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Iron Deficiency Anemia

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Abstract: **Anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. It is defined as a decrease in the level of hemoglobin in the blood below the reference level for the age and sex of individual. There are many types, but globally, the most significant contributor to the onset of anaemia is iron deficiency. Children, pregnant and non-pregnant women are the most susceptible groups for Iron deficiency anemia. Although iron deficiency may be due to physiological demands in growing children, adolescents and pregnant women, the underlying cause(s) should be sought. .There is a great variation in the clinical picture of the disease and its consequences. IDA may be effectively diagnosed in most cases by full blood examination and serum ferritin level. Serum iron levels should not be used to diagnose iron deficiency. This paper aims to identify the prevalence of IDA in KSA and comparing this with other countries , to study the IDA by means of descriptive epidemiology , to identify the possible risk factors and causes , To give an account of the methods of prevention of this problem , To identify the steps by which the main strategies improved food consumption and dietary practices, food fortification, supplementation, and public health measures,To identify appropriate indicators for monitoring programme implementation, To identify high-priority, action-oriented, and operational research needed to enable and accelerate effective programme implementation.**

Keywords: **Anemia, global public health problem, IDA, Children, pregnant women, public health.**

1. INTRODUCTION

Anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. It occurs at all stages of the life cycle, but is more prevalent in pregnant women and young children [1]. It is defined as a decrease in the level of hemoglobin in the blood below the reference level for the age and sex of individual [Table1]. Alternation in the level of Hemoglobin (Hb) may occur as an absolute change or relative as a result of change in the plasma volume. A reduction in the plasma volume will lead to a spuriously high Hb – this is seen in dehydration and in the clinical condition of apparent polycythaemia. A raised plasma volume produces a spurious anemia, even when combined with a small increase in red cell volume as occurs in pregnancy [2].

Table 1: WHO's Hemoglobin thresholds used to define anemia

Age or gender group	Hb threshold (g/dl)
Children 0.5 – 5.0 years	11.0
Children 5 - 12 years	11.5
Teens 12 - 15 years	12.0
non pregnant Women >15 years	12.0
Women (pregnant)	11.0
Men > 15 years	13.0

Anemia is a sign of illness rather than to be a disease itself. The incidental finding of a low hematocrit or hemoglobin level suggests an underlying condition that range from trivial to life –threatening. Anemia is classified according to the main corpuscular volume of the RBCs into, microcytic hypocromic, macrocytic hypocromic and normocytic normocromic. This classification simplify approaching the underlying pathology for the physician. The microcytic hypocromic types for example may arises as a result of iron deficiency anemia (IDA) - the most common , thalassemia , lead poisoning , sidroblastic anemia and sometimes chronic diseases[2].

Globally, anaemia affects 1.62 billion people (95% CI: 1.50–1.74 billion), which corresponds to 24.8% of the population (95% CI: 22.9–26.7%). The highest prevalence is in preschool-age children (47.4%, 95% CI: 45.7–49.1), and the lowest prevalence is in men (12.7%, 95% CI: 8.6–16.9%) . However, the population group with the greatest number of individuals affected is non-pregnant women (468.4 million, 95% CI: 446.2–490.6) [3] [Table 2] .

WHO regional estimates generated for preschool-age children and pregnant and non-pregnant women indicate that the highest proportion of individuals affected are in Africa (47.5–67.6%), while the greatest number affected are in South-East Asia where 315 million (95% CI: 291–340) individuals in these three population groups are affected [4] [Table 3].

Table 2: Global anaemia prevalence and number of individuals affected

Population group	Prevalence of anaemia		Population affected	
	%	95% CI	Number (millions)	95% CI
Preschool-age children	47.4	45.7-49.1	293	283-303
School-age children	25.4	19.9-30.9	305	238-371
Pregnant women	41.8	39.9-43.8	56	54-59
Non-pregnant women	30.2	28.7-31.6	468	446-491
Men	12.7	8.6-16.9	260	175-345
Elderly	23.9	18.3-29.4	164	126-202
Total population	**24.8**	**22.9-26.7**	**1620**	**1500-1740**

2. CLASSIFICATION OF ANAEMIA AS A PROBLEM OF PUBLIC HEALTH SIGNIFICANCE

The prevalence of Hb values below the population-specific Hb threshold was used to classify countries by the level of the public health problem. The prevalence of anaemia as a public health problem is categorized as follows: <5%, no public health problem; 5-19.9%, mild public health problem; 20-39.9%, moderate public health problem; ≥40%, severe public health problem [5] [Table 4] .

The Number of countries categorized by public health significance of anaemia is shown in Table 4.

Figures 1,2,3 showing Anaemia as a public health problem by country.

Table 3: Anaemia prevalence and number of individuals affected in preschool-age children, pregnant women, and non-pregnant women in each WHO region

WHO region	Preschool-age children		Pregnant women		Non-pregnant women	
	Prevalence (%)	**# affected (millions)**	**Prevalence (%)**	**# affected (millions)**	**Prevalence (%)**	**# affected (millions)**
Africa	67.6 (64.3-71.0)[b]	83.5 (79.4-87.6)	57.1 (52.8-61.3)	17.2 (15.9-18.5)	47.5 **(43.4-51.6)**	69.9 (63.9-75.9)
Americas	29.3 (26.8-31.9)	23.1 (21.1-25.1)	24.1 (17.3-30.8)	3.9 (2.8-5.0)	17.8 (12.9-22.7)	39 (28.3-49.7)
South-East Asia	65.5 (61.0-70.0)	115.3 (107.3-123.2)	48.2 (43.9-52.5)	18.1 (16.4-19.7)	45.7 (41.9-49.4)	182 (166.9-197.1)
Europe	21.7 (15.4-28.0)	11.1 (7.9-14.4)	25.1 (18.6-31.6)	2.6 (2.0-3.3)	19 (14.7-23.3)	40.8 (31.5-50.1)
Eastern Mediterranean	46.7 (42.2-51.2)	0.8 (0.4-1.1)	44.2 (38.2-50.3)	7.1 (6.1-8.0)	32.4 (29.2-35.6)	39.8 (35.8-43.8)
Western Pacific	23.1 (21.9-24.4)	27.4 (25.9-28.9)	30.7 (28.8-32.7)	7.6 (7.1-8.1)	21.5 (20.8-22.2)	97 (94.0-100.0)
Global	47.4 (45.7-49.1)	293.1 (282.8-303.5)	41.8 (39.9-43.8)	56.4 (53.8-59.1)	30.2 (28.7-31.6)	468.4 (446.2-490.6)

Table 4: Global anaemia prevalence and number of individuals affected

Prevalence of anaemia (%)	Category of public health significance
≤4.9	No public health problem
5.0–19.9	Mild public health problem
20.0–39.9	Moderate public health problem
≥40.0	Severe public health problem

Table 5: Number of countries categorized by public health significance of anaemia

Public health problem[a]	Preschool-age children[b]	Pregnant women	Non-pregnant women
	Number of countries	Number of countries	Number of countries
None	2	0	1
Mild	40	33	59
Moderate	81	91	78
Severe	69	68	54

Anaemia is the result of a wide variety of causes that can be isolated, but more often coexist. Globally, the most significant contributor to the onset of anaemia is iron deficiency so that IDA and anaemia are often used synonymously, and the prevalence of anaemia has often been used as a proxy for IDA. It is generally assumed that 50% of the cases of anaemia are due to iron deficiency, but the proportion may vary among population groups and in different areas according to the local conditions [6].

In 2002, iron deficiency anaemia (IDA) was considered to be among the most important contributing factors to the global burden of disease [7] .

In the kingdom of Saudi Arabia, Iron deficiency is the most prevalent nutritional problem and the most common cause of anemia especially among female [1]. A study (by Fatin Al-Sayes et al , 2010) was designed to determine the prevalence of iron deficiency and iron deficiency anemia among apparently healthy Saudi young female university students studying at King Abdulaziz University in Jeddah province . The prevalence was found to be 24 %, 26 % for iron deficiency and IDA respectively [1]. (Dr Saad Elzahrani: 2012) found the prevalence 22.6% among pregnant women who attending the antenatal clinics at Al-Hada Hospital , irrespective of the trimester of the pregnancy . This is in contrast to Mahfouz AA in which his found the prevalence increases to 31 % [8] .

Children are the second target population for risk of developing IDA. Several studies in the Kingdom of Saudi Arabia indicated a high prevalence of anaemia among schoolchildren in different regions ranging between 26 and 41.3%. (El Hazmi & Sebai, 1981; El Hazmi, 1982; Hammouda et al., 1988; Rasheed et al., 1989; National Nutrition Survey, unpublished data, 1994; El Hazmi & Warsi, 1998) [9] . A recent study by Mamdooh Gari, 2008 found the prevalence of iron deficiency 25.2 % comparing to and iron defiency anemia 10.6 % [10] .

However, the literature is deficient in studies directed toward Saudi male. Abdullah H.Al-Assaf, 2007 study was the first one to evaluate the IDA among adult male and results illustrates that the iron intake was adequate and anemia was not found among adult males [11]. His result was not in agreement with result of alhamdan: 2004 who found 38 % of adult male living in Riyadh nursing home anemic based on their hemoglobin concentration values. Reason for this difference is the difference in sampling. Al-Assaf study recruited healthy adult males by volunteer whereas Alhamdan study recruited males from nursing homes. Subjects living in nursing homes are more likely to be undernourished compared to subjects living in ordinary homes [11] .

In short, Iron deficiency is the most prevalent nutritional problem in many parts of the world and the most common cause of anemia in Saudi Arabia especially among pregnant and non pregnant female and young children. The adult male are spared. Till now no studies in KSA to evaluate the disease in infancy period, elderly for both male and female

(post-menopausal female) . There are many recommendations by the previous studies will be mentioned later hoping for eradication of the disease because of is major burden.

3. METHODOLOGY

This essay paper is done as an assignment for community medicine department in Taibah University in 2012 trying to make a quick review of literature about iron deficiency anemia in KSA and to compare this with other developed countries. As the disease is one of the preventable disease with minimal resources, this essay aiming to clarify the burden of the problem to be handled efficiently.

The specific objects of the paper are to identify the prevalent of IDA in KSA, to study the IDA by means of descriptive epidemiology, to identify the possible risk factors and causes, To give an account of the methods of prevention of this problem, To identify the steps by which the main strategies improved food consumption and dietary practices, food fortification, supplementation, and public health measures - could be more effectively implemented at each level. To

identify appropriate indicators for monitoring programme implementation. To identify high-priority, action-oriented, and operational research needed to enable and accelerate effective programme implementation.

As a background for writing this review, an online search was performed to find relevant articles and reports. The heading terms" anemia " " Iron deficiency anemia " " IDA in KSA " " prevalence of IDA among Saudis" " new guidelines for management of IDA" .

Furthermore, a variety of websites were reviewed, including international organizations such as World Health Organization (WHO), Centers for Disease Control (CDC).

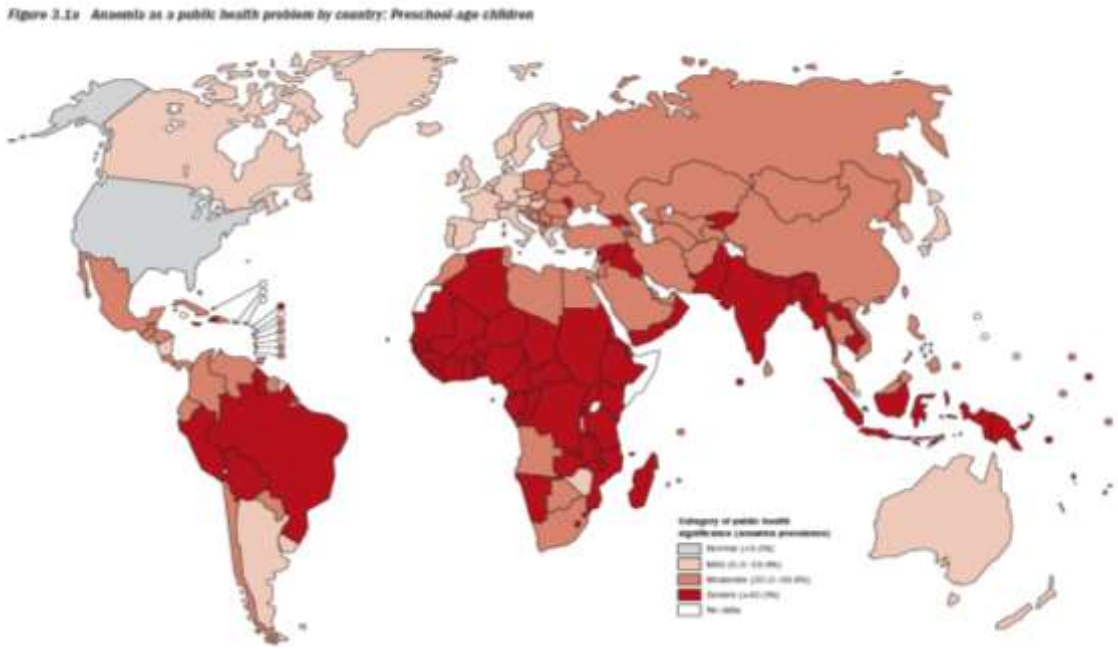

Figure 1 : anemia as public health by country – Pre-school age children

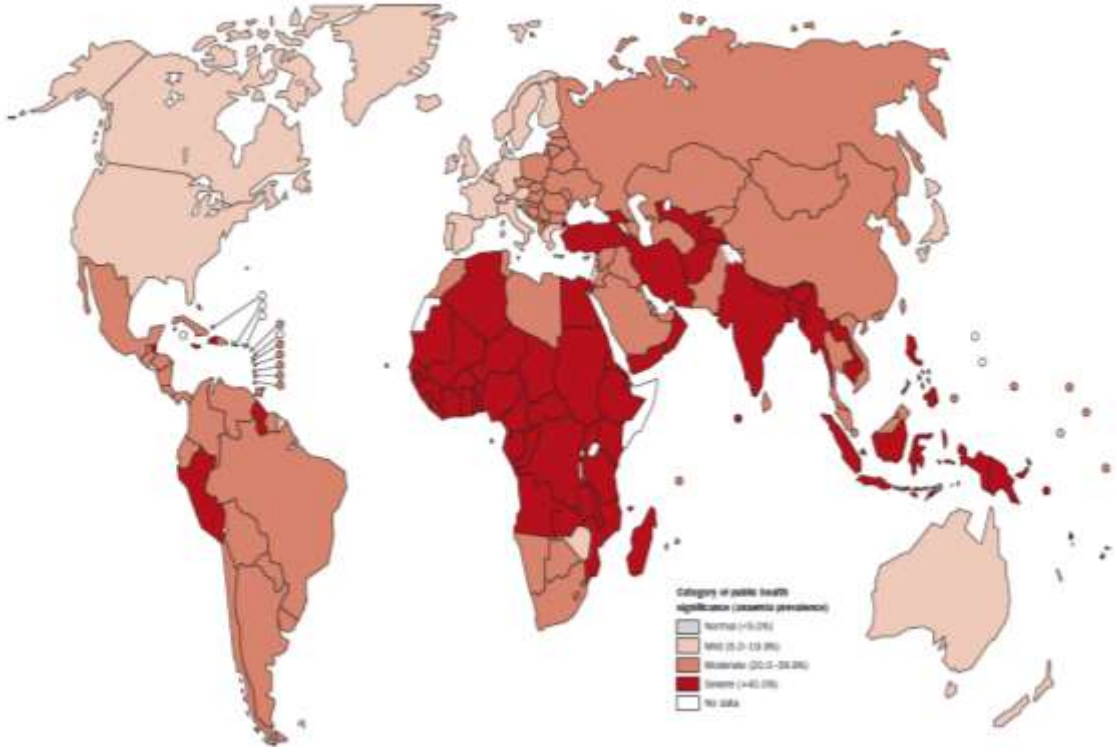

Figure 2 : anemia as public health by country – Pregnant women

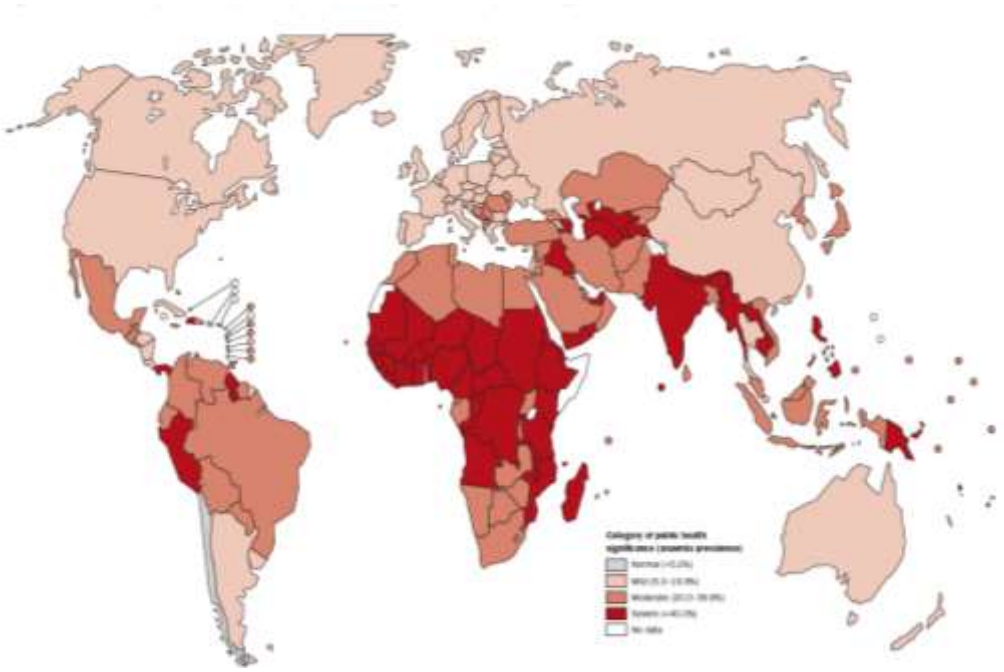

Figure 3: anemia as public health by country – Non-pregnant women of reproductive age Magnitude of IDA Worldwide

Iron deficiency is the most common and widespread nutritional disorder in the world. As well as affecting a large number of children and women in non-industrialized countries, it is the only nutrient deficiency which is also significantly prevalent in virtually all industrialized nations. There are no current global figures for iron deficiency, but using anaemia as an indirect indicator it can be estimated that most preschool children and pregnant women in non-industrialized countries, and at least 30-40% in industrialized countries, are iron deficient [7] .

Nearly half of the pregnant women in the world are estimated to be anaemic: 52% in non-industrialized - as compared with 23% in industrialized - countries. In industrialized countries, however, most pregnant women are thought to suffer from some degree of iron deficiency [7] .

Anaemia is particularly prominent in south Asia. In India, for example, up to 88% of pregnant and 74% of non-pregnant women are affected. Throughout Africa, about 50% of pregnant and 40% of non-pregnant women are anaemic. West Africa is the most affected, and southern Africa the least. In Latin America and the Caribbean, prevalences of anaemia in pregnant and non-pregnant women are about 40% and 30% respectively. The highest levels are in the Caribbean, reaching 60% in pregnant women on some islands [7] .

Prevalence data for various age groups are not available for all countries. However, the prevalence rate among preschool children is usually similar to, or higher than, the rate among pregnant women. Epidemiological mapping of prevalence requires cut-off levels, or criteria for grading the public health severity of anaemia [7] .

In most industrialized countries, the prevalence of anaemia among pregnant women is around 20%. It is therefore considered reasonable to classify these populations as having a medium prevalence, since a prevalence of up to 5% may not necessarily be regarded as abnormal in any population [7] .

Epidemiology [7]

The prevalence of iron deficiency varies greatly according to host factors: age, gender, physiological, pathological, environmental, and socioeconomic conditions.

4. HOST FACTORS

1- Age:

Full-term infants are normally born with adequate iron stores in the liver and haematopoietic tissue, because of destruction of fetal red blood cells soon after birth. This leads to deposition of iron in these tissues, especially if the cord is ligated after it stops pulsating. Breast milk is relatively low in iron, although the iron in breast milk is much better absorbed than that in cows' milk. Iron deficiency commonly develops after six months of age if complementary foods do not provide sufficient absorbable iron, even for exclusively breastfed infants.

Iron requirements on a body weight basis are proportional to growth velocity. Accordingly, in addition to women in their reproductive years as a result of physiological losses, iron deficiency is most common in the preschool years and during puberty. Another peak may occur in old age, when diets frequently deteriorate in quality and quantity and increase the prevalence of pathologies like neoplasms .

2- Gender:

Anemia is considered one of the most common disorder in female especially pregnant ones. the prevalence is much more common than male . Following menarche, adolescent females often do not consume sufficient iron to offset menstrual losses. As a result, a peak in the prevalence of iron deficiency frequently occurs among females during adolescence.

3- Nutrional status:

Many studies found nutritional problem and imbalanced diet was the major risk factor in KSA. Infants who feed cow`s milk considered susceptible hosts for developing IDA because the iron contents in cow`s milk is low. Iron-fortified formulas and breast milk are the best sources of iron for infants.

Abdulaziz Al-Othaimeen et al found iron deficiency anaemia is highly prevalent among the primary school girls in Riyadh City, which affect most seriously the growth of the 7- and 14-year-old girls and Food consumption pattern might be the most important factor for causation of anaemia in which the dietary questionnaire revealed that 16.5% of the girls did not take breakfast at home and depend on snacks offered in the school canteen which consist mostly of biscuits, chocolate bars, potato chips and carbonated cola drinks. IDA which originates as a result of underlying pathology e.g diabetes mellitus , hematological disorders like sickles , etc is considered to be very low .

4- Socioeconomic status:

Abdulaziz Al-Othaimeen et al studied the magnitude of IDA in relation to Socioeconomic status and Illiteracy was found to be high among the parents of these children as 49.4 and 24% respectively of the mothers and fathers were illiterate. Most of the fathers are Government employees (69.1%) while 20.1% are self-employed and the rest are labourers. However, only 12.5% of the mothers are employed. The monthly earnings of the families range between 3 000 and 10 000 Saudi Riyals (3.75 SR = 1 US$) and these families are considered middle class.

5- Pregnancy and lactation:

The prevalence is higher in pregnant female than in non pregnant ones .Substantial amounts of iron are deposited in the placenta and fetus during pregnancy. This results in an increased need of about 700-850 mg in body iron over the whole pregnancy. Overall, iron absorption is increased during pregnancy, when menstruations stop. Pregnant women still do not absorb sufficient additional iron, however, and the risk of iron deficiency increases.

Lactation results in loss of iron via breast milk. Consequently, for some women a deficiency developed during pregnancy may be perpetuated during lactation. In terms of iron balance, however, lactational amenorrhea more than compensates for iron lost through breast milk. Dr. Saad. S. Elzahrani and Joharah M. Al-Quaiz tried to find the relationship between epidemiological variables and anemia in pregnancy.

Dr. Saad. S. Elzahrani found the age of the mother (increase prevalence as the mother increases in the age), gestational age (the prevalence is high in the 3rd trimester), Gravida ,family size(more than 5 members) , prophylactic use of iron and folic acid supplementation are statistically significant. Other variables (educational level , interpregnancy spacing , income ,occupation , eating habits) were not found to have significant statistical association with anemia.

This is not in agreement with Joharah M. Al-Quaiz study in which there is no statistical significant association regarding multiparity , and iron supplement during the pregnancy , and a clear statistical significant association regarding the dietary habits where those who don't eat red meat and vegetables frequently are at risk .Moreover , Joharah M. Al-Quaiz studied variables of gynecologicl history in relation to anemia and found more than 8 days duration of the period, presence of clots during the period and flooding of the period all are considered as statistically significant . Other variables like freguency of the period , using of contraceptive and use of intra- utrine contraceptive device don't appear to be significant .

6- Health status:

Common infections, especially those which are chronic and recurrent, may impair haematopoiesis and consequently cause anaemia. Malaria by haemolysis and some parasitic infections, e.g. hookworm, trichuriasis, amoebiasis, and schistosomiasis (both vesical and intestinal forms), cause blood loss directly. This blood loss contributes to iron deficiency.

Other important causes of anaemia include genetic factors, e.g thalassemia, sickle cell trait, and glucose-6-phosphate dehydrogenase deficiency (G6PD).

Both Fatin Al-Sayes et al and Joharah M. Al-Quaiz are agree that previous history of IDA represent significant association with recurrence of the disease .

7- Socioeconomic status:

Iron deficiency is most common among groups of low socioeconomic status.

Environmental factors:

A given diet may be low in iron or may contain adequate amounts of iron which are of low bioavailability. Other nutrients necessary for haematopoiesis may also be deficient. These include folic acid, vitamins A, B12, and C, protein, and copper and other minerals. Trauma or childbirth can result in acute or chronic blood loss, with consequent iron deficiency and anaemia.

Pathophysiology of Iron Deficiency Anemia:

Iron deficiency anemia arises when there is imbalance between input and output of the iron. Many factors contribute to this situation and they need to be understood to have a fuller appreciation of iron balance. Iron balance is regulated by several conditions: (a) the amount of iron ingested, (b) the amount of iron absorbed, (c) red blood cell formation using recycled and new iron, (d) iron stores, and (e) iron loss through blood loss or other sources [12] .

Input of iron **output of iron**

Iron:

Dietary intake:

The average daily diet in the UK contains 15-20 mg of iron, although normally only 10% of this is absorbed. Absorption may be increased to 20-30% in iron deficiency and pregnancy. Non-haem iron is mainly derived from cereals, which are commonly fortified with iron; it forms the main part of dietary iron. Haem iron is derived from haemoglobin and myoglobin in red or organ meats. Haem iron is better absorbed than non-haem iron, whose availability is more affected by other dietary constituents [2].

Absorption:

Once iron is ingested, it is absorbed in the gastrointestinal (GI) tract and then transported into the circulation. The main portion of the GI tract involved is the duodenum and jejunum of the small intestine, where on average only about 10% of ingested iron is absorbed. This absorption rate is not static, however, and it decreases or increases relative to iron stores and the bodys needs. Once absorbed, the iron molecule is converted from the Fe^{3+} (ferric) to the Fe^{2+} (ferrous) state by stomach acid, and then the iron molecules are transported through the circulation to the bone marrow via transferring [2] .

Transferrin, the transport vehicle, is a plasma protein formed in the liver that assists iron delivery to the erythroblasts in the bone marrow. Transferrin receptors on the pronormoblast bind iron, so that iron molecules can immediately start being incorporated into the heme molecule during erythropoiesis. The willingness for the transferrin receptor to bind iron is influenced by the iron being delivered, the pH of the body, and, on the molecular level, the influence of an iron regulatory factor, ferritin repressor protein. An essential ingredient to seamless iron absorption and transport is a healthy

GI tract. Procedures such a gastrectomy or gastric bypass, atrophic gastritis, or celiac disease may compromise iron absorption [12]. There are several factors affecting the iron absorption showed in table 6.

Table 6: Factors affecting iron absorption

Haem iron is absorbed better than non-haem iron
Ferrous iron is absorbed better than ferric iron
Gastric acidity helps to keep iron in the ferrous state and soluble in the upper gut
Formation of insoluble complexes with phytate or phosphate decreases iron absorption
Iron absorption is increased with low iron stores and increased erythropoietic activity, e.g. bleeding, haemolysis, high altitude
There is a decreased absorption in iron overload, except in hereditary haemochromatosis, where it is increased

Iron stores [2]

About two-thirds of the total body iron is in the circulation as haemoglobin (2.5-3 g in a normal adult man). Iron is stored in reticuloendothelial cells, hepatocytes and skeletal muscle cells (500-1500 mg). About two-thirds of this is stored as ferritin and one-third as haemosiderin in normal individuals. Small amounts of iron are also found in plasma (about 4 mg bound to transferrin), with some in myoglobin and enzymes.

Ferritin is a water-soluble complex of iron and protein. It is more easily mobilized than haemosiderin for Hb formation. It is present in small amounts in plasma.

Haemosiderin is an insoluble iron-protein complex found in macrophages in the bone marrow, liver and spleen. Unlike ferritin, it is visible by light microscopy in tissue sections and bone marrow films after staining by Perls' reaction.

Requirements [2]

Each day 0.5-1.0 mg of iron is lost in the faeces, urine and sweat. Menstruating women lose 30-40 mL of blood per month, an average of about 0.5-0.7 mg of iron per day. Blood loss through menstruation in excess of 100 mL will usually result in iron deficiency as increased iron absorption from the gut cannot compensate for such losses of iron. The demand for iron also increases during growth (about 0.6 mg per day) and pregnancy (1-2 mg per day). In the normal adult the iron content of the body remains relatively fixed.

Iron deficiency [12]

Iron deficiency denotes a deficit in total body iron resulting from a sustained increase in iron requirements over iron supply. The continuum of decreased body iron is shown in Figure 4. Three successive stages of iron lack can be distinguished. A decrement in storage iron without a decline in the level of functional iron compounds is termed iron depletion. After iron stores are exhausted, lack of iron limits the production of hemoglobin and other metabolically active compounds that require iron as a constituent or cofactor. Iron-deficient erythropoiesis develops, although the effect on hemoglobin production may be insufficient to be detected by the standards used to differentiate normal from anemic states. Further diminution in the body iron produces frank iron-deficiency anemia.

Etiology and Pathogenesis:

The foremost task in the evaluation of patients with iron deficiency is identifying and treating the underlying cause of the imbalance between iron requirements and supply that is responsible for the lack of iron [Table 7]. Overall, the iron requirement for an individual includes not only the iron needed to replenish physiologic losses and meet the demands of growth and pregnancy but also any additional amounts needed to replace pathologic losses. Physiologic iron losses generally are restricted to the small amounts of iron contained in the urine, bile, and sweat; shedding of iron-containing cells from the intestine, urinary tract, and skin; occult gastrointestinal blood loss; and, in women, uterine losses during menstruation and pregnancy. In normal men, the daily basal iron loss is slightly less than 1.0 mg/day. In normal menstruating women, the daily basal iron loss is approximately 1.5 mg/day. The median total iron loss with pregnancy is approximately 500 mg, or almost 2 mg/day over the 280 days of gestation. Genetic factors may influence the risk of iron deficiency, but the mechanisms responsible have not been identified.

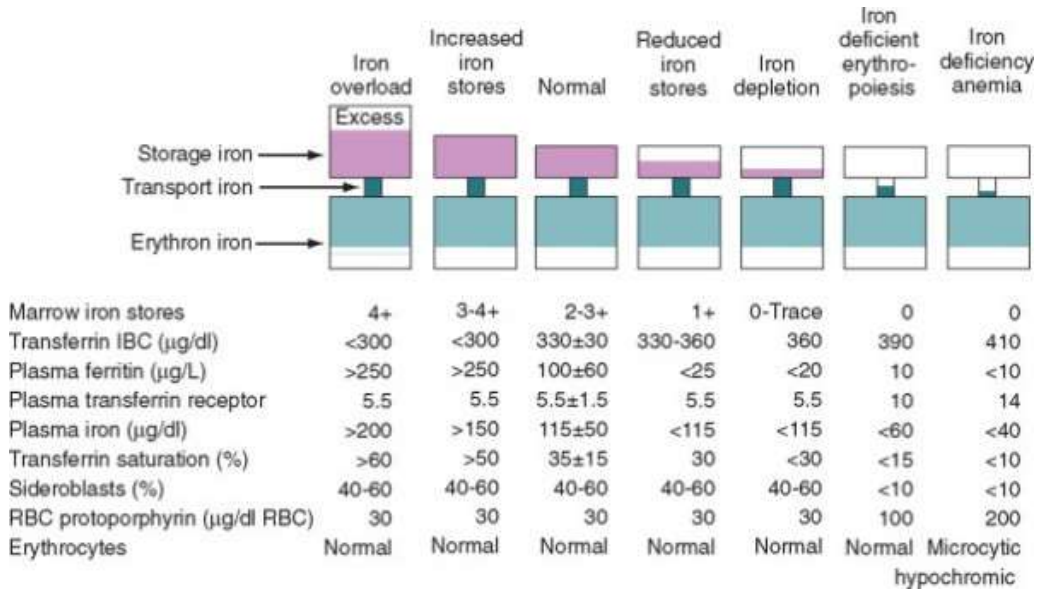

Figure 4: Continuum of changes in iron stores and distribution in the presence of increased or decreased body iron content. Abnormalities indicating the onset of specific stages of negative iron balance are enclosed in boxes. In iron overload, excess storage iron may increase from the normal range of 1 g or less to as much as 40 to 50 g. Marrow iron stores are increased as shown only in disorders of iron overload with reticuloendothelial iron loading, such as transfusional iron overload. Marrow iron stores may be normal or even absent in hereditary hemochromatosis.

TABLE 7: Causes of Iron Deficiency

Increased Iron Requirements
Blood loss
Gastrointestinal tract
Genitourinary tract
Respiratory tract
Blood donation
Growth
Pregnancy and lactation
Inadequate Iron Supply
Dietary insufficiency of bioavailable iron
Impaired absorption of iron
Intestinal malabsorption
Gastric surgery
Impaired iron transport

The most common pathologic cause of increased iron requirements leading to iron deficiency is blood loss [table 8] . In men and post-menopausal women, iron deficiency almost inevitably signifies gastrointestinal blood loss. Within the gastrointestinal tract, any hemorrhagic lesion may result in blood loss, and the responsible lesion may be asymptomatic. Iron deficiency often is the first sign of an occult gastrointestinal malignancyor other unrecognized conditions such as coeliac disease, or autoimmune, atrophic, or Helicobacter pylorigastritis. Chronic ingestion of drugs such as alcohol, salicylates, steroids, and nonsteroidal antiinflammatory drugs may cause or contribute to blood loss. Worldwide, the most frequent cause of gastrointestinal blood loss is hookworm infection, but other helminthic infections, such as *Schistosoma mansoniand Schistosoma japonicum*, and severe *Trichuris trichiurainfection* also may be responsible.

In women of childbearing age, genitourinary blood loss with menstruation adds to iron requirements. Menstrual losses tend to decrease with use of oral contraceptives but increase with use of intrauterine devices. Other, less frequent causes of genitourinary bleeding should be considered, including chronic hemoglobinuria and hemosiderinuria resulting from paroxysmal nocturnal hemoglobinuria or from chronic intravascular hemolysis.

Uncommonly, respiratory tract blood loss resulting from chronic recurrent hemoptysis of any cause produces iron deficiency. In two rare conditions, Goodpasture syndrome and idiopathic pulmonary siderosis, hemoptysis and intrapulmonary bleeding may be inapparent but lead to sequestration of iron in pulmonary macrophages.

TABLE 8: Pathological contributors to iron deficiency anemia in the UK with prevalence as percentage of total

Occult GI blood loss	
Common	
Aspirin/NSAID use	10—15%
Colonic carcinoma	5—10%
Gastric carcinoma	5%
Benign gastric ulceration	5%
Angiodysplasia	5%
Uncommon	
Oesophagitis	2—4%
Oesophageal carcinoma	1—2%
Gastric antral vascular ectasia	1—2%
Small bowel tumours	1—2%
Cameron ulcer in large hiatus hernia	<1%
Ampullary carcinoma	<1%
Ancylomasta duodenale	<1%
Malabsorption	
Common	
Coeliac disease	4—6%
Gastrectomy	<5%
Helicobacter pylori colonisation	<5%
Uncommon	
Gut resection	<1%
Bacterial overgrowth	<1%
Non-GI blood loss	
Common	
Menstruation	20—30%
Blood donation	5%
Uncommon	
Haematuria	1%
Epistaxis	<1%

GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug.

Although still within the body, the sequestered iron is "lost" from systemic use, and severe iron-deficiency anemia may develop. Recurrent blood donation may lead to iron deficiency, particularly in menstruating women.

In infants, children, and adolescents, the need for iron for growth may exceed the supply available from diet and stores. Premature infants, who have a lower birth weight and a more rapid postnatal rate of growth, are at high risk for iron deficiency unless given iron supplements. With rapid growth during the first year of life, the body weights of term infants normally triple, and iron requirements are at high levels.

Iron requirements decline as growth slows during the second year of life and into childhood but rise again with the adolescent growth spurt.

Without supplemental iron, pregnancy entails the net loss of the equivalent of 1200 to 1500 mL of blood. After delivery, resumption of menstruation usually is delayed for months. If the infant is breastfed, lactation necessitates an intake of approximately 0.5 to 1.0 mg of iron daily.

In some instances, an insufficient supply of iron may contribute to the development of iron deficiency. In infants or in women who have experienced heavy menstrual losses or multiple pregnancies, the risk of iron deficiency may be further increased by diets with insufficient amounts of bioavailable iron, such as those with little or no heme iron and with small amounts of enhancers or large amounts of inhibitors of nonheme iron absorption. For older children, men, and postmenopausal women, the restricted availability of dietary iron is almost never the sole explanation for iron deficiency, and other causes, especially blood loss, must be considered.

Impaired absorption of iron in itself infrequently produces iron deficiency. Intestinal malabsorption of iron may occur as a manifestation of more generalized syndromes. Atrophic gastritis and the attendant achlorhydria may impair iron absorption. In persons of all ages and both genders, but particularly in pregnant women and children, pica, the compulsive chewing or ingestion of food or nonfood substances, may contribute to iron deficiency if the material consumed inhibits

iron absorption. Iron deficiency frequently complicates gastric surgery, such as partial or total gastric resection or gastroenterostomy for bypass of the duodenum.

Increased iron requirements and an inadequate supply of iron often work in concert to produce iron deficiency. Infants fed cow's milk receive a diet that not only contains small amounts of iron of low bioavailability but also increases iron losses by causing gastrointestinal bleeding. Menstruating women, who have some of the highest iron requirements, may consume diets that have a low content of iron and contain inhibitors of iron absorption, such as calcium. Patients with ulcer disease and increased gastrointestinal blood loss may habitually take antacids, which diminish dietary iron absorption.

5. CLINICAL PICTURE OF THE DISEASE

Patients with anaemia may be asymptomatic. A slowly falling level of Hb allows for haemodynamic compensation and enhancement of the oxygen-carrying capacity of the blood. A rise in 2,3-BPG causes a shift of the oxygen dissociation curve to the right, so that oxygen is more readily given up to the tissues. Where blood loss is rapid, more severe symptoms will occur, particularly in elderly people [2]. By far, the most common cause of asymptomatic anemia is iron deficiency [13]. There are non-specific symptoms which are shared by all types of anemia and specific symptoms vary according to the underlying cause. The non-specific symptoms include headache, fatigue, faintness, dizziness, breathlessness, palpitation ,claudication and intermittent angina.

These symtoms vary from patient to patient and according to the degree of severity, grade 1 (Mild Anemia): 10 g/dl - cutoff point for ages, Grade 2 (Moderate Anemia): 7-10 g/dl , Grade 3 (Severe Anemia): below 7 g/dl [14] . A British survey, however, found no relationship between the frequency of the non-specific symptoms and the level of hemoglobin (ranging from 8 – 12 g/ 100 ml) among women found to have IDA during screening program. In- direct evidence showed that level of less than 8g / 100 ml were associated with symptoms sever enough to prompt a presentation to the physician.

Symptoms and signs of IDA are showed in table 9.

The potential consequences of IDA are of major concern in which there is great impact on patients suffering from the disease as showed in table 10.

Investigation and Screening for the disease

Investigations [2-12]

1- CBC (Complete Blood Count), and peripheral smear (see table 11)

	Male	Female
RCC **[low]**	< 4.5	< 3.9
PCV **[low]**	< 0.4	< 0.37
Hb **[low]**	13.5	11.5
MCV **[low]**	< 80	
MCH **[low]**	< 27	
MCHC **[low]**	< 32	
RDW **[high]**	> 15	
Peripheral blood	There is poikilocytosis (variation in shape) and anisocytosis (variation in size)	

RCC :Red cell counts (10^{12} / L)
PCV : Packed cell volume (L /L)
Hb : hemoglobin (g/ dl)
MCV : main corpuscular volume (Fl)
MCH : main corpuscular hemoglobin (pg)
MCHC : main corpuscular hemoglobin concentration (g/dl)
RBW : red blood cell distribution width (%)

TABLE 9: General symptoms and specific signs of IDA

Non specific symptoms	Specific signs
▪ **headache** ▪ **fatigue** ▪ **faintness** ▪ **dizziness** ▪ **breathlessness** ▪ **palpitation** ▪ **claudication and** ▪ **intermittent angina** ▪ Lethargy ▪ Ringing in ears ▪ Taste disturbances ▪ Restless leg syndrome	▪ brittle nails ▪ spoon-shaped nails (koilonychia) ▪ Glossitis ▪ atrophy of the papillae of the tongue ▪ angular stomatitis ▪ brittle hair ▪ a syndrome of dysphagia and glossitis (Plummer-Vinson or Paterson-Brown-Kelly syndrome ▪ Blue sclera ▪ Pica

TABLE 10: Potential Consequences of Iron Deficiency

Potential Consequences of Iron Deficiency	
Decreased maximum aerobic capacity Decreased athletic performance Lowered endurance Decreased work capacity Impaired temperature regulation Depressed immune function Increased rates of infection	**Impaired cognitive functioning and memory** **Decreased school performance** **Compromised growth and development** **Increased lead and cadmium absorption** **Increased risk of pregnancy complications, including prematurity and fetal growth retardation**

TABLE 11: Combining the Reticulocyte Count and Red Blood Cell Parameters for Diagnosis

MCV	RDW	**Reticulocyte Count <75,000/µL**	**Reticulocyte Count >100,000/µL**
Low	Normal	Anemia of chronic disease	
Normal	Normal	Anemia of chronic disease	
High	Normal	Chemotherapy/antivirals/alcohol Aplastic anemia	Chronic liver disease
Low	High	Iron deficiency anemia	Sickle cell-β-thalassemia
Normal	High	Early iron, folate, vitamin B_{12} deficiency Myelodysplasia	Sickle cell anemia, sickle cell disease
High	High	Folate or vitamin B_{12} deficiency Myelodysplasia	Immune hemolytic anemia Chronic liver diseases

Hypochromic anaemia occurs in other disorders, such as anaemia of chronic disorders and sideroblastic anaemias and in globin synthesis disorders, such as thalassaemia. To help to differentiate the type, further haematinic assays may be necessary [table 12]. Difficulties in diagnosis arise when more than one type of anaemia is present—for example, iron deficiency and folate deficiency in malabsorption, in a population where thalassaemia is present, or in pregnancy, when the interpretation of red cell indices may be difficult.

2- Serum iron and iron-binding capacity. The serum iron falls and the total iron-binding capacity (TIBC) rises in iron deficiency compared with normal. Iron deficiency is regularly present when the transferrin saturation (i.e. serum iron divided by TIBC) falls below 19% [Table 12].

3- Serum ferritin. The level of serum ferritin reflects the amount of stored iron. The normal values for serum ferritin are 30-300 µg/L (11.6-144 nmol/L) in males and 15-200 µg/L (5.8-96 nmol/L) in females. In simple iron deficiency, a low serum ferritin confirms the diagnosis. However, ferritin is an acute-phase reactant, and levels increase in the presence of inflammatory or malignant diseases. In these cases, measurement of serum iron/TIBC, serum ferritin and soluble transferrin receptors is used.

4- Serum soluble transferrin receptors. The number of transferrin receptors increases in iron deficiency. The results of this immunoassay compare well with results from bone marrow aspiration at estimating iron stores. This assay can help to distinguish between iron deficiency and anaemia of chronic disease (Table 5), and may avoid the need for bone marrow examination even in complex cases.

5- Reticulocytes. As a marker of red blood cell production, the reticulocyte count provides important information in directing the initial investigation of anemia. Modern flow cytometers accurately determine the reticulocyte count using fluorescent probes that bind to the residual ribonucleic acid present in newly released red blood cells. These measurements are useful, are accurate, and reflect the state of erythropoiesis. However, when significant numbers of nucleated red blood cells or nuclear debris are present in the peripheral blood, this diagnostic accuracy declines, and manual counting methods are generally preferable.

In the absence of anemia, the normal absolute reticulocyte count is between 25,000 and 75,000/µL. In the presence of anemia, an absolute reticulocyte count of less than 75,000/µL is indicative of a hypoproliferative process, whereas an absolute reticulocyte count of greater than 100,000/µL is indicative of hemolysis or an appropriate erythropoietic response [Table 13]. Reticulocyte counts between 75,000 and 100,000/µL require interpretation in the context of other available clinical data including the severity of anemia present.

6- Bone marrow. Erythroid hyperplasia with ragged normoblasts is seen in the marrow in iron deficiency. Staining using Perls' reaction (acid ferrocyanide) does not show the characteristic Prussian-blue granules of stainable iron in the bone marrow fragments or in the erythroblasts. Examination of the bone marrow is not essential for the diagnosis of iron deficiency but it may be helpful in the investigation of complicated cases of anaemia, e.g. to determine if iron deficiency is present in a patient with anaemia of chronic disease.

TABLE 12: Microcytic anaemia: the differential diagnosis

TABLE 12 : Microcytic anaemia: the differential diagnosis				
	Iron deficiency	**Anaemia of chronic disease**	**Thalassaemia trait (α or β)**	**Sideroblastic anaemia**
MCV	Reduced	Low normal or normal	Very low for degree of anaemia	Low in inherited type but often raised in acquired type
Serum iron	Reduced	Reduced	Normal	Raised
Serum TIBC	Raised	Reduced	Normal	Normal
Serum ferritin	Reduced	Normal or raised	Normal	Raised
Serum soluble transfer receptors	Increased	Normal	Normal or raised	Normal or raised
Iron in marrow	Absent	Present	Present	Present
Iron in erythroblasts	Absent	Absent or reduced	Present	Ring forms

TABLE 13: Usefulness of the Reticulocyte Count in the Diagnosis of Anemia

Diagnosis	Value
Hypoproliferative anemias	
Anemia of chronic disease **Anemia of renal disease** **Congenital dyserythropoietic anemias** **Effects of drugs or toxins** **Endocrine anemias** **Iron deficiency** **Marrow replacement**	***Absolute reticulocyte count <75,000/µl***
Maturation abnormalities	
Vitamin B_{12} deficiency Folate deficiency Sideroblastic anemia	***Absolute reticulocyte count <75,000/µl***
Appropriate response to blood loss or nutritional supplementation	
Hemoglobinopathies **Immune hemolytic anemias** **Infectious causes of hemolysis** **Membrane abnormalities** **Metabolic abnormalities** **Mechanical hemolysis**	***Absolute reticulocyte count >100,000/µl***

7- Other investigation [15]

These will be indicated by the clinical history and examination and including:

6. UPPER AND LOWER GI EVALUATION

Upper and lower GI investigations should be considered in all postmenopausal female and all male patients where IDA has been confirmed unless there is a history of significant overt non-GI blood loss. In the absence of suggestive symptoms (which are unreliable), the order of investigations is determined by local availability, although all patients should be screened for celiac disease with serology (B) See Table 14 .

TABLE 14: Grade of Recommendations

Level	Type of evidence	Grade of recommendation
IA	Meta-analysis of randomised controlled trials or inception cohort studies	A
IB	At least one randomised controlled trial or well-designed cohort studies with good follow-up	A
IIA	At least one well-designed controlled study without randomisation or a meta-analysis of case–control studies	B
IIB	At least one study with quasi-experimental design or case–control study	B
III	At least one non-experimental study (such as a descriptive study)	C
IV	Expert committee reports or reports by recognised authorities	C

If oesophagogastroduodenoscopy (OGD) is performed as the initial GI investigation, only the presence of gastric cancer or coeliac disease, as explained below, should deter lower GI investigation (B). In particular, the presence of oesophagitis, erosions and peptic ulcer disease should not be accepted as the cause of IDA until lower GI investigations have been carried out. Small-bowel biopsy samples should be taken at OGD if coeliac serology was positive or not performed. Colonoscopy has the following advantages over radiology: it allows biopsy of lesions, treatment of adenomas, and identification of superficial pathology such as angiodysplasia and NSAID damage. Performing gastroscopy and colonoscopy at the same session speeds investigation and saves time for both the hospital and the patient, because only one attendance for endoscopy is required. Radiographic imaging is a sufficient alternative where colonoscopy is contraindicated. The sensitivity of CT colography for lesions >10 mm in size is over 90%. Barium enema is less reliable, but is still useful if colonoscopy or CT colography are not readily available.

7. SCREENING FOR AND FURTHER INVESTIGATION OF COELIAC DISEASE

Ideally coeliac serologydtissue transglutaminase (tTG) antibody or endomysial antibody if tTG antibody testing is not availabledshould be undertaken at presentation, but if this has not been carried out or if the result is not available, duodenal biopsy specimens should be taken. If coeliac serology is negative, small-bowel biopsies need not be performed at OGD unless there are other features, such as diarrhoea, which make coeliac disease more likely (B). The pretest probability of coeliac disease in those with IDA alone is w5%. The negative likelihood ratio for the tTG antibody test using human recombinant tTG is 0.06. Thus, if the tTG antibody test is negative, the post-test probability of coeliac disease is 0.3%, which is less than in the general population. This means that duodenal biopsy samples will need to be taken from w330 tTG antibody-negative patients to detect one extra patient with coeliac disease at an estimated additional cost of £35 000.

If coeliac serology is positive, coeliac disease is likely and should be confirmed by small-bowel biopsy. Although concurrent testing for IgA deficiency, which is found in 2% of patients with coeliac disease, has been recommended, we do not consider it necessary to test for it routinely, because it only results in the post-test probability of coeliac disease with a negative tTG antibody test changing slightly from 0.3% to 0.2%, which is not clinically significant. However, it is advised if low absorbance readings are shown in the IgA tTG antibody assay.

Further GI investigations are not usually necessary if celiac disease is diagnosed. However, the lifetime risk of GI malignancy in patients with coeliac disease is slightly increased, particularly within 1 year of diagnosis, so investigation with colonoscopy should be considered if additional risk is presentdfor example, if age is >50 years or if there is a significant family history of colorectal carcinoma. If IDA develops in a patient with treated coeliac disease, upper and lower GI investigation is recommended in those aged >50 in the absence of another obvious cause. In the rare case of normal small-bowel histology with positive serology, we recommend that investigation should proceed as if coeliac serology was negative.

8. FURTHER EVALUATION

Further imaging of the small bowel is probably not necessaryunless there is an inadequate response to iron therapy, especially if transfusion dependent (B).

Follow-up studies have shown this approach to be reasonably safe provided that dietary deficiency is corrected, NSAIDs have been stopped, and the Hb concentration is monitored.

In those with an inadequate response, video capsule endoscopy or enteroscopy may be helpful to detect angiodysplasia, Crohn's disease and small-bowel neoplasia. Video capsule endoscopy has a diagnostic yield of 40 -55% in this setting. However, it seldom results in a beneficial subsequent intervention. Many lesions detected by both enteroscopy and video capsule endoscopy are within the reach of a gastroscope, and repeat OGD should be considered before these procedures.

Bleeding lesions identified by video capsule endoscopy may be amenable to treatment by push or double-balloon enteroscopy. However, the benefits of these procedures after a normal video capsule endoscopy in the context of IDA are unproven. Small-bowel imaging (MRI enteroclysis, CT enterography or barium studies) should also be considered in patients with symptoms suggestive of small-bowel disease, transfusiondependent IDA, and rapid recurrence of anaemia after normalization of Hb concentrations. However, many small intestinal lesions that cause asymptomatic anaemia are mucosal and flat or nearly so and most small intestinal imaging modalities apart from video capsule endoscopy are only efficient at identifying mass lesions. CT has the additional advantage of being able to identify extraintestinal pathology such as renal tumours and lymphomas.

Helicobacter pylori colonisation may impair iron uptake and increase iron loss, potentially leading to iron deficiency and IDA. Eradication of H pylori appears to reverse anaemia in anecdotal reports and small studies. H pylori should be sought by non-invasive testing, if IDA persists or recurs after a normal OGD and colonoscopy, and eradicated if present (C). H pylori urease (CLO) testing of biopsy specimens taken at the initial gastroscopy is an alternative approach. ***Autoimmune gastritis*** has been identified as a potential cause of IDA in up to a quarter of cases, but, although of interest, its diagnosis is currently of little practical value. **Giardia lamblia** has occasionally been found during the investigation of IDA. If there is associated diarrhoea, then smallbowel biopsy samples will be taken anyway and may detect this. Where giardiasis is suspected, stool should be sent for ELISA, even if histology of duodenal biopsy samples is negative.

Radiological imaging of the mesenteric vessels is of limited use but may be of value in transfusion-dependent IDA for demonstrating vascular malformations or other occult lesions. Similarly, diagnostic laparotomy with on-table enteroscopy is rarely required in cases that have defied diagnosis by other investigations. There is no evidence to recommend labelled red cell imaging or Meckel's scans in patients with IDA.

Other investigations, including routine assessments of the liver and renal function, and clotting studies are of no diagnostic value unless the history suggests systemic disease. Faecal occult blood testing is of no benefit in the investigation of IDA (B), being insensitive and non-specific.

Management:

Aim of treatment:

After attending to any discovered underlying cause, the aim of treatment should be to restore Hb concentrations and red cell indices to normal, and replenish iron stores. If this cannot be achieved, consideration should be given to further evaluation.

Iron therapy:

Treatment of an underlying cause should prevent further iron loss, but all patients should have iron supplementation both to correct anaemia and replenish body stores (B). This is achieved most simply and cheaply with ferrous sulphate 200 mg twice daily.

Lower doses may be as effective and better tolerated and should be considered in patients not tolerating traditional doses. Other iron compounds (eg, ferrous fumarate, ferrous gluconate) or formulations (iron suspensions) may also be tolerated better than ferrous sulphate. Oral iron should be continued for 3 months after the iron deficiency has been corrected so that stores are replenished.

Ascorbic acid (250-500 mg twice daily with the iron preparation) may enhance iron absorption, but there are no data for its effectiveness in the treatment of IDA.

For those intolerant or not responding to oral iron, there are three parenteral preparations available, two of which can only be administered intravenously (iron sucrose (Venofer) and ferric carboxymaltose (Ferinject)), and one that can be given either intravenously or by deep gluteal intramuscular injection (iron (III) hydroxide dextran (Cosmofer)), although this can be painful and requires several injections. A comparison of intravenous iron compounds is shown in table 15 .

Table 15

Table 2 Comparison of the intravenous iron preparations

Intravenous iron preparation	Maximum single dose	Duration of infusion	Cost/g of iron†
Iron dextran* (Cosmofer)	20 mg/kg	6 h	£79.70
Iron sucrose (Venofer)	200 mg	10 min	£70.80
	500 mg	4 h	
Ferric carboxymaltose (Ferinject)	1000 mg	15 min	£217.50
	But ≤15 mg/kg		

*Can also be given intramuscularly.
†Costs according to British National Formulary.

The principal advantage of ferric carboxymaltose, a recent addition to intravenous therapy, is the abbreviated duration of infusion, without the need for a test dosed15 min compared with 6 h with Cosmofer (consisting of a 15 min test dose, 45 min observation, 4 h infusion, then 1 h observation). Although drug costs are higher, length of stay in a day-case or primary-care facility is reduced. Intravenous iron sucrose is reasonably well tolerated (35% of patients have mild side effects including abdominal pain, nausea, headache and diarrhoea), with a low incidence of serious adverse reactions (0.03-0.04%).Bolus intravenous dosing of iron sucrose (200 mg iron) over 10 min is licensed andmore convenient than a 2 h infusion. Intravenous iron dextran can replenish iron and Hb concentrations in a single infusion, but serious reactions can occur (0.6-0.7%) and there have been fatalities associated with infusion (31 reported between 1976 and 1996).

The incidence of side effects with ferric carboxymaltose are similar to other intravenous compounds (22-29%), but no anaphylaxis has been reported to date. The cautions and contraindications found in the manufacturers' instructions and in the British National Formulary should be noted. Anaphylaxis may occur, and resuscitation facilities should be available for all these agents when given intravenously.

Although the initial rise in Hb is more rapid with parenteral iron, the rise in Hb at 12 weeks is similar to that observed during oral iron therapy. Blood transfusions should be reserved for patients with symptomatic anaemia despite iron therapy or at risk of cardiovascular instability because of their degree of anaemia (C), particularly if they are due to have endoscopic investigations before a response from iron treatment is expected. Transfusions should aim to restore Hb to a safe level, but not necessarily normal values. Iron treatment should follow transfusion to replenish stores.

Follow-up:

Once normal, the Hb concentration and red cell indices should be monitored at intervals. We suggest 3 monthly for 1 year, then after a further year, and again if symptoms of anaemia develop after that. Further oral iron should be given if the Hb or red cell indices fall below normal (ferritin concentrations can be reserved for cases where there is doubt).

Further investigation is only necessary if the Hb and red cell indices cannot be maintained in this way. It is reassuring that iron deficiency does not recur in most patients in whom a cause is not found after upper GI endoscopy, testing for coeliac disease, and large-bowel investigation.

9. SUMMARY FLOW CHART FOR INVESTIGATION

An abbreviated investigation flow chart is shown in **figure 5**.

Special Considerations:

Investigation of premenopausal women IDA occurs in 5 e12% of otherwise healthy premenopausal women and is usually due to menstrual loss, increased demands in pregnancy and breast feeding, or dietary deficiency.The yield of GI investigation in these 'patients' has been investigated in several studies. Malignant tumours have been found in 0-6.5% of patients, but the two studies with highest detection rates have been criticised as non-representative. It therefore seems likely that, although malignant tumours may occur in asymptomatic premenopausal women, they are extremely uncommon. Coeliac disease is present in up to 4% of premenopausal women in these studies. All premenopausal women with IDA should be screened for coeliac disease (B). Age is the strongest predictor of pathology in patients with IDA, and thus GI investigation as outlined above is recommended for asymptomatic premenopausal women with IDA aged 50 years or older (B).

OGD should be considered for any premenopausal women with IDA and upper GI symptoms according to the Department of Health referral guidelines for suspected upper GI cancer.

Colonic investigation in premenopausal women aged <50 years should be reserved for those with colonic symptoms, a strong family history (two affected first-degree relatives or just one first-degree relative affected before the age of 50 years), or persistent IDA after iron supplementation and correction of potential causes of losses (eg, menorrhagia, blood donation and poor diet).

Although it is convenient to use the term premenopausal, it is menstruation that influences the investigative pathway. Thus those premenopausal women who have IDA but no menstruation (eg, after hysterectomy) should be fully investigated.

Patients with significant comorbidity:

The appropriateness of investigating patients with frailty and/or severe comorbidity needs to be considered on a case-by-case basis. Factors to be taken into account include the severity and recurrent nature of the anaemia, the risk of bowel preparation before lower GI investigation, and the potential fitness of the patient to withstand treatment in the event that a colorectal cause was identified. The least invasive test should be used where deemed appropriate. There are no data in the literature about the detection rate of cancer in patients with IDA being investigated with unprepared CT or minimally prepared CT compared with standard CT colography or colonoscopy. Provisional data from the national bowel cancer screening programme show a pick up rate of 6.9% for minimal or unprepared CT (101 patients) compared with 11% for colonoscopy (>33 000 patients).

Thus, although unprepared CT may miss occasional cancers, we continue to recommend this for very frail patients in whom bowel preparation may be risky. An older patient with weight loss may benefit from an initial CT scan of the abdomen, pelvis and thorax, and, if malignancy is found, endoscopy may not be necessary.

Patients awaiting surgery:

Prompt and effective iron replacement is needed before urgent surgery, and intravenous iron is a likely cost-effective solution that may obviate the need for blood transfusion.

Young men:

Although the incidence of important GI pathology in young men is low, there are no data on the yield of investigation in those with IDA. In the absence of such data, we recommend that young men should be investigated in the same manner as older men (C). Where there is an obvious cause of blood loss (eg, blood donation), it is reasonable to avoid investigations unless anaemia recurs despite correction of the cause of blood loss.

Pregnant women:

Mild IDA is common in pregnancy, and iron replacement should be encouraged as soon as the diagnosis is made. A careful history and examination should be made, specifically seeking a family history of gastrointestinal neoplasia or

coeliac disease. Coeliac serology should be carried out. If it is positive, endoscopy and duodenal biopsy can be performed, as there is no evidence this is unsafe in pregnancy. If there is concern about lower GI pathology, further investigation should be considered, although in some patients this may be delayed until after delivery. Performing unsedated flexible sigmoidoscopy in pregnancy is considered quite safe. However, there are insufficient data on the safety of performing colonoscopy in pregnancy, and, because of its potential to cause serious adverse events, it should be reserved for very strong indications. MR colography is believed to be safe for mother and fetus and should be preferred to radiological imaging. The National Radiological Protection Board considers it prudent to avoid MRI in the first trimester

Post-gastrectomy:

IDA is very common in patients with partial or total gastrectomy, probably because of poor chelation and absorption of iron as a result of loss of ascorbic acid and hydrochloric acid, and loss of free iron in exfoliated cells. However, these patients also have a two- to three-fold increased risk of gastric cancer after 20 years, and probably an increased risk of colon cancer. Investigation of IDA in post-gastrectomy patients aged >50 years of age is therefore recommended (C). Bariatric surgery can lead to iron deficiency, but iron supplementation is usually recommended after surgery to prevent the problem.

Use of warfarin and aspirin:

No significant difference in the prevalence of GI cancer was found in patients taking aspirin or warfarin, either alone or in combination, compared with patients not taking these drugs. IDA should therefore not be attributed to these drugs until GI investigations have been completed.

Use of proton pump inhibitor:

There are no data to indicate that proton pump inhibitors cause IDA in humans. Patients taking these drugs should not be considered less likely to have malignancy.

Figure 1 An abbreviated flow chart of the investigation of iron deficiency anaemia. GI, gastrointestinal; Hb, haemoglobin; OGD, oesophagogastroduodenoscopy; tTG Ab, tissue transglutaminase antibody. *See text for details of significant family history.

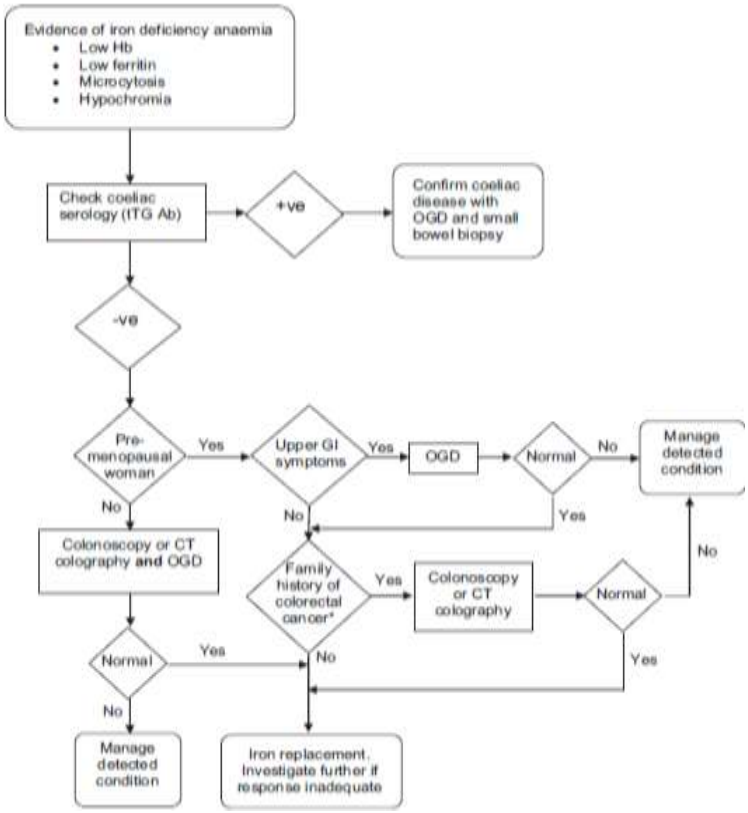

Figure 5: Iron deficiency without anaemia

Iron deficiency without anaemia (confirmed by low serum ferritin-hypoferritinaemia) is three times as common as IDA, but there is no consensus on whether these patients should be investigated, and further research is needed. The largest study shows very low prevalence of GI malignancy in patients with iron deficiency alone (0.9% of postmenopausal

women and men, and 0% of premenopausal women). Higher rates have been reported only in more selected groups. In the absence of firm evidence, we tentatively recommend coeliac serology in all these patients but that other investigation be reserved for those with higher-risk profiles (eg, age >50 years) after discussion of the risks and potential benefits of upper and lower GI investigation (C). All others should be treated empirically with oral iron replacement for 3 months and investigated if iron deficiency recurs within the next 12 months (C).

Prevention strategies[16]

Iron deficiency, like most nutritional deficiencies of public health concern, is mainly a consequence of poverty. Even in developed countries, it affects a significant proportion of people in groups which are particularly vulnerable.

Prevention strategies must, if they are to be sustainable, involve the input and resources of a wide range of sectors and organizations. This is especially true for iron deficiency. For example, the agriculture, health, commerce, industry, education, and communication sectors should be included in any strategy. These, in turn, should work in concert with communities and with local nongovernmental organizations.

Efforts should be targeted to:

1- reduce poverty;

2- improve access to diversified diets;

3- improve health services and sanitation; and

4- promote better care and feeding practices.

These are fundamental elements of any programme to improve nutritional well-being in general, but are especially important in the improvement of iron status in particular.

A. Food-based approaches:

1- Dietary improvement

Food-based approaches represent the most desirable and sustainable method of preventing micronutrient malnutrition. Such approaches are designed to increase micronutrient intake through the diet.

Food-based approaches should therefore include strategies to:

- improve the year-round availability of micronutrient-rich foods;
- ensure the access of households, especially those at risk,
- to these foods; and change feeding practices with respect to these foods.

One of the greatest strengths of these food-based strategies lies in their potential to result in multiple nutritional benefits. These benefits can, in turn, achieve both short-term impact and long-term sustainability.

In practice, food-based approaches should first address the production, preservation, processing, marketing, and preparation of food. Secondly, they should address feeding practices, such as intra-family food distribution and care for vulnerable groups.

Applied to iron deficiency, efforts should be directed towards promoting the availability of, and access to, iron-rich foods. Examples include meat and organs from cattle, fowl, fish, and poultry; and non-animal foods such as legumes and green leafy vegetables.

Similarly, focus should be upon foods which enhance the absorption or utilization of iron. Examples include those of animal origin, and non-animal foods – such as some fruits, vegetables, and tubers - that are good sources of vitamins A and C, and folic acid. Finally, effective nutrition education - and information on health and nutrition for both supply and demand aspects of programmes – may be needed to increase the demand for and consumption of such foods.

The first step in this process involves obtaining and analysing information on the various foods consumed and on the way they are processed, mixed, and prepared for a meal.

Annex 4 suggests proposed strategies for obtaining such information, adapted from the approach currently used with success in some programmes to promote consumption of foods rich in vitamin A.

The interpretation of values concerning iron status which have been obtained using this methodology will vary according to the bioavailability of iron from local food mixtures and meal patterns. Accordingly, this approach should be adapted to, and its value assessed under, local conditions.

Once all the information has been analysed, appropriate recommendations can be made for changing dietary components and the timing of their consumption, altering food processing or preparation, or changing meal patterns. The focus should be on changes that will improve the bioavailability, as well as the amount, of iron in the diet.

Interpretation of bioavailability is limited by the scarcity of accurate information concerning the content of phytates and iron-binding polyphenols in various foods.

Such information is urgently needed to facilitate the promotion of correct food choices.

Recommendations should be adapted to regional and local variations in diet, the age group concerned,seasonal availability, and other factors that cause food intake and meal patterns to vary. It should be noted that food-frequency questionnaires are not a sufficient base from which to draw inferences on likely iron status unless they are combined with information on meal composition and food consumption patterns.

Methods of food preparation and processing influence the bioavailability of iron. Cooking, fermentation, or germination can, by thermal or enzymatic action, reduce the phytic acid and the hexa- and penta-inositol phosphate content. All inositol phosphates inhibit iron absorption in proportion to the total number of phosphate groups. Processing procedures that lower the number of phosphate groups improve bioavailability of non-haem iron.

Building food-based approaches around the needs and activities of women can be especially effective. This is particularly important in recognition of the multiple roles women play as food providers and primary caregivers.

For example, promoting home gardens and small animal husbandry, and improving food preservation and home or community processing technologies, can be especially useful in improving iron status. These interventions are enhanced by efforts to generate additional income for women and by effective nutrition education.

The primary goal of dietary modification to improve and maintain the iron status of a population involves changes in behaviour, leading to an increase in the selection of iron-containing foods and a meal pattern favourable to increased bioavailability. Although sometimes difficult to achieve, such changes in dietary habits can bring about important sustainable improvements, not only in iron status but also for nutrition in general. Such changes must be rooted in issues that take into account food security, actual availability, and education.

Bioavailability of food iron is strongly influenced by enhancers and inhibitors in the diet. Presently, there is no satisfactory in vitro method for predicting the bioavailability of iron in a meal.

Iron absorption can vary from 1% to 40%, depending on the mix of enhancers and inhibitors in the meal. Therefore, the adequacy - i. e. bioavailability - of iron in usual diets can be improved by altering meal patterns to favour enhancers, lower inhibitors, or both.

Enhancers *of* iron absorption include:

- haem iron, present in meat, poultry, fish, and seafood;
- ascorbic acid or vitamin C, present in fruits, juices,potatoes and some other tubers, and other vegetables such as green leaves, cauliflower, and cabbage; and some fermented or germinated food and condiments, such as sauerkraut and soy sauce (note that cooking,
- Some fermentation, or germination of food reduces the amount of phytates).

Inhibitors of iron absorption include:

- phytates, present in cereal bran, cereal grains, high-extraction flour, legumes, nuts, and seeds;
- food with high inositol content;
- iron-binding phenolic compounds (tannins); foods that contain the most potent inhibitors resistant to the influence of enhancers include tea, coffee, cocoa, herbal infusions in general, certain spices (e.g. oregano), and some vegetables; and

- calcium, particularly from milk and milk products.

Examples of simple but effective alterations in meal patterns that enhance iron absorption might include:

- 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;
- include in the meal fruit juices such as orange juice, or another source of ascorbic acid such as tubers, cabbage, carrots, or cauliflower;
- consume milk, cheese, and other dairy products as a between-meal snack, rather than at mealtime; and
- consume foods containing inhibitors at meals lowest in iron content, e.g. a breakfast of a low-iron cereal (bread or corn tortilla) consumed with tea or milk products; this meal pattern can provide adequate calcium without hampering iron nutrition.

Other actions that indirectly affect iron status might include:

- parasitic disease control programmes, in particular those directed to hookworm, schistosomiasis and malaria control; these programmes can enhance iron deficiency anaemia control programme effectiveness in a population with moderate to severe levels of infection; and
- Incentive policies and improved farming systems that favour the development, availability, distribution, and use of foods that enhance iron absorption.

10. FOOD FORTIFICATION

There is a consensus that enrichment (or fortification) of food is an effective long-term approach to improving the iron status of populations. Once a fortification programme is established, it is a cost-effective and sustainable means of achieving this purpose. The technical, operational, and financial feasibility should, however, be carefully assessed before embarking on such a fortification programme. An effective iron fortification programme requires the cooperative efforts of governments, the food industry (producers, processors, and marketers) and consumers. Appropriate food vehicles and fortificants must be selected.

Essential requirements for implementing fortification strategies include the identification of an appropriate food vehicle that reaches the target population, that is centrally processed, and that is widely available and consumed in relatively predictable amounts by vulnerable population groups. It is essential that the final product not be significantly changed in terms of its organoleptic quality, shelf life, or price; and that the food as prepared be acceptable to the population.

The dietary habits of the population are an important consideration in selecting a food for fortification. For example, possible appropriate food vehicles range from wheat flour or pasta and condiments like sugar, salt, curry powder, haldi, monosodium glutamate (MSG), to bouillon cubes and soy sauce.

In subsistence farming areas in most developing countries, a fortified-food approach has limited potential because few households ever consume commercially processed foods. Instead, fortified food supplements can be effectively and widely distributed through general food distribution programmes, e.g. school lunch or other supplemental or emergency feeding programmes.

Fortified foods for young children:

Normal-birth-weight infants who are exclusively breastfed do not need iron supplements for the first 4 to 6 months of life. When complementary feeding begins, and certainly after 6 months of age, infants need an additional source of iron to maintain adequate iron nutrition and prevent iron deficiency anaemia.

Since cereals are widely used as early complementary foods, they should be fortified during their commercial preparation, by extrusion, cooking, or mixing processes. Centrally processed milk-based foods designed for infants and preschool children should also be fortified. Other forms of iron have been used for infant cereals: small-particle-size metallic iron is the form most widely used.

An iron complex with ammonium-orthophosphate - which is less reactive and has better absorbability - is used successfully in Sweden, and its use should be explored elsewhere. Iron pyrophosphate and orthophosphate should not be used, because of their poor bioavailability.

Finally, the practice of including iron-rich complementary foods for young children should be encouraged, both at home and in the community. Ferrous sulphate is the most widely used fortificant for cows' milk or modified infant formula.

Iron supplementation:

Iron supplementation is the most common strategy currently used to control iron deficiency in developing countries. This is likely to remain the case until either significant improvements are made in the diets of entire populations or food fortification is achieved.

Supplementation is most often used to treat existing iron deficiency anaemia. It should also be considered as a preventive public health measure to control iron deficiency in populations at high risk of iron deficiency and anaemia. Supplementation programmes, 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 iron deficiency anaemia in that country.

Various delivery systems and modalities, under conditions of varied efficiency, reach a wide range of target groups. Small controlled studies of supplementation have been shown to be particularly successful, and a few large-scale supplementation programmes clearly demonstrating positive biological impact are reported from some developing countries. Countries should identify specific problems and constraints limiting the effectiveness of supplementation programmes and those key elements responsible for successes and failures. Only then will information be sufficient to introduce effective and efficient solutions, if traditional approaches and practices are to continue.

Traditionally, target groups for supplementation programmes have been pregnant women and infants. This practice is due to the short- and long-term health benefits of these programmes for both groups. To a large extent, they are reached with relative ease through the health system in urban areas.

However, it has become increasingly evident that the main target group for supplementation to prevent iron deficiency should be all women of childbearing age (in addition to infants older than 6 months, preschool children, and adolescent girls). This target group should not be limited to pregnant women, who are often accessible only through the health system and late in pregnancy.

One problem is that all of these groups are often difficult to contact through the health services. An exception involves adolescent girls, who may be reached through the school system.

Therefore, efforts should concentrate on supplementation programmes for women of childbearing age. If women enter pregnancy with adequate iron reserves, iron supplements provided during pregnancy will be more efficient at improving the iron status of the mother and of the fetus. As a result, the risk of maternal anaemia at delivery and of anaemia in early infancy will be reduced.

Iron supplementation to prevent iron deficiency anaemia:

Low-birth-weight infants:

A daily dosage of 2 mg iron/kg of body weight in the form of a liquid preparation should be given to all low-birth-weight infants, starting at 2 months and continuing to 23 months of age (universal supplementation).

Infants and children below 2 years of age:

Where the diet does not include fortified foods, or prevalence of anaemia in children approximately 1 year of age is severe (above 40%), supplements of iron at a dosage of 2 mg/kg of body weight/day should be given to all children between 6 and 23 months of age. There have been some reports of stained teeth after iron supplementation with some solutions. Good oral hygiene and the use of ferrous carbonate can prevent this condition. Ferrous carbonate is not soluble, but present as a suspension or a solution of iron-EDTA (Sodium iron ethylenediaminetetraacetic acid (NaFeEDTA), known as iron-EDTA, is a potentially valuable fortificant that has hitherto had limited use)

Children above 2 years of age:

The recommended WHO regimen (4) - based on daily supplementation as summarized in Table 16 - should be followed. However, supervised weekly, or biweekly supplementation of preschool and school-aged children and adolescent girls has been reported to be effective in several countries .

Table 16: Dosage schedules for iron supplementation to prevent iron deficiency anaemia

Age groups	Indications for supplementation	Dosage schedule	Duration
Low-birth-weight infants	Universal supplementation	Iron: 2 mg/kg body weight/day	From 2 months of age up to 23 months of age
Children from 6 to 23 months of age	Where the diet does not include foods fortified with iron or where anaemia prevalence is above 40%	Iron: 2 mg/kg body weight/day	From 6 months of age up to 23 months of age
Children from 24 to 59 months of age	Where anaemia prevalence is above 40 %	Iron: 2 mg/kg body weight/day up to 30 mg	3 months
School-aged children (above 60 months)	Where anaemia prevalence is above 40 %	Iron: 30 mg/day Folic acid: 250 µg/day	3 months
Women of childbearing age	Where anaemia prevalence is above 40 %	Iron: 60 mg/day Folic acid: 400 µg/day	3 months
Pregnant women	Universal supplementation	Iron: 60 mg/day Folic acid: 400 µg/day	As soon as possible after gestation starts - no later than the 3rd month - and continuing for the rest of pregnancy
Lactating women	Where anaemia prevalence is above 40 %	Iron: 60 mg/day Folic acid: 400 µg/day	3 months post-partum

Women of childbearing age: pregnant women:

A total amount of about 700-850 mg of iron is needed to meet the iron requirements of a mother and fetus during pregnancy, at delivery, and during the perinatal period. Iron needs during the first trimester are lower than pre-pregnancy needs; they increase the most during the second half of the pregnancy and especially during the last trimester. For unknown reasons, dietary iron absorption in iron-sufficient women is reduced during the first trimester and increased in the second half of pregnancy.

The average woman of reproductive-age needs about 350-500 mg additional iron to maintain iron balance during pregnancy. Potentially, this iron could be provided either from the mother's iron stores or from iron supplements. However, it is not reasonable to expect that this additional iron can come from iron stores, since they very seldom reach this level in women in either developed or developing countries (the mean iron content of the body reserves - ferritin and haemosiderin - is often only around 200-250 mg).

Furthermore, in developing countries 25-30% of women have no iron reserves at all. Because the situation is especially serious among pregnant teenagers, it is important to promote all measures - with emphasis on pubertal girls – that will improve iron reserves before pregnancy.

All pregnant women (universal supplementation) should be given 60 mg iron and 400 µg folic acid daily during the second half of pregnancy to control iron deficiency anaemia. There is some evidence, however, that smaller doses of 30 mg daily could achieve similar results.

Combined with other micronutrients, folic acid should always be given with iron during pregnancy. This combination is important because of the increased folic acid requirement of pregnant women and the fact that both deficiencies are common in pregnancy. In addition, folic acid supplementation prior to pregnancy will also have an impact on maternal folic acid status, which is expected to reduce the risk of neural tube defects.

Women of childbearing age: lactating women:

In populations with a severe prevalence of anaemia (>40%), it is recommended that iron supplementation begin during pregnancy. Supplementation should continue during lactation for at least three months post-partum, at the same dosage - 60 mg iron and 400 µg folic acid daily - as during pregnancy.

Women of childbearing age: non-pregnant women:

In areas where the prevalence of anaemia among women of childbearing age is severe (> 40%), preventive iron supplementation of 60 mg/day iron with 400 µg folic acid for 3 months should be considered.

Adolescents:

Where prevalence of anaemia in pubertal girls is severe (>40%), preventive iron supplementation of 60 mg/day iron with 400 µg folic acid for 3 months should be considered. Adolescent boys should also receive preventive iron

supplementation where prevalence of anaemia among them is severe (>40%). As with adolescent girls, supplementation should continue throughout adolescence, following the same schedule of 60 mg/day iron with 400 µg folic acid for 3 months.

Problems associated with iron supplementation:

Delivery system:

Much of the success of an iron supplementation programme depends on the effectiveness of the delivery system. The framework of the programme will be provided by the health system of the country in question. It may also include primary health care facilities and community health workers, such as traditional birth attendants and volunteers . Ideally, iron supplementation should be community-based: the community should embrace the need for the programme and provide support on its behalf.

To this end, 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. Involvement and participation of the private health system will also help to achieve maximum coverage.

Adherence:

Irregular consumption of prescribed iron supplements, due in part to side-effects (see below), has plagued most supplementation programmes. For this reason, definitive results of tests of iron preparations with fewer side-effects are eagerly awaited. Even if new iron preparations are more expensive than ferrous sulphate, they may ultimately be more cost-effective if they improve adherence .

Possible side-effects associated with iron medication

- Epigastric discomfort, nausea, diarrhoea, or constipation may appear with a daily dose of 60 mg or more. If these symptoms occur, supplement should be taken with meals.
- Faeces may turn black, which is not harmful. Treatment should continue.
- All iron preparations inhibit the absorption of tetracyclines, sulphonamides, and trimethoprim. Thus, iron should not be given together with these agents.
- High-dose vitamin C supplements should not be taken with iron tablets, because this would likely cause epigastric pain.

The side-effects of iron tablets generally increase with higher dosages. These side-effects can be reduced if supplements are taken with meals, but absorption is reduced by about 40% . If the supplement is administered in the form of a single tablet, it is best ingested at bedtime. Adherence frequently diminishes due to intolerence when more than one iron tablet of 60 mg is required. Under such circumstances, prescribing one daily tablet instead of two is justified as a general policy or for the particular subjects who experience intolerance. One tablet taken consistently is preferable to the risk of total rejection or non-acceptance of supplements.

11. AWARENESS AND MOTIVATION

Motivating the target group to take iron tablets according to the prescribed schedule, thereby improving adherence, is of utmost importance. Accordingly, communities, families, mothers, and health workers need to be well informed about the health benefits - as well as the side-effects - of iron supplementation for both the mother and fetus.

One approach is a comprehensive education and information programme, organized through the health and other community infrastructures. Such a programme should emphasize the benefits of iron supplementation and provide advice concerning possible side-effects. Community leaders, volunteer health workers or local cadres, schoolteachers, and students can reinforce these messages as a demonstration of their involvement in and commitment to the community

The training of community workers involved in programme implementation is essential. Social marketing techniques can be used to great advantage.

Of course, the design of messages should take into account local terms, perceptions, and cultural factors related to anaemia.

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Of course, the design of messages should take into account local terms, perceptions, and cultural factors related to anaemia.

Quality and packaging of iron supplements:

Improvements are needed in the quality of iron tablets, especially in their stability (e.g. avoidance of cracking, and disintegration, and absorption of moisture) and other physical characteristics (e.g. their colour and odour). Development of improved packaging to minimize deterioration before distribution, and innovative and safe ways of dispensing the tablets, is also needed.

The design and testing of all of these aspects of iron supplementation are significant in improving adherence. They are especially important in preventing accidental iron poisoning, particularly in children.

Risk of iron overload with iron supplementation:

The above-mentioned supplementation strategies are not considered to be associated with any increased risk of iron overload .

Monitoring and evaluation:

Iron supplementation programmes should be carefully assessed, and their efficiency and effectiveness monitored, to improve critical aspects of the system.

Other complementary public health interventions:

Iron supplementation programmes should be integrated into broader public health programmes which are directed to the same population target groups.

Iron supplementation during pregnancy and lactation is a major component in reducing maternal morbidity and mortality. Emphasis should therefore be placed upon increasing the capacity of antenatal, postnatal, and child health clinics to provide iron supplementation for mothers and children.

For maximum effectiveness, links should be established with programmes such as those targeting:

1. malaria prophylaxis;
2. hookworm control;
3. immunization;
4. environmental health;
5. control of micronutrient malnutrition; and
6. community-based primary health care.

Community participation within the framework of the concept of primary health care (and beyond) should be actively encouraged.

Iron supplementation to correct iron deficiency anaemia:

As mentioned earlier in this chapter, it is important to differentiate between supplementation for the prevention of iron deficiency anaemia and supplementation for its correction. The amounts of iron supplementation recommended to treat iron deficiency anaemia for adults is **120 mg/day** iron for **3 months**. For infants and younger children, it is 3 mg/kg/day, **not to exceed 60 mg daily.**

12. GUIDELINES FOR TREATMENT OR REFERRAL OF SEVERE ANEMIA IN PRIMARY CARE SETTINGS [17]

Severe anemia usually comprises a small proportion of the cases of iron deficiency in a population but may cause a large proportion of the severe morbidity and mortality related to iron deficiency. It is important that primary health care providers are able to recognize these cases and treat or refer individuals with severe anemia. The training and supervision of this activity in primary health care settings becomes a priority activity when the prevalence of severe anemia in population groups (e.g., pregnant women) exceeds 2%.

Iron deficiency is not the only cause of severe anemia. Other possible causes include malaria, folate deficiency, hemoglobinopathies such as sickle c ell anemia or thalassemias, and the anemia of chronic disorders such as HIV infection, tuberculosis, or cancer. In primary care settings, health care workers should know when to refer individuals who do not respond to oral iron therapy or who are at urgent risk of serious complications.

Detection of Severe Anemia:

Severe anemia is defined clinically as a low hemoglobin concentration leading to cardiac decompensation, that is, to the point that the heart cannot maintain adequate circulation of the blood. A common complaint is that individuals feel breathless at rest. In practical settings, severe anemia may be defined by using a hemoglobin or hematocrit cutoff or by extreme pallor. If the hemoglobin or hematocrit can be determined, cutoffs of hemoglobin below 7.0 g/dL or hematocrit below 20% should be used to define severe anemia[17] .

In addition, any child with kwashiorkor or marasmus should be assumed to be severely anemic and treated for severe anemia (Table 17). However, oral iron therapy should not be started until the child regains appetite and is gaining weight. This is usually about 14 days after nutritional rehabilitation has begun.

Table 8. Guidelines for oral iron and folate therapy to treat severe anemia

Age group	Dose	Duration
< 2 years	25 mg iron + 100-400 µg folic acid daily	3 months
2-12 years	60 mg iron + 400 µg folic acid daily	3 months
Adolescents and adults, including pregnant women	120 mg iron + 400 µg folic acid daily	3 months

Notes:
- After completing 3 months of therapeutic supplementation, pregnant women and infants should continue preventive supplementation regimen.
- Children with kwashiorkor or marasmus should be assumed to be severely anemic. However, oral iron supplementation should be delayed until the child regains appetite and starts gaining weight, usually after 14 days.

Treatment or Referral of Cases:

Once an individual is determined to have severe anemia, a decision must be made regarding whether to treat in the local setting or refer to a hospital. Treatment should be given in a hospital if the individual is a pregnant woman beyond 36 weeks gestation (i.e., in the last month of pregnancy) or if signs of respiratory distress or cardiac abnormalities (e.g., labored breathing at rest or edema) are present [17] . Other individuals should be treated as indicated in Table 17.

Summary for public health measures [16:]

1. Universal supplements for pregnant and lactating women and low-birth-weight infants.
2. Supplementation for women of childbearing age including adolescent girls and school-aged children, if anaemia prevalence exceeds 40%.
3. Screening - only if anaemia prevalence is mild or moderate (<20%) and protocols and guidelines for action are available.
4. Integration with the activities of primary health care and maternal and child health clinics.
5. Using channels outside the health system, building on existing programmes in the communities.
6. Sharing facilities, training and supervision.
7. Providing adequate supplies and logistics.
8. Ensuring shelf-life under prevailing climatic conditions.
9. Identifying and addressing factors leading to low adherence.
10. Forewarning on side-effects (black faeces and dyspepsia) by providers.

11. Creating awareness, linking iron deficiency anaemia to conditions which people recognize as undesirable symptoms or patterns of distress.

12. Stressing undesirable consequences of IDA during pregnancy

13. and delivery for infants.

14. Encouraging positive expectations as a result of supplements.

15. Motivating and training personnel for IDA prevention.

16. Reduction of the prevalence of infectious diseases in general (e.g. diarrhoeal and respiratory diseases, measles).

17. Reduction in the prevalence of hookworms, trichuriasis, and schistosomiasis infestations. Ideally, parasite control should be complemented with primary preventive measures to break the transmission cycle and environmental health measures to reduce parasitism (especially hookworms). This is particularly important for pregnant women, who should receive an appropriate anti-helminthic after the third month of pregnancy.

18. Reduction in the prevalence of malaria and other infection , which contribute for IDA

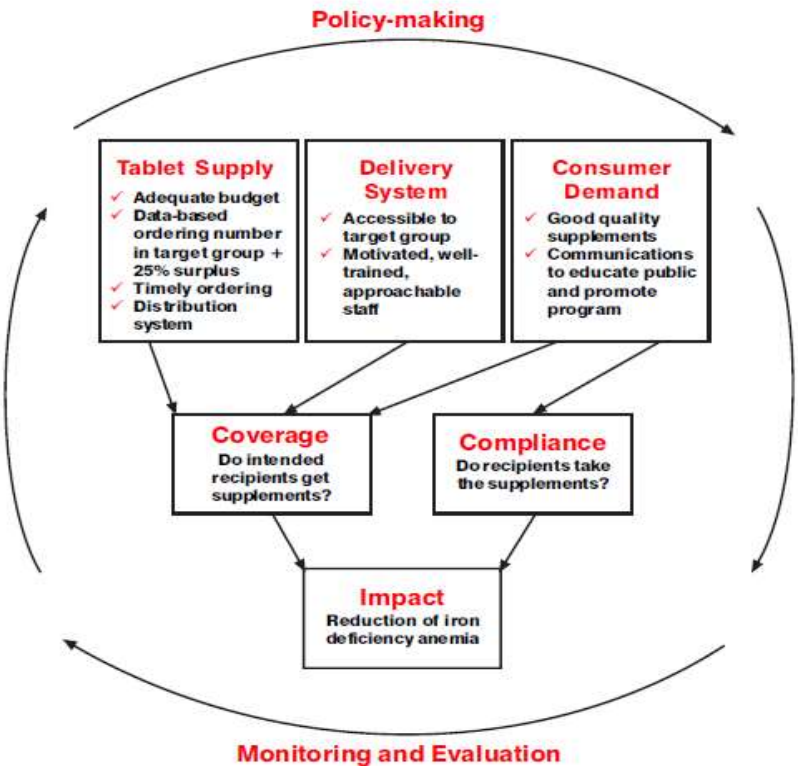
13. DEVELOPING A PROGRAM [17]

The evidence is indisputable that iron supplements can substantially reduce iron deficiency anemia. However, there are also many experiences that show that iron supplementation programs do not always work. Fortunately, although every program will have its unique aspects, some general elements of a successful iron supplementation programs are beginning to emerge from these experiences. These elements are summarized in Figure 1.

Developing an iron supplementation program or revitalizing an established program that is not working well is a process that involves several interactive steps.

There are lessons to be learned at each step of the process that might necessitate adjustments in decisions made in previous steps. One may set out to take each stepin turn to establish the perfect program, but in reality, **the best programs develop from constant learning and adjusting, especially at the beginning. Here is a summary of the key steps:**

Figure 1. Elements of Successful Iron Supplementation Programs



1. Establish a Policy:

Policies are needed to legitimize program activities, establish standard practices within programs, and engender the resource base necessary to bring programs to life. These resources include not only funds, but people.s time, equipment, and space and the credibility and influence of the policy-setting organization. If a policy for the control of iron deficiency anemia is not in place, it is important to establish one. Policy makers often do not fully understand the cost of iron deficiency anemia informed of the prevalence of anemia in the population or targeted subgroups (e.g., pregnant women and infants); the major causes of anemia; its consequences for the individual, the family, the community and the economy; and the cost effectiveness of interventions. In many situations, all of this information is not available before a program is implemented, which illustrates the interactive nature of these various steps. As the program gains experience and is monitored and evaluated, there needs to be a regular flow of information back to policy makers so that policies can be adjusted and strengthened.

2. Get the Right Product:

There are a wide variety of iron supplements in use around the world, and their quality varies. The quality of a supplement and its attractiveness to users is a major key to success. Iron supplementation programs to pregnant women typically use tablets, which are relatively inexpensive and easy to transport and store.

UNICEF has supported the production of a tablet that contains 60 mg iron (as ferrous sulfate) and 250 µg folic acid but is now changing to a tablet that contains 60 mg iron plus 400 µg folic acid. Children younger than 2 years will likely need a liquid supplement that can be dropped into their mouth, although a powder or crushable tablet could be mixed with an infant food. The higher costs associated with a liquid formulation for young children must be weighed against the greater ease of its use and potential for greater compliance.

The appearance and packaging of supplements may greatly influence their attractiveness to users. The color used to coat tablets can carry positive or negative connotations for women. In many cultures, women prefer a red, sugar-coated tablet. The coating of tablets also influences their stability in different storage conditions and their taste. The packaging of a product not only influences its appeal, but its cost and the frequency of contacts needed to deliver it (i.e., how long one package will last). The size and quality of the packaging also determines its safety in the household. Packages of iron supplements that contain a total of More than 1 g iron (e.g., 16 tablets each containing 60 mg iron) could cause serious injury or death if ingested by a child, and as little as 400 mg may be fatal to an infant. It may be possible to work with a local pharmaceutical company to develop a product and packaging uniquely suited to the tastes and beliefs of the population.

Once a product is chosen, a system must be made for ordering, storing, and transporting supplements to their point of distribution to consumers. Although these processes may seem straightforward, they have been major problem areas in the past. A lack of supplies within programs is a well-documented problem. The number of supplements needed in a given period should be based on the actual number of intended recipients (e.g., pregnant women or children younger than 2 years). Usually this number can be estimated from census information. A good rule of thumb is to procure the estimated number needed plus a 25% surplus. The frequency of procurements will depend upon the storage life of the supplements. This needs to be carefully planned, as out-of-date supplements represent lost money and lost opportunities to improve people.s health.

3. Choose Effective Delivery Systems:

People planning iron deficiency anemia control programs are encouraged to explore nontraditional modes for delivering supplements. Traditionally, iron supplementation programs have been delivered through health centers, but a wider variety of delivery systems are being tried to increase coverage and compliance.

One innovative approach is to distribute iron tablets during national immunization days. Increasingly, the private sector is an important means of making ironsupplements available to consumers. This requires collaboration with pharmaceutical industries to market the iron tablets attractively, regulate their quality and labeling, and ensure they are available in small villages. In several places people have discovered that even the poor are willing to spend small amounts on medications and tonics. Use of traditional healers and birth attendants, schools, religious centers, community centers, women.s groups, and factories are all being tried.

Qualitative research (e.g., focus groups and interviews) with target groups in representative communities should focus on their access to different delivery systems and users. perceptions of them. It is essential to realistically assess the coverage through different mechanisms. Where they exist, community health committees should be important partners in developing and implementing appropriate supplementation strategies.

A key to the success of any delivery system is the people who work there. Do women or other users feel good about interacting with these people? Can the people become truly committed to implementing the iron supplementation program, or are there important structural barriers (e.g., staff lack facilities and time), social barriers, or political barriers? The answers to the latter question will depend in part on the strength of the policy, because strong policies can create the resource base needed to overcome existing barriers.

4. Linking with Other Health and Nutrition Activities:

As described in the first part of this document, supplementation may be an essential intervention for some target groups in the population, but supplementation must be combined with other interventions to effectively control anemia. Building linkages with these programs will broaden the efforts to combat iron deficiency anemia and may increase the base of support for iron supplementation programs.

Contacts with young children, pregnant women, and perhaps other groups through health services can be used to ensure or reinforce supplementation. Immunization programs provide an opportunity for reminding child caregivers of supplementation protocols and for providing or selling supplements for young children or lactating women. Where other nutrition interventions are being implemented, aspects of the anemia control strategy may be effectively integrated. Examples include periodic distribution of anthelminthics with vitamin A supplements and screening for severe anemia in growth-monitoring programs for young children. Important linkages may also be made with agriculture or nutrition programs that carry out nutrition education or that might generate food intake data needed to plan an iron fortification program. Other potential partners are food industries that might participate in fortification efforts, family planning programs,obstetricians and midwives, pediatricians, and malaria and helminth control programs.

5. Develop a Communications Strategy:

A strategy is needed to communicate the plan and purpose of the program at multiple levels. To start a new program or to revitalize an existing one, many agents.from community members to health planners.need to act in new ways. Evaluations of unsuccessful programs have shown that health care personnel at all levels were confused or ignorant about the program plan and objectives.

Often health care workers need to be educated about iron deficiency anemia almost as much as do community members. Even health care workers who are not directly involved in distributing supplements should be knowledgeable about the program so that they reinforce the program messages in their work. Materials can be developed to help recipients remember to take supplements and to help health care workers (or other distributors) to distribute supplements appropriately and counsel pregnant women (or other users) about their use.

Some examples are included in Appendix B. Communications strategies need to be reviewed and adjusted as people.s experience and knowledge evolve. For example, as women become used to taking iron supplements, different messages may be needed to promote long-term compliance. Some of the most important objectives of the communications strategy and also potential points of resistance are summarized in Table 18.

6. Monitoring and Evaluation

Monitoring and evaluation are essential to the life of any program and should be planned and integrated from the start of the program. Monitoring is the continual activity of collecting information about the different parts of the program, whereas evaluation may be periodic and involves judgement about whether the program is working. These activities provide opportunities to reward excellence within the system, identify and solve problems in program implementation, and provide the additional information that policy makers need to revise and strengthen policies. Several types of monitoring and evaluation activities can be carried out; these may be grouped into two general categories.

In the first category of activity, specific program activities are monitored to assess whether all parts of the system are working as planned (sometimes called process evaluation). This level of evaluation is essential to all programs. This level may be expanded to include the assessment of knowledge, attitudes, and practices of program agents and beneficiaries,

and the compliance of beneficiaries with supplement usage. Measurable outcomes are listed in Table 19. Data on these outcomes will provide information about whether the implementation plan is functioning. It is critical that the information is compiled and reported so that the people implementing the program learn from the evaluation.

The second category of activity is to measure changes in iron deficiency anemia in target groups (sometimes called impact evaluation). One approach is to periodically conduct surveys of anemia (or iron deficiency anemia, if possible) in the target groups in the community.

Table 18

Table 10. Scope and behavior goals of an effective communications strategy for iron supplementation programs

Agent	Behavior Goal	Challenges
Pregnant women, mothers	Obtain and use iron supplement at right frequency and dose	Women not asking for services or knowing where they are Lack of awareness of anemia and how to prevent it Lack of knowledge of how to manage side effects Fears, beliefs, and suspicions (e.g. that iron pills will make baby too big) Forgetfulness
Health care providers	Distribute or sell iron supplements and counsel women properly about their use	Lack of awareness and knowledge Poor communication skills Infrequent contacts with pregnant women Providers may act disrespectfully to women
Health planners and drug managers	Train and supervise staff, monitor supplies, and manage resources	Lack of awareness of purpose of program May be part of poorly functioning system
Agents in complementary activities, such as family planning workers, midwives, and pediatricians	Support and reinforce messages of iron supplementation program, integrate anemia education into their activities	Lack of awareness of anemia and iron supplementation activities False sense of competition or threat between health care agents
Policy makers	Make and enforce necessary policies and allocate sufficient resources	Lack of awareness of cost of iron deficiency anemia to health and economy of society

Table 19:

Table 11. Measurable outcomes in process evaluation

- A budget dedicated and spent
- Supplements and other supplies procured
- Quality of supplements
- Provision of adequate storage
- Distribution system in place
- Availability of supplements at distribution points
- Training activities planned and conducted for health care workers and others as needed
- Knowledge, attitudes, and practices of health care workers and other agents
- Community education programs in place
- Knowledge, attitudes, and practices of community leaders, family decision makers, and mothers
- Number of supplements distributed
- Number of supplements reported received by mothers
- Program coverage (percentage of intended recipients who actually received supplements)
- Number of supplements consumed by women/infants

Ideally, a survey is carried out before the program is initiated, and follow-up surveys are conducted at intervals of 2.5 years after the program has begun. Demographic and health surveys in several countries now include hemoglobin measurements, and these are excellent resources for program evaluation. Coverage and compliance of iron supplementation by target individuals can also be ascertained within periodic surveys. It is especially important to do this if compliance (i.e., how many supplements are actually consumed) is not assessed as part of program monitoring. These periodic surveys let health planners and policy makers know whether anemia prevalence is declining. It is difficult to conclude with certainty that the changes observed in anemia rates result directly from the activities of the supplementation program. However, evidence from this type of evaluation can be very influential in maintaining political support for policies and programs or advocating for additional iron deficiency anemia control activities. Usually program effect, if it is assessed at all, is assessed in this way .

Sometimes resources are available to do a more in-depth evaluation of effect. The strength of evidence about program effect will be increased if iron status is linked to coverage and compliance at the level of the individual.

If data are collected to show that the general nutritional status of the population has not changed, improvements in women.s hemoglobin levels can be attributed with greater confidence to program activities. The strongest level of evidence about effect is obtained if individuals. iron status is measured before and after supplementation (e.g., early and late in pregnancy or postpartum or in infants at 6 and 12 months), and the change in status is linked to degree of iron supplement usage.

7. Development of an Applied Research Program to Support Program Activities:

Experience has shown that programs to control anemia and other forms of malnutrition are most successful in countries where they are supported by one or more teams of researchers dedicated to carrying out applied research related to nutrition interventions.

A few noteworthy examples are Chile, Argentina, and Venezuela in the control of anemia and Indonesia and Guatemala in the control of vitamin A deficiency. In each of these countries, scientists at local universities or institutes carried out critical research needed to develop, evaluate, and refine program strategies; and in each of these countries the nutritional problem has been substantially reduced.

Where such linkages between applied research and programs do not already exist, they should be encouraged in every way by program planners and implementers. These collaborations provide technical support for programs and also provide invaluable opportunities for nutrition and public health scientists to carry out research that will have an enduring effect in their country.

14. ACTION-ORIENTED RESEARCH NEEDS [16]

A. Dietary improvement:

1. Develop simple methods of dietary assessment, including screening foods or meals for their value as important sources of bioavailable iron and other nutrients.

2. Develop laboratory methods for assessing iron bioavailability from individual meals.

3. Update analytical databases on food, condiments, and spices, with respect to iron content and availability, as well as content of folic acid, vitamin C, tannins, phytates, vitamin A, and carotenoids.

4. Evaluate traditional forms of food preparation that may favourably affect bioavailability of iron, which are decreasing in use (e.g. fermentation); and explore ways in which these methods can be made more practical and/or less time-consuming.

5. Investigate methods of improving dietary patterns (e.g. food selection and preparation, addition of enhancers or removal of inhibitors of iron absorption).

6. Research practical methods of food preparation that will reduce the content of tannins and phytates, such as the use of commercial phytase, malting of cereals, prolonged cooking at high and low temperatures, germination and fermentation.

7. Expand knowledge about interactions among and between nutrients and/or non-nutrient factors (e.g. condiments and vitamins A and C, which influence micronutrient bioavailability, especially that of iron).

8. Conduct operational research to improve community nutrition and related education, and implement a social marketing approach with the ultimate goal of improving the quality and quantity of the food supply and its use.

9. Explore methods of introducing adventitious iron sources, such as the use of iron cooking pots.

Evaluate approaches to improving the delivery and adoption of agricultural inputs and technologies by nutritionally vulnerable or iron-deficit households.

10. Evaluate approaches to improving the delivery and adoption of agricultural inputs and technologies by nutritionally vulnerable or iron-deficit households.

11. Develop means to extend outreach to women farmers through agriculture extension services.

12. Explore methodologies for improving the marketing of foods rich in iron and vitamins A and C.

13. Improve methods for documenting the cost-effectivenessof horticultural interventions.

B. Iron fortification:

1. Expand research on iron-EDTA to include not only its current areas of application, but also its use in non-traditional vehicles (e.g. an adequate fortificant, its effect on absorption of other minerals, and the effectiveness of its absorption to influence meal iron bioavailability compared with that from ferrous sulphate).

2. Continue research to determine how EDTA promotes the absorption of the non-haem iron pool.

3. Continue to explore the potential for multiple fortification of foods with micronutrients.

4. Improve fortification technology to make fortification feasible in remote areas and in the community (e.g. premixes for home fortification use and microencapsulation).

5. Conduct pilot fortification studies to assess biological effectiveness, acceptability, and costs.

6. Develop methods for quality assurance control of fortification.

C. Iron supplementation:

1. Assess relative effectiveness of weekly supplements in various vulnerable population groups and under various conditions of programme implementation.

2. Conduct operational research on ways to improve the effectiveness and efficiency of preventive and therapeutic iron supplementation programmes.

3. Explore new approaches to iron supplementation, which may have better absorption and fewer side-effects.

4. Determine the cost-effectiveness of universalsupplementation of infants in areas where a high prevalence of iron deficiency is found among them.

5. Conduct operational research on practical surveillance systems, use of sentinel sites, etc.

6. Undertake operational research on community-based infrastructures for the distribution of iron and folic acid to pregnant women, and monitoring its effects among them.

7. Study effects of zinc supplementation in areas where iron deficiency is highly prevalent.

8. Conduct bioavailability tests on preparations containing multiple micronutrients.

9. Study combined pharmaceutical micronutrient preparations and super-fortified foods, including their feasibility, stability, and effectiveness.

10. Study the role, effectiveness, and cost-effectiveness of treating hookworm infections as a means of alleviating or preventing anaemia and iron deficiency.

15. GENERAL RECOMMENDATIONS [16]

In order to reduce substantially the prevalence of iron deficiency anaemia and in support of national programmes for the prevention of iron deficiency, the following actions are recommended:

For governments:

1. Undertake appropriate studies to collect or update information on the prevalence and severity of anaemia in various age groups and by gender in the principal ecological zones and socioeconomic groups of the country; results should be made rapidly available and used as the basis for advocacy and programme planning and monitoring.

2. Formulate and implement, as part of the national plan of action for nutrition, a programme for the prevention of iron deficiency, based on a combination of dietary improvement, food fortification (where feasible) and iron supplementation; public health measures integrated into maternal and child health, and primary health care programmes should also be part of the plan.

3. Establish a surveillance system to ensure appropriate monitoring of iron status and of programme implementation, using indicators outlined in this report; locally applicable programme indicators should be further developed.

4. Undertake a feasibility study of iron fortification programmes with emphasis upon reaching at least the major vulnerable populations.

5. Review, and strengthen as necessary, national legislation or regulations dealing with fortification and the marketing of appropriate fortified foods; strengthen appropriate food control and quality assurance systems; and foster effective working relationships with the food industry and consumer groups.

6. Develop appropriate support activities, e.g. human resources development (training of programme managers, sector specialists, extension agents, and laboratory and field staff, each for his or her respective role); advocacy; information, education, and communication; and applied research; and provide at least the minimum facilities necessary to those activities, including those for anaemia assessment.

7. Develop suitable managerial mechanisms, including integration into appropriate community programmes, e.g. those promoting sustainable agriculture and rural development, primary health care, maternal and child health, and prevention of other micronutrient deficiencies.

8. Mobilize the effective participation of community groups, the private sector, and nongovernmental organizations, in these programmes.

For supporting organizations and institutions:

1. Stimulate and provide technical, material, and financial support for the formulation, implementation, and monitoring and evaluation of national and local programmes.

2. Assist in mobilizing and training necessary human resources.

3. Provide support for appropriate applied and operational research.

4. Ensure the organization of necessary global, regional, and subregional advocacy, and of appropriate meetings, communications, and information systems.

5. Develop rosters of available human resources in various categories, and in all countries, and ensure the widespread circulation of those rosters.

6. Initiate, if possible, systems for continuous collection and periodic dissemination of information on the prevention of iron deficiency, and systems to ensure adequate communication on iron deficiency prevention initiatives, especially through widely circulated periodicals, bulletins, and newsletters.

7. Ensure that adequate and appropriate global and national information systems are established in connection with iron deficiency, including information on the implementation of prevention programmes.

8. Foster action-oriented research, and networking to increase collaborative efforts and cross-cultural trials.

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