Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: September 30, 2023

Citation: Ramachandran P and Kalaivani K, 2023. Prevention and management of Anaemia in Pregnancy in India: Challenges and Opportunities, Medical Research Archives, [online] 11(9).

https://doi.org/10.18103/mra.v11i9.4404

DOI
https://doi.org/10.18103/mra.v11i9.4404

ISSN: 2375-1924

RESEARCH ARTICLE

Prevention and management of Anaemia in Pregnancy in India: Challenges and Opportunities

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ABSTRACT

Seven decades ago, over 80% of Indian pregnant women were anaemic. About 3/4th of anaemia was due to nutritional deficiencies of: iron (most common), folic acid (second) and vitamin B12 (not as common). Anaemia in pregnancy was associated with higher maternal morbidity and mortality, low birth weight and high perinatal mortality. Detection and appropriate management of anaemia, including parenteral iron therapy and intensive care for severe anaemia were important components of antenatal care in India, but only about 10% of women had access to antenatal care.

In 1970s the national programme for anaemia in pregnancy focussed on identifying all pregnant women and providing them iron and folic acid (IFA) supplementation. The coverage and compliance with supplementation were low.

In 1990 when the primary health care infrastructure was established, the anaemia control programme embarked on testing and providing appropriate treatment to anaemic women. The tertiary care centres operationalised this "test and treat" strategy. In primary and secondary care settings, accurate test for diagnosis of anaemia was not available. In the absence of accurate Hb estimation at all levels of care, it was not possible to provide appropriate treatment based on Hb levels. So, all pregnant women continued to receive one tablet of IFA throughout pregnancy. Over the next two decades, coverage under antenatal care and IFA supplementation improved but compliance with supplementation was low because about a third of pregnant women had gastrointestinal side effects with IFA. Despite these problems, between 2002 and 2015, there had been a decline in the prevalence of severe and moderate anaemia.

To accelerate the decline in anaemia in pregnancy the country is focusing on the 'test and treat' strategy in pregnant women using an accurate method for Hb estimation and providing appropriate treatment. Nutrition education to improve iron intake prior to and during pregnancy, is focussing on dietary diversification and use of iron fortified salt or cereals. Progress will be monitored through national surveys and locale specific appropriate mid-course modifications in the programme will be made.

Introduction

India had and continues to have the highest prevalence of anaemia in pregnancy in the world and is the home of the largest number of anaemic pregnant women[1-3]. Six decades ago, the country invested in research studies for defining the dimensions, determinants, health consequences of anaemia to the mother-child dyad and interventions for management of anaemia in pregnancy. These studies showed that over 80% of pregnant women were anaemic and anaemia in pregnancy was associated with higher maternal morbidity and mortality, low birth weight and high perinatal mortality[4-6]. Anaemia was mainly due to low vegetable consumption (not readily available, affordable and not tasty) and low flesh food consumption (cannot afford economically or ecologically) leading to iron, folate and vitamin B12 deficiency[4,6,7]. Poor bioavailability of dietary iron in habitual fibre, phytate rich Indian diets aggravated iron deficiency[4,7].

The country accorded high priority to interventions aimed at prevention and management of anaemia in pregnancy. Research studies in the 70s reported that iron and folic acid supplementation to pregnant women resulted in improvement in Hb levels; but the addition of vitamin B12 did not result in further improvement in Hb[4,8]. In 1970, India initiated the National Anaemia Prophylaxis Programme aimed at identifying all pregnant women and providing them at least 90 tablets of 60mg of elemental iron and 500 µg of folic acid[9]. In 1990 when the primary health care infrastructure was established, the country embarked on anaemia control programme aimed at detection and treatment of anaemic pregnant women as a major component of antenatal care[10]. Interventions for detection and management of anaemia in pregnancy have been implemented across the country but the content, coverage and utilisation varied between states and in different levels of health care in urban and rural areas. Review after three decades showed that there has been a reduction in the severity and magnitude of anaemia and adverse health consequences associated with anaemia in pregnancy, but the pace of reduction has been slow[11]. Some of the unmet challenges responsible for the tardy reduction in anaemia in pregnancy include problems in:

- diagnosis of anaemia using accurate estimation of Hb;
- operationalising the 'test and treat' strategy for management of anaemia in primary health care level and monitoring impact of treatment using accurate estimation of Hb;
- grading of anaemia based on functional decompensation and providing appropriate treatment;
- assessing nutritional deficiencies associated with anaemia and tailoring the supplementation to correct them;
- improving Hb levels in women prior to pregnancy and prevention of anaemia in pregnancy; and
- estimating impact of interventions in prevalence of anaemia.

The present review explores how these challenges can be transformed into opportunities for achieving sustained decline in anaemia in pregnancy[12].

Diagnosis of Anaemia

All technical documents on anaemia start with the statement that symptoms reported by anaemic persons such as the inability for sustained manual work, easy fatiguability and shortness of breath are seen in many other conditions and are non-specific[13-15]. Clinical signs of anaemia such as pallor are difficult to detect and quantify; koilonychia is a specific sign of anaemia but there is a large time gap between onset of anaemia and development of the sign[15]. Koilonychia disappears only when new nail grows months after correction of anaemia. For nearly a century it has been well recognised that the only method of diagnosis of anaemia is by Hb estimation[15].

HAEMOGLOBIN ESTIMATION

Scientists prefer the measurement of circulating Hb mass for diagnosis of anaemia but this is not feasible under clinical care conditions; hence globally Hb g/dL in circulating blood is accepted as the parameter for diagnosis of anaemia[13,14]. There is an increase in Hb mass during pregnancy, but there is a reduction in circulating Hb g/dL because of haemodilution. The cut-off Hb g/dL for defining anaemia in pregnant women had taken this into account[14]. In hospital settings where blood from venepuncture is collected for other investigations, Hb estimation is done from venous blood so that the woman is spared of a finger prick. Haemoglobin estimations in pregnant women in primary health care settings is done using finger prick because no other investigation is done, finger prick is the preferred option for the woman and the service provider and processing of venous blood is not possible in community settings[15]. Under service or survey conditions feasibility, convenience and acceptability will determine whether finger prick or venous blood is used for Hb estimation. Most of the studies comparing Hb values estimated from venous blood, with Hb estimated from finger prick blood in the same person at the same time report that venous

blood values were higher by 0.1 to 0.5 g/dL[16]. It is preferable that when Hb results are reported in publications the source of blood is indicated, so that it is taken into account while comparing results.

Choosing the accurate, appropriate and affordable method for Hb estimation is a critical requirement for the management of anaemia in pregnancy. The majority of women in India access antenatal care in primary health care settings. Five decades ago, India lacked laboratory facilities in primary health care settings and hence used WHO haemoglobin colour scale (HCS). In HCS, Hb markings are at 2 g/dL interval and optical colour matching from dried blood is difficult[17-18]. Because of these problems, WHO no longer recommends use of the Hb colour scale[19]. India supplied Sahli's haemoglobinometer to primary health care institutions because it was inexpensive, did not require electricity or colorimeter. But this method is time consuming and not accurate[20].

Cyanmethaemoglobin method for Hb estimation was described nearly nine decades ago and remains the gold standard for Hb estimation even today[21]. This is because:

- RBCs get lysed and evenly distributed in the Drabkin's reagent,
- almost all forms of Hb combine with the Drabkin's reagent to form stable cyanmethaemoglobin,
- the method is precise and the samples can be directly compared with the standard, and
- Hb estimation by cyanmethaemoglobin method can be done using a wide range of equipment from colorimeter, spectrophotometer to auto-analyser.

In many secondary and tertiary care hospitals in India, Hb estimation by cyanmethaemoglobin method using colorimeter, spectrophotometer or haematology auto-analyser is in vogue.

In community settings it is not possible to perform Hb estimation using direct cyanmethaemoglobin method. In the 1970s, National Institute of Nutrition (NIN), India standardised Hb estimation by cyanmethaemoglobin with 20µl of blood from finger prick deposited on filter paper and dried. Dried filter paper is put in a zip lock bag, labelled and sent to the laboratory[14]. In India finger prick collection of 20µl of blood from finger prick is taught to laboratory (lab) technicians and nurse midwives. Their accuracy in pipetting and Hb estimation in hospital[20] and community settings[22] and national surveys[23-25] has been well documented. Hb estimation by cyanmethaemoglobin method is one of the assigned tasks of the lab technicians at all levels of care.

Newer technologies which did not require skilled technicians who could accurately measure 20µl of blood, and provide results within minutes after finger prick blood collection (eg Hemocue), non-invasive methods of Hb estimation which did not require invasive procedures such as finger prick or venepuncture for blood collection had been developed and are being tested for use as point of care devices for Hb estimation[16]. Evaluations show that none of them match the gold standard cyanmethaemoglobin method for accuracy, feasibility and cost effectiveness. Experts from developed countries often recommend that a less accurate method eg Hemocue can be used to get immediate results especially in emergency situations and Hb estimation using accurate methods of Hb estimation can be done later in well-equipped lab. In India Hb estimations are done in primary health care settings to detect pregnant women with anaemia and provide appropriate treatment. Majority of women screened in community settings cannot afford the time and cost of going to hospital for confirmatory Hb estimation. Therefore. Hb estimation by cyanmethaemoglobin method remains the accurate, feasible and affordable method of Hb estimation for diagnosis of anaemia and monitoring impact of treatment in pregnant women in primary care settings[15]. When personnel undertaking the Hb estimation and those treating anaemia know that Hb estimation is being done by an accurate method and improvement following treatment can be carefully monitored, they will rapidly operationalise the 'test and treat' strategy in the country and when communities recognise the improvement in quality of care provided to India's 30 million pregnant women, they will optimally utilise the services[15].

In the last few years haematology auto-analysers which rapidly provide accurate estimations of haematological parameters are available and increasingly used in secondary care settings with high case load. As and when 'test and treat' strategy is operationalised in the primary health care settings, secondary care centres will have to manage high referral caseloads of anaemic pregnant women not responding to iron and folic acid supplementation. Auto-analysers will help these centres to cope with the increasing lab workload without deploying more personnel. There had been some discussion whether auto-analyser could be introduced in primary health care setting for Hb estimation in pregnant women. Introduction of auto-analysers in primary health care settings in India is neither required, feasible nor affordable. Care providers at primary care level do not have

the knowledge and skill to interpret all the information provided by the auto-analysers or have access to drugs for management of anaemia using the information provided by the auto-analyser. At primary health care settings, the focus will have to continue to be on Hb estimation for detection of anaemia, providing appropriate dose of iron folic acid supplementation, monitoring improvement through Hb estimation and referring the non-responders to secondary care institutions.

ASSESSMENT OF WOMEN WHO DO NOT RESPOND TO IRON AND FOLIC ACID SUPPLEMENTATION

It is estimated that in India about 2/3rd to 3/4th of anaemia in pregnancy is due to nutritional deficiencies and majority of such women respond to iron and folic acid (IFA) therapy. Non-response to IFA supplementation could be due to poor compliance with supplementation, iron intolerance, or vitamin B12 deficiency. Non response could also be due to non-nutritional causes for anaemia such as haemoglobinopathies and infections like malaria. The non-responders in primary care settings are referred to secondary care centres for management of anaemia. To assess whether persistence of anaemia is due to inadequacy of iron, folic acid and/or vitamin B 12, the pathologists in the secondary or tertiary care centres used the time-tested RBC bio-response in terms of morphological changes in RBC to the nutritional milieu in anaemic individuals and obstetricians provided appropriate treatment based on these indictors:

- normocytic (continue IFA supplementation), and
- microcytic hypochromic (IFA treatment with close monitoring of the intake and response),
- dimorphic (IFA and vitamin B12 supplementation and monitoring) and
- macrocytic (refer to tertiary care centres for investigation).

Reticulocyte count was used for assessing bone marrow response (as expected - continue supplementation, low - refer to tertiary care centres for investigation)[26]. Progress was assessed after 4 weeks by Hb and peripheral smear. Though these algorithms are well known, they are not widely used[26]. As and when these algorithms get operationalised, there will be substantial reduction in the number of women who need referral to tertiary care centres.

In endemic areas. haemoglobinopathies, malaria, hook worm infestation are important factors responsible for pregnant women not responding to iron and folic acid supplementation. Diagnosis and treatment of malaria and hook worm infestation is possible in primary health care settings in endemic areas. In non-endemic areas all pregnant women not responding to IFA supplementation are referred to secondary care centres for diagnosis and management. Physicians in these centres will screen women for these problems and if confirmed treat them[26].

BIOMARKERS FOR IRON, FOLIC ACID AND VITAMIN B12 STATUS

Initially assays for biomarkers of iron, folic acid and vitamin B12 status were available only in research laboratories; over years many tertiary care institutions have access to these assays and have been using them for investigating the women who had not responded to IFA supplementation. Iron deficiency is the most common nutrient deficiency in anaemic pregnant women[27,28]. Iron metabolism is very tightly controlled because both deficiency and iron excess are associated with health hazards. Serum iron, iron binding capacity and % saturation of total iron binding capacity were earlier used for assessing iron status. Currently ferritin (iron stores), soluble transferrin receptor (balance in tissue iron), and hepcidin (iron absorption, iron egress and ingress to the cells) which are expressed in serum are used to assess iron nutritional status[29,30]. The WHO recommends assessing iron status using serum ferritin as biomarker for iron storage depletion and soluble transferrin receptor (sTfR) which indicates tissue iron deficiency[31-32]. Inflammation from any cause results in rise in both these parameters[33,34] and this could mask the presence of iron deficiency. Estimation of C reactive protein and other inflammatory markers and making appropriate adjustments in ferritin levels have been recommended to overcome this problem[33,34].

Studies in India confirm that iron deficiency as assessed by ferritin levels below 12 ng/ml is the most common cause of anaemia in pregnancy[27,28]. However, not all anaemic women with iron deficiency (having microcytic hypochromic anaemia) have low ferritin levels. Almost all women who had received intramuscular (IM) iron therapy[35] and majority of women who received IFA supplementation[28] showed improvement in both Hb and ferritin levels. But ferritin levels remained unchanged in some women who had shown improvement in Hb and some women who did not show improvement in Hb[28]. This is perhaps due to complex interaction between absorption, transport and storage of iron modulated by hepcidin, transferrin and ferritin.

Earlier studies in India had shown high prevalence of folic acid deficiency[7] but over time there had been reduction folic acid deficiency (folic acid <3

ng/ml) and some increase in vitamin B12 deficiency (<200pg/ml)[28,36-38]. Addition of vitamin B12 to IFA did not result in further improvement in Hb[8,28]. Supplementation with IFA and vitamin B12 resulted in a reduction in vitamin B12 deficiency but not all women with B12 deficiency prior to supplementation showed such a reduction[28]. In health care settings decisions on management of individual pregnant women who had not shown improvement in terms of Hb have to be made and implemented within the limited time available in pregnancy. Given complexities and difficulties in interpreting the assay results for individual non-responders, it is preferable that even when assay results are available, they are considered along with the peripheral smear RBC morphology in deciding the management of the women and assessing the response to therapy.

Management of Anaemia in Primary Health Care Settings

Studies in the 1960s and 70s had shown that anaemia in pregnancy was mainly due to iron and folic acid deficiencies[4,7]. Research studies in India reported that iron-folic acid supplementation to pregnant women resulted in improvement in Hb levels[4,8]. India was the first developing country to initiate National Anaemia Prophylaxis Programme in 1972[9]. At that time, primary health care institutions were not established in India and antenatal care was accessed by less than 10% of pregnant women. The programme therefore aimed at identifying pregnant women and providing them with 90 tablets of iron (60mg) and folic acid (500µg) to bring about a reduction in prevalence and severity of anaemia in pregnancy. Evaluation of the national anaemia prophylaxis programme showed that coverage was low; compliance with supplementation was low because of the side effects associated with iron supplementation[39]. Studies undertaken by the Task Force of Indian Council of Medical Research reported that even women who had taken 90 tablets of IFA during pregnancy did not show any improvement in Hb levels[40]. Expert groups which reviewed the results felt that dosage of iron might be inadequate and increased iron dose from 60mg to 100mg/day[10].

By late 1980 India's primary health care system had been established and attempts were made to improve coverage and content of antenatal care. The National anaemia control programme aimed at screening pregnant women by Hb estimation and treating anaemia[10]. Non-anaemic women were to receive 1 tablet of 100mg of elemental iron and 500 µg of folic acid; anaemic women were to receive 2 tablets daily from second trimester of pregnancy and improvement in Hb was to be monitored[10]. Data from national surveys[23-25,41-46] indicate that:

- screening all pregnant women by Hb estimation for detection of anaemia and treating anaemic women was not being done in primary health settings;
- there had been substantial improvement coverage under antenatal care and IFA supplementation but compliance under the supplementation programme was low due to the side effects of iron tablets.
- Over the last two decades there has been some reduction in the severity and prevalence of anaemia in pregnancy but the pace of reduction in the prevalence of anaemia is tardy[3,11].

The Ministry of Health and Family Welafre (MoHFW) of Govt of India reviewed these data and the National Iron Plus Initiative (NIPI) reemphasised the need to operationalise the test and treat strategy[47].

Five years later MOHFW reviewed problems in the implementation of the NIPI programme. Factors responsible for the slow decline in anaemia include:

- inability to screen all pregnant women for anaemia by accurate Hb estimation to identify anaemic and non-anaemic pregnant women; and consequent inability to provide higher dosage of IFA to anaemic pregnant women;
- problems in ensuring a continuous and adequate supply of IFA;
- lack of uniformity in the dose of iron, micronutrient composition and dose in supplements provided in different states;
- low coverage under the programme especially in the remote rural and tribal areas; and
- low compliance with the IFA supplementation because of the troublesome minor gastrointestinal side effect.

Research studies showed that 60-120 mg of elemental iron in IFA supplementation is adequate to bring about improvement in anaemia in over two thirds of anaemic pregnant women[8,28]. Higher and divided doses of iron/day may not be associated with increase in absorption or utilisation of iron but might be associated with increase in side effects. Taking all these into consideration, the Intensified National Iron Plus initiative (I-NIPI)[48]:

- emphasised the importance of operationalising the 'test and treat' strategy in pregnant women using an accurate method for Hb estimation);
- reduced the dosage of iron to 60mg for anaemia prophylaxis and 120mg of elemental iron to be taken together after a meal for treatment of anaemia in pregnant women;

- emphasised need for increasing iron intake and Hb status of the entire population through dietary diversification and use of iron fortified food stuffs such as salt, and
- recommended IFA supplementation to vulnerable segments of the population.

The multi-pronged strategy envisaged in the I-NIPI is getting operationalised across the country and is expected to accelerate the reduction in prevalence of anaemia.

Management of Anaemia in Pregnancy in Tertiary Care Hospitals

In the 1960s and 70s obstetricians in tertiary care hospitals had documented that anaemia was one of the most important causes of maternal morbidity, mortality, low birthweight and perinatal mortality[4,5]. Indian obstetricians defined the Hb cut-off for mild, moderate and severe anaemia in pregnancy on the basis of the functional decompensation associated with anaemia and evolved appropriate regimens for management of different grades of anaemia in pregnancy[4,26].

Data from Indian studies showed that women with mild anaemia (Hb between 8-10.9g/dL) reported fatigue with habitual exercise, but went through pregnancy and labour without any adverse consequences, because they were well compensated[5]. Women with moderate anaemia (Hb between 5-7.9g/dL) had easy fatiguability, reduction in work capacity and difficulty in coping with household chores and child care and higher prevalence of morbidity due to common acute infections such as diarrhoea and respiratory infections. Pregnant women with moderate anaemia showed immune depression as assessed T and B cell count[49], but there was no alterations in the phyto-hemagglutinin induced lymphocyte transformation or humoral immunity. The changes in T and B cells and immunoglobulins were reversed within 6-12 week by parenteral iron therapy and improvement in haemoglobin levels, indicating that these alterations are due to anaemia per se and not due to co-existent under-nutrition[49]. Women with moderate anaemia had difficulty in coping with blood loss prior to or during labour. Substantial proportion of maternal deaths due to antepartum and post-partum haemorrhage, pregnancy induced hypertension and sepsis occurred in women with moderate anaemia. Moderate anaemia was associated with a doubling of low-birth-weight rate due to prematurity and intrauterine growth retardation and 2-to-3-fold increase in the perinatal mortality rates[5,6]. Women with Hb below 5.0g/dL were a very high-risk group. There was an 8 to 10-fold increase in maternal mortality rate when the Hb was below 5 g/dL. Studies carried out in the 1970s and 80s showed that, anaemia was directly or indirectly responsible for 40% of maternal deaths in India[5,6].

In view of the high prevalence anaemia and serious consequences of moderate and severe anaemia in pregnancy, screening for anaemia by Hb estimation was made a mandatory component of antenatal care and appropriate management of anaemia in pregnancy was accorded a very high priority in obstetric practice. In 1970s and 80s in majority of tertiary care settings accurate Hb estimation was done and anaemic and non-anaemic pregnant women were identified. Iron folic acid supplements (60mg elemental iron and 500µg of folic acid/day) were given to non-anaemic women to prevent fall in Hb in pregnancy. Women with mild anaemia (Hb between 8.0-10.9g/dl) were advised to have two tablets of IFA from second trimester till delivery. But regularity of women attending antenatal clinics and taking IFA supplementation was low and improvement in Hb levels was suboptimal[26]. Taking into account the higher risk of adverse maternal and foetal outcomes in women with Hb between 5.0 and 7.9 g/dl and the poor continuation and compliance with IFA supplementation, IM and intravenous (IV) iron therapy which ensured that the needed iron dose was delivered in a short time was preferred mode of treatment for women with moderate anaemia. Women with Hb below 5 g/dL were admitted and provided intensive care irrespective of their period of gestation. Management of severe anaemia detected late in pregnancy, through intensive care and blood transfusion became the hallmark of good obstetric practice in tertiary care hospitals and resulted in reduction in hospital maternal mortality.

In 1970s and 80s medical college hospitals had abundant case load of moderate anaemia. Indian obstetricians working in these hospitals conducted what were at that time the world's largest series of studies exploring feasibility, safety and efficacy of intramuscular iron dextran and iron sorbitol citric acid complex and intravenous iron therapy using iron dextran. Intravenous administration of iron to anaemic pregnant women was considered useful because it was possible to administer the total dose to the woman who had been admitted in the hospital, observe her for a day and then discharge her[50]. However, use of IV iron was discontinued, because of the rare anaphylactic reaction to IV iron preparations, which resulted in maternal death in spite, of intensive resuscitative efforts in medical college settings[26]. In the last three decades several newer iron compounds for IV use have been developed and used mainly in renal dialysis

patients with chronic anaemia. In India there had been small scale studies in pregnant women on use of these newer compounds as single or multiple IV injections[51]. Rare fatalities had been reported[52] and overtime there appears to be a decline in IV iron use in pregnant women. Over decades there has been a steep decline in pregnant women with severe anaemia in pregnancy getting admitted in urban hospitals and requiring heroic measures to ensure maternal survival.

Indian studies in the 1970s and 80s established the safety and efficacy of IM iron therapy[53-57]. Based on these experiences, obstetric text books[58,26] national policy[59] and programme guidelines[47] had recommended use of IM iron for the management of moderate anaemia in pregnancy. However, IM iron therapy was not widely used even in tertiary care centres and seldom used in secondary care institutions because of the troublesome side effects such as myalgia and arthralgia seen in about a third of the women receiving IM iron dextran injections. Studies in the last two decades have demonstrated the use of iron sorbitol citric acid injections was associated with lower side effects and IM iron therapy is feasible in urban primary health care institutions[20,35]. In the last decade there had been considerable reduction in number of women with Hb between 5-7.9 g/dL. It is possible that with effective implementation of INIPI, there will be substantial decline in moderate anaemia requiring IM iron therapy.

Improving Haemoglobin Status of Women Prior to Pregnancy

Two-thirds to three-fourths of pregnant women in India are anaemic and face adverse health consequences associated with it. Along with interventions to detect and treat anaemia in pregnancy, it is desirable to initiate interventions to reduce the prevalence of anaemia prior to pregnancy. In India, anaemia begins right from infancy; infants born to anaemic mothers have low iron stores; the low iron content in breast milk and complementary foods result in anaemia during infancy. Inadequate iron and folate intake results in an increase in the prevalence of anaemia in childhood. Prevalence and severity of anaemia increase during adolescence in girls due to menstrual blood loss. Increased requirements for iron and folic acid during pregnancy aggravate anaemia and postpartum blood loss perpetuates anaemia. The prevalence of anaemia is high not only among under-nourished persons but also in normal and over-nourished individuals[11]. To improve micronutrient intake and accelerate the pace of decline in anaemia, the Intensified National Iron Plus Initiative (I-NIPI) envisages the effective implementation of a three-pronged strategy: iron-folic acid supplementation to vulnerable groups; use of iron-fortified foodstuffs to improve iron intake of the population; and increase in consumption of micronutrient-rich vegetables[48].

IRON AND FOLIC ACID SUPPLEMENTATION

In countries where anaemia in all age groups is a major public health problem, WHO had recommended intermittent or continuous IFA supplementation to children, adolescents and women in reproductive age group[60-62]. The I-NIPI programme envisages that all children between 6 months 10 years, adolescents between 10-19 years, pregnant women (from the second trimester) lactating women (during first six months of lactation) and women in reproductive age should receive iron folic acid supplementation either as daily supplementation for three months every year or once a week supplementation throughout the year[48].

Research studies have shown that, in situations where prevalence of anaemia is high, daily iron folic acid supplementation in pre-school children, adolescents and women for three months or longer resulted in improvement in mean Hb (of about 0.5 to 1 g/dL) and ferritin levels[63-65]. Intermittent iron supplementation improves haemoglobin concentrations and reduces the risk of having anaemia or iron deficiency in children younger than 12 years of age, adolescent girls and women in reproductive age when compared with a placebo or no intervention. However, it is less effective than daily supplementation to prevent or control anaemia. There is inadequate data to assess the impact of continuous or intermittent supplementation on mortality, morbidity, developmental outcomes[64-65]. The WHO guidelines had recommended daily IFA supplementation for 3 months every year in settings where prevalence of anaemia is 40% or higher[61]. Not all anaemic persons become non-anaemic after three months of daily IFA supplementation; once supplementation is stopped some of those who did become non-anaemic may become anaemic again. Compliance with daily supplementation was more difficult to maintain on a long-term basis. Taking into consideration the operational difficulty in daily supervised administration of iron folic acid tablets to adolescent girls, the WHO guidelines had recommended weekly IFA supplementation[62]. However, such intermittent supplementation has to be continued throughout the year and year after year. Year round supervised weekly IFA supplementation may pose problems in many settings.

Available global and Indian experience show that except in pregnant women, coverage under IFA supplementation programmes was low and difficult to sustain. Compliance was poor because all these persons were asymptomatic, did not know whether they were anaemic or not and one-third or more of the persons receiving the supplements had troublesome minor gastro-intestinal side effects. The drug cost of IFA supplementation was low but cost of logistics of supply, administration of IFA and monitoring of the impact were labour intensive and therefore expensive. The focus of limited human resources for health on these massive supplementation programmes may come in the way of effective implementation of other urgently required interventions. Given these constraints in IFA supplementation, WHO suggests that food fortification may be an effective, inexpensive and sustainable method of improving iron intake, especially, among the poorer segments of the population[67].

FOOD FORTIFICATION

Low dietary intake of iron especially low vegetable intake and poor bio-availability of iron are major factors responsible for high prevalence of anaemia across all age and sex groups in India. The estimated average intake of iron is about 13-14 mg/day in non-pregnant women and about 14 mg/day in pregnant women[42]. The bio-availability of iron from habitual Indian diets has been estimated to be between 5-8%. The Indian estimated average requirement (EAR) for iron ranges from 11 mg/day in men to 30-32 mg/day in pregnant women (depending upon body weight and pregnancy weight gain)[66]. The high prevalence of anaemia across age groups is because the dietary intake of iron is inadequate to meet the requirements. Given the widespread iron deficiency in Indians, food fortification offers a ready, relatively inexpensive and sustainable method of increasing the iron intake without altering dietary habits.

India had invested in the development and evaluation of iron-fortified iodised salt (double fortified salt - DFS) for increasing iron intake of the population because:

- salt is used by all segments of the population;
- salt is relatively inexpensive and fortification cost is low;
- risk of excessive as well as low consumption of salt is small[68].

Surveys conducted by National Nutrition Monitoring Bureau and research studies had shown that the average consumption of salt was about 10 gm/day[42]. Formulations of DFS contain 1mg of iron in 1 gram of salt and use of DFS will bridge the gap between iron intake and iron requirement in the population. The National Institute of Nutrition, Hyderabad, India had developed the technology for DFS and reported that use of DFS was associated with improvement in Hb and ferritin[69].

Cochrane review of efficacy studies on impact of DFS concluded that there was a small but significant improvement in Hb and ferritin levels[70]. A recent research study in India showed that DFS use for 12 months resulted in improvement in mean Hb in children (0.8 gm/dl) women (0.4 gm/dl) and men (0.3 gm/dl). Improvement in Hb was higher in anaemic women, men and children[71]. There was no change in mean Hb in non-anaemic persons. There was a small improvement in ferritin in women who have low ferritin but no change in ferritin in women and men with normal ferritin. These data suggest that the absorption of iron is well modulated to cope with varying iron status in DFS users[71].

Food Safety and Standards Authority of India (FSSAI) has approved two technologies for manufacture of DFS[72]. In an attempt to increase dietary intake of iron, use of DFS has been made mandatory in hot cooked meals under the Mid-Day Meal (MDM) and Integrated Child Development Service (ICDS) programmes. Some states are currently providing DFS through the Public Distribution System (PDS) in selected districts. Centralised production and preexisting programmes for fortification of salt with iodine offer a very ready platform to launch iron-fortified iodised salt. With scaling up of production, distribution and sustained use, DFS can bring about improvement in iron intake and reduction in iron deficiency anaemia in India and enable the country to achieve the SDG target of 50% reduction in prevalence of anaemia in reproductive age by 2030[71].

Globally the technology for iron, folic acid and B12 fortification of wheat flour and rice fortification with iron and other micronutrients have been developed and used. A recent Cochrane review concluded that fortification of wheat flour with iron may reduce anaemia in the general population, but its effects on other outcomes are uncertain[73]. Another Cochrane review concluded that fortification of rice with iron alone or in combination with other micronutrients may make little or no difference in the risk of having anaemia or preventing iron deficiency; or improvement in Hb levels in the general population older than 2 years of age[74]. Cereal fortification is difficult to sustain in countries like India with diverse dietary habits among the population. Both rice and wheat flour are not

centrally processed; it is difficult to ensure quality of fortification in diverse settings. The cost of fortifying 250-300 grams of wheat flour or rice/person/day is far more as compared to the cost of fortifying 10 grams of salt/person/day.

It is now well documented that excess intake of iron can lead to iron overload and associated adverse health consequences. The gap between iron requirements for growing children and pregnant women and the tolerable upper limit (TUL) for iron is narrow. Concerns have been raised about the potential problem that iron consumed from multiple fortified food stuffs may cross the TUL especially if the consumers were not iron deficient.[75,76]. In India use of iron fortified iodised salt and iron fortified wheat flour or rice in hot cooked meal in ICDS and MDM programme has been initiated in selected districts in some states[77]. As the ICDS and MDM programmes provide only one-third of the nutrient requirement, there is no risk of iron overload in these food supplementation programmes. Currently, the availability and consumption of multiple food stuffs fortified with iron in general population is low. As and when the country moves towards universal access to DFS, concurrent steps will have to be taken to ensure that no other foodstuff fortified with iron is available, so that the potential adverse consequences of iron overload are avoided.

DIETARY DIVERSIFICATION

The estimated average intake of iron from Indian diets ranges from 10-15 mg per day[42]. This intake is not much lower than the iron intake in developed countries. But the bio-availability of iron from phytate and fibre-rich Indian diets is only 5-8%, whereas bio-availability of iron from animal food is about 40%. Dietary diversification, with increase in the consumption of vegetables, especially green leafy vegetables which are the richest source of iron and folate in a vegetarian diet, is an essential medium-term intervention for sustainable improvement in iron and folate intake. Increase in vegetable consumption will also reduce the risk of over-nutrition and non-communicable diseases. Interventions under the National Horticultural Mission have led to a substantial increase in vegetable production in India. But farmers face economic constraints because of high wastage and the cyclical glut in vegetables. Investments are urgently needed in grading, storage, processing and marketing of vegetables, which will make horticulture remunerative for the farmer. Consumers do not buy and consume larger quantities of vegetables because of the high cost. India has a tradition of sun drying vegetables when they are available in abundance and using them when they are scarce. Drying prevents glut and distress sale of vegetables, improves shelf life of the vegetables and availability of vegetables at affordable cost throughout the year to the consumer. Processing of green vegetables and making tasty dishes is a time-consuming task. Dried vegetables can cut the processing time and help in increasing vegetable consumption. Once these are achieved, nutrition education will ensure improvement in dietary diversification and increased intake of vegetables.

Prevalence of Anaemia in Pregnancy

India is a vast and varied country and the existing health management information system could not provide accurate, timely information on coverage under the anaemia control programme and its impact in different states over time. The country invested in periodic national surveys to provide the data on access to antenatal care, coverage under IFA supplementation and impact on prevalence of anaemia in pregnancy[23-25,41-46]. NFHS surveys used Hemocue for Hb estimation. All other surveys in India used cyanmethaemoglobin method for Hb estimation.

Data on prevalence of anaemia in a representative sample from all states was provided for the first time by NFHS 2 (1998-99). This survey reported a far lower prevalence of anaemia in pregnancy as compared to the earlier studies. The reduction in prevalence of anaemia was interpreted as being due to the successful implementation of the National Anaemia Control programme in the 1990s. Obstetricians felt that there had not been any substantial reduction in prevalence of anaemia in the 1990s. A survey done in the same villages covered by NFHS 2 in 7 states, using cyanmethaemoglobin method of Hb estimation showed that the prevalence of anaemia in pregnancy continued to be very high[78]. Subsequently several surveys[23-25,42] confirmed that the prevalence of anaemia was much higher than those reported by NFHS 2. Research studies comparing Hb estimation in the same samples, using Hemocue and cyanmethaemoglobin method, showed that Hemocue under-estimated Hb, and that there was no linear correlation between Hb values estimated by these two methods[79-81].

Analysis of data on prevalence of anaemia reported in NFHS 2-5 showed that there was no clear and consistent time trend in prevalence of anaemia[3]. The small rise in prevalence of anaemia in some surveys and overall lack of reduction in the prevalence of anaemia over two decades had been interpreted that the national anaemia control programme had been implemented poorly. Analysis of data from DLHS 2 and 4 and AHS conducted between 2002-2015 with substantially

larger sample of pregnant women than NFHS showed that there was a substantial reduction both in overall prevalence of anaemia and severity of anaemia across all districts and states[3]. The difference in the reported prevalence of anaemia in pregnant women between NFHS and other surveys is likely to be due to the difference in the method used for Hb estimation.

Demographic and Health Surveys were carried out in low- and middle-income countries to provide comparable data on major health and demographic parameters in these countries. Many of these countries did not have adequate skilled manpower or lab support to undertake Hb estimation by the gold standard method. Hemocue was a feasible option for Hb estimation because there was no need to accurately pipette 20µl of blood or access a lab and results were available immediately. These surveys aimed at the categorisation of the public health significance of anaemia in different countries on the basis of prevalence of anaemia: (severe ≥ 40%, moderate 20-39.9% and mild 5-19.9%). For this limited purpose Hemocue provided adequate information.

India had been using data from national surveys to assess the impact of the on-going anaemia control programme. It was therefore imperative to use accurate Hb estimation, so that relatively small changes in Hb over time could be identified. The country had the necessary laboratory infrastructure and trained skilled manpower to carry out large scale Hb surveys using accurate Hb estimation techniques. These surveys (NNMB, DLHS 2 and 4 and AHS) demonstrated that it was possible for India to undertake large scale national surveys on prevalence of anaemia using accurate affordable Hb estimation methods and demonstrate the changes in prevalence of anaemia over time in different segments of population, states and urban and rural areas[23-25,42]. Such data can be used for initiating state and district specific midcourse modifications in I NIPI. Currently a National Diet and Biomarker Survey is being initiated to document household food security, individual nutrient adequacy based on dietary intake data and nutritional status, Hb, macro- and micro-nutrient status as assessed by blood biomarkers in all age and sex groups in selected households. It is expected that this survey will provide insights to further refine ongoing interventions to improve nutrition and Hb status.

Conclusion

India had and continues to have the highest prevalence of anaemia in pregnancy in the world. There had been some reduction in the prevalence of anaemia especially severe and moderate anaemia and concurrent reduction in the adverse health consequences of anaemia in mother child dyad. These might be attributable more to improvement in the nutritional and health status of pregnant women and access to health care than interventions aimed at reducing anaemia in pregnancy. Currently, India's abundant human resources for health can effectively implement the anaemia control programme and the aware rational families can utilise available services. It will be possible to accelerate the pace of reduction in prevalence of anaemia in the next decade by:

- operationalising the 'test and treat' strategy using accurate method for Hb estimation at all levels of care and providing appropriate treatment;
- monitoring improvement in Hb and referring non-responders for investigation and management; and
- improving Hb status of all family members by increasing access to DFS and vegetables at affordable cost.

Conflict of interest: None

Funding Statements: None

Acknowledgements: The authors gratefully acknowledge Nutrition Foundation of India for permitting us to undertake this review.

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