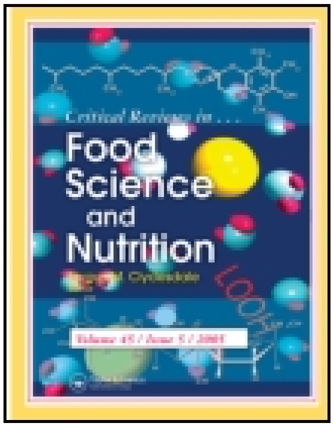

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

A Question Mark on Iron Deficiency in 185 Million People of Pakistan: Its Outcomes and Prevention

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Accepted author version posted online: 14 Jun 2013.Published online: 28 Feb 2014.

To cite this article: Anwaar Ahmed , Asif Ahmad , Nauman Khalid , Angel David , Mansoor Abdullah Sandhu , Muhammad Atif Randhawa & Hafiz Ansar Rasul Suleria (2014) A Question Mark on Iron Deficiency in 185 Million People of Pakistan: Its Outcomes and Prevention, Critical Reviews in Food Science and Nutrition, 54:12, 1617-1635, DOI: 10.1080/10408398.2011.645087

To link to this article: http://dx.doi.org/10.1080/10408398.2011.645087

Critical Reviews in Food Science and Nutrition, 54:1617–1635 (2014)

ISSN: 1040-8398 / 1549-7852 online
DOI: 10.1080/10408398.2011.645087

A Question Mark on Iron Deficiency in 185 Million People of Pakistan: Its Outcomes and Prevention

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Micronutrient deficiency especially the iron deficiency is the bane of our lives, affecting all strata of society. Unfortunately, the women during pregnancy, adolescence, and children are under this curse particularly in developing countries like Pakistan. It is one of the biggest reasons of complications during pregnancy and malnourished children under five years of age. Maternal death, still-births, and underweight births are most common consequences of iron deficiency and these outbreaks as iron-deficiency anemia in Pakistan. Disastrous nature of iron deficiency requires an urgent call to eradicate it. Hence, the solution should not be frail comparing with the huge economic loss and other incompatibilities. Flour fortification, supplementation, dietary diversification, and especially maternal education are possible solutions for combating this micronutrient deficiency.

Keywords Iron, iron-deficiency anemia, pregnancy, Pakistan, out ways

BACKGROUND

In this challenging environment, the population of developing countries is on peak than world's average population (Hochman et al., 2009; Population Division, 2009; McMahon, 2010). There is a need of real hard effort with full food revolution especially in poor and developing countries to solve food scarcity and availability (Huang et al., 2002), but it requires consistent and determined efforts of all leaders and scientists all around the world. In comparison of total population, about 65% of world's total population is starving (Food Security Statistics, 2008) and lives below the poverty line. Malnutrition and under nutrition are found among people where food supply and diet diversification are lacking. In this 21st century, the developing world is under severe threat of micronutrient malnutrition because of the consumption of diet that are rich in phytates and these limits bioavailability of essential nutrients (Hussain et al., 2010).

The deficiency of essential vitamins and minerals are now regarded as "hidden hunger" and it affects more than one-third of the world's population, threatens women and children, resulting devastating consequences for public health, social development, and future of the country. It is estimated that as many as 2 billion people are at a risk of zinc deficiency and has insufficient iodine intake (Boy et al., 2009). These micronutrient deficiencies contribute significantly to the burden of diseases and linked to adverse functional outcomes such as stunting, wasting, increased susceptibility to infections during pregnancy, decreased IQ level, cognitive losses, blindness, and premature mortality (Boy et al., 2009). Literature reviews estimate that 40% of the world's population may be at a risk of inadequate dietary intake of zinc and iron. The populations at highest risk are located in South and Southeast Asia, Sub-Saharan Africa, Central America, and the Andean region. Premature and small-for-gestational-age infants, and preschool children, mostly in between 6 and 23 months of age comes in most vulnerable list and need extreme

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attention from NGOs and Government bodies (Boy et al., 2009).

Anemia is a major public health problem affecting 1.62 billion people globally (McLean et al., 2009; Balarajan et al., 2011). The prevalence of anemia is estimated at 9% in countries with high development rate in contrast to countries with low development, where the prevalence is 43% (McLean et al., 2009; Balarajan et al., 2011). Children and women of reproductive age are most serious, with global anemia prevalence estimates of 47% in children younger than five years, 42% in pregnant women, and 30% in nonpregnant women aged 15–49 years (McLean et al., 2009; Balarajan et al., 2011) and with Africa and Asia accounting for more than 85% of the absolute anemia burden in high risk groups. Anemia is estimated to contribute to more than one, 15,000 maternal deaths and five, 91,000 prenatal deaths globally per year (Ezzati et al., 2004). Figures 1, 2, and 3 depict the global prevalence of anemia in children, pregnant, and nonpregnant women.

In many developing countries, one out of two pregnant women and more than one out of every three preschool children are estimated to be anemic (WHO, 2008). In countries where meat consumption is low, such as India and many in sub-Saharan Africa, up to 90% of women are or become anemic during pregnancy (Allen et al., 2006). Among all micronutrients, iron deficiency holds greatest share toward burden of diseases (WHO, 2008). It is obvious with the statistics that DALY (Disability Adjusted Life-Years) loss contributed by iron is 25 million (Codex Alimentarius Commision, 2001). People more prone to iron-deficiency anemia are children under the age of 5 (Sitti-Noor et al., 2006) and women during gravidity (Lone et al., 2004). This is because of increased iron requirement during growth and pregnancy (Black et al., 2008b). Anemic mothers increase the chances of iron-deficiency anemia (IDA) in their infants (Nestle and Ritu, 2000) and also the neonates have susceptibility to develop IDA (Batra and Seth, 2002). Pregnancy outcomes get worsen if iron-deficiency anemia occurs during the antenatal period (Gregory and Taslim, 2001). Maternal mortality cases occur due to low blood reserves infection and post-partum hemorrhages (Ramanthan and Aruthmaran, 2006). Fetal life-threatening results of IDA include pre-term births, low birth weight (LBW) infants, intrauterine growth and fetal growth retardation, or still-births (Rasmussen, 2001). Iron-deficiency anemia results in reduction of IQ in children and emotional imbalance. The most pronounced behavior noticed in children due to IDA is that they become unhappy, unconfident, fatigued, and self-centered (Lozoff et al., 2007).

The WHO and UNICEF guidelines recommend that interventions for the prevention and control of iron deficiency should follow an integrated, long-term approach (Allen et al., 2006). The solution to this problem lies in basic four approaches as suggested by WHO. These approaches to the prevention of iron-deficiency anemia are: (1) dietary change and diversification to increase iron intake; (2) supplementation with medical iron; (3) fortification of a suitable staple food with iron; and (4) the control of infection through public health activities (Allen et al., 2006).

Pakistan is a developing country and since its birth malnutrition has recognized as a key factor that significantly affecting infants, children, and women. Malnutrition affects the physical growth in terms of body development, physical work capacity, and producing risk for several chronic diseases in children. In Southeast Asia, it was estimated at 43%, whereas in Pakistan 50% of children fewer than five were stunted, 40% were under weight, and 9% were wasted (Bellamy, 2000). This situation

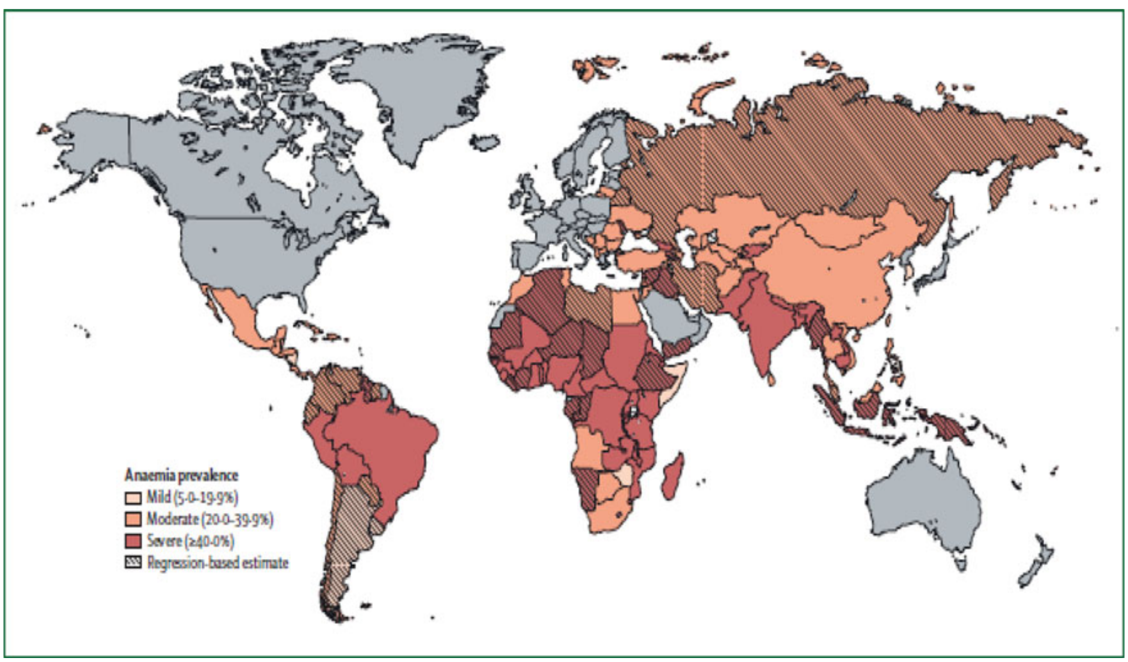

Figure 1 Global anemia prevalence in preschool age (0–5) children. (Color figure available online.)

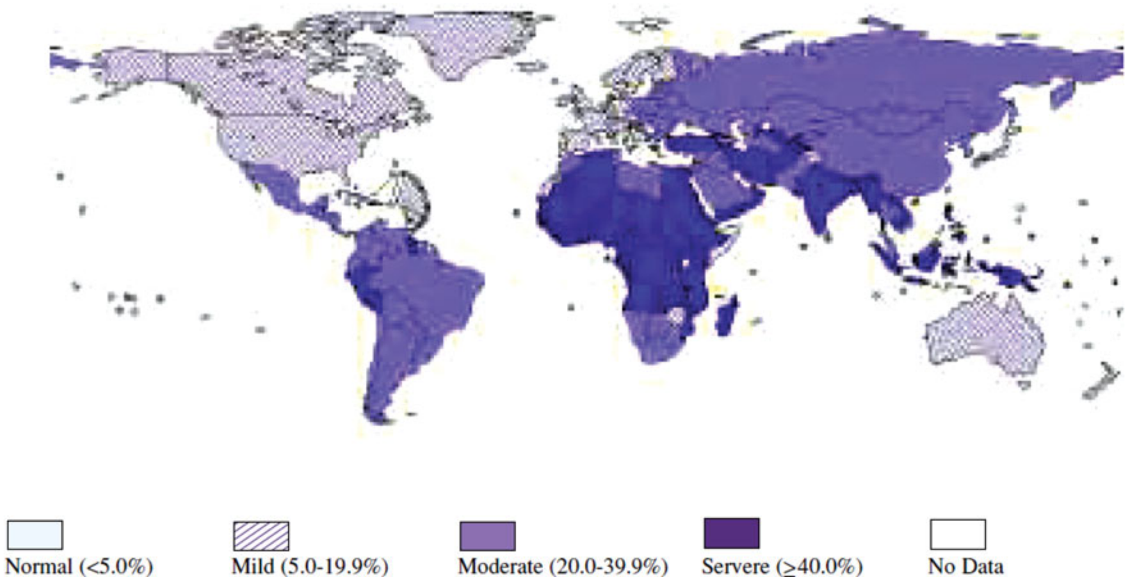

Figure 2 Anemia as a public health problem in pregnant women of global village. (Color figure available online.)

has not changed much in the region; recent reports showed that stunting is 37%, underweight 38%, while wasting is progressively increased to 13%, indicating lack of proper nutritional and health interventions at the national level (Diaz et al., 2003). Pakistan is suffering from high rates of childhood malnutrition and has made little progress in the past 20 years due to bad governess and less attention paid by NGOs. The burden of child malnutrition in South Asia (India, Bangladesh, and Nepal) is considered much higher than most of the countries in Sub-Sahara Africa (Bhutta, 2000; Ahmed and Farooq, 2010).

The last National Nutrition Survey (NNS, 2004) conducted in (2001–2002), pointed out that 66.5% of 0–5-year old were found to be iron deficient (35.6% with IDA). Among pregnant women, 41% had iron deficiency and 45% had zinc deficiency. In calculation, more than 50% people in Pakistan suffer from micronutrient deficiencies that gives alarming call for urgent attention of Government, but still it is a question mark.

Micronutrient deficiencies, such as iron, zinc, and vitamin A are responsible for 0.4 million and 0.6 million deaths respectively in children with less than five years of age, whereas

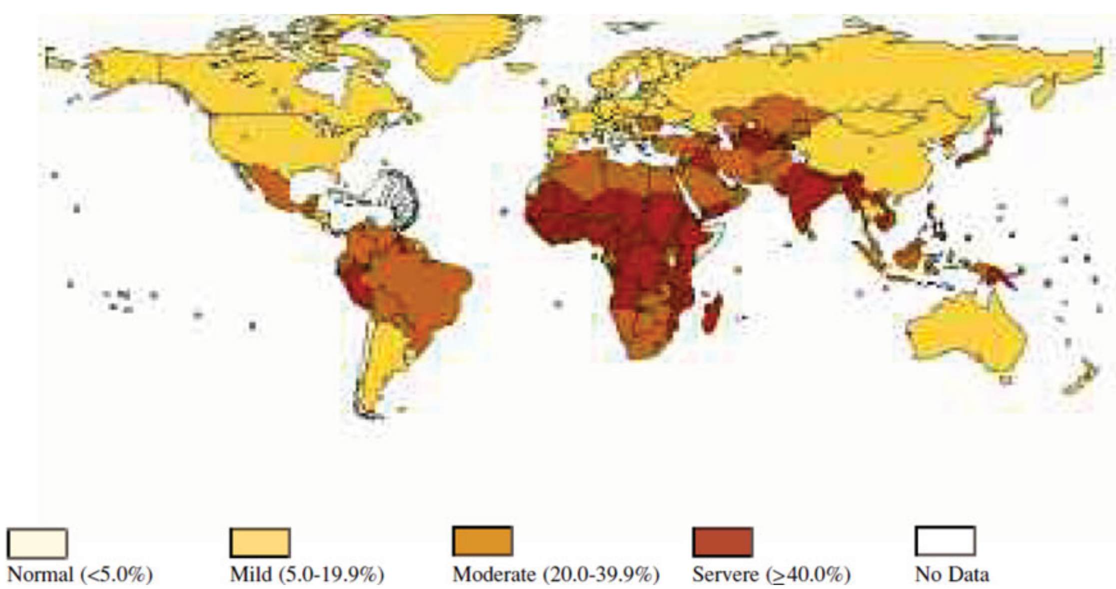

Figure 3 Anemia as a public health problem in nonpregnant women of global village. (Color figure available online.)

iron-deficiency anemia is found in 40–50% of infant and children (Black et al., 2008a).

IRON AS AN IMPORTANT NUTRIENT FOR SUSTAINING LIFE

Iron plays a central role in many biochemical processes in the body. The key function of iron is to facilitate oxygen transport by hemoglobin, the oxygen-carrying pigment of erythrocytes. It is also involved in oxygen storage by myoglobin, an iron-containing protein that transports and stores oxygen within muscles and releases it to meet increased metabolic demands during muscle contraction.

Iron is vital for the proliferation of all cells including those of the immune system. Iron deficiency causes several defects in both humoral and cellular immunity (Bowlus 2003), inhibition of thymocyte proliferation (Bowlus 2003), and a reduction in IL-2 (Interleukin 2) production (Bergman et al., 2004). Reduced IL-2 production may partly explain the increased susceptibility to infections and cancer in patients with iron-deficiency anemia (Bergman et al., 2004). There is also evidence that iron may be implicated in the pathogenesis of auto-immune disorders, including SLE (Systemic Lupus Erythematosus), scleroderma, type 1 diabetes, goodpasture syndrome, and multiple sclerosis (Bowlus, 2003). Current evidence suggests that moderately elevated iron stores may be associated with an overall increased risk for cancer, especially colorectal cancer (McCarty, 2003). Additionally, it has been proposed that iron may increase HIV replication (Olsen et al., 2004).

Both haem and nonhaem iron are a part of many enzymes that are involved in cellular respiration, amino acid metabolism (e.g., carnitine), detoxification (as part of cytochrome P450 enzymes in the liver), protection against free radical damage, synthesis of nutrients such as vitamin A, synthesis of hormones and neurotransmitters (serotonin and noradrenaline), and synthesis of collagen and elastin (Bowlus, 2003).

PHARMACOKINETICS OF IRON IN HUMAN BODY

Iron is an essential mineral found in the body in both haem and nonhaem form. In average, human body contains 2–4 g of iron. Iron exists in nature as metal and it has many different oxidation states, but only ferrous and ferric forms are stable in the aqueous form of a living body (Groff and Gropper, 2000). In terms of composition, iron in human body locates in forms of hemoglobin (65%); myoglobin (10%); enzymes (1–5%); the transport form, transferrin (0.05%); and in storage forms ferritin (4–9%) and hemosiderin (1–4%). In terms of solubility, haem form of iron is more soluble than the nonhaem form and is absorbed 2–3 times more readily. The absorption takes place via mucosal cells in the small intestine. Nonhaem iron is bound to other substances in food, and must first be released by gastric secretions mostly from hydrochloric acid and pepsin (Groff and Gropper, 2000).

Sources of Iron in Human Body

About 50–60% of the iron in animal sources is in the haem form. Sources include liver, lean red meat, poultry, fish, oysters, clams, shellfish, kidney, and heart. The nonheam iron is found in plant and dairy products in the form of iron salts and makes up about 85% of the average intake. Sources include nuts, legumes, fruit, dried fruit, and vegetables including beetroot, grains, and tofu. Dairy is a relatively poor source of iron. Iron is also obtained through many chemical sources such as ferrous sulfate, ascorbate, carbonate, citrate, fumarate, gluconate, lactate, succinate, and tartarate; among all these ferrous sulfate has a significantly greater bioavailability than from ferrous glycine chelate or ferric EDTA (Ferreira da Silva et al., 2004). Other ferric forms include ammonium citrate, chloride, citrate, pyrophosphate, and sulfate. Amino acid chelates, such as iron glycine, are also available (Davila-Hicks et al., 2004). It is noteworthy that cooking in iron pots may also improve iron status (Geerligs et al., 2003).

Factors Affecting Absorption of Iron in Human Body

The absorption is significantly affected by a number of factors (Table 1). The solubility from nonheam iron can be increased by ascorbic acid. The addition of 20 mg ascorbic acid has been shown to increase nonhaem iron absorption by 39% (Hallberg et al., 2003). The addition of red meat increases nonhaem iron absorption by 85% (Hallberg et al., 2003). There are many inhibitors that restrict the absorption from nonhaem sources like polyphenols, including tannin derivatives of gallic acid. Tea has been reported to reduce iron absorption by 60% and coffee by 40% (Kaltwasser et al., 1998; Morck et al., 1983). Recent studies have reported that tea catechins can inhibit intestinal nonhaem iron absorption (Ullmann et al., 2005). Other factors include Phytic acid (whole grains), oxalic acid (spinach, chard, chocolate, berries), and calcium. It has been recently reported that calcium phosphate in foods especially in milk reduces iron absorption by up to 70% (Hallberg et al., 1991).

The consumption of milk or the equivalent amount of calcium from fortified food does not appear to decrease nonhaem iron absorption (Grinder-Pedersen et al., 2004). But it remains to be shown in iron-deficient persons (Molgaard et al., 2005). Zinc competes with iron for absorption (Solomons, 1982). The inorganic zinc supplements reduce iron absorption by 66–80% (Crofton et al., 1989), but supplements containing both iron and zinc may not be as effective as the same doses given in isolation (Fischer Walker et al., 2005; Lind et al., 2003). Manganese also reduces absorption by 22–40% (Rossander-Hultén et al., 1991).

Table 1 Factors influencing dietary iron absorption (WHO, 2008)

Heme iron absorption	Nonheme iron absorption
Iron status of subject	Iron status of subjects
Amount of dietary heme iron, especially as meat Food preparation (time, temperature)	Amount of potentially available nonheme iron (adjustment for fortification iron and contamination iron)
Content of calcium in meal (e.g., milk, cheese)	Balance between enhancing and inhibiting factors
PROMOTING FACTORS	INHIBITING FACTORS
Ascorbic acid (e.g., certain fruit juices, fruits, potatoes, and certain vegetables)	Phytates and other inositol phosphates (e.g., bran products, bread made from high extraction flour, breakfast cereals, oats, rice, pasta products, cocoa, nuts, soya beans, and peas)
Meat, chicken, fish, and other seafood	Iron-binding phenolic compounds (e.g., tea, coffee, cocoa certain spices, certain vegetables)
Fermented vegetables (e.g., sauerkraut), fermented soy sauces, etc.	Calcium (e.g., milk, cheese)
	Soy proteins

IRON REQUIREMENTS OF HUMAN BODY

The total amount iron lost is estimated to be at 14 μg/kg body weight/day (Green, 1968). A nonmenstruating 55 kg woman loses about 0.8 mg Fe/day and a 70 kg man loses about 1 mg. The range of individual variation has been estimated to be $\pm 15\%$ (FAO/WHO, 1988). In case of infant, the requirement of iron is about 75 mg/kg body weight and it only fulfilled from human milk that only contain small amount of iron. During the first year of development, the infant almost doubles its total iron stores and triple its body weight. The change in body iron during this period occurs mainly during the first 6–12 months of life. Between one and six years of age, the body iron content is again doubled. The requirements for absorbed iron in infants and children are very high in relation to their energy requirements (Table 2). For example, in infants 6–12 months of age, about 1.5 mg of iron need to be absorbed per 4.184 MJ and about half of this amount is required up to the age of four years (WHO, 2008).

During the weaning period, the iron requirements in relation to energy intake are the highest of the lifespan except for the last trimester of pregnancy, when iron requirements to a large extent have to be covered from the iron stores of the mother. The rapidly growing weaning infant has no iron stores and has to rely on dietary iron. It is possible to meet these high requirements if the diet has a consistently high content of meat and foods rich in ascorbic acid (WHO, 2008).

Table 2 Iron intakes required for growth under the age of 18 years

Group	Age (years)	Body weight (kg)	Required iron intake (mg/day)
Children	0.5–1	9	0.55
	1–3	13.3	0.27
	4–6	19.2	0.23
	7–10	28.2	0.32
Males	11–14	45	0.55
	15–17	64.4	0.6
	18 onward	75	
Females	11–14A	46.1	0.55
	11–14B	46.1	0.55
	15–17	56.4	0.35
	18 on wards	62	
Menopause		62	
Lactating		62	

A, menstruating females; B, nonmenstruating females (WHO, 2008).

Iron requirements are also varies in adolescents, particularly during the period of rapid growth (Rossander-Hulthén and Hallberg, 1996). Menstrual blood losses are very constant from month to month for an individual, but vary markedly from one woman to another (Hallberg, 1966). The main part of this variation is genetically controlled by the content of fibrinolytic activators in the uterine mucosa even in populations which are geographically widely separated (Rybo, 1966; Rybo and Hallberg, 1966). The mean menstrual iron loss, averaged over the entire menstrual cycle of 28 days, is about 0.56 mg/day. The frequency distribution of physiologic menstrual blood losses is highly skewed. Adding the average basal iron loss (0.8 mg) and its variation allows the distribution of the total iron requirements in adult women to be calculated as the convolution of the distributions of menstrual and basal iron losses (Fig. 4). The mean daily total iron requirement is 1.36 mg. In 10% of women it exceeds 2.27 mg and in 5% it exceeds 2.84 mg (Hallberg and Rossander-Hulthénm, 1991). In 10% of menstruating (still-growing) teenagers, the corresponding daily total iron requirement exceeds 2.65 mg, and in 5% of the girls it exceeds 3.2 mg/day. The marked skewness of menstrual losses is a great nutritional problem because personal assessment of the losses is unreliable.

IRON-DEFICIENCY SIGNS AND SYMPTOMS

Iron deficiency is the most common nutritional deficiency in the world and gets second position in all micronutrient deficiencies (Gillespie et al., 1991). It may occur with or without anemia and divided into primary deficiency and secondary deficiency. Primary deficiency is most common in vegetarians, the elderly, those with protein calorie malnutrition, and during periods of increased iron requirement due to expanded blood volume in infancy, adolescence, and pregnancy (Gillespie et al., 1991).

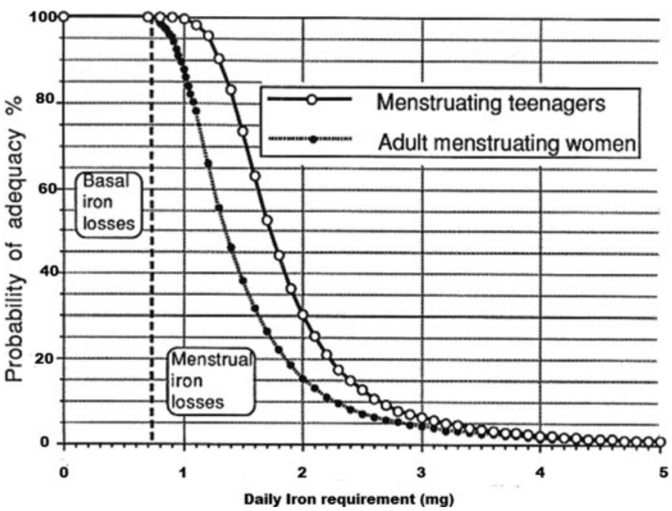

Figure 4 Distribution of daily iron requirements in menstruating adult women and teenagers: the probability of adequacy at different amounts of iron absorbed.

The secondary deficiency includes: iron-deficiency anemia including blood loss, inefficient absorption due to gastrointestinal disturbances, and increased destruction of red blood cells. Blood loss includes (menstruation, menorrhagia, bleeding hemorrhoids, parasites, bleeding peptic ulcer, malignancy, *H. pylori* infection, gastrointestinal bleeding). Inefficient absorption (chronic gastrointestinal disturbances, malabsorption syndromes, celiac disease) also comes in secondary deficiencies (Annibale et al., 2001). Iron-deficiency anemia, also known as hypochromic microcytic anemia, results in reduced work capacity in adults and a reduced ability to learn in children. Signs and symptoms include: fatigue and lethargy, decreased resistance to infection, cardiovascular and respiratory changes, which can progress to cardiac failure, decreased selenium and glutathione peroxidase levels, pale inside lower eyelid or mouth, pale-colored nail bed, pale lines on stretched palm (palmar creases), ridged, spoon-shaped, thin flat nails, brittle hair, impaired cognitive and motor function, adverse pregnancy outcomes, and increased perinatal maternal mortality (NMCD, 2011).

TYPES OF ANEMIA

There are over a dozen different types of anemia, some due to a deficiency of either a single or several essential nutrients and others from conditions that are not related to nutrition such as infections. People throughout the Asia suffer from nonnutritional anemia (such as sickle-cell anemia and thalassaemia, which are induced by genetic disorders), but these are few in comparison to the number of people, children, women, and men with nutritional anemia. The most important types of nutritional anemia includes; anemia of B_{12} deficiency, anemia of chronic disease, anemia of folate deficiency, drug-induced immune hemolytic anemia, hemolytic anemia, hemolytic anemia due to g6pd deficiency, idiopathic aplastic anemia, idiopathic autoimmune hemolytic anemia, immune hemolytic anemia, iron-deficiency anemia, pernicious anemia, secondary aplastic anemia, and sickle cell anemia (UNICEF, 2002).

Nutritional anemia develops slowly after the normal stores of iron have been depleted in the body and in the bone marrow. Women, in general, have smaller stores of iron than men and have increased loss through menstruation, placing them at higher risk for nutritional anemia. In men and postmenopausal women, anemia is usually due to gastrointestinal blood loss associated with ulcers, the use of aspirin or nonsteroidal anti-inflammatory medications (NSAIDS), and parasite infestations. High-risk groups include: women of child-bearing age who have blood loss through menstruation; pregnant or lactating women who have an increased requirement for iron; infants, children, and adolescents in rapid growth phases; and people with a poor dietary intake of iron through a diet of little or no meat or eggs for several years. Risk factors related to blood loss are peptic ulcer disease, long-term aspirin use, colon cancer, uterine cancer, and repeated blood donation (UNICEF, 2002).

EPIDEMIOLOGY

The presence of anemia is basically defined as a red blood cell count, which is below the accepted lower level of the normal range (Greer et al., 2008). In the daily clinical routine, anemia is defined by a hemoglobin (Hb) concentration, which is below the recommended lower thresholds established by epidemiological population surveys or by the local laboratory. In order to perform useful comparisons between countries, it is preferred to use the hemoglobin thresholds defined by the World Health Organization (WHO) shown in Table 3.

Anemia can be broadly classified into decreased erythrocyte production (ineffective erythropoiesis) as a result of impaired proliferation of red-cell precursors or ineffective maturation of erythrocytes; or increased loss of erythrocytes through increased destruction (hemolysis) or blood loss; or both. These processes are broadly determined by nutrition, infectious disease, and genetics (Balarajan et al., 2011; Tolentino and Friedman, 2007). Anemia is characterized by reductions in hemoglobin concentration, red-cell count, or packed-cell volume, and the subsequent impairment in meeting the oxygen demands of tissues (Warrell et al., 2003). Physiological characteristics such as age, sex, and pregnancy status, as well as environmental factors such as smoking and altitude affect hemoglobin concentration. There

Table 3 Threshold level of hemoglobin and total number of people effect by anemia (WHO, 2008)

Age or gender group	Hb threshold (g/L)	Anemia (%)	Population effected (Millions)
Children (6 months to under 5 years)	110	47	293
Children (5 years to under 12 years)	115	25	305
Children (12 years to under 15 years)	120	13	260
Nonpregnant women (15 years and over)	120	30	468
Pregnant women	110	42	56

is no specific threshold value for epidemiological surveillance, monitoring, and targeting (Beutler and Waalen, 2006; Dallman et al., 1978). The use of moderate-to-severe anemia (hemoglobin $<$90 g/L) has been recommended for disease surveillance, especially in high-prevalence countries, as changes in the high end of the distribution are likely to shift more rapidly than those at the low end, so are more helpful in monitoring progress (Stoltzfus et al., 1999).

Iron-Deficiency Anemia (IDA)

Recent studies suggested that weekly administration of iron is an effective strategy for the treatment and prevention of iron deficiency and iron-deficiency anemia in most population groups including pregnant women and children (Agarwal et al., 2003; Mukhopadhyay et al., 2004; Siddiqui et al., 2004; Sungthong et al., 2004; Yang et al., 2004) and is associated with lower cost, fewer side effects, and improved compliance (Haidar et al., 2003). Sixty children (age 5–10 years) with iron-deficiency anemia were given ferrous sulfate (200 mg) daily or weekly for two months with similar efficacy and fewer side effects in the once weekly group (Siddiqui et al., 2004). In another study, children receiving weekly doses of ferrous sulfate (300 mg) had similar improvements in hemoglobin, but a significantly higher increase in IQ than those taking the same dose of iron 5 days per week (Sungthong et al., 2004). The doses used in these trials may be higher than those actually required to correct deficiency. Patients, such as the elderly, who are particularly vulnerable to the dose-dependent adverse effects of iron supplementation, should be given the lowest effective dose. A randomized trial of 90 hospitalized elderly patients demonstrated that 15 mg of liquid ferrous gluconate produced similar improvements in hemoglobin and ferritin over 60 days to 150 mg of ferrous calcium citrate tablets without the negative side effects (Rimon et al., 2005). In all cases, the lowest safe and effective dose at the lowest frequency of dosing should be used to correct iron deficiency with or without anemia.

Pregnancy

A supplement of 40 mg ferrous iron/day from 18 weeks of gestation appears adequate to prevent iron deficiency in 90% of the women and iron-deficiency anemia in at least 95% of the women during pregnancy and postpartum (Milman et al., 2005). A single weekly dose of 200 mg elemental iron, however, may be sufficient as this has been shown to be comparable with 100 mg elemental iron daily on erythrocyte indices (Mukhopadhyay et al., 2004). Although iron supplementation is often used as stand-alone treatment in pregnant iron-deficient women, one RCT (Root Canal Therapy) indicated that a combination of iron and folate therapy (80 mg iron protein succinylate with 0.370 mg folinic acid daily) for 60 days produces a better therapeutic response than iron-only supplementation (Juarez-Vazquez et al., 2002). Due to the possibility of uncontrolled lipid peroxidation, predictive of adverse effects for mother and fetus, iron supplementation should be prescribed on the basis of biological criteria, not on the assumption of anemia alone (Lachili et al., 2001).

Postpartum Anemia

Postpartum anemia is associated with breathlessness, tiredness, palpitations, maternal infections, and impaired mood and cognition. A Cochrane 2004 review suggested that further high-quality trials were required before the benefits of iron supplementation or iron-rich diets in the treatment of postpartum anemia could be established (Dodd et al., 2004). Since then a randomized placebo-controlled study of iron sulfate (80 mg daily) for 12 weeks starting 24–48 hours after delivery demonstrated an improvement in hemoglobin levels and iron stores (Krafft et al., 2005) and supplementation of ferrous sulfate (125 mg) with folate (10 μg) and vitamin C (25 mg) demonstrated improvements in cognitive function, as well as depression and stress compared with folate and vitamin C alone (Beard et al., 2005). However, further studies are still warranted.

Unexplained Fatigue without Anemia

Iron supplementation is sometimes used in women who are not anemic (hemoglobin $>$117 g/L) yet complain of fatigue. A recent, double-blind, randomized placebo-controlled trial designed to determine the subjective response to iron therapy in nonanemic women (hemoglobin $>$117 g/L) with unexplained fatigue found that supplementation with oral ferrous sulfate (80 mg/day elemental iron) for four weeks reduced the level of fatigue in the iron group by 29% compared with 13% in the placebo group. Subgroup analysis showed that only women with ferritin concentrations $<$50 μg/L improved with oral supplementation. This was common in 85% of subjects and 51% of subjects had ferretin concentrations $<$20 μg/L (Verdon et al., 2003). This study suggests that iron-deficiency anemia may be present despite hemoglobin and ferritin levels being within the "normal" range and that the lower reference levels for women may need to be revised.

Folate and Vitamin B_{12}

It is concluded that anemia is linked with vitamin deficiencies and nearly one-third (32%) of the women were deficient in riboflavin, 40% had vitamin B6 deficiency, and 28% had vitamin B_{12} deficiency (Fig. 5). The most common vitamin deficiency producing anemia is folate deficiency (Benoist, 2008; Khatib et al., 2006; Milman, 2011). Folate deficiency causes a specific form of anemia termed megaloblastic anemia. It has been estimated that in developing countries, folate deficiency occurs

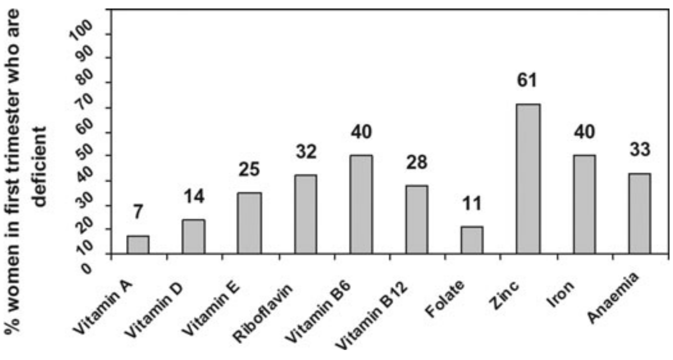

Figure 5 Multiple nutrient deficiencies occur in women in first trimester, Sarlahi Nepal.

in as many as 25–72% of women of reproductive age (Khatib et al., 2006). In the fetus and newborn baby, folate deficiency is associated with a high risk of neural tube defects as well as other defects (Khatib et al., 2006). Folate is present in food of plant origin, e.g., green leafy vegetables, grains, etc. The folate is highly sensitive toward heat treatment. The modern processing and eating habits further reduces the availability of folate.

Vitamin B_{12} deficiency is the second most common vitamin deficiency causing anemia (Greer et al., 2008). In developing countries, vitamin B_{12} deficiency constitutes a significant problem (Khatib et al., 2006) and studies from Lebanon and Turkey have revealed that about 40% of women of reproductive age have vitamin B_{12} deficiency (Keraglu et al., 2010), which in addition to insufficient dietary vitamin B_{12} intake, may be due to the food cobalamin malabsorption syndrome or pernicious anemia (Benoist, 2008). The prevalence of IDA is mostly in young children and females especially adolescents. The body of adolescent females grew very rapidly and during their first menstrual cycle, there is appreciable loss of iron, followed by women of reproductive age, pregnant women, and lastly lactating women (Table 4).

IRON DEFICIENCY IN INFANCY AND EARLY CHILDHOOD

Significant emphasis is placed on reducing the prevalence of iron deficiency in infancy and early childhood, because a large body of evidence indicates that poor iron status negatively affects cognitive, motor, and social development during this period of rapid growth and development (Gleason and shrimshaw, 2007). Iron-deficiency anemia has been shown to have significant adverse effects on infants between 6 months and 24 years of age, that include decreases in responsiveness and activity, as well as increases in body tension and fatigue. Depending on the age at which anemia occurs and its severity, some developmental deficits can be improved or even corrected with iron treatment, but with iron deficiency in infancy some cognitive and social differences can remain permanent (Lozoff et al., 2000).

Table 4 Public health significance of different prevalence of anemia (WHO, 2008; Milman, 2011)

Prevalence of anemia (%)	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	Severe public health problem

The risk of iron deficiency is high during infancy because only about 50% of the iron requirement of a normal six-month old can be obtained from breast milk, and by this age the stores received at birth are likely to have been used to support normal functions and growth even in children born at term of well-nourished mothers. If the mother is anemic and/or the child is of LBW, the stores are depleted much earlier. Continued breastfeeding alone will supply only half of the infant's iron needs, while the other half, approximately 4 mg/day, must come from complementary foods or an iron-containing supplement if iron-deficiency anemia is to be avoided.

The high risk of iron-deficiency anemia in children 6–24 months of age is clearly shown in analysis of pooled data from 18 Demographic and Health Surveys (DHS) from 11 developing countries. Cohorts of children selected by months of age from 6 to 24 months from more than 31,000 children for which hemoglobin had been measured found approximately 50% anemia among cohorts of children in each monthly age group (Fig. 6). For infants younger than six months, especially in developing countries, several factors may lead to an iron status inadequate for normal growth and development. Studies have also found the infants of mothers suffering from anemia during pregnancy have lower iron stores at birth. Cutting the pulsing umbilical cord before iron-rich cord blood is transferred to the newborn also results in lower iron in the infant at birth. LBWs account for up to 20% of infants in poorly nourished populations, and these infants receive low levels of iron stores based on lower overall tissue and blood volume at birth. These facts, compounded by the increased iron needs associated with the rapid weight gain of LBW infants, are the basis for the WHO and UNICEF recommendation that LBW infants receive supplementary iron beginning at two months (Llewelyn-Jones, 1965; Beischer, 1968), and continuing up to 24 months of age (Stoltzfus, 1998).

IRON DEFICIENCY IN PAKISTAN

In Pakistan, despite an increase in per capita food availability and resultant rise in per capita calorie and protein intake, the prevalence of malnutrition has not improved over last 20 years (PDHS, 2007). At the time of the on-set of the Ninth Plan, i.e., 1997–1998, the estimated number of malnourished children was about 8 million. Nearly half of the children under five years of age were found underweight of age at a level that corresponds to general malnutrition of protein energy malnutrition (PEM). Approximately 5% of these were severely underweight and 10% were moderately underweight. Recent studies show that

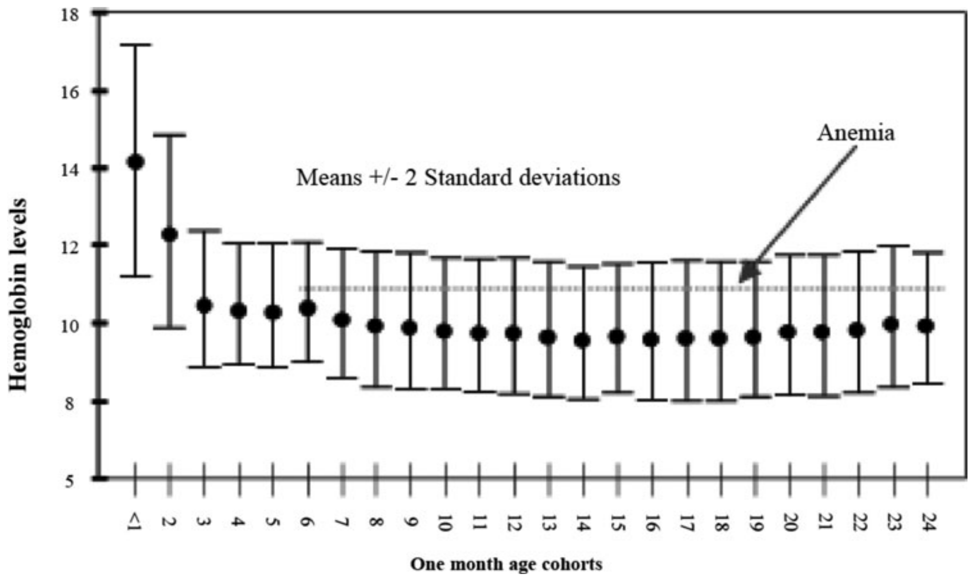

Figure 6 Mean hemoglobin levels (g/dL) of children. Grouped by age in months from 19 population surveys (total $n = 31{,}859$).

Pakistan is lacking to achieve its Millennium targets goal to reduce malnutrition and it is clearly depicted from Fig. 7.

The nutritional and demographic surveys, conducted during last two decades, indicate extremely poor state of female and child nutrition. According to the National Nutrition Survey (NNS, 1988), nearly 65% of the young children and 45% of pregnant and lactating women suffered from anemia due to iron deficiency. Nearly 28% of pregnant and 46% of lactating women consumed less than 70% of recommended daily allowance (RDA) of calories. Almost 10–20% children of age under five years received less than 70% of the RDA of protein, nearly 30–40% received less than 70% of the RDA for calories, and 25% children of the age group 4–5 years received less than 70% of the RDA for iron. An overview of the hemoglobin level in married and pregnant women of Pakistan is presented in Fig. 8.

IDA in Pakistan

Anemia in children can be linked with iron deficiency in mothers during pregnancy; hence a few surveys regarding iron deficiency in women have been conducted in Pakistan. The Fig. 9 presents the data given by World Health Organization (WHO, 2001) regarding prevalence of anemia and mean hemoglobin concentration in Pakistan. Fig. 9 shows that among the total population, 29.4% women are anemic and out of them 24.9% (maximum number of anemic women) are of the age of 19 years (43.5%). This percentage decreases after the age of 40 years. On comparing the prevalence of anemia areawise, its occurrence is higher in the rural area than the urban areas of Pakistan.

The National Nutrition Survey (NNS) report defines anemia by Hb level less than 10 g/dL and states that 45.2% pregnant and lactating mothers were anemic in Pakistan (NNS, 1988). The

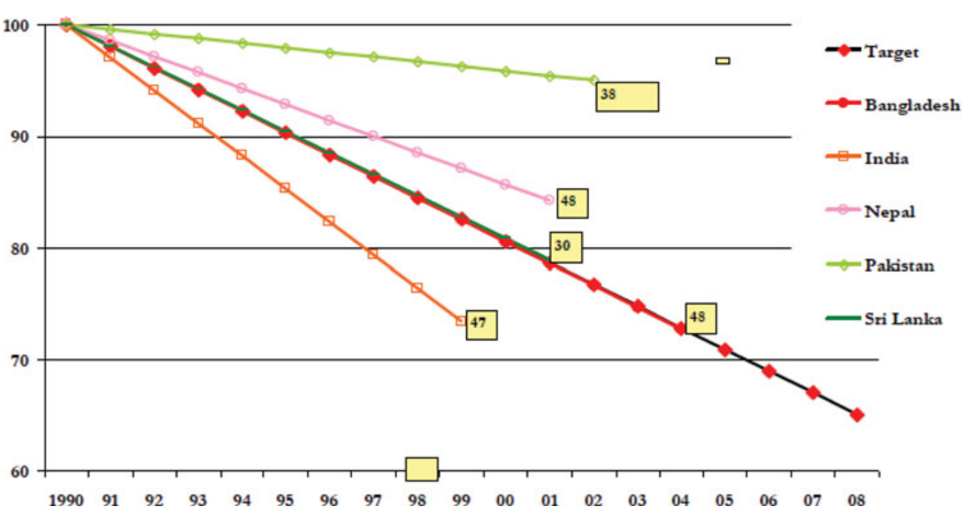

Figure 7 Millennium target goal (MDG) on reduction in malnutrition (weight for age) (1990 = 100%, target reduction to 50% of 1990 level by 2015). (Color figure available online.)

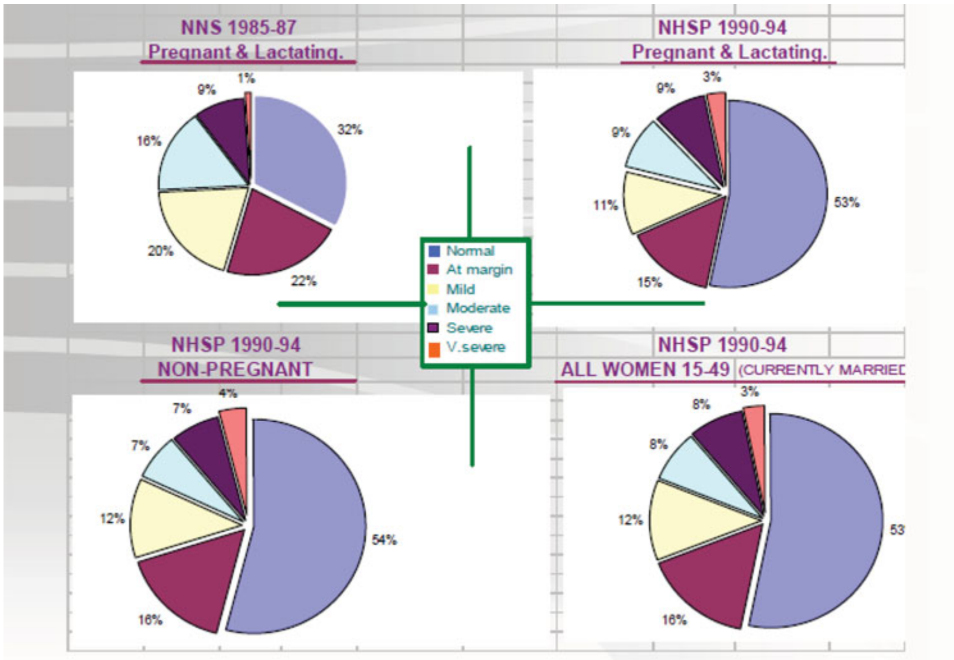

Figure 8 Status of hemoglobin in married and pregnant women. (Color figure available online.)

survey conducted later in Pakistan manifests prevalence of IDA, iron deficiency, and anemia in mothers up to 25%, 45%, and 29.4%, respectively. This percentage was even higher in children, i.e., 35.6%, 66.5%, and 50.9%, respectively (NNS, 2004).

Agha et al. (1992) studied iron deficiency among 270 Pakistani students, ages 13–20, from low-income families attending government schools in the suburbs of Islamabad. Their findings indicated that both boys and girls suffer from overall iron depletion and anemia to a similar extent. A recent study by Sabah et al. (2010) on nutritional deprivation among female patients of reproductive age group proved that the lack of the balanced diet especially protein group has much stronger association with iron-deficiency anemia. The study by Khalil et al. (2007) showed that out of the total samples, 48.2% of the pregnant women were found to be anemic in Pakistan. Later on in Hyderabad (Pakistan), Ansari et al. (2008) found 90.5% anemic women in his observational study of 1369 pregnant women enrolled at 20–26 weeks of gestation and followed to 6 weeks postpartum. Among these 75.0% were mildly anemic, 14.8% were moderately anemic, and 0.7% were severely anemic. Khan et al. (2010) conducted research on 262 male and 259 female students of Peshawar University in order to evaluate the prevalence of anemia. Their findings showed that out of 521 participating students. 23.9% females have anemia in comparison to males 1.5%. Similarly, Irshad et al. (2011) determined the incidence of anemia on the basis of ferritin in three socioeconomic groups, i.e., poor, middle, and upper classes during three trimesters of pregnancy. They concluded that total mean serum ferritin (ng/mL) level were 18.5, 14.6, and 14.7 in first, second, and third trimesters, respectively. They also mentioned that serum ferritin was very low in all three socioeconomic groups and it was lowest in poor class in comparison with middle and upper class (Arshad et al., 2011).

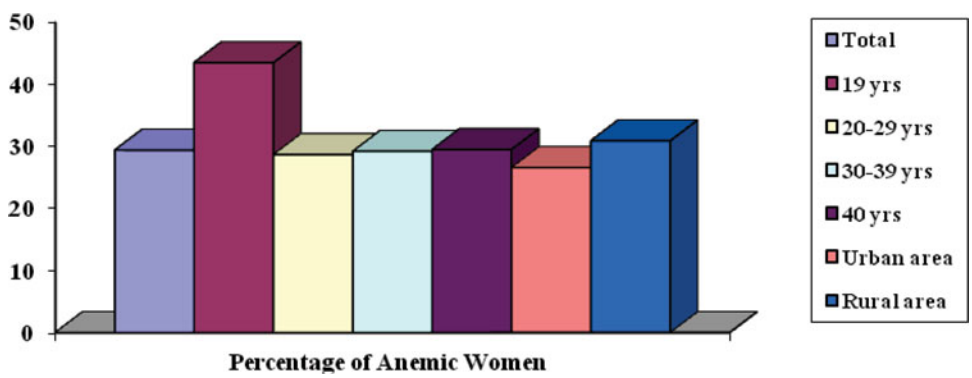

Figure 9 Prevalence of anemia and mean hemoglobin concentration in Pakistan. (Color figure available online.)

Infants born to anemic mothers are more likely to be moderate or severely anemic than those born to nonanemic mothers (Nestle and Ritu, 2000). The Pakistan National Nutrition Survey found that 65% of children between the ages of 7–60 months were anemic (NNS, 1988), with hemoglobin of less than 11 g/L.

Causes of IDA in Pregnant Women

IDA in pregnant women is related to the socio-economic factor, such as poor dietary habits, lack of awareness, and access to iron supplements (Awan et al., 2004). During a survey in Multan, Pakistan they found that 88% of the subjects had breast fed their children and faced multiple pregnancies. Moreover, food choices and food access impart decisive role in prevalence of IDA especially during pregnancy (Sabah et al., 2010). In another study conducted by Abbassi et al. (2009), 76.42% of pregnant women were anemic due to nutritional deficit.

Breast feeding is also an important stress on the nutritional status of the mother. All these factors deplete the micronutrient stores of the mother, to the extent that she becomes anemic even in the first trimester in next pregnancy. This brings a more severe outcome for the mother and the baby (Awan et al., 2004). Another reason of IDA is poor iron stores at the pre-pregnancy stage (McMahon, 2010).

The requirement of iron is calculated on the basis of iron losses from the body, intake of iron sources, and already stores of iron present in the body (Beard, 2000b). Talking about the losses, the foremost form of blood loss is through the menstruation cycle; later in pregnancy iron loss due to greater demand of iron in second and third trimesters contributes in developing anemia among pregnant women (Huma et al., 2007). Study by Asif et al. (2007) at Pakistan Institute of Medical Sciences Hospital, Islamabad showed decrease in serum ferritin and hemoglobin during second trimester followed by third trimester. This requirement increases to 6.7 and 10–12 mg per day in second and third trimesters, respectively (Beard, 2000b). Iron needs are sectioned some of iron is required for the red blood cells expansion, whereas some iron is needed to meet the requirement of growing fetus and placenta (Kozuma, 2009). Additional loss of iron occurs during and after delivery (Beard, 2000a). Therefore, women are generally advised to take iron supplements during pregnancy and, in some circumstances, during early lactation (WHO, 2001; 2008).

Consequences of IDA

The pregnant and lactating women and growing children especially in the developing world are vulnerable to IDA. The major consequences for pregnant women are the premature delivery and LBW (Ali et al., 2011). This in turn is linked to increased risk of prenatal and infant mortality. Anemia in early pregnancy can be harmful to the development of unborn baby. It increases chances of mother having miscarriages or still-birth; in women, it also accelerates the mortality and morbidity rate (Abu-Saad and Fraser, 2010).

Anemia in mothers results in low reserves of iron in the infants (Nestle and Ritu, 2000). In children, IDA retards growth, impairs cognitive performance, and reduces physical activity (Hotz et al., 2008). The physical activity is impaired due to IDA because of the feeling of exertion, dizziness, and general weakness as IDA is also responsible for the frail immune system (Kasumi et al., 2006; Rashid et al., 2009).

PREGNANCY OUTCOME OF IDA IN PAKISTAN

Serious outcomes of IDA are expected in case of pregnancy (Jilani and Iqbal, 2010). Second and third trimesters are the most critical trimesters in which chances of iron deficiency are at its peak (Zimmermann and Hurrell, 2007).

Preterm Birth

Prematurity is a consequence of anemia during gestation which leads to the release of placental stress hormones (CRH, Norepinephrine) followed by the fetal release of ACTH (adrenocorticotropichormone) and cortisol. These induce production of uterine contraction stimulating hormones (estrogen, connexin) and inhibition of insulin like growth factor (IGF), an important anabolic hormone for fetal development (Haram et al., 2003). Many studies showed that the increased level of CRH results in greater risk of preterm birth and constrained growth of the fetus (Wadhwa et al., 2004). Other than CRH release, maternal infections and hypoxia induced by IDA become the reason for premature births (Haram et al., 2003; Kozuma, 2009).

Lone et al. (2004) observed four times increase in the threat of premature births in their study conducted at Agha Khan University Hospital. These studies too found hypoxia and CRH the reason for gestational period to be less than 37 weeks. A study in Rawalpindi supported these figures; in the study, threat of preterm birth was 3.8 times higher than normal deliveries (Waqar et al., 2008).

Another study conducted at Department of Gynecology & Obstetrics at Baqai Medical University to ascertain the major reason for premature births validated that anemia was carrying the load (Tufail et al., 2009). Similarly, the study at MirPur Khas revealed iron-deficiency anemia to be the cause of preterm births. In this study, it was found that among 75% pregnant women 9% cases resulted in preterm babies in a study conducted by Rizwan et al. (2010). Another study conducted in Sindh showed alarming statics of preterm births, i.e., 23.5% (Jaleel and Khan, 2008).

Birth Weight

Similar low indices in the anthropometric measurements were observed by Golub et al. (2006), but no other causality was observed in his study. On the other hand, scientists working on IDA during pregnancy revealed incidences of preterm births and LBW babies and maternal mortalities. The lower level of hemoglobin is directly proportional to the incidences of LBW babies (Rizvi et al., 2007). Lone et al. (2004) found that possibility of low birth weighed children to anemic mothers was 2.2 times higher than the nonanemic ones. Almost similar results were quoted by Waqar et al. (2008), i.e., risk of LBW babies is 2.1 times higher in anemic mothers. Whereas a study conducted in Rawalpindi revealed that the risk of LBW babies was 3.4 times higher (Bakhatwar et al., 2007). Preterm births were not only alarming in the study but also the LBW ratio was found to be highest in Sindh region of Pakistan (Jaleel and Khan, 2008).

It has been also studied that the relationship of maternal hemoglobin concentrations and birth weight shows a U-shaped association (Rasmussen, 2001). Abnormally high hemoglobin concentrations usually indicate poor plasma volume expansion, which is also a risk for LBW (Steer, 2000).

Maternal Mortality and Morbidity

Maternal mortality is a threat usually near and at delivery till first week after delivery; the possibility of maternal deaths is even high after still-births and unsafe abortions (Ronsmans and Graham, 2006). Anemia leads to the starvation of muscles for oxygen mainly affecting heart muscles that retard altogether causing heart failure. This ultimately causes death. Anemia in the moderate stage cannot cause death directly, but it may induce some other problems that become fatal. Some common examples are hemorrhages, lack of tolerance for any blood loss. It has been studied that a healthy pregnant woman at the time of delivery can withstand 1 L loss of blood. On the other hand, 150 mL loss of blood for the anemic mother can be fatal. Another important reason for maternal mortality is the susceptibility for anesthesia and operative risk. Moreover, postpartum hemorrhages are major cause of maternal deaths. Study at Ayub Medical teaching Hospital Pakistan revealed that 90% postpartum hemorrhages are caused due to anemia (Naz et al., 2008).

Pakistan is unfortunately among those developing countries that experience maternal mortality at a huge count, i.e., 1 out of every 23 women dies during child birth (PHS, 2001). Planning commission revealed the maternal mortality rate in Pakistan as 350 deaths per 100,000 births. This number increased in 2005 to 400 deaths per 100,000 births according to Pakistan Social and Living Standard Measurement Survey (PSLSMS, 2005). Recent survey by Pakistan Demographic and Health Survey estimates that among every 89 pregnant women one dies due to maternal complications (PDHS, 2007). A study conducted in Peshawar concluded that maternal mortality rate is 1311/100,000 births with direct causes having precedence over the indirect ones (Rahim et al., 2006). Similar situation is prevailing in Sindh Province, out of 21 maternal deaths 8% was found to be due to anemia. In Karachi, MMR 1578/100,000 live births shows gruesome effect of IDA in Pakistan (Sheikh et al., 2010).

Table 5 Iron requirements during pregnancy (WHO, 2008)

	Iron requirements (mg)
Iron requirements during pregnancy	
Fetus	300
Placenta	50
Expansion of maternal erythrocyte mass	450
Basal iron losses	240
Total iron requirement	1040
Net iron balance after delivery	
Contraction of maternal erythrocyte mass	+450
Maternal blood loss	−250
Net iron balance	+200
Net iron requirements for pregnancy if sufficient maternal iron stores are present (1040−200 = 840)	840

Iron During Pregnancy and Lactation

Iron requirements during pregnancy are well established (Table 5). The importance of iron during pregnancy can be judged by the following fact that 13% of maternal deaths in Asia and 4% in Africa are directly caused by anemia (UNICEF, 2009) also anemia contributes to the over 30% of deaths that are due to hemorrhage. Most of the iron required during pregnancy is used to increase the hemoglobin mass of the mother, which occurs in all healthy pregnant women who have sufficiently large iron stores or who are adequately supplemented with iron. The increased hemoglobin mass is directly proportional to the increased need for oxygen transport during pregnancy and is one of the important physiologic adaptations that occurs in pregnancy (Hallberg, 1988; Hallberg, 1992). A major problem for iron balance in pregnancy is that iron requirements are not equally distributed over its duration. The exponential growth of the fetus implies that iron needs are almost negligible in the first trimester and that more than 80% relates to the last trimester. The total daily iron requirements, including the basal iron losses (0.8 mg), increase during pregnancy from 0.8 mg to about 10 mg during the last six weeks of pregnancy.

Iron absorption during pregnancy is determined by the amount of iron in the diet, its bio-availability (meal composition), and the changes in iron absorption that occur during pregnancy. There are marked changes in the fraction of iron absorbed during pregnancy. In the first trimester, there is a marked, somewhat paradoxical, decrease in the absorption of iron, which is closely related to the reduction in iron requirements during this period as compared with the nonpregnant state. In the second trimester, iron absorption is increased by about 50%, and in the last trimester it may increase by up to about four times. Even considering the marked increase in iron absorption, it is impossible for the mother to cover her iron requirements from diet alone, even if its iron content and bio-availability are very high. It can be calculated that with diets prevailing in most

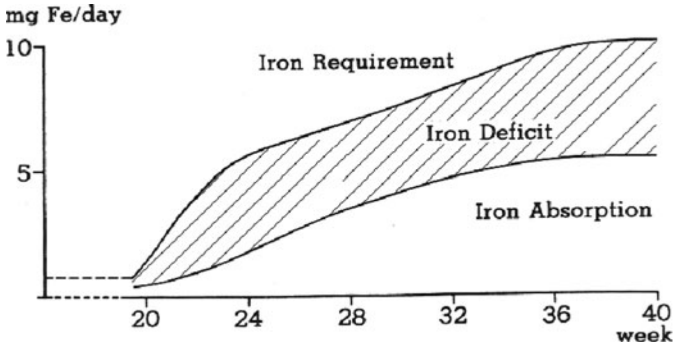

Figure 10 Daily iron requirements and daily dietary iron absorption in pregnancy.

industrialized countries, there will be a deficit of about 400–500 mg in the amount of iron absorbed during pregnancy (Fig. 10).

An adequate iron balance can be achieved if iron stores of 500 mg are available. However, it is uncommon for women today to have iron stores of this size. It is therefore recommended that iron supplements in tablet form, preferably together with folic acid, be given to all pregnant women because of the difficulties in correctly evaluating iron status in pregnancy with routine laboratory methods. In the nonanemic pregnant woman, daily supplements of 100 mg of iron (e.g., as ferrous sulphate) given during the second half of pregnancy are adequate. In anemic women higher doses are usually required. During the birth process, the average blood loss corresponds to about 250 mg iron. At the same time, however, the hemoglobin mass of the mother is gradually normalized, which implies that about 200 mg iron from the expanded hemoglobin mass (150–250 mg) is returned to the mother. To cover the needs of a woman after pregnancy, a further 300 mg of iron must be accumulated in the iron stores in order for the woman to start her next pregnancy with about 500 mg of stored iron. Such restitution is not possible with present types of diets. There is an association between low hemoglobin values and prematurity. An extensive study (Lieberman et al., 1988) showed that a woman with a hematocrit of 37% had twice the risk of having a premature birth as did a woman with a hematocrit between 41% and 44% ($P \leq 0.01$).

A similar observation was reported in another extensive study in the United States of America (Garn et al., 1981). These materials were examined retrospectively and the cause of the lower hematocrit was not examined. In lactating women, the daily iron loss in milk is about 0.3 mg. Together with the basal iron losses of 0.8 mg, the total iron requirements during the lactation period amount to 1.1 mg/day. In early pregnancy, there are marked hormonal, hemodynamic, and hematologic changes. There is, for example, a very early increase in the plasma volume, which has been used to explain the physiologic anemia of pregnancy observed also in iron-replete women. The primary cause of this phenomenon, however, is more probably an increased ability of the hemoglobin to deliver oxygen to the tissues (fetus). This change is induced early in pregnancy by increasing the content of 2, 3-diphospho-D-glycerate in the erythrocytes, which shifts the hemoglobin–oxygen dissociation curve to the right.

The anemia is a consequence of another observation has likewise caused some confusion about the rationale of giving extra iron routinely in pregnancy. In extensive studies of pregnant women, there is a U-shaped relationship between various pregnancy complications and the hemoglobin level (i.e., there are more complications at both low and high levels). There is nothing to indicate, however, that high hemoglobin levels (within the normal nonpregnant range) per se have any negative effects. The hemoglobin increase is caused by pathologic hormonal and hemodynamic changes induced by an increased sensitivity to angiotensin II that occurs in some pregnant women, leading to a reduction in plasma volume, hypertension, and toxemia of pregnancy. Pregnancy in adolescents presents a special problem because iron is needed to cover the requirements of growth. In countries with very early marriage, a girl may get pregnant before menstruating. The additional iron requirements for growth of the mother are then very high and the iron situation is very serious.

STRATEGIES TO COMBAT IDA IN PAKISTAN

The devastating effects of IDA demand its prevention and were mentioned as one of the aims in National health objectives (US) to reduce iron deficiency to less than 3% among children till five years and women of childbearing age till the year 2000. Further Millennium Development Goals were laid, setting up to reduce maternal and child mortality up to three quarters and two-third respectively till 2015 (PMDGR, 2005). Similarly, Pakistani policy makers are seriously dealing with children and maternal health issues by aligning their policies and setting their goals similar to International Millennium Development Goals (Government of Pakistan, 2008). This requires the application of some intervention strategies. It includes: (1) dietary change and diversification to increase iron intake, (2) iron supplementation, and (3) fortification of a suitable staple food with iron (Allen et al., 2006).

Dietary Diversification

Dietary diversification or modification has the potential to prevent deficiencies of iron and other coexisting limiting micronutrients simultaneously, without risk of antagonistic interactions (Gibson and Anderson, 2009). Diets in low-income countries are plant based and consumption of animal source foods, such as meat, poultry, and fish, is often limited because of economic, cultural, and/or religious constraints. As a result, the iron content of such diets is low and the efficiency of absorption is limited. Dietary inadequacy is probably the primary cause iron deficiency. To increase the iron content in the diets, small-livestock husbandry, aquaculture, and production of other indigenous iron-rich food can be promoted. At the household level, reduction of phytate content of the diet can be achieved by using simple techniques to activate phytase, which is present naturally in cereals and legumes. A combination of dietary strategies involving increased consumption of animal source foods and phytate reduction is the preferred approach to enhance both the content and bioavailability of zinc and iron in the diets of rural households in low-income countries (Gibson, 2006). Such strategies have the added advantage of simultaneously improving the content and bioavailability of iron, vitamin B_{12}, vitamin A, and calcium while enhancing protein quality and digestibility. Dietary diversification also involves creating awareness among people to increase consumption of meat, poultry, and fish, which are naturally rich in iron (Zlotkin, 2003). Addition of vitamin C or its natural presence in a food enhances the iron absorption. That is why, vitamin C is recommended to be ingested with iron-rich food especially (Killip et al., 2007).

Fortification and Supplementation

Food fortification has been defined as the addition of one or more essential nutrients to a food, whether or not it is normally contained in the food, for the purpose of preventing or correcting a demonstrated deficiency of one or more nutrients in the population or specific population groups (WHO 2001).

Cereal foods can be successfully fortified with iron. Among the cereals, wheat has additional advantage to be used as vehicle. The bioavailability of iron added to wheat is several times greater than other staples such as maize and rice (Cook and Reusser, 1983; Cook et al., 2003). Wheat flour is a relatively dry and free flowing powder making it easy to blend small quantities of micronutrients with little segregation or separation. In Pakistan, leavened flat bread (khameeri roti) is consumed by all population segments and socioeconomic strata. Bread is taken daily and in relatively constant amounts. Fortification is truly invisible to the consumer. While consumers must be educated to purchase fortified products the flour products are already part of the diet and no individual compliance is necessary. Iron-fortified whole wheat flour constitutes a familiar, convenient, acceptable, nutritious, and comparatively low-cost food ration for the target population and ensures a better nutritious diet for them (Anjum et al., 2006).

Wheat flour is a good vehicle for delivering additional iron in Pakistan because it is so widely consumed and because iron can be added with no effect on product quality or appearance and at very low cost (Anjum et al., 2006). Since iron is a mineral it will not diminish during production, storage, or baking. However, over time interactions between ferrous sulfate and the fat naturally contained in flour will cause rancidity leading to changes in color and flavor. This interaction between ferrous sulfate and fat tends to increase with humidity, length of storage as well as the amount of iron added (Cook and Reusser, 1983).

Okley (2002) fortified flour with folic acid and discussed with reference to concern about safety of folic acid fortification for adults; lack of evidence of adverse effects of folic acid fortification and protective action of folic acid against cardiovascular disease. It is suggested that the health benefits of folic acid fortification of flour justify introduction of folic acid fortification without more randomized controlled trials, and that folic acid fortification is a simple inexpensive and effective intervention to prevent major human diseases. Similarly, Ranum (2000) reported that as staples, milled cereals are relatively inexpensive; they are grown and consumed worldwide by all economic classes, versatile in preparation, and use and generally processed in large centralized plants. Consequently, milled cereals are good vehicle for fortification.

Davidson (1996) reported that cereal-based foods may be fortified with reduced iron of small particle size, ferrous fumarate or ferrous succinate, while milk-based foods may be fortified with ferrous sulfate. In cereal-based foods, the inhibitory effect of phytate may be inhibited by adding ascorbic acid or exogenous phytase to degrade the phytate. Layrisse et al. (1996) reported that for the past 60 years, fortification of flour with iron and vitamins has been demonstrated to be a cost effective way of reducing the prevalence of anemia in many countries of the world. In Venezuela, e.g., fortification of wheat flour with iron led to the reduction of anemia from 39 to 16% in children of age 16 during the period 1992–1994. Awan et al. (1995) reviewed the fortification of whole wheat flour. The authors reviewed in detail the problems of malnourishment especially protein deficiency, strategies to improve the protein level of the food and benefits of fortifying the whole wheat flour with protein-rich minerals such as cereals, tubers, milk, milk products, fish, fish protein concentrate, oil seed flour, oil seed meal, and different legumes. The authors also reviewed the use of composite flour technologies to eliminate protein deficiency. Foods in which composite flour have been employed include cookie, biscuits, nans, breads, chapaties, and miscellaneous products.

The available studies clearly show that iron fortification can increase total daily iron absorption, it is reasonable to say that individuals at risk of iron deficiency who consume iron fortified foods will have enhanced iron status. Most absorption studies also show that adding iron to food does not adversely affect the absorption of other minerals, like zinc. Food fortification is toting up essential nutritional elements in a food to combat respective deficiency. That food to be fortified should be affordable, consumed regularly, and available in predictable amount to the target population. Many countries are practicing fortification to fight back micronutrient deficiencies because of the economic (Fig. 11) (Huma et al., 2007).

Iron supplementation during pregnancy can lower the adverse outcomes of anemia by minimizing the threat of iron-deficiency anemia (Berglund et al., 2010). It was suggested through a study conducted at Hospitals in Islamabad and Taxila that daily oral iron supplementation increases the hemoglobin level more than oral iron twice a week (Mumtaz et al., 2000). However, at 16 weeks, a twice weekly dose of iron increases the hemoglobin level more than oral iron given once a week (De-Souza et al., 2000). Maternal hemoglobin at four weeks becomes higher and hemoglobin level > 11 g/dL at birth was more frequent, with intravenous iron, as compared with oral

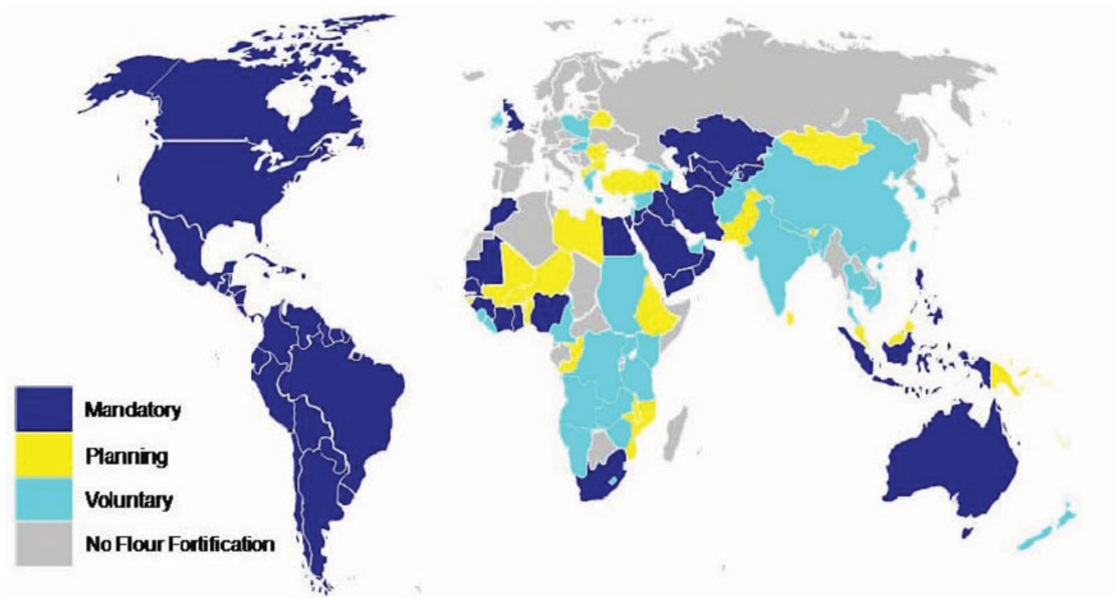

Figure 11 Fortification status in world till March 2011. (Color figure available online.)

iron (Bayoumeu et al., 2002). In a study, oral iron was found to be better than intramuscular iron (Zutshi et al., 2004), which in turn produced better hematological parameters than intravenous iron (Wali and Nilofour, 2002). A very recent study carried out by Yakoob and Bhutta (2011) to study the effect of routine iron supplementation with or without folic acid on anemia during pregnancy and they concluded that daily supplementation results in 73% reduction in the incidence of anemia and 67% in terms of iron-deficiency anemia as compared to no supplementation. Their study was based on Child Health Epidemiology Reference Group (CHERG) guidelines. Similarly, Haider et al. (2011) studied the effect of multiple micronutrient supplementation during pregnancy on maternal and birth outcomes, they depicted that there was significant benefits of MMN supplementation during pregnancy on reducing small-for-gestational age birth as compare to only iron-folate supplementation.

Recommendations to Overcome IDA in Pakistan

Although, iron intake of 31 mg/day by the Pakistani population through diet looks more than sufficient, but its bioavailability may be low due to its dietary composition. As major portion of Pakistani diet is based on plant food (71%), followed by milk products (17%) and other miscellaneous item, while consumption of animal food is only 5 per cent. Intake of tea is also very common in Pakistan. The composition of our food shows that phytate in plant food and tannin, polyphenols in tea and calcium may inhibit absorption of iron (Akhtar et al., 2005). Therefore, high intake of cereals and low intake of animal food could be a cause of iron-deficiency anemia in Pakistan.

Food Support Program for households has been integrated into Benazir income support Program throughout the country for wider coverage has been launched so that balance food will be accessed by every common man.

Bearing in mind the micronutrient deficiency, Pakistan government is taking firm steps to eradicate it through Micronutrient Deficiency Control Program. Under this project, wheat flour fortification has been expanded to 82 flour mills. This will result in most available iron fortified flour to all the citizens of Pakistan (Government of Pakistan, 2008). Micronutrient initiative with collaboration of gain, world food program, and government of Pakistan are expanding and encouraging the use of iron-fortified flour (MI, 2004). As vitamin A deficiency is common and vitamin A has a vital role in iron absorption. Ninety-five percent of children of 6–59 months age are being administered the vitamin A drops through National Immunization Days, to reduce vitamin A deficiency. In order to spread public awareness especially the most vulnerable group in our population, (pregnant women and children under five years) are being given the supplements to combat micronutrient deficiency. Awareness is being spread through trained Lady Health Workers (LHW) under the project of nutrition through Primary Health Care. For the purpose, 96,000 LHW are working for the antenatal care during gravidity (Khan et al., 2009).

To avoid the parasitic disease like Malaria, Pakistan launched Malaria Eradication Program with the collaboration of WHO in 1960. Now it has been converted to Malaria Control Program. Its five-year plan is to achieve WHO global Roll Back Malaria target of 50% reduction in malaria burden by year 2010. All above-mentioned projects designed will ultimately reduce the prevalence of IDA and improve the awareness regarding healthy dietary habits resulting in healthier nation of Pakistan (Government of Pakistan, 2008). A study conducted in Sindh province of Pakistan showed that by increasing the general practitioners availability of antenatal care is possible for almost every pregnant women resulting in safer motherhood (Khan and Hall, 2004).

CONCLUSION

Maternal malnutrition is one of the leading causes of numerous diseases and nutrient deficiencies in children around the world. The situation is worst in the developing countries where there is lack of access to balanced and diversified diet. Micronutrient deficiency especially iron deficiency is a common malnutrition among all. This deficiency results in IDA. The most susceptible group of society affected by iron deficiency is pregnant women and women of child-bearing age. The numbers of people experiencing this micronutrient malnutrition is higher in developing countries. Therefore, the situation is quite worse in Pakistan. Iron is important in maintaining normal pregnancy outcomes. Anemia in early pregnancy can be harmful to the development of fetus. It increases the risk of mother having a miscarriage or still-birth or delivering an LBW baby, which in turn is linked to increased risk of perinatal and infant mortality. Maternal consequences of anemia are also well known and include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, poor peripartal blood reserves and finally increased incidence of blood transfusion in the postpartum period. In children, iron-deficiency anemia retards growth, impairs cognitive performance, and reduces physical activity. It also accelerates the mortality and morbidity rate in women. It is important to assess the deficiency correctly in order to work against it. The different parameters help to differentiate between iron deficiency, iron-deficiency anemia, and β-thalessemia. Moreover, the portrayal of mass effect of IDA shows that it is important to find a solution to this problem. The strategy must be followed that results in alleviation of this form of malnutrition to strengthen the most prone and important group of the society. The prevention strategies that can be opted are iron supplementation, food fortification, diet diversification, and control of malarial and parasitic diseases. According to the feasibility, any of the tools or combination of these can be implemented. The strategies and struggle of Pakistani government will lead to a positive result in eradicating IDA from Pakistan.

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