversaturation is thought to play a key role in some of the adverse reactions from other parenteral preparations. Changes in serum transferrin saturation (TSAT) and ferritin levels may be measured reliably just 48 hours after the IV administration of iron sucrose.[7]

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Experience with the Use of IV Iron Sucrose Reaffirming Safety

Iron sucrose was introduced into the European market in 1950, and since then an impressive wealth of data on its safety have accumulated. Most relates to use in nonpregnant patients, especially hemodialysis patients, but in recent years, there has also been an accumulation of data on both efficacy and safety profiles in pregnancy. Arguably, the greatest experience with iron sucrose in pregnancy comes from the unit of Christian Breymann in Switzerland, although other centers have also published extensively, and the authors describe below the Indian experience too. The most frequently adverse effects, reported during treatment in hemodialysis patients, are hypotension, cramps, and nausea. General side effects include metallic taste, local irritation, and dizziness. A small selection of work illustrating the safety of iron sucrose is presented below.

1. Using data collected and analyzed from semiannual safety reports submitted to worldwide regulatory authorities that incorporate information from greater than 1,600 patients enrolled in 36 clinical trials of iron sucrose, the number of vials of iron sucrose was estimated to quantitate the number of doses and patients treated between 1992 and February 2001.[8] This summary concluded that only 52 anaphylactoid reactions occurred consequent to the administration of 20 million doses of iron sucrose injection to 1,004,477 patients worldwide. Of these, 22 cases were considered serious, an incidence of 0.002%, and all patients recovered uneventfully.
2. Van Wyck, *et al*[9] in an open-label, single-arm, prospective study of 23 patients, who had previously shown sensitivity to iron dextran, found that these patients did not show adverse reactions to iron sucrose. This study proved that even though the patients had reactions with iron dextran, they did not have similar adverse reactions with iron sucrose. Patients were segregated into two groups according to the severity of dextran-related side effects. The mild-reaction group had experienced symptoms of urticaria, pruritus, or back pain, whereas the severe-reaction group had experienced symptoms of dyspnea, wheezing, stridor, angioedema, or hypotension. The mild-reaction group patients were administered iron sucrose as 100-mg IV push doses during 10 sequential hemodialysis sessions. The severe-reaction group was administered iron sucrose as either ten 100-mg IV injections over 5 minutes or 100-mg infusions of iron sucrose in 0.9% sodium chloride over 15 to 30 minutes. A total of 223 doses of iron sucrose were administered by the end of study. Overall, no serious drug reaction was recorded, and no individual discontinued the study because of an adverse drug reaction. Intradialysis blood pressure monitoring showed no hypotensive effects attributable to iron sucrose.
3. Very low rate of anaphylactoid reactions with iron sucrose was recently confirmed in a study involving 61 centers in the United States. No anaphylactoid reactions occurred after administration of 8,590 iron sucrose doses to 665 hemodialysis patients.[10]
4. Christian Breymann and his group have published extensively on the efficacy and safety of iron sucrose in pregnancy. They have promoted the safety of administration of the iron by bolus injection with syringe, maintaining that the patient can leave after 5–10 minutes, which is very important for their ambulatory management. It is not necessary to survey the patients or monitor their blood pressure, and they have reported 100% compliance.[11,12]

5. al-Momen, *et al*[13] reported on a study where 111 women were included, 52 receiving IV therapy and 59 receiving 300 mg of oral ferrous sulfate daily. The mean hemoglobin level, MCV, and ferritin levels were all significantly higher in the IV group compared to the orally treated group. With regards to safety and side effects, they reported no major adverse effects in pregnant women with iron-deficiency anemia receiving IV iron sucrose, compared to 6% that could not tolerate the oral intake of ferrous sulfate.
6. Divakar and Manyonda (2008): In a low resource setting such as India, it is vital to research approaches which are not only cost-effective and safe, but also convenient. In one such program of research, women between 20 and 24 weeks of pregnancy with Hb < 11 g/dL were randomized to receive a slow IV infusion of iron sucrose in 100 mL saline over 30 minutes (Group A, n = 75), or to receive the iron sucrose as a rapid IV bolus-push over 2–5 minutes, administered through a venous butterfly cannula once the correct positioning in the vein had been tested with normal saline (Group B, n = 77). No test dose was given to either group, and all women were closely observed for up to 30 minutes for adverse reactions (after the first dose), such as nausea, burning sensation at infusion site, local pain, rashes, and breathlessness during or immediately after the injection. If an adverse reaction occurred and did not settle in 15–20 minutes, one vial of hydrocortisone (100 mg) was given intravenously. The women were also advised to contact the unit, if they developed any subsequent symptoms.

After the first dose, 5 of the 75 women in group A (6.7%) experienced minor adverse reactions, whereas 15 of the 77 women (19.5%) did so in group B (Fig. 5.1). The nature of the adverse reactions was minor in both groups and

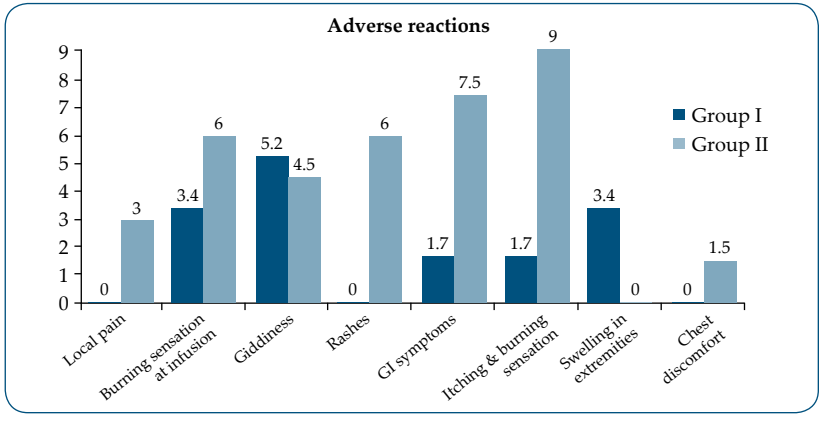

Fig. 5.1. Types and frequency of adverse reactions following the first dose of IV iron sucrose.

included giddiness, generalized itching/burning, local pain, gastrointestinal symptoms, such as nausea, burning at the infusion site, swelling in extremities, and chest discomfort (Fig. 5.1). Only two women in group B required IV hydrocortisone 100 mg when they developed rashes and GI symptoms lasting more than 20 minutes, and all symptoms and signs resolved within the next 20 minutes after administering the hydrocortisone. No woman experienced any major side effects necessitating hospitalization.

Of the 19 women lost to follow-up in group A, 2 had adverse reactions, whereas among the 22 women lost to follow-up in group B, 4 had adverse reactions after the first dose, suggesting that occurrence of adverse events may not have been the reason for not returning for follow-up.

None of the women developed major reactions or side effects, and in a low resource setting, minor side effects could be traded for the advantages of convenience and cost-savings.

Divakar and Manyonda demonstrated safety and efficacy and of the bolus-push technique, although the side effect profile was less advantageous compared to the slow infusion. None of the women developed major reactions or side effects, and in a low resource setting, minor side effects could be traded for the advantages of convenience and cost-savings.

Safety of Iron Sucrose Preparation in India

Subtle changes in the manufacture of iron sucrose can have a profound impact on the safety profile of a given preparation. The preparations that the authors can vouch for, based on their experience, are iron hydroxide–sucrose complex. The authors have been concerned by the apparently high incidence of anaphylactic reactions that colleagues have reported to them using other brands of iron sucrose.

Blood Transfusion

Blood transfusion, used in appropriate circumstances, can be life-saving, but it must always be borne in mind that it can have significant side effects, some of which can be fatal. Due care and consideration should, therefore, be taken whenever blood is to be transfused, and it is well to remember that in contemporary practice blood is often transfused when alternatives could be used effectively, or when the potential need could have been anticipated, and therefore preventative measures taken that would have avoided the need for blood transfusion.

The hazards of blood transfusion include:

- transfusion of incorrect blood,
- infection risks,
- immunological risks, and
- hazards or risks related to the erythrocyte damage caused by storage.

Transfusion of Incorrect Blood

It is remarkable that despite the extensive guidelines and measures taken in most units, administration of the incorrect blood remains by far the commonest transfusion-related complication, accounting for approximately 50% of transfusion-related complications. Other complications, especially immunological ones, can then ensue, some of which could be fatal. Meticulous measures, to avoid this human-based error, do not seem to be watertight.[14]

Infection Risks

Overall, it is estimated that transmission of infections account for 3–5% of transfusion-related complications.[15]

The range of infections transmitted and their estimated incidence are as follows:

- Hepatitis B (1:50,000–1.5 million)
- Hepatitis C (1:50,000–1.5 million)
- Human immunodeficiency virus (1:1–1.12 million)
- Bacteria (1:2000)
- Prions (incidence unknown)[16]
- Parasites, such as malaria (incidence unknown)
- Other viruses, e.g. EBV, CMV (incidence unknown)[17]

The incidences above are based on units in developed countries, with supposedly robust services, but even then these figures will vary from country to country. There are no reliable figures for developing countries, including India.

Immunological Hazards

The transfusion of blood involves the introduction of powerful immunogens, even when the blood has been cross-matched correctly. The potential immune reactions and their estimated contribution to transfusion-related complications (where known from studies) are as follows:

- Acute transfusion reaction (15%)
- Delayed transfusion reaction (14%)
- Post-transfusion purpura (6%)
- Transfusion-related acute lung injury (TRALI) (8%)
- Transfusion-related graft *versus* host disease (TR-GVHD) (2%)

De novo formation of antibodies to blood group antigens or to HLA antigens have also been reported, as have the development of a range of allergies. In most cases, it is not possible to predict the immunological hazards, and fortunately overall they are not common. They can only be effectively avoided by the avoidance of blood transfusion.

Risks Related to the Erythrocyte Damage Caused by Storage

Storage of erythrocytes has the following adverse effects on the properties of erythrocytes:

- Hemolysis
- Reduced survival
- Reduced 2,3-DPG content
- Microaggregation and increased agglutination tendency
- Histamine, kinin, and cytokine accumulation
- Membrane defects, such as increased rigidity

These adverse effects of storage are likely to increase the risks of immunological reactions and also lower the efficacy of the erythrocytes in improving organ perfusion and oxygenation.[18]

Blood Transfusion: Safety Issues

Reduce the Chances of the Need for a Blood Transfusion

Anemia should be treated: If the hemoglobin level is less than 10.5 g/dL in the antenatal period, consider hematinic deficiency once hemoglobinopathies have been excluded. Oral iron should be the preferred first-line treatment. Parenteral iron is indicated when oral iron is not tolerated, absorbed, or patient compliance is in doubt.

Parenteral therapy offers a shorter duration of treatment and a quicker response than oral therapy. It is, however, more invasive and expensive to administer. Iron sucrose is given in multiple doses whereas iron dextran may be given as a single total-dose infusion.

Anemia, not due to hematinic deficiency (for example, hemoglobinopathies and bone marrow failure syndromes), should be managed by blood transfusion where appropriate in close conjunction with a hematologist.

Blood loss at delivery should be minimized: Active management of the third stage of labor is recommended to minimize blood loss. Clear evidence from randomized trials supports the active management of the third stage of labor as a method of decreasing postpartum blood loss.

Women at high risk of hemorrhage should be advised to deliver in hospital. Optimal management of women on anticoagulants, such as low-molecular-weight heparin, will minimize blood loss.

Blood Should Only be Sourced from Robust Blood Transfusion Services

The WHO recommends that all donated blood should be tested, as a minimum, for the following pathogens: HIV 1 and HIV 2; hepatitis surface antigen, and *Treponema pallidum* antibodies. Where possible and/or appropriate, donor blood should also be tested for hepatitis C, Chagas' disease, and malaria.

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Need for National Guidelines

- In practice, this is not always possible, but at the very least, hospital-specific criteria for the prescription of blood should be available and strictly adhered to.
- Protocols for the administration of donated blood should be adhered to, and this may minimize many of the hazards, e.g. systematic checks on patient identification and matching patient to the correct blood will minimize the risks of administering the wrong blood.
- There should be facilities in place for monitoring and intervention, if transfusion-related complications occur. These include emergency resuscitation facilities in the event of an acute anaphylactic reaction.

Thus to conclude, the clinician has to offer individualized treatment, keeping the safety as a priority, without compromising on the efficacy.

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Chapter - 6

Intravenous Iron Therapy

- Introduction
- Rendering IV Iron Available to the Populace
- Challenges Posed by Storage
- Equipment Requirements and Expertise in Administration
- Slow IV Infusions: Reducing Cost and Inconvenience
- The Cost of IV Iron Sucrose
- Cost of Blood Transfusion *vs.* Current Cost of IV Iron
- Repeated Infusions: Challenges

Intravenous Iron Therapy

Introduction

The advantages of intravenous (IV) iron, in terms of safety and efficacy, are beyond debate, but in low resource settings, such as India, there are major challenges to the widespread use of this effective drug. These include the following:

- The logistics of getting the iron sucrose to where it is needed the most: the sprawling villages strewn across the massive Indian sub-continent where the majority of the population resides.
- Challenges of storage of the drug so that it is readily available when it is needed: this brings into question the stability of the drug in the high temperatures prevalent in most of India, and the actual infrastructural requirements.
- The need for health care workers trained in the administration of a drug that has to be given by the IV route, and requiring patient-specific dosing.
- The difficulties of giving a drug that may require several visits by the patient who starts with a hemoglobin (Hb): the maximum iron sucrose dose is officially 200 mg per sitting, given on alternate days—the woman with a Hb of 6 will need at least 6 visits to achieve a hemoglobin in excess of 11 g/dL. This poses major challenges for keeping track of these women, and their ability to attend for the desired number of treatments.
- The economic challenges: the basic costs of the drug, which are way higher than the oral preparations; additional costs of administering the drug—the IV equipment, the need for a short-stay bed, and the inconvenience of IV administration.

Anemia is the direct cause in 20% of cases of maternal mortality in India; this represents the loss of hundreds of women every year in a country that is

regarded as an emerging economic giant on the world stage. It is imperative that everything possible is done to overcome this blight on India's reputation. Innovations by obstetricians and gynecologists, government, and the pharmaceutical industry will go a long way towards meeting the challenges outlined above and more—team work is required, since no single player in this great challenge could succeed in isolation.

Rendering IV Iron Available to the Populace

Intravenous iron is easily and widely available for use in the private sector in all the pharmaceutical outlets throughout India. However, the vast majority of women in India have no access to private medical care, and therefore, no easy access to this vital drug. There is an urgent need to render this drug "always available" if women attend a health center needing IV iron but are asked to return due to lack of availability, research has shown that less 20% would come back—a real lost opportunity, for most of the rest of the women would then only present in labor, often with very low hemoglobin and therefore, at major risks from all the complications of severe anemia.

A number of measures can be implemented to render IV iron more available to every woman who needs it in India.

- If IV iron is designated an "emergency drug", by law this renders the drug always available.
- A collaborative effort by obstetricians, government, and the pharmaceutical industry would help promote policies that will render the drug available (see later).

India does not suffer the problems of accessibility with the exception of very few remote and inaccessible areas, but these areas are not heavily populated. In essence, therefore, there is no significant problem of transportation of the drug to where it is required.

Challenges Posed by Storage

In reality, storage, from the point of view of stability of the drug, is not a problem, since iron sucrose is a stable compound with a long shelf life.[1] No refrigeration is required and the drug can be stored at room temperature; thus, there are no additional logistic problems, such as the need for refrigeration, and, of course, the need for a reliable source of electricity. However, there may be infrastructural problems of space for the actual physical storage of the drug; this, however, should not be a realistic problem for the people with sufficient ingenuity to drive the economy of their country the way India's is going!

Equipment Requirements and Expertise in Administration

The IV equipment (cannulae, syringes, and infusion sets), required for the administration of IV iron, are no different from those required for any other IV drug. Thus, neither special equipment nor technology is needed, and the actual technique of administration is similar to that of any other IV injection, and therefore, no special training and expertise is required. However, of course, some basic minimum training is required with respect to building the confidence level of providers, including specialists, medical officers, and staff nurses. This is especially with regards to awareness of potential anaphylaxis and how to deal with it, whereas every health care provider, administering iron sucrose, should be familiar with how to manage anaphylaxis; it should be stressed that most adverse reactions are minor and anaphylaxis very rare indeed (refer to chapter 5 on Safety Issues in the Treatment of Gestational Anemia). No test dose is required, and no deaths have been reported in over 50 million women on whom this drug was used.

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Dose Calculations

Conventionally, the dose of iron infusion required is calculated by the following formula:

Dose = Body weight (kg) × Hb deficit × 0.3 (where Hb deficit is the target Hb − measured Hb).

Since most women with iron-deficiency anemia (IDA) will also have deficient iron stores, additional iron is required to replenish the stores, and the latter is calculated by the formula:

Dose = Body weight × 10.

Thus, the total amount of iron required is:

(Body weight (kg) × Hb deficit × 0.3) + (body weight × 10) mg.

To illustrate this with a woman starting with an Hb of 8 g/dL, who weighs 45 kg and where the target Hb is 11 g/dL, the dose required is:

(45 × 3 × 0.3) + (45 × 10) = 815 mg

Clearly, the above dose calculation is cumbersome. We would suggest a user-friendly dose calculation which assumes that (i) all anemic women have depleted iron stores which can be adequately replenished with 500 mg of iron, and (ii) 100 mg of IV iron will raise the Hb by 1 g/dL. Thus, for a woman who starts with an Hb of 8 g/dL where the target Hb is 11 g/dL, the

calculation becomes very simple since the dose requirement is calculated as follows:

Dose required = 500 + 300 = 800 mg. The 500 mg is to replenish the stores, and the 300 mg is to raise the Hb by 3 units from 8 to 11 g/dL. This requires 4 visits if the iron sucrose is to be administered at 200 mg per visit.

Another example: a woman starts with an Hb of 6 g/dL, and target Hb is again 11 g/dL:

Dose required = 500 + 500 = 1000 mg. This requires 5 visits if the iron sucrose is administered at 200 mg per visit.

Yet another illustrative example: for a woman presenting with Hb of 7 g/dL, with target Hb as 11 g/dL

And deficit is, therefore, 4 g/dL.

Dose required = 400 + 500 = 900 mg. This requires 5 visits, and with only 100 mg being administered on the 5th visit.

Slow IV Infusions: Reducing Cost and Inconvenience

By conventional 200 mg elemental iron diluted in 100 mL 0.9% normal saline and infused over 30 minutes every 3–7 days up to the total calculated dose, for example, three visits for a patient needing 600 mg as total dose with 200 mg administered at each visit. This approach requires a temporary bed, as well as IV infusion giving sets—with obvious cost implications. Research has now shown that iron sucrose can in fact be administered a "rapid push" over 2–5 minutes in an outpatient setting, without the requirement of a bed. When it is considered that in busy institutions, as many as 50 women per day may need iron sucrose, the advantages of the rapid push technique become immediately obvious.

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Examples of research showing the benefits of the rapid push technique are as follows:

- A recent study by Macdougall *et al.* established the safety of iron sucrose 200 mg as a 2-minute push for a total of 2297 injections.[2,3] The most common adverse reaction was metallic taste in 17.9% and anaphylactoid reactions during 7 injections that resolved completely within 30 minutes with no hospitalization.

- In a study by Van wyk and associates, 10 doses of iron sucrose were administered, each administered undiluted as a 100 mg IV push over 5 minutes, and recorded blood pressure and adverse events after the injection were recorded. No serious adverse drug reactions were seen after a total of 757 doses.
- Jayaseelan T, Saravanan AK, *et al.* from the Dialysis Unit, Chennai Transplant Centre, Madras Medical Mission and SRMC,[4] Chennai, conducted a prospective study in maintenance hemodialysis (MHD) patients of the administration of iron sucrose as IV push. The aim of the present study was to investigate the cost, safety, and efficacy of administering a 100 mg IV bolus (push) of iron sucrose to prevalent MHD patients. They did a comparison of the cost, safety, and efficacy of parenteral iron in two groups of patients who were on MHD at a tertiary care center. Group A (18) received iron as an infusion therapy in normal saline over 30–60 minutes at the end of dialysis. Group B (20) received iron as a push at the end of dialysis. A total of 194 injections were given, including 93 times in group A and 101 times in group B. There were no serious adverse reaction either immediate or delayed observed in both group A and group B. There was an increase in Hb by at least 1 g/dL in both groups (1–2 g). In group A, 2 patients developed low-grade fever which responded to antipyretics. There were no incidences of thrombophlebitis. There were no serious adverse reactions in either group and the efficacy was similar. However, there was a great difference in the cost analysis, favoring IV push as the treatment of choice. The 2–3 minutes is a practical dosing regimen, resulting in considerable savings in time. Hence, they recommend IV push in patients who are receiving parenteral iron.

They used a maximal permissible dose of 200 mg of IV iron sucrose at one sitting—to minimize the number of visits and thus, maximize compliance.

- Divakar and Manyonda (2009) conducted a prospective randomized controlled trial in which they compared the efficacy, safety, and cost of providing IV iron sucrose in an Indian rural pregnant population with iron-deficiency anemia via a "bolus push" technique over 2–5 minutes *versus* the conventional slow IV infusion. They used a maximal permissible dose of 200 mg of IV iron sucrose at one sitting—to minimize the number of visits and thus, maximize compliance. Women with an Hb < 11 g/dL were recruited from two rural antenatal clinics in Southern India between November 2008 and February 2009, at gestational age of 20–24 weeks. Those previously investigated and confirmed to be carriers of either the thalassemia or sickle cell gene were

excluded. Women who were already on oral iron supplementation or had received a blood transfusion within the previous year were also excluded. All women were de-wormed with two tablets of Mebex Plus (Mebendazole and Pyrantel Pamoate) prior to commencement of treatment. Each woman received a total dose of 400 mg IV iron sucrose divided into two equal (200 mg) doses administered 2–4 days apart, regardless of the pretreatment Hb, measured before intervention.

- Women were randomized to receive a slow IV infusion of iron sucrose in 100 mL saline over 30 minutes (group A, $n = 75$), or to receive the iron sucrose as a rapid IV bolus-push over 2–5 minutes, administered through a venous butterfly cannula, once the correct positioning in the vein had been tested with normal saline (group B, $n = 77$). No test dose was given, and all women were closely observed for up to 30 minutes for adverse reactions (after the first dose), such as nausea, burning sensation at infusion site, local pain, rashes, and breathlessness during or immediately after the injection. The women were also advised to contact the unit if they developed any subsequent symptoms. These women were not given any further oral iron supplementation. Post-treatment Hb was measured at 4 weeks after the second dose of iron sucrose in all women available for follow-up. The nature of the adverse reactions was minor in both the groups and included giddiness, generalized itching/burning, local pain, gastrointestinal symptoms, such as nausea, burning at the infusion site, swelling in extremities, and chest discomfort. No woman experienced any major side effects necessitating hospitalization. After the first dose, 5 of the 75 women in group A (6.7%) experienced minor adverse reactions whereas 15 of the 77 women (19.5%) did so in group B. Both groups showed a statistically significant ($P < 0.05$) rise in Hb at 4 weeks, as compared to baseline, with a mean Hb of 10.2 g/dL (± SD 0.8) in group A and 10.3 g/dL (± SD 0.7) in group B.
- Cost analysis: The costs, involved in the infusion method, included the cost of 100 mL of 0.9% normal saline, IV set, cannula and infusion charges, and bed occupancy charges for 1 hour (30 minutes infusion + 30 minutes observation) amounting to 200 Indian rupees (INR) per injection in group A. In group B, the cost amounted to 30 INR for the use of 10 mL 0.9% saline and syringe with needle. Thus, the bolus-push technique was seven times cheaper than the slow infusion technique. The use of the bolus-push technique has potential for cost savings because of the avoidance of the need for a hospital bed and other paraphernalia associated with the conventional infusion technique currently used in the administration of iron sucrose.

Divakar and Manyonda's study showed that this is indeed a feasible approach, with similar efficacy to the conventional, and thereby corroborating the report by Macdougall *et al*.

The Cost of IV Iron Sucrose

There can be no argument that IV iron sucrose is vastly more expensive than the oral preparations. Equally, there can be no justification for perpetuating a treatment (routine oral supplementation) that has failed to eradicate the problem. Although vastly cheaper per unit cost, the total sums of money spent on free oral iron supplements, represents a colossal waste of money due to lack of efficacy (refer to the chapter on "The Iron–Folic Acid Supplementation Program in India: Profound Failure of an Idyll").

What is the solution to this conundrum? Perhaps another way of asking the same question is "what value is placed on a woman's life in India"? If IDA in pregnancy could be eradicated, this would make a major dent in the embarrassing maternal mortality rates in India, which are higher than those in Sri Lanka in the Indian sub-continent and Botswana in Southern-Central Africa!

It is clearly a challenge for government and the pharmaceutical industry. Government needs to place value on women's lives and provide the necessary resources. The pharmaceutical industry needs to make profits, but it could make profits while at the same time, providing a drug at an affordable cost. The authors of this article are neither economists/politicians nor industrialists, but it seems quite obvious that a meeting of minds between government and the pharmaceutical industry could go a long way towards resolving the problems. India is one of the most populous countries in the world—the sheer numbers of women needing iron therapy mean that pharmaceutical companies could cut the cost of the drug and yet realize their profits through bulk sales. If there were the political will, an understanding could be reached where government would be able to make available iron sucrose to all women who need it. In this regard, the challenge for the obstetrician is to work with both, the government and the pharmaceutical industry, to bring about change. The increased use of iron sucrose in a variety of settings might drive down costs, and such situations include the following:

- In every situation where the desired response to oral iron is not obtained
- Using IV iron sucrose as the first line therapy in all cases of moderate and severe anemia
- Using IV iron sucrose more frequently in the postpartum anemia

- Many women enter pregnancy already anemic: IV iron sucrose should be considered in women with anemia due to heavy menstrual loss, adolescence with significant anemia, or women destined for gynecological surgery, especially those destined for myomectomy where blood loss can be considerable.

The additional indications would enhance the usage of IV iron sucrose, which would inevitably scale up the volumes, and with appropriate discussions/negotiations/political pressure—this would translate into cost reductions. In the long term, generic preparations would inevitably affect prices in favor of the patient.

Cost of Blood Transfusion *vs.* Current Cost of IV Iron

In a typical rural setting, when a woman with moderately severe anemia goes into labor, she is at significant risk of postpartum hemorrhage. A requisition is made for a couple of units of blood or blood products, but these are not easily available. The hazards of blood transfusions are only too well known. The alternative would have been for this woman to have entered labor with a normal hemoglobin, her anemia having been effectively treated in the antenatal period with IV iron. Even at current costs, IV iron sucrose is cheaper than emergency blood transfusion. Thus, it is false economy to withhold IV iron sucrose due to cost—the expense incurred for 4 to 5 pints of blood/blood product transfusion is much more than what the IV sucrose administration in the antenatal period would cost—and the expense may also include the young woman's life!

Many women enter pregnancy already anemic: IV iron sucrose should be considered in women with anemia due to heavy menstrual loss, adolescence with significant anemia, or women destined for gynecological surgery, especially those destined for myomectomy where blood loss can be considerable.

So, here is an issue government should consider: if government wishes to save women's lives, one option with regards to anemia and peripartum blood loss would be to set up several thousands of blood banks or blood storage units in peripheries. This is a pipe dream, both in terms of cost and in terms of logistics. A cheaper, achievable, and more realistic option is to invest in making IV iron sucrose available. Many district hospitals and large government institutions, where IV sucrose has been used on a wide scale, have documented a steep decline in the need for blood transfusion. The lower cost of decreasing the number and severity of cases of obstetric hemorrhage, and thereby saving lives, surely makes a compelling case for

government to invest in making IV iron sucrose more readily available rather than trying to manage the complications of peripartum hemorrhage to the mother and the child.

Repeated Infusions: Challenges

With the current iron sucrose, the maximum permissible dose to be administered at one sitting is 200 mg, and then a minimum 24 hours must elapse before the next dose can be given. Thus, a woman, who presents with a hemoglobin of 6 g/dL, would need five visits over a minimum 10 days to achieve a target hemoglobin of 11 g/dL. A number of challenges immediately arise:

- Very few women will complete the five visits, either because it is just too inconvenient on their time, too expensive to travel that many times to the health center, or the idea of five separate IV injections is daunting, or a combination of these and other factors.
- Many women present late in pregnancy. The woman, who presents at 38 weeks gestation, is unlikely to have the time required to complete the treatment course before she goes into labor, even if she were compliant.

Ferric carboxymaltose, a novel iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell, allows for controlled delivery of iron to target tissues.

The potential solution lies in the use of IV iron available as a total dose infusion. In the chapter on "Safety Issues in the Treatment of Gestational Anemia", the risks of anaphylaxis associated with iron dextran, which can be used as a total dose infusion, were discussed. The risks are not massive, but they are enough to dissuade many practitioners from using this preparation routinely, and iron dextran would not seem to be a rationale solution to the huge problem posed by anemia in India. In the West, the preparation ferric carboxymaltose[5] is already available which is an iron sucrose preparation with all the advantages of Orofer, but which can be given at a dose as high as 1000 mg at one sitting over 15 minutes. Ferric carboxymaltose,[6] a novel iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell, allows for controlled delivery of iron to target tissues. Administered intravenously, it is effective in the treatment of iron-deficiency anemia, delivering a replenishment dose of up to 1000 mg of iron during a minimum administration time of less than or equal to 15 minutes.

Ferric carboxymaltose is a macromolecular ferric hydroxide carbohydrate complex, which allows for controlled delivery of iron within the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of release of

large amounts of ionic iron in the serum. Intravenous administration of ferric carboxymaltose results in transient elevations in serum iron, serum ferritin, and transferrin saturation, and, ultimately, in the correction of hemoglobin levels and replenishment of depleted iron stores. The total iron concentration in the serum increased rapidly in a dose-dependent manner after IV administration of ferric carboxymaltose. Ferric carboxymaltose is rapidly cleared from the circulation and is distributed primarily to the bone marrow (approximately 80%) and also to the liver and spleen.

Results of several randomized trials have shown that intravenously administered ferric carboxymaltose rapidly improves hemoglobin levels and replenishes depleted iron stores in various populations of patients with iron-deficiency anemia, including those with inflammatory bowel disease, heavy uterine bleeding, postpartum iron-deficiency anemia, or chronic kidney disease. It was well tolerated in clinical trials. Ferric carboxymaltose is, therefore, an effective option in the treatment of iron-deficiency anemia in patients for whom repeated visits can be an issue. There are discussions and arguments over relative costs, but the avoidance of several visits may in the long term mean that ferric carboxymaltose may turn out to be cheaper. For India, this is a potential solution that would overcome most of the difficulties discussed above—ferric carboxymaltose has yet to be licensed and marketed in India.

The partial solution in the meantime is educate and encourage women to attend for antenatal care early in the second trimester so that any anemia can be diagnosed and treatment commenced early. Some, in India, have already experimented with the administration of 400 mg of iron sucrose, and by all accounts, this approach seems to be safe and efficacious, but the pharmaceutical industry continues to recommend the maximum of 200 mg and until rigorous safety and efficacious studies have been conducted and the results published, the authors of this article cannot and do not recommend a change in practice.

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Chapter - 7

Management of Postpartum Anemia

- Introduction
- Prevalence
- Consequences of Postpartum
- Management of ID and IDA in the Postpartum Woman
- Role of IV Iron in the Postpartum Period
- Use of IV Iron in the Postpartum
- Blood Transfusion in the Management of Postpartum Anemia
- Approaches to the Management of Postpartum ID and IDA in India
- Proposed Protocol for the Management of Postpartum Anemia
- Management of Postpartum Anemia based on Hb Level
- Conclusion

Management of Postpartum Anemia

Introduction

Postpartum iron-deficiency anemia (IDA) is defined as a hemoglobin (Hb) of <10 g/dL and ferritin of <15 μg/L at 24–48 hours post-delivery. After childbirth, Hb levels may drop during the first 24 hours due to the loss of blood during delivery. However, the levels should rise over the next few days and return to normal by the 7th day. Due to physiological changes and fluid shifts, a spontaneous restoration of ferritin levels is also expected to occur postpartum.

Prevalence

It is teleological sound to suppose that the iron status should significantly improve after delivery for the following reasons:

- Maternal body iron stores are enhanced as the expanded red cell mass of pregnancy contracts at delivery.
- Maternal iron requirements radically decline with the birth of the infant, whose iron needs take precedence over the mother's during pregnancy.
- Iron losses are significantly reduced by postpartum amenorrhea and the relatively small amount of iron lost through breast milk.

Though it is, therefore, thought that the postpartum period is a time of low risk of IDA, the reality is different. Recent investigations in ethnically diverse low-income populations in the US have reported that postpartum iron deficiency (ID) and IDA are far more common than previously thought.[1] Blood loss at delivery appears to be a contributing factor, with 5% of deliveries involving loss of more than one liter (irrespective of mode of delivery).

In the National Pregnancy Nutrition Surveillance System, 29.8% of women, who were not previously anemic during pregnancy, become anemic after

delivery.[2] Bodnar LM *et al.* (2002) identified ID as the principal cause and reported that postpartum Hb levels of <10 g/dL are observed in up to 30% of women, with more severe anemia (Hb < 8 g/dL) seen in 10%.[3]

In a recent cross-sectional study of 59,428 women, participating in the Special Supplemental Program for Women, Infants, and Children (WIC), the prevalence of anemia among non-Hispanic black women ranged from 38.3% to 48.0% from 4 to 26 weeks' postpartum and was roughly twice that of non-Hispanic white women at each week postpartum.[1] These data also showed that, of the 9129, women who entered WIC with a normal hemoglobin concentration in the third trimester, 21.3% had anemia at their postpartum return visit.

The scenario in India can hardly be expected to be any better since a significant number of women are anemic during pregnancy, and enter labor with a low Hb. Blood loss during delivery would be expected to worsen the situation, and therefore, increase the likelihood of postpartum anemia. In a study by Patra Somdatta in the village of Haryana, it was found that 70% of the women were anemic at 6 weeks' postpartum. Thus, poor postpartum iron status is a public health problem that warrants greater attention.[4]

Not only is IDA a major risk factor for maternal and perinatal mortality and morbidity, it also significantly contributes to several other problems, such as poor postpartum wound healing, depression, and impaired lactation.

Consequences of Postpartum

The impact of ID and IDA on the pregnant woman, fetus, newborn, and child has been dealt with in chapter 4 under "Western and Indian Experience with Intravenous Iron Sucrose: Exercising Caution in the Use of a New Medication."[4] Therefore, suffice here to merely summarize:

On the Mother

Not only is IDA a major risk factor for maternal and perinatal mortality and morbidity, it also significantly contributes to several other problems, such as poor postpartum wound healing, depression, and impaired lactation. It is well known that women with anemia suffer increased cardiovascular strain, reduced exercise tolerance and a variety of symptoms, including feelings of reduced wellbeing, headaches, tiredness, and dizziness. All these symptoms can be debilitating and negatively impact on a woman's quality at a time when she faces the demands of caring for a newborn. Fatigue alone can affect a person's physical and mental health, their motivation to participate in everyday activities and even the desire to interact socially. It can impact

on her maternal role attainment and may place her at greater risk for postnatal depression, impair cognitive function, increase stress and anxiety, and interrupt mother-child bonding.[5] The everyday challenges of fatigue are significantly compounded after childbirth. In addition to a new mother's demanding tasks of caring for a child, postpartum fatigue can impact her postpartum maternal role attainment and may place her at greater risk for postpartum depression.[6]

On the Neonate

It is well known that gestational anemia is associated with increased risk of preterm birth and low birth weight, and is associated with an estimated 24% of perinatal deaths.[7] Studies have shown that infants of anemic mothers were developmentally delayed, possibly due in part to the fact that anemic mothers were significantly more "negative" towards their baby, engaged less in goal setting, and were less "responsive" than nonanemic mothers.[8]

Management of ID and IDA in the Postpartum Woman

The Center for Disease Control (CDC) and Institute Of Medicine (IOM) recommend that women who have had ''anemia continued through the third trimester, excessive blood loss during delivery, and a multiple birth'' should be supplemented with iron from delivery to the 4- to 6-week postpartum visit. Data are lacking on current postpartum ID prevention and treatment strategies employed by clinicians in public and private settings in India.

Oral Iron Therapy

The American College of Obstetricians and Gynecologists on anemia of pregnancy (ACOG) guidelines suggest that, in most circumstances, oral iron preparations are appropriate and sufficient. The guidelines cited a randomized controlled clinical study by Bhandal and Russell (2006)[9] comparing oral *versus* intravenous (IV) iron sucrose for postpartum anemia, finding that women treated with IV iron had higher hemoglobin levels in the short term (on days 5 and 14) but that by day 40, there was no significant difference in the hemoglobin levels of the two groups. Various forms of oral iron preparations may be considered:

- **Ferrous sulfate** – An amount of 325 mg orally three times daily between meals separately from other medications. Ten mL syrup orally three times daily between meals separately from other medications.

An increase in the hemoglobin concentration of at least 2 g/dL after 3 weeks of therapy generally is used as the criterion for an adequate therapeutic response.

- **Carbonyl iron** – This form of iron may be less toxic than iron salts. However, bioavailability is only 2.7% compared to 10.4% offered by ferrous sulfate.
- **Iron ascorbate 100 mg** – Ascorbic acid enhances absorption making the bioavailability at 40%. It is far superior to other salts and is responsible for improving efficacy. It has fewer side effects and is better tolerated. This leads to improved compliance. An added advantage may be the prevention of oxidative damage *in vivo*.

Role of IV Iron in the Postpartum Period

Although the standard treatment for mild to moderate postpartum ID and IDA remains oral iron supplementation, the effectiveness of this approach in cases of severe anemia is doubtful as the iron has to be taken for prolonged episodes and the associated side effects compromise compliance, whereas responses are often slow. There is, therefore, a need to explore or consider alternative potentially more effective treatment strategies. Guidelines from the ACOG (2008) stated that parenteral iron is useful in the rare patient who cannot tolerate or will not take modest doses or oral iron. Patients with malabsorption syndrome and severe IDA may benefit from parenteral therapy. The guidelines note that anaphylactic reactions have been reported in 1% of patients receiving parenteral iron dextran. In comparison with patients who take iron dextran, patients who take iron sucrose have fewer allergic reactions (8.7 *versus* 3.3 allergic events per 1 million doses) and a significantly lower fatality rate 31 *versus* 0, $P < 0.001$).

Use of IV Iron in the Postpartum

Bhandal N *et al*. 2006[9]

In this prospective randomized controlled trial (RCT), conducted at the Women's Centre, John Radcliffe Hospital (Oxford, UK), 44 women with an Hb of <9 g/dL and ferritin of <15 μg/L at 24–48 hours postdelivery were randomized to receive either oral ferrous sulfate 200 mg twice daily for 6 weeks or IV ferrous sucrose 200 mg given as two doses on days 2 and 4 following recruitment. By day 5, the Hb level in women treated with IV iron had risen from 7.3 ± 0.9 to 9.9 ± 0.7 g/dL, though there was no change in

those treated with oral iron. Women treated with IV iron had significantly higher Hb levels on days 5 and 14 ($P < 0.01$). Throughout the study, ferritin levels rose rapidly in those treated with IV iron and remained significantly higher than in those treated with oral iron ($P < 0.01$). Thus, this study showed that IV iron sucrose increases the Hb level more rapidly and replenishes iron stores more effectively than oral ferrous sulfate in women with postpartum IDA.

Van Wyck *et al.* 2005[10]

This study was designed to compare the efficacy of rapid, large-dose IV ferric carboxymaltose *versus* oral iron supplementation, as evidenced by hematologic parameters and maternal health-related quality of life assessments. Forty-three sites (40 in the United States and 3 in Mexico) participated in this open-label, phase III, randomized trial where 361 postpartum anemic women were randomized to oral iron or IV iron. At each treatment interval after day 7, the proportion of patients who achieved a rise in Hb of 3.0 g/dL or more was greater in the IV iron treatment group. The IV iron group also had a greater proportion of patients who experienced correction of anemia (achieving Hb more than 12 g/dL) at each treatment interval and overall (90.5% *versus* 68.6%, $P < 0.001$). Patients with the most severe anemia showed the greatest improvement in anemia correction when treated with IV ferric carboxymaltose. Serum ferritin was significantly increased in the IV iron group, whereas the oral group showed no increase.

Breymann *et al.* 2008[11]

In this open-label RCT, 349 postpartum anemic women (Hb < 10.5 g/dL) from 20 centers in Romania, Russia, and Poland were randomized in a 2:1 ratio to receive IV ferric carboxymaltose or oral iron sulfate. All patients received their first dose of medication within 7 days postpartum and then attended follow-up visits after 1, 2, 4, and 12 weeks. There was a mean compliance of greater than 90% in the oral group and, with the exception of two patients, 100% compliance in the ferric carboxymaltose group. Hemoglobin levels in both groups increased throughout the study but "no significant differences between the increases in Hb in the two groups" time during the study. Despite the nonsignificant results, the Hb levels of the IV treatment group did rise more rapidly by week 1 when compared to the oral control group. Ferritin levels in the treatment group, however, increased significantly throughout the study. At week 1, the ferritin levels of the IV group were significantly elevated at 568.2 μg/L), though the control group showed only minimal increases at week 2 of 34.8 μg/L.

By the end of the study, there was still a significant elevation in the IV treatment group's ferritin level, compared to that of the oral control group (161.2 μg/L *versus* 43.3 μg/L, respectively).

Seid *et al.* 2008[12]

This was an RCT which compared the safety, effectiveness, and tolerability of IV ferric carboxymaltose to oral ferrous sulfate in women with postpartum anemia. A total of 291 women at less than 10 days after delivery with Hb < 10 g/dL were randomized to receive ferric carboxymaltose (n = 143) 1000 mg or less intravenously over 15 minutes or less, repeated weekly to a calculated replacement dose (maximum 2500 mg) or ferrous sulfate (n = 148) 325 mg orally thrice daily for 6 weeks. Ferric carboxymaltose-treated subjects were significantly more likely to: (i) achieve an Hb > 12 g/dL in a shorter time period, with a sustained Hb > 12 g/dL at day 42, (ii) achieve Hb rise >3 g/dL more quickly, and (iii) attain higher serum transferrin saturation and ferritin levels. Drug-related adverse events occurred less frequently with ferric carboxymaltose.

Westad *et al.* 2008[13]

Postpartum anemic women (n = 128) with Hb 6.5–8.5 g/dL were randomized to receive IV iron sucrose (600 mg) or oral ferrous sulfate (200 mg daily). After 4 weeks, the mean Hb levels of both groups increased, however, there was no significant difference between the groups. The treatment group's Hb level increased from 7.9 g/dL to 11.9 g/dL and the control group's Hb level increased from 7.7 g/dL to 12.3 g/dL. Hemoglobin levels continued to increase from week 4 to week 8 with no significant difference between the groups, and then leveled off around week 8 for both groups. The nonsignificant hemoglobin results included patients who received blood transfusions. A sub-analysis of 113 women was conducted to exclude patients who required blood transfusions. This sub-analysis showed a significantly higher proportion of subjects, treated with IV iron sucrose, achieving an Hb increase of at least 2 g/dL (P = 0.04). Also, the treatment group showed significantly higher mean Hb levels at weeks 8 and 12 (P = 0.02). The mean serum ferritin value after 4 weeks was significantly higher in the IV group compared to the oral group (13.7 *vs.* 4.2 μg/L, P < 0.001). This study used the SF-36 to look at four main measures of a mother's quality of life: the physical function score, the pain index, the vitality score, and the mental health score. At week 12, there was a significant difference in the pain index in favor of the treatment group. The fatigue score comprised physical, mental, and total fatigue ratings. In both

groups, the physical fatigue scores improved and the IV treatment group showed significantly greater improvements at weeks 4, 8, and 12 ($P = 0.02$, $P = 0.02$, $P = 0.03$, respectively).

Giannoulis *et al.* 2009[14]

Postpartum women ($n = 104$) with an Hb < 8 g/dL and ferritin < 10 μg/dL were randomized to receive a total of 300 mg IV iron sucrose over 3 days ($n = 78$) or oral iron protein succinylate 800 mg daily for 4 weeks ($n = 26$). Adverse reactions to the treatment were mild but more prominent in the oral iron group, comprising mostly constipation and bloating. By the end of the study, Hb increase was significantly higher in the IV iron group (mean increases 4.6 *vs*. 2.3 g/dL, $P = 0.0001$). The increase in ferritin levels was similarly higher in the IV iron group (mean rise 105 *vs*. 68 μg/L, $P = 0.0004$).

Blood Transfusion in the Management of Postpartum Anemia

In both groups, the physical fatigue scores improved and the IV treatment group showed significantly greater improvements at weeks 4, 8, and 12 ($P = 0.02$, $P = 0.02$, $P = 0.03$, respectively.

The trigger for blood transfusion in postpartum anemia appears to be largely clinician dependant, since a number of studies and audits have shown that the level of Hb when a blood transfusion is done, varies widely between medical teams and institutions, and it would appear that a significant proportion of transfusions done inappropriately.[15] The hazards of allogenic blood transfusion have been addressed in another chapter in this book, and include the transfusion of the wrong blood, infection, anaphylaxis, and lung injury, any of which could be devastating for the new mother. These hazards, together with the national shortage of blood products, mean that transfusion should be viewed as a last resort in otherwise young and healthy women, transfusion being reserved for women with hemodynamic instability and continued bleeding. The demand on blood transfusion services, to provide adequate and yet safe products, means that alternative yet effective treatment strategies should be explored. Intravenous iron therapy would seem the obvious option, yet its role in situations where blood transfusion is usually given has yet to be rigorously evaluated. The concerns regarding the risks of anaphylaxis associated with iron dextran are significantly minimized by the use of iron sucrose, and there are undoubtedly major potential cost-savings in the use of IV iron *versus* blood transfusion.

As yet there are no randomized studies showing a beneficial effect of IV iron on transfusion requirements. A study by Broche *et al.*[16] however, is indicative

of the beneficial effect. The need for transfusion after delivery was compared in two groups of women, one before and one after IV iron became available. Of 103 women in the first group, 15 received transfusions compared to 5 of 112 in the second group. Twenty-three women in the latter group would have received transfusions, based on their Hb levels, if IV iron were not available.

One study has explored the potential benefits of adding recombinant human erythropoietin (rhEPO) to the use of IV iron in postpartum anemia. Wågström *et al*. (2007)[17] working in a Swedish hospital, randomized 60 women with postpartum Hb < 8.0 g/dL to 3 different treatment groups within 72 hours of delivery. All 3 groups were given a total dose of 450 mg IV iron sucrose. In addition, 2 groups were given 20,000 or 40,000 U of total rhEPO (day 0 and 3). In comparison with IV iron alone, the addition of rhEPO did not further increase hemoglobin concentration in women with postpartum anemia.

Approaches to the Management of Postpartum ID and IDA in India

There can be no doubt the high prevalence of ID and IDA in association with reproduction in India, and the major negative impact extensively dealt with elsewhere in this book. It is also the case that the prevalence of postpartum anemia is high, and defined measures are required to address the issue. Here we propose options for the management of postpartum ID and IDA. In essence, we advocate a central role for IV iron sucrose for the following reasons:

In terms of cost-analysis, 3 doses of iron sucrose infusion are cheaper than 1 unit of blood.

Intravenous iron sucrose produces a more rapid increase in Hb concentration than oral iron and intramuscular iron dextran: IV iron can allow up to a 5-fold erythropoietic response to significant blood loss anemia in normal individuals.[18,19]

- For iron-deficient patients, 50% of IV iron is incorporated into Hb within 3–4 weeks.[20] There is now good evidence to show that IV iron treats IDA and restores iron stores more effectively and faster than oral iron in conditions, such as chronic renal disease, inflammatory bowel disease, and pregnancy, and reduces the requirement of red cell transfusion.[9,21,22]
- In terms of cost-analysis, 3 doses of iron sucrose infusion are cheaper than 1 unit of blood.

- It has been argued that iron sucrose requires multiple dosing and this disadvantage can be overcome by administration of iron carboxymaltose. Although the drug cost of latter is twice that of iron sucrose, both cost-effective- and cost-benefit analysis showed that the use of iron carboxymaltose is cheaper than that of iron sucrose due to fewer hospital visits.[23]

Proposed Protocol for the Management of Postpartum Anemia

All women should have a postnatal Hb estimation. Ideally, this should be on day 3, but a pragmatic approach is required to meet specific situations, e.g. an earlier Hb estimation would be required for the following:

- Women who sustained a blood loss of >500 mL
- Women who underwent a cesarean section delivery
- Women who had an instrumental delivery
- Women who sustained a 3rd- or 4th-degree perineal tear
- Women who were anemic in the antenatal period

Women who Might Require a Blood Transfusion

Women with an Hb < 8 g/dL with associated symptoms of breathlessness, dizziness, and/or other signs of cardiovascular compromise, such as tachycardia and tachypnea, are likely to require a blood transfusion. Hemoglobin level alone should not be the trigger for a blood transfusion, since many women with Hb < 8 g/dL will be asymptomatic and can be managed with IV iron.

Management of Postpartum Anemia based on Hb Level

1. Hb > 10 g/dL with low ferritin (below cut off level): treat with oral iron (ferrous sulfate) 200 mg twice daily. Ascorbate, given as vitamin C tablets or orange juice taken at the time of iron ingestion, will enhance iron absorption.
2. Hb between 8 and 10 g/dL: treat with IV iron to bring the Hb between 11.5 and 12 g/dL.
3. Hb between 6 and 8 g/dL: look for symptoms and signs of anemia. If symptomatic, transfuse 1–2 units followed by iron infusion to raise the Hb to target level.

4. Hb < 6: if symptomatic, transfuse to restore Hb level to 7–8 g/dL followed by iron infusion. If asymptomatic, do not transfuse automatically: give iron infusion and monitor closely.
5. If the woman received a blood transfusion and iron infusion, repeat Hb the next day and then on the 14th (after the last infusion) and 28th day, and also measure serum ferritin.
6. If the woman received iron infusion, repeat Hb and ferritin on 14th (after the last infusion) and on 28th day.
7. Repeat Hb and ferritin in 4 weeks, if on oral iron only.

Contraindications to Iron Infusion

- History of anaphylaxis
- History of reaction to iron infusion
- Signs and symptoms of active acute or chronic inflammation
- Acute renal failure
- Chronic liver disease

Conclusion

The authors emphasize that the above protocol is their suggestion, open to constructive criticism and suggestions. However, many will find it beneficial as a starting point, although they would urge each maternity unit to develop its own protocol in the hope of drastically reducing the mortality and morbidity associated with IDA in the maternity population of India.

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Iron-Deficiency Anemia: Good Clinical Practice Recommendations

- **Introduction**
- **Classification**
- **Indian Guidelines**

Iron-Deficiency Anemia: Good Clinical Practice Recommendations

Introduction

Anemia, the most common hematologic abnormality, is a reduction in the concentration of erythrocytes or hemoglobin in blood. The two most common causes of anemia in pregnancy and the puerperium are deficiency and acute blood loss. Iron requirements increase during pregnancy, and a failure to maintain sufficient levels of iron may result in adverse maternal–fetal consequences. The purpose of this document is to provide recommendations for screening and clinical management of anemia during pregnancy in India.

Classification

The definition of anemia recommended by the Centers for Disease Control and Prevention is a hemoglobin (Hb) or hematocrit (Hct) value less than the fifth percentile of the distribution of Hb or Hct in a healthy reference population based on the stage of pregnancy.

Classification derived from an iron-supplemented population lists the following levels as anemic:

Hb (g/dL) and Hct (percentage) levels:

- below 11 g/dL and 33%, respectively, in the first trimester;
- below 10.5 g/dL and 32%, respectively, in the second trimester; and
- below 11 g/dL and 33%, respectively, in the third trimester.

This is the standard to be accepted in India. Expert group also agreed upon the ICMR classification for severity of anemia (Box).

Indian Guidelines

A recent report estimates that in a low income, mostly minority population, rates of iron-deficiency anemia are 1.8% in the first trimester, 8.2% in the

Box. ICMR classification for severity of anemia	
Severity of anemia	**Hb in g/dL**
Mild	10–10.9
Moderate	9.9–7
Severe	6.9–4
Very severe	<4

See Annexure for other categories of classification.

second trimester, and 27.4% in the third trimester in the West. As against this, the incidence of IDA in India is 60% in urban and 69% in the rural population. In the light of this, following recommendations are made with respect to evaluation and management.

The following recommendations are based primarily on consensus and expert opinion (Level C):

Who should be screened for anemia during pregnancy?

All pregnant women should be screened for anemia during pregnancy. Those with iron-deficiency anemia should be treated with supplemental iron, in addition to prenatal vitamins. Patients with anemia, other than iron-deficiency anemia, should be further evaluated.

How should asymptomatic pregnant women with mild to moderate anemia be evaluated?

All pregnant women should be screened for anemia during pregnancy.

The spectrum of iron deficiency ranges from iron depletion, when both stored and transport iron are low, to iron-deficiency anemia, when stored, transport, and functional iron are low. Measurements of serum Hb concentration of Hct are the primary screening tests for identifying anemia but are nonspecific for identifying iron deficiency.

Iron deficiency can be defined as abnormal values on biochemical test results, increases in hemoglobin concentrations of more than 1 g/dL after iron treatment, or absent bone marrow iron stores as determined by a bone marrow iron smear.

Evaluation at a PHC is limited to clinical examination and Hb estimation by: Sahli's method, Pbs, and hematocrit.

At First Referral Units (FRU's) distinct hospital and institutes depending on facilities available, the following could be done:

- Complete blood count
- Peripheral smear
- Semen ferritin
- Hb electrophoresis

What is the practical approach to treatment?

The Centers for Disease Control and Prevention recommend screening for iron-deficiency anemia in pregnant women and universal iron supplementation to meet the iron requirements of pregnancy except in the presence of certain genetic disorders, such as hemochromatosis.

The rationale for universal supplementation is that treatment maintains maternal iron stores and may be beneficial for neonatal iron stores. Iron-deficiency anemia during pregnancy has been associated with an increased risk of low birth weight, preterm delivery, and perinatal mortality.

Iron supplementation decreases the prevalence of maternal anemia at delivery. In practise, the diagnosis of mild to moderate iron-deficiency anemia is often presumptive. In patients without evidence of causes of anemia other than iron deficiency, it may be reasonable to empirically initiate iron therapy without first obtaining iron test results. The standard treatment is oral supplementation with 60 mg of elemental iron once or twice daily from second trimester of pregnancy.

- Deworming
- Treatment of malaria
- Dieting advice—jaggery, green leafy vegetables
- Avoid tea/parboiled rice
- Cook in iron pots/vessels
- 60 mg elemental iron $FeSO_4$/Fe-ascorbate

When pregnant women with moderate iron-deficiency anemia are given adequate iron therapy, reticulocytosis may be observed 7–10 days after iron therapy, followed by an increase in Hb and Hct levels in subsequent weeks.

Failure to respond to iron therapy should prompt further investigation and may suggest an incorrect diagnosis, co-existing disease, malabsorption (sometimes caused by the use of enteric-coated tablets or concomitant use of antacids), noncompliance, or blood loss.

When should parenteral iron be used in pregnant patients?

In most clinical circumstances, oral preparations are appropriate and sufficient.

Guidelines for giving parenteral iron sucrose:

- Hb < 9 g% iron
- 14-day oral dose failure
- No hemoglobinopathy

Parenteral Iron

High molecular weight iron dextrose is not recommended for use. Newer preparations, such as iron sucrose, are effective and safe with minimal adverse reactions. In comparison with patients who take iron dextran, patients who take ferrous sucrose have fewer allergic reactions (8.7 *versus* 3.3 allergic events per 1,000,000 doses) and a significantly lower fatality rate (31 *versus* 0, $P < 0.001$), hence, it is the preferred molecule of choice. Iron sucrose molecule used should have molecular weight 30,000–100,000 daltons.

Dosage and Technique of Administration

Iron sucrose administered as either a bolus (undiluted) over 5–10 min on outpatient basis or short infusion over 30 min [in 200 mL NaCl (9 g/L)]. Maximum cumulative doses 1600 mg in pregnancy (200 mg twice per week to a target Hb of 11 g/dL or for a maximum of 4 weeks), Mean treatment duration 21 days (8–29 d).

When should blood transfusions be used?

Severe anemia with maternal Hb levels less than 6 g/dL has been associated with abnormal fetal oxygenation, resulting in nonreassuring fetal heart patterns, reduced amniotic fluid volume, fetal cerebral vasodilatation, and fetal heart death. Thus, maternal transfusion should be considered for fetal indications in case of severe anemia.

- Postpartum anemia with signs of shock
- Severe acute blood loss following spontaneous delivery or lower segment cesarean section
- Severe anemia during pregnancy associated with maternal decompensation

Annexure

- **Anemia Classification**
- **Anemias Characterized by Mechanism**
- **Anemias Classified by Mean Corpuscular Volume**
- **Normal Iron Indices in Pregnancy**
- **Biochemical Tests for Diagnosis of Anemia**
- **Signs and Symptoms of Iron-Deficiency Anemia**
- **Red Blood Cell Distribution Width**
- **Action**
- **Increase Demand**

Anemia Classification

Acquired

- Deficiency anemia (e.g. iron, vitamin B12, folate)
- Hemorrhagic anemia
- Anemia of chronic disease
- Acquired hemolytic anemia
- Aplastic anemia

Inherited

- Thalassemias
- Sickle cell anemia
- Hemoglobinopathies (other than sickle cell anemia)
- Inherited hemolytic anemias

Anemias Characterized by Mechanism

Decreased red blood cell production

- Iron-deficiency anemia
- Anemia associated with vitamin B12 deficiency
- Folic acid-deficiency anemia
- Anemia associated with bone marrow disorders
- Anemia associated with bone marrow suppression
- Anemia associated with low levels of erythropoietin
- Anemia associated with hypothyroidism

Increased red blood cell destruction

- Inherited hemolytic anemias
  - Sickle cell anemia
  - Thalassemia major
  - Hereditary spherocytosis
- Acquired hemolytic anemias
  - Autoimmune hemolytic anemia
  - Hemolytic anemia associated with thrombotic thrombocytopenic purpura
  - Hemolytic anemia associated with hemolytic uremic syndrome
  - Hemolytic anemia associated with malaria
- Hemorrhagic anemia

Anemias Classified by Mean Corpuscular Volume

Microcytic (MCV less than 80 fL)

- Iron-deficiency anemia
- Thalassemias
- Anemia of chronic disease
- Sideroblastic anemia
- Anemia associated with copper deficiency
- Anemia associated with lead poisoning

Normocytic (MCV 80–100 fL)

- Hemorrhagic anemia
- Early iron-deficiency anemia
- Anemia of chronic disease
- Anemia associated with bone marrow suppression
- Anemia associated with chronic renal insufficiency
- Anemia associated with endocrine dysfunction
- Autoimmune hemolytic anemia
- Anemia associated with hypothyroidism or hypopituitarism
- Hereditary spherocytosis
- Hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria

Macrocytic (MCV greater than 100 fL)

- Folic acid-deficiency anemia
- Anemia associated with vitamin B12 deficiency
- Drug-induced hemolytic anemia (e.g. zidovudine)
- Anemia associated with reticulocytosis
- Anemia associated with liver disease
- Anemia associated with ethanol abuse
- Anemia associated with acute myelodysplastic syndrome

Abbreviation: MCV, mean corpuscular volume

Normal Iron Indices in Pregnancy

Test	Normal value
Plasma iron level	40–175 μg/dL
Plasma total iron-binding capacity	216–400 μg/dL
Transferrin saturation	16–60%
Serum ferritin level	More than 10 μg/dL
Free erythrocyte protoporphyrin level	Less than 3 μg/g

Biochemical Tests for Diagnosis of Anemia

	Iron-deficiency anemia	**Thalassemia**	**Anemia of chronic disease**
Iron level	<level	Normal	<level
TIBC	>capacity	Normal	<capacity
Ferritin level	<level	Normal	>level
Iron/total iron-binding capacity	<18%	Normal	>18%

Signs and Symptoms of Iron-Deficiency Anemia

- Pale skin
- An elevated platelet count
- Inflamed tongue (glossitis)
- Spoon nails
- Blue sclerae
- Weakness
- Restless leg syndrome
- Fatigue
- Irritability
- Pica—A craving for peculiar substances, such as soil or clay or an abnormal appetite for foods, like cornstarch, tomatoes, lemons, and ice.

Trimester	Hemoglobin (g/dL)	Hematocrit (%)
First	<11	<33
Second	<10.5	<32
Third	<11	<33

Serum ferritin value	**Interpretation**	
≤45 ng per mL	Probable iron deficiency	
≥100	Not likely to be iron deficiency. Evaluate for other causes of anemia	
= 46 to 99	Obtain total iron-binding capacity (TIBC),serum iron (FE), and transferrin saturation (TSAT)	
	If TIBC is increased, serum iron is decreased, and transferrin saturation is decreased, most likely iron deficiency. Probable iron deficiency	If TIBC is decreased, serum iron is increased, and transferrin saturation is increased, not likely to be iron deficiency. Evaluate for other causes of anemia

Red Blood Cell Distribution Width

The Red blood cell distribution width (RDW) is usually elevated early in iron deficiency, but may also occur with vitamin B12 or folic acid deficiency. However, vitamin B12 or folic acid deficiency results in blood cells that are larger than normal (macrocytic anemia), whereas iron deficiency leads to the production of small red blood cells with an MCV of less than 80 fL (microcytic anemia).

In patients with thalassemia minor, the RDW is usually normal. The American College of Obstetricians and Gynecologists recommends that women of Southeast Asian or Mediterranean ancestry with a low MCV and normal iron status should be offered hemoglobin electrophoresis. All individuals of African descent should be offered hemoglobin electrophoresis regardless of their red blood cell indices.

Acquired or hereditary sideroblastic anemia may also present with an elevated RDW and low MCV. However, serum iron and serum ferritin are increased in sideroblastic anemia, because red blood cells are unable to use available iron to make hemoglobin. Instead, the iron accumulates in the red cell mitochondria producing sideroblasts.

Action

Proven, cost-effective interventions can reduce maternal anemia during pregnancy and lactation. The package of activities includes:

- In all countries:
  - provide iron-folic acid supplementation,
  - promote healthy timing and spacing of pregnancy,
  - and prevention of postpartum hemorrhage,
  - through active management of third stage of labor (AMTSL).
- In malaria endemic areas:
  - provide intermittent preventive treatment,
  - longlasting insecticide-treated bed nets,
  - indoor residual spraying,
  - and artemisinin-based combination therapy.
- Where hookworm prevalence exceeds 20%:
  - provide deworming medication as a routine part of antenatal care (ANC).

Increase Demand

Social marketing can be further utilized to create awareness of and demand for services and supplies.

Counseling at the community and health service level can help women understand and adhere to IFA supplementation, family planning, and other interventions.

- Use supportive supervision systems to reinforce adequate counseling of pregnant women and ensure that local realities are addressed in the counseling provided.
- Empower health workers and volunteers for quality counseling to improve adherence.
- Listen and take action to overcome the barriers women face in accessing anemia prevention and treatment to develop context-relevant approaches, such as the provision of the full course of IFA at first treatment.

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