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REVIEW ARTICLE

Iron Deficiency Anemia: Perspectives in Indian Pregnant Women

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ABSTRACT

Anemia is a major problem seen in most of the Indian pregnant women. Specially, Iron deficiency with anemia or without anemia has adverse effects on nervous system, physical response and pregnancy outcome (around 80%). These effects are exaggerated in pregnant women with iron deficiency anemia because of ability of fetus to extract its iron requirement even from iron deficient mothers. Maternal mortality was 7 % in anemic pregnant women as compared to controls (3%). Abnormally high hemoglobin concentrations usually indicate poor plasma volume expansion, which is also a risk for low birth weight. Iron supplements have been reported to increase hemoglobin, serum ferritin, mean cell volume, serum iron, and transferrin saturation. Iron status of the fetus and the infant, is quite independent of maternal iron status during pregnancy, except when infants are born to anemic women. Factors that affect IDA may be classified as Impaired RBC Production, Increased RBC Destruction, Blood Loss and Fluid Overload. Complete Blood Count, Total Iron Binding Capacity, Serum Ferritin, Serum Folic Acid, and Bone Marrow these methods are used for Hb estimation. Iron supplements can be given orally or parenterally. The common side effects are gastrointestinal in the form of heartburn, constipation, nausea and diarrhea. Overdose of iron leading to iron-poisoning as well as hypotension, tachypnoea, restlessness and cyanosis. If ingested in large dose, leads patient's death. Anemia during pregnancy affecting more and sometimes causes the death of the newly born child or the premature born or the growth restriction may occur.

Keywords: Anemia, hemoglobin content, bone marrow.

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INTRODUCTION

Anemia is blood related diseases, in which the oxygen carrying capacity is been reduced due to the destruction of the hemoglobin or the RBCs level from its normal range. Iron deficiency with anemia or without anemia has many adverse effects on nervous system, physical response and pregnancy outcome [1,2]. These effects are exaggerated in pregnant women with iron deficiency anemia because of ability of fetus to extract its iron requirement even from iron deficient mothers. The 50% of women in the child bearing age are anemic due to menstrual blood loss and inadequate intake or absorption [3,4]. During pregnancy, there is great demand for iron to meet of requirement for red blood cell mass expansion in mother, fetus and placental blood loss at delivery in addition to increased occult gastrointestinal blood loss [5,6].

Anemia happens when blood doesn't have enough hemoglobin. Hemoglobin helps red blood cells carry oxygen from your lungs to all parts of body. Iron deficiency anemia is the commonest medical disorder to occur in pregnant women affecting around 80% of the pregnant females, its incidence being particularly high in many developing countries where it remains a major contributing factor to maternal morbidity, mortality and also high perinatal mortality. The requirements of iron increase during pregnancy, as in the third trimester, a pregnant woman needs six times more iron than a non-pregnant woman. World Health Organization recommends a hemoglobin concentration value of a minimum 11.0 gm% during pregnancy [7-10].

Iron deficiency is an end result of a long period of negative iron balance, mainly due to poor dietary availability, rapid growth of the person, and blood loss.

The pathological stages are;
Pre-latent deficiency: Liver (Hepatocytes and macrophages), spleen and bone marrow show reduced iron stores (reduced-bone marrow iron and serum ferritin).

Latent deficiency: With very low or absent bone marrow iron stores there is progressive reduction in plasma iron; the bone marrow receives little iron for hemoglobin regeneration (bone marrow iron is absent, serum ferritin is <12ug/l, transferrin saturation is <16% and free erythrocyte porphyrin is increased); however, hemoglobin concentration remains normal.

Iron deficiency anemia: This is a very late stage of iron deficiency with progressive fall in hemoglobin levels and means corpuscular volume [5-7].

Causes of anemia
Iron deficiency anemia (IDA) is the most common type of anemia and it happens when the body doesn’t have enough iron. The need iron to make hemoglobin. This can happen when body loses blood from problems like heavy periods, ulcers, colon polyps, or colon cancer. A diet that

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doesn't have enough iron that can also cause IDA. Pregnancy can also cause IDA if there's not enough iron for the mother and fetus [8,9].

Risk factors

- Socio demographic factors (age, level of formal education, marital status, areas and cities of residence)
- Obstetrical factors (gravidity, parity, history of previous preterm or Small-for gestational- age deliveries, plurality of pregnancy multiple Or singleton)
- Behavioral factors (smoking or tobacco usage, alcohol usage, utilization of prenatal care services)
- Medical conditions (diabetes, renal or cardio-respiratory diseases, chronic hypertension AIP- anemia in pregnancy [5-7].

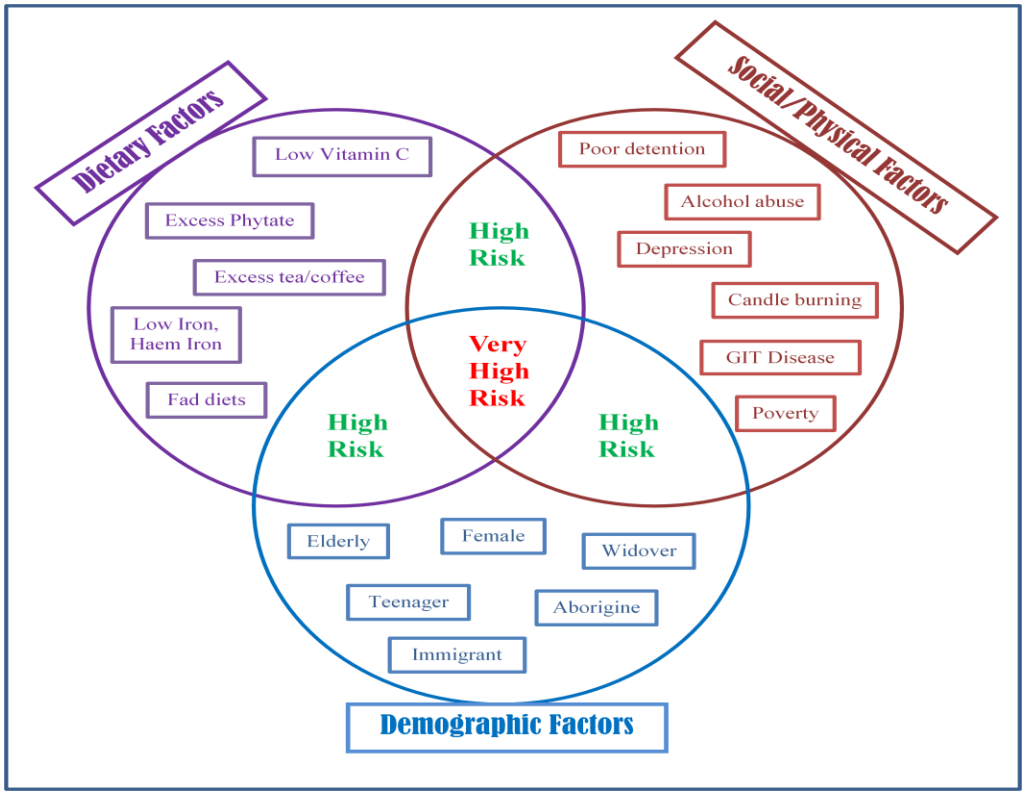

Fig 1. Risk factor causing Anemia

Signs and Symptoms of anemia [5-7]

Anemia takes some time to develop. In the beginning, the person may not have any signs or they may be mild. But as it gets worse, the person may have these symptoms:

- Fatigue
- Weakness
- Low body temperature

- Pale skin
- Rapid heartbeat
- Shortness of breath
- Chest pain
- Dizziness
- Irritability
- Numbness or coldness in your hands and feet
- Headache

Pregnancy outcome in anemia

In the case of moderate to severe anaemia, breathlessness, oedema, congestive heart failure and even cerebral anoxia have been observed. Pregnancy outcome in anemia, showed a higher incidence of premature labour and of preterm, low birth weight and stillbirth deliveries. Even the infants born alive had low Apgar scores, and the rate of neonatal deaths was higher. Maternal mortality was 7 % in anemic pregnant women as compared to controls (3%). Similar findings were reported in other Indian studies. Anemic mothers do not tolerate blood loss during childbirth; as little as 150 ml can be fatal. Normally, a healthy mother during childbirth may tolerate a blood loss of up to 1000 ml [11, 12].

Maternal anemia and birth weight

In several studies was observed between maternal hemoglobin concentrations and birth weight. Abnormally high hemoglobin concentrations usually indicate poor plasma volume expansion, which is also a risk for low birth weight. Lower birth weights in anemic women have been reported in several studies. Trials that included large numbers of iron-deficient women showed that iron supplementation improved birth weight [13-19].

Benefits of iron supplementation on maternal iron status

There is little doubt that iron supplementation improves maternal iron status. Even in industrialized countries, iron supplements have been reported to increase hemoglobin, serum ferritin, mean cell volume, serum iron, and transferrin saturation. These improvements are seen in late pregnancy, even in women who enter pregnancy with adequate iron status. Supplementation can reduce the extent of iron depletion in the third trimester. However, for women who enter pregnancy with low iron stores. Low compliance may affect some of this problem. The benefits of iron supplementation on maternal iron status during pregnancy become even more apparent postpartum. In addition, many women are anemic in the postpartum period because of blood loss during delivery especially in cesarean cases. Although a similar benefit could be obtained if women were supplemented during lactation, pregnancy is a time when iron absorption is particularly efficient to monitor the use of supplements. Insufficient attention has been paid to the extent to which anemia affects the mother's life,

including her level of fatigue and ability to cope with the stress of pregnancy and a young infant [20-27].

Benefits of maternal iron supplementation on iron status of the fetus and infant

It is generally assumed that the iron status of the fetus, and subsequently the infant, is quite independent of maternal iron status during pregnancy, except perhaps when infants are born to severely anemic women. Serum transferrin receptor concentrations were higher in infants born to anemic mothers. High prevalence of iron deficiency in infants after less than 6 months of age. There are more studies that assess the relation between the iron status of pregnant women and the iron status of their infants postpartum. Preterm delivery associated with iron deficiency could also contribute to lower fetal iron stores [28].

Factor affecting Iron deficiency in India

Factor affecting Iron deficiency anaemia may be classified as Impaired RBC Production; Increased RBC Destruction, Blood Loss and Fluid Overload. Indeed, the most common cause of anaemia is blood loss [29].

Impaired RBC production [30]

- Disturbance of proliferation and differentiation of stem cells.
    - Pure red cell aplasia
    - Aplastic anemia affecting all kinds of blood cells.
    - Anemia of renal failure, by insufficient erythropoietin production
    - Anemia of endocrine disorders
- Disturbance of proliferation and maturation of erythroblasts
    - Pernicious anemia is a form of megaloblastic anemia due to vitamin B_{12} deficiency dependent on impaired absorption of vitamin B_{12}.
    - Anemia of folic acid deficiency. As with vitamin B_{12}, it causes megaloblastic anemia.
    - Anemia of prematurity, by diminished erythropoietin response to declining hematocrit levels, combined with blood loss from laboratory testing. It generally occurs in premature infants at 2 to 6 weeks of age.
    - Iron deficiency, resulting in deficient heme synthesis.
    - Thalassemias, causing deficient globin synthesis.
    - Anemia of renal failure, also causing stem cell dysfunction.
- Other mechanisms of impaired RBC production
    - Myelophthisic anemia or Myelophthisis is a severe type of anemia resulting from the replacement of bone marrow by other materials, such as malignant tumors or granulomas.
    - Myelodysplastic syndrome
    - Anemia of chronic inflammation

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Increased RBC destruction [30-34]

Anemia of increased red blood cell destruction is generally classified as haemolytic anemia. These are generally featuring jaundice and elevated LDH levels.

✓ **Intrinsic abnormalities**

- Hereditary spherocytosis is a hereditary defect that results in defects in the RBC cell membrane, causing the erythrocytes to be sequestered and destroyed by the spleen.
- Hereditary elliptocytosis, another defect in membrane skeleton proteins.
- A betalipoproteinemia, causing defects in membrane lipids.

❖ ***Enzyme deficiencies***

- Pyruvate kinase and hexokinase deficiencies, causing defect glycolysis
- Glucose-6-phosphate dehydrogenase deficiency and glutathione synthetase deficiency, causing increased oxidative stress.

❖ ***Hemoglobinopathies***

- Sickle cell anemia
- Hemoglobinopathies causing unstable hemoglobins

❖ ***Paroxysmal nocturnal hemoglobinuria***

✓ **Extrinsic abnormalities**

- Antibody-mediated
- Cold agglutinin hemolytic anemia is primarily mediated by IgM. It can be idiopathic or result from an underlying condition.
- Rh disease, one of the causes of haemolytic disease of the newborn
- Transfusion reaction to blood transfusions
- Mechanical trauma to red cells
- Microangiopathic hemolytic anemias,
- Infections, including malaria
- Heart surgery

Blood loss [30]

- Anemia of prematurity from frequent blood sampling for laboratory testing, combined with insufficient RBC production.
- Trauma or surgery, causing acute blood loss.
- Gastrointestinal tract lesions, causing a rather chronic blood loss.
- Gynaecologic disturbances, also generally causing chronic blood loss.

Fluid overload [28]

Fluid overload causes decreased hemoglobin concentration and apparent anemia:

- General causes of hypervolemia include excessive sodium or fluid intake, sodium or water retention and fluid shift into the intravascular space.
- Anemia of pregnancy is anemia that is induced by blood volume expansion experienced in pregnancy.

Iron rich foods

Main sources of iron from foods like ground beef, clams, spinach, lentils, and baked potato with skin, sunflower seeds, and cashews. It also includes Pulses, cereals, jaggery, Beet root, Green leafy vegetables, meat, liver, egg, fish, legumes, dry beans, and iron reached white breads etc [5-9].

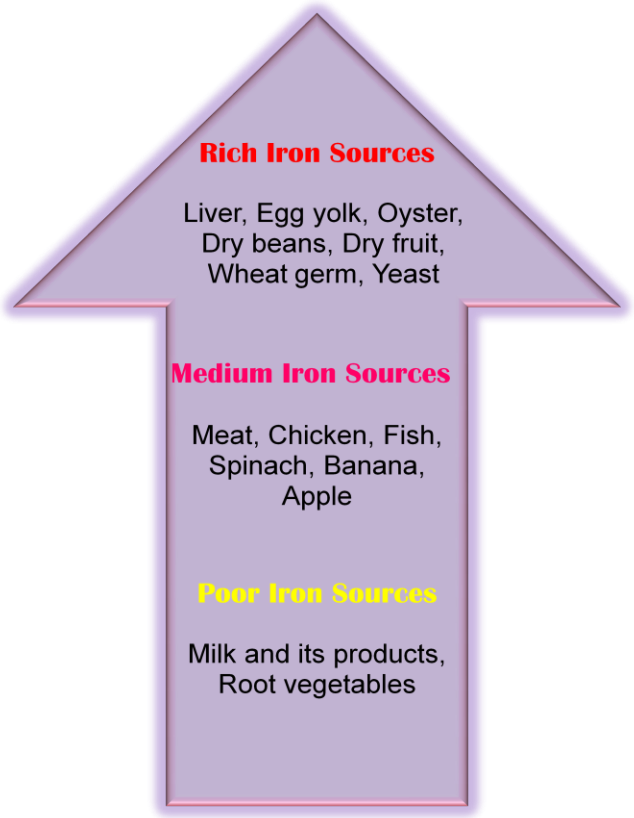

Fig 2. Nutritional food to improve iron status

Investigations

Hemoglobin estimation and study of peripheral smear is good indicator for diagnosis of anemia. There may be several methods for estimation of Hb. However in spite of limitation of present method of Hb estimation, it is a useful method of diagnosis for anemia. If the peripheral smear looks pale, there is hypochromia (large central vacuoles) and microcytosis (small deformed red cells). It suggests iron deficiency. Another test, Complete Blood Count is been done by the physician to check the anemia level; Other special laboratory investigations total iron binding capacity (TIBC), serum ferritin (SF), serum folic acid, bone marrow studies are

not available everywhere and expensive. Therefore they are not for routine use to diagnose pregnancy anemia [29-33].

Iron Supplementation

Iron can be given orally or parenterally.

Oral Iron therapy

Oral Iron is safe, inexpensive & effective way to administer iron. Oral route should be the route of choice in routine cases. Parentral route of iron therapy should only be considered when oral route is not possible due to any reason. If all pregnant women receive routine iron and folic acid, it is possible to prevent nutritional anemia in pregnant women. National nutritional anemia prophylaxis program advices 60 mg elemental iron and 500 µg of folic acid daily for 100 days to all pregnant women. However it is suggested that 120 mg of elemental iron and 1 mg folic acid are the optimum daily doses needed to prevent pregnancy anemia. The higher dose in Indian women is required as they start pregnancy with low or absent iron stores due to poor nutrition and frequent infection like hook worm and malaria [32-38, 43-50].

Parenteral iron therapy

Parenteral iron therapy is not more effective than oral. In addition, it is expensive and can be dangerous. It should never be prescribed routinely without one or more definite indications as enlisted below:

- Poor compliance to oral therapy in spite of repeated counseling
- Intolerance to oral iron
- Rapid blood loss which is difficult for oral iron to compensate
- Gastrointestinal disorders where oral iron may exacerbate the symptoms i.e. peptic ulcer, ulcerative colitis
- Mal-absorption syndromes
- Inability to maintain iron balance as seen in patients on haemodialysis
- Pregnant women with severe IDA, presenting late in pregnancy
- Patient donating large amount of blood for auto-transfusion programme

The defaulting rate with oral iron therapy in pregnant women is fairly high because of gastrointestinal side effects like nausea, vomiting, diarrhea and abdominal pain. Sometimes pregnant women present with severe anemia after 30-32 weeks of pregnancy and in those cases time is an important factor to improve hemoglobin status. In such situations Parenteral iron therapy is indicated. Parenteral iron can be given by intramuscular or intravenous route. Iron- sorbitol -citric acid complex 1.5ml is used for intramuscular route only. On the other hand iron-dextran can be used both by intramuscular and intravenous route. The main drawback of

intramuscular iron is the pain and staining of the skin at injection site, myalgia, arthralgia and injection abscess.

Intravenous route should be reserved for those who do not wish to have frequent intramuscular injections. Utmost caution is needed for total dose iron therapy via intravenous route because of severe anaphylactic reaction that may occur [32-38].

Management

A pregnant woman requires about 2 to 4.8 mg iron every day. To have it from the dietary sources, she must consume 20-48 mg of dietary iron. This is practically impossible in India because of average vegetarian diet does not contain more than 10-15 mg of iron and the phytate content in it further reduces iron absorption. Moreover majority of Indian women enter pregnancy already with iron depleted condition. The iron store is markedly diminished when there is fall in Hb values. Therefore in India there is a need for routine iron supplementation to all pregnant women [37-39].

Types of Iron Salts [39]

Various types of iron salts available are shown in Table-1. Of these ferrous salts are preferred as they are better absorbed than ferric forms. Ferrous sulfate is the best as it is also cost-effective.

Table-1 Percentage of Elemental Iron in various Iron Salts available in India

Iron Salts	Percentage of elemental iron
Ferrous sulphate. Anhydrous	37
Ferrous sulphate	20
Ferrous Fumarate	33
Ferrous gluconate	12
Ferrous fructose	25
Ferrous succinate	23
Ferrous lactate	19
Ferrous carbonate	16
Ferrous glycine citrate	23
Iron choline	12
Ferric sulphate	27
Ferric ammonium citrate	18
Colloidal iron	50

Side Effects

Most patients are able to tolerate oral iron therapy without much side effects, but 10-20% may develop symptoms attributable to oral iron. The most common side effects are gastrointestinal in the form of pyrosis (heartburn), constipation and diarrhea. Some patients do develop heartburn, nausea and abdominal cramps. A metallic taste may be experienced. Most

of the side effects are dose related. In a controlled study, iron was given in lower dosage 105mg/day. Incidence of side effects was similar in both placebo and a group which received iron. The patient who is unable to tolerate the full therapeutic dose should be tried with smaller dose to start with and gradually full dose can be reached.

In many instances, both severity and frequency of side effects are exaggerated. All ferrous salts had similar incidence of side effects. No significant differences were noticed amongst the three iron salts. Incidence of side effects was 13% in subjects taking placebo while 25% in those taking iron. Thus approximately 12% had symptoms ascribed to iron [40-41].

Overdose of iron

Overdose of iron leading to iron-poisoning usually results after accidental ingestion of iron preparations intended for adult use by infants and small children. The earliest manifestations are vomiting, often associated with hematemesis. This is followed by hypotension, tachypnoea, restlessness and cyanosis. If amount ingested is large, within few hours patient goes into coma followed by death. Usually, if medical aid is sought early and proper treatment is offered, most children survive [41].

The initial treatment is prompt evacuation of the stomach either by inducing emesis or gastric lavage. Gastric lavage should be done with sodium bicarbonate solution and at the end of lavage, 5 to 10 gm of Desferrioxamine solution with approximately 60 ml of sodium bicarbonate should be left in the stomach. Increased serum iron level does require intramuscular administration of Desferrioxamine in doses of 0.5 to 1 gm. The children, who survive initial 3-4 days usually recover without much sequelae. Gastric stricture, fibrosis and intestinal stenosis are rare late effects [41].

CONCLUSION

On the basis of this review, we can say that in India, anemia occurred more during pregnancy and affecting more Indian pregnant women. It may sometimes cause death of newly born child, the premature born or the growth restriction may occur. Leaving style of the public in India is not that much good, which can also affect to the public to, cause anemia. They can't get proper diet, because of the poverty is more in India as compare with other country, near about 40% or more than that public leaving under the poverty line. Patient's non-compliance is more in India and may lead to the anemia and affect the health of the patients as well as fetus also. Mostly oral therapy is choice of treatment, when the oral treatment goes fail or in emergency, the parentaral therapy is recommended. Parentaral iron therapy is used sparingly but having more effective.Limitation of this parentaral therapy is, experience persons required with adequate facilities. Time management is necessary for effectiveness of treatment and to avoid side effects. So the government of India tried to improve the status of the leaving style, providing medications and the nutritional food at free of cost or very low cost to the patients with anaemia.

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REFERENCES

[1] Fairbanks VF, Beutler E. Iron deficiency, In; Beultlere E, Lichtman MA. Coller BS. Kipps TJ, eds Williams Hematology. 5th edn. New York; Mc Graw-Hill Inc 1995; 490-511.

[2] Lieberman E. Ryan KJ. Monson RR. Schoenbaum SC. Am J Obstet Gynaecol 1998; 159: 107-114.

[3] DeMaeyer E, Adiels-Tegman M. World Health Stat Q 1985; 38; 302- 316.

[4] Hallberg L. Hogdalh AM. Nilsson L. Rybo G. Acta Obstet Gynaecol Scand 1966; 45: 320-351.

[5] Pitkin RM. Nutritional influences during pregnancy. In; Tyson JE ed. Medical Clinics of North America. Philadelphia; WB Saunders 1977; 61: 3-15.

[6] Romslo L. Haram K Sagen N. Augeennnsenn K. Br j Obstet Gynaecol 1983; 90: 101-107.

[7] Mehta BC. Iron deficiency anemia. In, G.S Sainani (ed). API textbook of medicine 6th ed. Mumbai: Association of Physicians of India, 1999;859.

[8] Whitfield CR. Blood disorders in pregnancy. In, Whitfield CR (ed). Dewhurst's textbook of obstetrics and gynecology for postgraduates. 5th ed. Carlton, Australia: Blackwell Science, 1995;228-9.

[9] India. National Child Survival and Safe Motherhood Programme. Programme interventions. Safe Motherhood newborn care. New Delhi: Ministry of Health and Family Welfare, MCH Division, 1994.

[10] Nutritional anemias. Report of a World Health Organization Group of Experts (Technical Report Series No. 503). Geneva: WHO, 1972.

[11] Agarwal KN . The effects of maternal iron deficiency on placenta and foetus. In advances in international maternal child health. Vol 4 Editors Jelliffe D B & Jelliffe F E P Clarendon ress pp 26-35, Oxford 1984.

[12] Kapur D, Agarwal KN, Agarwal DK. Indian J Pediatr 2002; 69: 607-616.

[13] Steer PJ. Am J Clin Nutr 2000; 71(suppl): 1285S–7S

[14] Murphy JF, O'Riordan J, Newcombe RJ, Coles EC, Pearson JF. Lancet 1986; 1: 992–5.

[15] Garn SM, Ridella SA, Tetzold AS, Falkner F. Semin Perinatol 1981; 5: 155–62.

[16] Hemminki E, Rimpela U. Arch Dis Child 1991; 66: 422–5.

[17] Agarwal KN, Agarwal DK, Mishra KP. Indian J Med Res 1991; 94: 277–80.

[18] Singla PN, Tyagi M, Kumar A, Dash D, Shankar R. J Trop Pediatr 1997; 43: 89–92.

[19] Hemminki E, Starfield B. Br J Obstet Gynaecol 1978;85:404–10.

[20] Puolakka J, Janne O, Pakarinen A, Vihko R. Acta Obstet Gynecol Scand 1980; 95(suppl): 43–51.

[21] Dawson EB, McGanity WJ. J Reprod Med 1987; 32: 478–87.

[22] Svanberg B, Arvidsson B, Norrby A, Rybo G, Solvell L. Absorption of supplemental iron during pregnancy—a longitudinal study with repeated bone-marrow studies and absorption measurements. Acta Obstet Gynecol Scand Suppl 1976;48:87–108.

[23] Milman N, Agger AO, Nielsen OJ. Dan Med Bull 1991; 38: 471–6.

[24] Simmons WK, Cook JD, Bingham KC, et al. Am J Clin Nutr 1993; 58: 622–6.

[25] De Benaze C, Galan P, Wainer R, Hercberg S. Rev Epidémiol Santé Publique 1989; 37: 109–18 (in French).

[26] Taylor DJ, Lind T. Br J Obstet Gynaecol 1979; 86: 364–70.
[27] Fleming AF, Ghatoura GBS, Harrison KA, Briggs ND, Dunn DT. Ann Trop Med Parasitol 1986; 80: 211–33.
[28] Institute of Medicine, Food and Nutrition Board. Iron deficiency anemia: guidelines for prevention, detection and management among U.S. children and women of childbearing age. Washington, DC: National Academy Press, 1993.
[29] Bainton DF, Finch CA. Am J Med 1964; 37: 62-65.
[30] Viswanath D, Hegde R, Murthy V, Nagashree S, Shah R. Ind J Pediatr 2001; 68; 1117-9.
[31] International Committee for Standardization in Haematology. Recommendations for the measurement of serum iron in human blood. Br J Haematol 1978;38:291-97.
[32] International Committee for Standardization in Haematology. The measurement of total and unsaturated iron-binding capacity in serum. Br J Haematol 1978;38:281-90.
[33] Bainton DE, Finch CA. Am J Med 1964; 37: 62-69.
[34] Finch CA. West J Med 1986; 145: 657-66.
[35] Zanella A. J Lab Clin Med 1989; 113:73-80.
[36] Skikne BS, Flowers CH, Cook JD. Blood 1990; 75: 1870-1876.
[37] Gaillard T, Fontan E, Civadier C, Emile L. Ann Biol Cin 2001; 59: 632-635.
[38] Rimon E, Levy S, Sapir A, et al. Diagnosis of iron deficiency anaemia in the elderly by transferrin receptor – ferritin index. Arch Intern Med 2002; 162:445-49.
[39] Punnonen K, Irjala K, Rajamaki A. Blood 1997;89: 1052‑7.
[40] Cook JD. Baillieres Clin Haematol 1994; 7: 787‑98.
[41] Kerr DNS, Davidson S. Lancet 1958; 2: 489-95.