Review of Literature

CHAPTER 2

REVIEW OF LITERATURE

The worldwide prevalence of anemia both in the developing and industrialized countries has evoked considerable interest due to its debilitating health consequences (Hereberg 1991). In the past few decades research in the field of nutritional anemia has grown, providing a more focussed perspective on the prevalence, etiology, prevention, and treatment of this nutritional disorder.

The most commonly practised measure for combating this problem is supplementation with medicinal iron, which has been reported to reduce the prevalence substantially by improving the Hb levels. However the efficacy of the supplementation is yet to be substantiated in major anemia control programs due to various constraints, compliance being one of them. Further, although the hematological responses of pregnant women to different dose levels of iron have been investigated, data on the effect of different dose levels of iron on maternal and infant outcome are very scarce.

The main goal of the present study was to determine the effect of a decentralized home based delivery system for

distribution of iron folic acid supplements on the coverage and compliance in pregnant women and to investigate the effects of different levels of iron (60 mg, 120 mg and 180 mg) with 1.5 mg folic acid delivered through this decentralized delivery system on specific parameters of maternal and infant outcome.

This chapter provides a review of selected studies in the literature related to the objectives. It begins with the current prevalence and etiology of anemia in pregnant women and then examines the iron requirements during pregnancy. The adverse health consequences of anemia are briefly outlined followed by the interventions for the prevention and control of anemia. The next section deals with iron supplementation trials conducted during pregnancy, and their impact in terms of hematological status and maternal and infant outcome. A brief account of the anemia control programme in India, its lack of impact and the reasons for the lack of impact are presented in the final section.

Prevalence of Anemia in Pregnancy

Anemia is diagnosed when the Hb concentration is lower than the level considered to be normal for the particular age/sex group. Although several cutoff levels have been used in the literature, currently the generally accepted levels

below which anemia is considered to exist are the ones given by WHO (1968) which are indicated below:

Children (6 months to 6 years)	11g/dl
Children (6 years to 14 years)	12g/dl
Adult males	13g/dl
Adult females (puberty to menopause) ..	12g/dl
Pregnant women	11g/dl

Based on the above criteria approximately 2170 million people worldwide are estimated to be affected by this disorder (WHO 1992). A compilation of the prevalence of anemia by DeMaeyer (1989) shown in Table 2.01, indicates that globally the highest prevalence is found in pregnant women and young children in the age group of 0-4 years, 59% and 51% respectively. Further it is apparent from Table 2.01 that this disorder is more prevalent among pregnant women in developing countries than in industrialized countries, 51% vs 14% (DeMaeyer 1989).

Another recent compilation by the World Health Organization (WHO 1992) has shown that the highest estimates of the prevalence of anemia in pregnant women within the developing countries are for the South Asian region (75%), followed by Oceania (71%) and Africa (52%). Among the South Asian countries, India has recorded the highest

Table 2.01 Estimated prevalence of anemia in different age/sex groups in the world

Population groups	Estimated prevalence of anemia %		
	Developing countries	Developed countries	World
Infants and children (0-4y)	51	12	43
Children (5-12y)	46	7	37
Men	26	3	18
Women (15-49y)			
Pregnant	59	14	51
All	47	11	35

Source De Maeyer 1989

prevalence of anemia in pregnancy (88%), closely followed by Indonesia (74%), Thailand (71%) and Sri Lanka (52-73%) (WHO 1992).

It is a matter of concern that prevalence of severe anemia (Hb < 7 g/dl) is also alarmingly high in pregnant women in India. The national evaluation of the anemia prophylaxis program in India (ICMR 1989) indicated that 12.6% of the 5779 pregnant women above 20 weeks of gestation surveyed were severely anemic (Hb <7 g/dl). An earlier study by Prema et al (1981a) in Hyderabad, India showed that 13.6% of 3461 pregnant women of varying gestational ages studied by them had Hb levels less than 8 g/dl.

Etiology Of Anemia in Pregnancy

Several factors contribute to the etiology of anemia, which vary according to the geographical locations, but the most predominant one is a poor dietary intake of iron coupled with a low bioavailability of the dietary iron (Narasinga Rao 1983, Hallberg 1984). Folic acid deficiency is also a contributory cause of anemia in pregnancy (INACG 1981). Intestinal infestations, especially hookworms, malaria and genetic causes are other significant factors, but the incidence of these vary in different countries. Table 2.02 summarizes the results of selected studies

Table 2.02 Factors associated with the etiology of anemia in pregnancy

Authors	Country	Factors associated with the etiology of anemia				
		Low Dietary Intake	Parasitic Infestation	Multi-partity	Age	Socio-economic factors
Barua and Foll 1960	Burma India		_/			
Lourdenadin 1964	Malaya			_/		
Akhand 1966	Pakistan	_/				
Vyas et al 1968	India		_/			
Cook et al 1971	Latin America		_/			
Hibbard and Hibbard 1972	Singapore	_/		_/		
Ratten and Beischer 1972	Australia			_/	_/	
Ross 1972	Ethiopia			_/		
Dawn 1973	India	_/				
Yusufji et al 1973	India			_/		_/
Garn et al 1977	USA					_/
Kusin et al 1980	Indonesia	_/				
Jackson and Jackson 1987	Liberia		_/			
Johnson et al 1982	Guyana					_/
Gupta et al 1989	India	_/				_/
Guldholt et al 1991	Sweden			_/		

concerning different factors in the causation of anemia during pregnancy in different areas of the world, and shows that low dietary intake of iron, parasitic infestation and multiparity are the commonly encountered ones in the etiology of anemia in pregnant women.

Dietary Factors

Although many hemopoietic nutrients like iron, folic acid, vitamin B_{12} and other co-factors are involved in the maintenance of the normal Hb concentration (Hercberg 1991) the most common nutrient deficiency from the public health point of view is iron deficiency (INACG 1977). The overall nutrient intake in developing countries including India is low and varies according to the social strata and income levels. Dietary intake of energy of adult women (non-pregnant, non-lactating) from low income groups in urban areas of India has been reported to be 1200-1600 Kcal per day which remains relatively unchanged during pregnancy (Ramachandran 1989). In India a significant correlation ($r = 0.769$) has been shown to exist between the dietary energy intake and iron intake (Narasinga Rao 1991). Thus the low levels of energy intake contribute substantially to the low levels of iron intake seen in these subjects.

Studies on dietary intake of iron in 200 pregnant women in Calcutta, India by Dawn (1973) showed that it was a meagre 10.4 mg for anemic women and was only slightly better for non anemic women, 15.8 mg. That some of these women maintained normal Hb levels at an intake which is only half that of the recommended allowance for Indian pregnant women (37.5 mg) suggests that either the availability of iron in these diets must have been high or that they must have had adequate liver iron stores, although information on these aspects is not available in the study. Shankar (1962) in Hyderabad reported the mean intake of iron in pregnant women to be 16.8 mg/day which was almost similar to mean daily dietary intakes (18 mg) reported by Venkatachalam (1962) for pregnant women earlier in Hyderabad.

Other studies in the literature have reported much higher intakes of iron for Indian pregnant women. Gopaldas et al (1986) in a study on urban pregnant women from Baroda found the mean intake to be 28-30 mg/day. In spite of this relatively higher intake of iron the prevalence of anemia (Hb $<$ 11 g/dl) in these pregnant women was found to be 88%. In a study of 48 pregnant women in South India, Sunderaraj and Pereira (1973) reported a mean daily intake of 24.4 mg. A higher mean intake of 36 mg/day has been reported by Vijayalakshmi and Shobana (1982) in Coimbatore and in spite

of this, these authors reported anemia to be a universal finding in these pregnant women.

Iron intake during pregnancy may also vary across different cultures depending on the composition of the diet. Analysis of the diets of an Iranian population (general) showed high iron concentration (98.9 mcg/g dry diet) in the representative village diets. This was attributed to the ingestion of Tanok' an unleavened wholemeal wheat bread which accounted for 50% of the food intake (Haghshenass et al 1972). A mean intake of 318 mg/day in poorer women and 253 mg/day in women with higher income levels has been reported by Ross (1972) in Ethiopian pregnant women consuming Teff' (Eragrotis abysinnica), a staple containing high amount of iron.

These data reveal that while low dietary intake of iron is not uncommon among pregnant women, even at apparently normal intakes, the prevalence of anemia is quite high which suggests that other factors relating to iron absorption may play an important role.

The process of iron absorption is complex but can be divided into three phases: luminal, mucosal and corporeal (Narasinga Rao 1981). In the luminal phase iron absorption is affected by dietary ingredients that are concomitantly present along with iron. The mucosal phase which involves

transfer of iron from lumen to the mucosa has been the subject of intensive study as the intestinal mucosa have been found to regulate iron absorption by as yet not a very well understood mechanism. The mucosal behaviour is influenced by the iron content of the body, with percent absorption increasing as the body iron content falls. The last is the corporeal phase in which iron is bound to transferrin in plasma and carried to the liver.

Besides these, the form in which iron is present in the diets determines the extent to which iron is absorbed. Heme iron present in meat, poultry and fish is absorbed to a greater extent than nonheme iron (15% vs 2%). Unlike heme iron, nonheme iron absorption is affected by a number of concomitant factors in the diet as mentioned above, which include inhibitors like tannic acid, phytic acid, and oxalic acid and enhancers like ascorbic acid, meat-fish-poultry (Cook and Monsen 1977; Morck and Cook 1981). In the Indian and South Asian diets, the inhibitors far outnumber the enhancers resulting in very low absorption of iron. Studies by Narasinga Rao (1981) have shown that typical vegetarian diets in India have only 2-3% of bioavailable iron, which explains the paradoxical finding of widespread anemia even among populations whose intakes appear to be apparently adequate.

In the face of iron deficiency, the intestinal mucosa absorbs higher quantities of iron which becomes apparent when iron salts are administered to iron deficient subjects (Hallberg 1970). The absorption of iron from $FeSO_4$ given with the meal in iron deficient individuals in the initial period of therapy has been shown to be as high as 20% while in the same individuals after 40 days of therapy, the absorption was reduced to 8% (Bothwell et al 1979).

Besides these pregnancy per se has also been shown to influence the iron absorption. Apte and Iyengar (1970) showed that iron absorption increased from 7.4% in the first trimester to 25.7% and 31.25% in the 2nd and 3rd trimesters for non anemic women and 37.9% and 34.5% for anemic women in the second and third trimesters.

Investigations carried out by Svanberg et al (1975) in Sweden also showed a similar trend of increased absorption in pregnancy although the percent absorption figures in general were much lower. In nonanemic women iron absorption was estimated to be about 1.5% in the first trimester and 5.8% in the second trimester, which increased to a maximum of 14.6% in the third trimester.

Inspite of these compensatory mechanisms, iron absorption in Indian pregnant women does not appear to be adequate to meet the requirements resulting in a large

percentage manifesting anemia as discussed earlier. Deficiency of folic acid during pregnancy as a contributory cause of anemia has also been reported by several investigators (Cook et al 1971, Hibbard and Hibbard 1972, Yusufji et al 1973, Coleman et al 1975, Simmons and Gurney 1982). In a cross sectional study of 114 pregnant women from low income groups, Iyengar (1971) reported a progressive fall in the serum folic acid concentration with advancing gestation. Sixty three percent of the pregnant women studied by them had serum folic acid levels below normal (<3 mg/ml) in the last trimester of pregnancy. Yusufji et al (1973) found a significant correlation between maternal serum folic acid level and Hb ($r = 0.81$), in a study of 1000 pregnant women in southern India. This and the observation that serum folic acid levels in the pregnant women studied by them were lower than that in the non pregnant women suggests that folic acid deficiency is common among the pregnant women and that it is a contributory factor in the anemia of pregnancy.

Parasitic Infestations

Studies on parasitic infestations have established the role of hookworm (Ancylostoma duodenale and Necator americanus) and Schistosoma in the etiology of anemia due to chronic blood loss (DeMaeyer 1989). Blood loss due to hookworm infestation varies from 2 to 100 ml/day (DeMaeyer

1989) according to the severity of infestation (0.15-0.25 ml/worm/day for Ancylostoma duodenale and 0.04 ml/worm/day for Necator americanus) (Roche and Layrisse 1966, Farid et al 1965). This would have tremendous implications as continuous loss of blood would deplete the individual of all the iron stores. Iron loss with an infestation of 1000 eggs of Necator americanus per gram of feces is estimated to be about 0.8 mg/day, which is almost the same as the daily iron requirement of an adult woman.

Lower mean Hb levels (9.5 g/dl) were reported by Jackson and Jackson (1987) in pregnant women with hookworm infestation than those without hookworm infestation (10 g/dl). A significant negative correlation was also reported by the same authors between hookworm infestation and Hb levels ($r = -0.38$). In a study of 1074 pregnant women in Malaysia, a 76.2% prevalence of anemia was found of which 14% was ascribed to hookworms (Lourdenadin 1964). Cook et al (1971) implicated hookworm as a contributory cause of anemia in women from low socio-economic groups in seven Latin American countries, although prevalence figure for infestation was not reported by them. In Varanasi (India), Agarwal et al (1986) found that there was a higher incidence of hookworm infestation (73.8%) in anemic non-pregnant women than in non anemic ones (19.4%).

Malaria

During pregnancy, women especially the primigravidae, demonstrate an increase in prevalence and severity of malaria, although the mechanism of altered host susceptibility has not been clearly understood (Brabin 1983). Studies conducted with isotopically labelled chromium and iron (Woodruff et al 1979) have indicated that anemia in malaria is compounded by three factors : the destruction of erythrocytes by parasites growing within them, mild and transient depression of erythropoiesis, and hemolysis, which is the most important factor.

Epidemiological evidence from the African countries (Gambia, Kenya, Nigeria, Tanzania and Uganda) which are malaria endemic regions has indicated a more frequent and severe incidence of malaria in primigravidae than in multigravidae during pregnancy (Gills et al 1969, Brabin 1983, Brabin et al 1986, Oppenheimer 1986a). These investigators also reported lower Hb levels in both primi and multigravidae who were infested with the malarial parasite compared to those without parasitemia. Therefore oral administration of iron has been recommended for the treatment of anemia in holoendemic regions (ACC/SCN 1989).

In view of the immuno suppressive effect of iron deficiency it is also believed that the net effect of iron

supplementation in malaria endemic regions could be a reduction in the prevalence of malaria (ACC/SCN 1989).

Pregnancy Related Factors

Maternal age and parity have been shown to contribute significantly to the prevalence of anemia, as increasing parity diminishes the iron stores and close birth spacing does not allow enough time for the replenishing of iron stores (WHO 1993). Ratten and Beischer (1972) who made a study of anemia in 15,321 obstetric subjects in Melbourne, Australia found a lower anemia prevalence of 8% and 3.4%, in women aged 19 and below, or 40 and above. Higher prevalence was found in women aged 20-30 years (61%). The same authors reported a 30.3% prevalence of anemia in primiparous women and 69.7% in multiparous women.

Ross (1972) reported a slight downward trend in Hb with increasing parity in 497 women in Addis Ababa. Hibbard and Hibbard (1972) in a study of 545 pregnant women from a mixed population of Chinese, Malay, and Indian reported that multigravidae in all ethnic groups had higher incidence of anemia which was consistant with the findings of Lourdenadin (1964) in a similar mixed population of 1074 pregnant women of Chinese, Indian, Malaysian, European, and Eurasian background. Kuizon et al (1985) reported lower Hb levels in

multiparous Philippino women than in primiparous women. A multicentric study by the Nutrition Foundation of India in five urban cities showed that severe anemia was three fold higher in women with para 4 compared to those of para 3 or less (NFI 1988).

Significant associations between the prevalence of anemia (Hb < 10 g/dl) and birth spacing were reported by Luwang et al (1980) in 232 pregnant women in Varanasi. Prevalence of anemia was the highest in women with birth spacing of less than 12 months.

Genetic Factors and Others

Genetic disorders, such as sickle cell anemia and thalassemia are the other factors in the etiology of anemia. However, a study by Crane et al (1974) showed that despite the presence of thalessemia and endemic malaria, iron deficiency emerged as the major cause of anemia in Coastal New Guinea.

Geographical discrepancies attributable to socioeconmic factors have been shown to contribute significantly to the prevalence of anemia. A significant difference in the prevalence of anemia (Hb < 10 g/dl) was reported between literate and illiterate women in Varanasi (Luwang et al 1980). In Ajmer, India, Gupta et al (1989) found that

prevalence of anemia was highest among those with a monthly income of Rs.300-499 per month, and lowest in those with an income of Rs.1000-1999, although they did not find any consistency of association between income and prevalence of anemia. Johnson et al (1982) in a survey of 103 households in Guyana reported that a number of socio demographic factors like house ownership, distance from health facility, type of dwelling, distance from drinking water, toilet facility and presence of kitchen garden were significantly associated with the prevalence of anemia. Several of these socio-economic factors may operate through food choices, low dietary intakes and increased infections.

Iron Requirements In Pregnancy

Physiological changes occurring during pregnancy lead to increased demands for iron. During pregnancy growth of the fetus and placenta and expansion of the red cell mass result in an increased need for nutrients especially iron. An increase of 45% in blood volume, 50% in plasma volume, and 35% in red cell mass have been reported for well nourished pregnant women from the developed countries (Bothwell et al 1979). The underprivileged pregnant women in India have been shown to register even a higher increase in plasma volume, about 65%, which apparently facilitates the transfer of more nutrients to the fetus (Rajalakshmi and

Raman 1985). The changes in total blood volume, plasma volume and red cell volume in underprivileged Indian pregnant women are shown in Table 2.03.

Table 2.03 Changes in blood volume in pregnancy

Blood Components Volume in Litres	Nonpregnant Women	Pregnant Women at term	% Increase Trimester I	II	III
Total blood volume	3051	4894	<-----	60	----->
Plasma volume	1975	3192	2.3	63	-
Red cell volume	1021	1650	-	6	50

Source: Rajalakshimi and Raman 1985

As seen from Table 2.03, much of the increase in plasma volume occurs in the 2nd trimester, while a major part of the increase in red cell volume occurs in the 3rd trimester, with relatively little change taking place in the 1st trimester. This and the observation that iron transfer to the fetus is significant in the 2nd and 3rd trimester, account for the rather high requirements for iron during the last two trimesters of pregnancy.

Based on the blood volume changes and the iron content of the fetuses at different gestational ages, the iron requirements for pregnancy in an iron replete non-anemic

woman has been estimated and as shown in Table 2.04, amount to a total of 1200 mg.

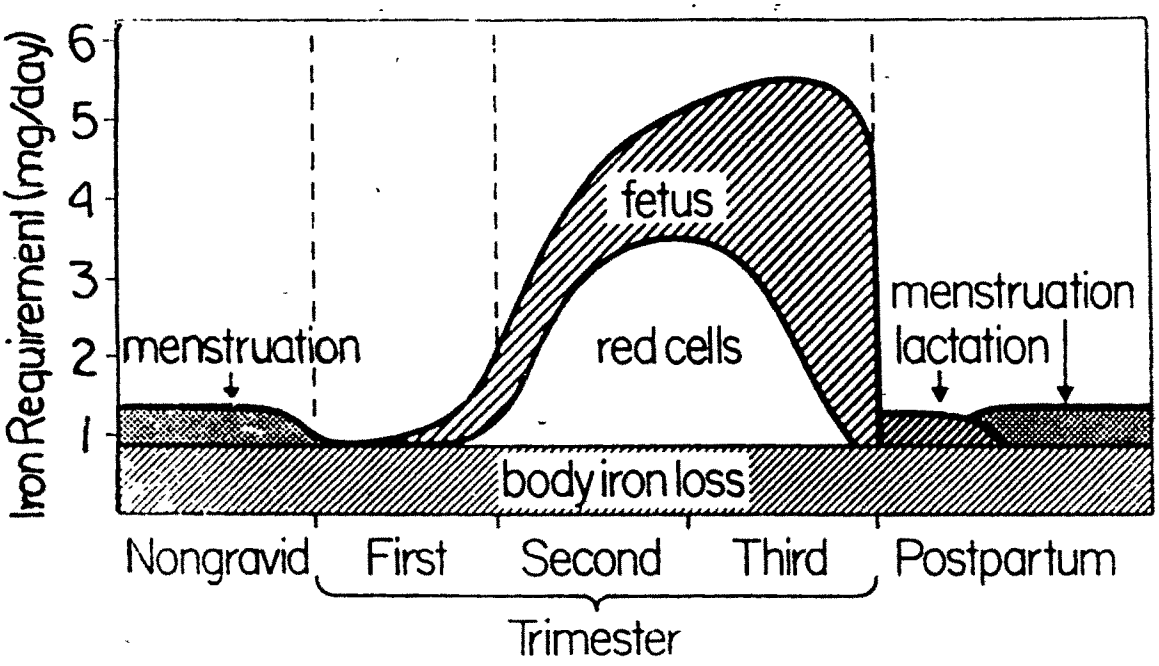
Table 2.04 Iron cost of pregnancy

Requirement	mg iron
Fetus (at term)	280
Expansion of red cell mass	450
Placenta and umblical cord	90
Maternal blood loss	150
Obligatory loss	230
Total iron cost	1200

Source: INACG 1981

As seen from Fig 2.01 the increase in iron requirements during the first trimester is minimal as menstruation losses are nil and transfer to the fetus has not begun but the increase during the second and third trimester is quite large for reasons already mentioned. The absorbable iron requirements are worked out to be 0.8 mg/day during the first trimester and 6.3 mg/day during the second and third trimesters. Requirements for the first trimester can be met easily by dietary iron, but subsequently as the requirements increase during second and third trimester, supplementation with medicinal iron becomes increasingly more important.

FIG. 2.01 Requirements of iron during pregnancy in an iron replete non-anemic woman.



adapted from
Bothwell et al (1979)

The computation of iron requirements for correction of anemia and pregnancy needs have been worked out by Narasinga Rao (1991) and are shown in Table 2.05. These estimates indicate that 60 to 100 mg of supplemental iron may be necessary for pregnant women who are anemic and have Hb levels between 7 g/dl to 11 g/dl to provide for pregnancy demands as well as correction of anemia.

Adverse Effects of Anemia in Pregnancy

It is well documented that anemia leads to a reduction in physical work capacity and productivity (Basta et al 1979, Edgerton et al 1979, Rahamathulla 1983). Impairment in selected cognitive functions have also been demonstrated in children (Seshadri and Gopaldas 1989).

Laboratory studies have shown reduced bactericidal activity of leucocytes and reduced T lymphocyte population in anemic individuals (Prema et al 1982a). A progressive reduction in these parameters was shown in pregnant women with decreasing levels of Hb, the fall becoming significant when Hb levels reached less than 8 g/dl (Prema et al 1982a).

However, effect of anemia on morbidities is not as clearcut as on the other functional effects. Investigators from NIN (NIN 1983) have studied the morbidity profile of anemic and non-anemic pregnant women in the second and third

Table 2.05 Daily iron requirements for correction of anemia and provision of pregnancy needs

Hb g/dl		Daily iron requirement (mcg/kg/day)			Daily iron required for a 45 Kg woman (mg)	Daily dose of iron supplement (mg)
Initial	Final	Correcting anemia	Pregnancy demand[a]	Total		
12	12	0	110	110	5.0	62.5[b]
11	12	22	110	132	6.0	60[c]
10	12	44	110	154	7.0	70
9	12	66	110	176	8.0	80
8	12	88	110	198	9.0	90
7	12	110	110	220	10.0	100

a. Assuming 75% of total iron requirement to be provided in the last 100 days

b. Absorption 8% in nonanemic

c. Absorption 10% in anemic

Source: Narasinga Rao 1991.

trimester from urban and rural backgrounds by clinical examination. No significant difference was found between anemic and non-anemic urban pregnant women, but there was a trend towards increased prevalence of infectious morbidity with decreasing levels of Hb in the rural pregnant women which became more marked when Hb levels fell below 8 g/dl (25%, 34%, and 56% prevalence in women with Hb $\geq$11 g, 8-10.9 g, and $<$8.0 g respectively). The type of infectious morbidities that showed a higher prevalence in anemic rural women were respiratory infection, fever and skin infection.

In addition to the above effects, in pregnancy, anemia may have several other serious consequences. Anemia, especially severe anemia has been shown to be an associated cause of maternal mortality in several developing countries (WHO 1993) as shown in Table 2.06, chiefly by increasing postpartum hemorrhages and blood loss.

Table 2.06 Maternal deaths attributable to anemia

Country	Deaths per 100,000 live-births due to anemia	Anemia deaths as percent of all maternal deaths
Kenya	82	11
Malawi	48	8
Nigeria	83	9
Senegal	35	5
Bangladesh	47	4
Bhutan	55	7
India	38	16
Pakistan	194	7

Source: WHO 1993

Anemia is also associated with increased risk of premature delivery. Studies carried out by Prema et al (1981a) on women from urban low socio-economic status in India found a progressive increase in the premature deliveries as the Hb levels dropped from 11 g/dl to less than 5 g/dl, the incidence rates at the two extremes being 10.2% and 34.5%. Similar findings have been reported by Garn et al (1981) for black and white pregnant women in USA, for Hb levels of < 8 g/dl to > 12 g/dl (21.5% incidence at Hb < 8 g/dl and 14.7% incidence with more than > 12 g/dl). In several large scale studies similar findings of increased incidence of premature delivery with low Hb levels has been reported for Australian women (Beischer et al 1970, Rattan and Beischer 1972) and for Malaysian pregnant women (Lourdenadin 1964).

Extensive studies conducted in various countries have shown significant relationships between Hb levels in pregnant women and incidence of low birthweight and perinatal mortality. In India a study of 3461 pregnant women by Prema et al (1981a) revealed that low birthweight incidence was 23.1% in women with Hb > 11 g/dl and 62.3% in those with Hb < 5 g/dl. A progressive increase in birthweight with increasing levels of maternal Hb was reported by these investigators (Table 2.07).

Table 2.07 Pregnancy outcome in relation to mean Hb levels

	Hemoglobin (g/dl)			
	< 5	5 - 7.9	8 - 10.9	> 11
Mean birthweight (g)	2400	2530	2660	2710
Unfavourable outcomes				
Prematurity %	34.5	18.2	12.5	10.2
Low birthweight %	62.3	38.4	26.4	23.1
Perinatal mortality (rate/1000 births)	400.6	130.9	64.1	44.9

Source: Prema et al 1981a

Severe anemia was shown to cause higher degrees of low birthweight (Prema et al 1981a, Singla et al 1978, Badole et al 1992). Mitchell and Lerner (1992) showed a significant correlation (r = 0.068) between Hb at term of the mother and birthweight of the infant, even when controlled for gestational duration. The multiple analysis of variance showed that final Hb accounted for 3.7% of the variability in birthweight.

Higher incidence of fetal death, short gestation lengths, low birthweight and medical abnormalities have been found to occur in the more affluent populations at both ends of the hematological distributions, significant at Hb $\geq$13.0 g/dl and Hb less than 10.0 g/dl (Garn et al 1981, Higgins et al 1982, Murphy et al 1986).

Interventions for the Control of Anemia in Pregnancy

Several avenues have been explored for the control and prevention of anemia in the developing countries. Four basic approaches have been suggested: supplementation with iron and folic acid, dietary modification, fortification of selected food items and control of parasitic infestation (DeMaeyer 1989).

Supplementation with Iron and Folic Acid

This has been the most popular approach, especially in developing countries with a high prevalence of anemia, due to its specific advantage of being targeted to appropriate population groups and being able to produce rapid improvements in Hb levels. However the efficacy of the oral supplementation is dependent upon the compliance of the women, and the incidence of side effects. Most controlled studies of iron supplementation in pregnancy which are reviewed later have shown a significant improvement in Hb levels, although field level supplementation programmes without supervision have generally shown little impact. This is reviewed in a later section.

Dietary Modification

The high correlation (r= 0.7369) observed between dietary energy and iron intake (Narasinga Rao 1983) suggests that total intake of iron can be increased if the energy gap can be bridged. Increasing the consumption of iron-rich foods, or improving the bioavailability by inclusion of enhancers like ascorbic acid and animal protein (meat, fish and poultry), may be expected to improve iron status and Hb levels in underprivileged pregnant women but hard data to support this are lacking. Dietary modifications are long term measures and do not yield immediate results, and are therefore of greater significance in situations where anemia control does not have to be achieved within a limited span of time. During pregnancy, especially in areas where anemia is widely prevalent in its more severe forms, dietary modifications may contribute little to assuage the situation in view of the high requirements for iron during pregnancy.

Fortification of Foods with Iron Salts

The procedure of fortifying a commonly consumed staple (wheat flour, bread etc) with iron has been widely practised in many industrialised countries and can be targeted to all population groups. Fortification of wheat flour has been in operation in Sweden, UK and USA (INACG 1977). In India,

where the staple food varies with each ethnic group, salt has been used as a vehicle for iron fortification as it is universally consumed and centrally processed. Although fortification of salt with iron at the level of 1 mg/g has been shown to produce a significant rise in Hb levels of school children (Food and Nutrition Board and UNICEF 1981) the amount that can be derived from fortified salt (about 10-15 mg per day based on average salt consumption of 10-15 g) is very inadequate for the increased demands during pregnancy. Therefore it can only be used as a complementary measure for combating the problem of iron deficiency anemia in pregnant women. In Thailand fortification of fish sauce has shown great promise in improving the iron status of the general population (Garby and Areekul 1974).

Control of Parasitic Infestation

As discussed earlier it is well established that heavy hookworm infestation plays a significant role in the etiology of anemia. Hence deworming has been suggested as one of the measures to prevent anemia. The results of interventions which have included deworming prior to iron supplementation or by itself as a major intervention have shown a better effect in terms of Hb (Gopaldas et al 1983, Food and Nutrition Board and UNICEF 1981). However, several factors relating to worm infestation play a role in

influencing Hb levels and it is not uncommon to find studies which report no differences in Hb between infested and non-infested subjects (Sood et al 1975).

From the foregoing discussion it is evident that currently supplementation with medicinal iron is the most important intervention for the control of anemia in pregnancy especially in a country like India, where the prevalence of anemia among pregnant women is very high.

Therapeutic Supplementation Trials With Iron And Other Hemopoietic Nutrients During Pregnancy

Compliance

Failure of iron supplementation to produce the expected results in anemia prevalence and Hb levels may often be due to poor compliance, inadequate dose and/or limitations of absorption. Very few studies, however, have addressed the issue of compliance. Assessing compliance is also plagued by the lack of an objective measurement of compliance.

In controlled supplementation trials ingestion of supplements is supervised, providing reliable estimates of tablet consumption. This is not feasible in field situations due to enormous coverage involved. In India, evaluation of the anemia control programme (ICMR 1989) revealed that the

tablet consumption was monitored periodically only in 35% of the pregnant women while 65% of the women reported that there was no monitoring of the consumption of iron supplements. As the distribution of tablets in India is chiefly clinic based, monitoring compliance becomes difficult. The leftover tablets are usually not brought to the clinic and mother's recall has to be relied on.

Although mother's recall has generally been believed to be unreliable (Bonnar et al 1969, Schultink et al 1993) the only available study in the literature by Simmons (1990) reported a significant correlation between compliance as measured by counting the leftover tablets and that by the recall of the mothers. Both are, however, subject to certain limitations such as memory lapse, loss or spillage and tablet consumption by any one other than the subject and therefore have limited reliability.

In view of the fact that obtaining stool samples in the field situation are fraught with problems, other objective measures such as marking on a mother retained card or a calendar type of device needs to be tested out extensively, as it has been shown to be a reliable measure of compliance in the Thailand study (Charoenlarp et al 1988). The investigators of the Thailand study provided calendars every month depicting messages that iron makes pregnant women and

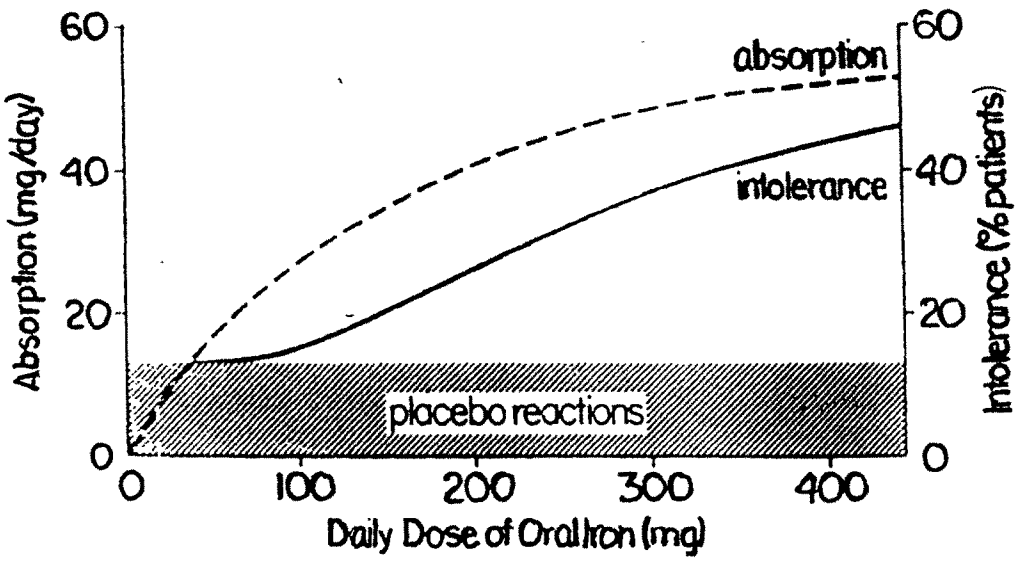
their babies stronger. The calendar was reported to serve as an effective compliance measure and also as a motivational tool to consume the tablets.

Side Effects

Of the several controlled iron supplementation trials available in the literature, only a few have reported in detail on side effects. Earlier studies indicated that side effects were psychological in origin (Kerr and Davidson 1958) as the placebo group also reported of side effects. Controlled trials carried out later indicated higher incidence of side effects in subjects under iron medication than in the ones given placebo (Bothwell et al 1979). Fig 2.02 illustrates the incidence of side effects with increasing doses of iron and increasing levels of iron absorbed. As shown in the figure the side effects increased in proportion to the amount of iron absorbed as the dose levels were increased from 100 mg to 400 mg/day. Other studies in the literature have also revealed that the incidence and severity of side effects were dose related (Kuizon et al 1983, Charoenlarp et al 1988, Reddiah et al 1989, ICMR 1992), as shown in Table 2.08.

Whether or not side effects are experienced appear to depend on whether the iron is administered as a single dose or as divided doses and their timing. When pregnant women

FIG. 2.02 Side effects of oral iron therapy



adapted from
Bothwell et al (1979)

Table 2.08 Side effects with different levels of iron therapy in pregnant women

Reference	Dose level of iron (mg) per day	Duration of Fe therapy (weeks)	% with side effects	Nature of side effects	Frequency of recording side effects
Kuizon et al 1983	260	4	36.4	vomiting	NA
	390		49.0	nausea	
	260		25.6		
	260		40.0		
Charoenlarp et al 1988	120	10-15	10.0	abdominal discomfort, nausea, fatigue vomiting, dizziness	-
	240		20.0		
Reddiah et al 1989	60	15±1	3.4	nausea, vomiting, abdominal pain, burning of abdomen	Once in 4 w
	120		40.5		
	240		72.2		
ICMR 1992	60	14	14.0	nausea/vomiting gastric/dysentry diarrhoea constipation abdominal distension	NA
	120		14.2		
	180		21.3		

NA - Not available

were supplemented with 30 mg or 60 mg of iron in divided doses, the incidence of side effects was found to be less than 5% (Bonnar et al 1969, Iyengar and Apte 1970), while 60 mg of iron administered as a single dose was shown in another study to result in a 9% incidence of side effects (ICMR 1989). Reddiah et al (1989) reported very high incidence of side effects of 32.1%, 49% and 72% when the tablets were administered two hrs after the meal as a single dose at dose levels of 60, 120 or 240 mg iron per day. Most of the undesirable manifestations reported by them were confined to the gastrointestinal tract. These included vomiting, nausea, constipation, diarrhoea, and epigastric discomfort. Investigators of the Thailand study (Charoenlarp et al 1988) however reported that the incidence of side effects were the highest during the first three days, but reduced in frequency and severity thereafter.

While it is well documented that side effects are related to the dose level of iron, there are no convincing studies to show that the high dropout rates in iron supplementation programmes is due primarily to the high incidence of side effects. Iron supplementation studies reviewed in the later section have shown that only a very small percentage of dropouts (1-4%) were due to side effects. Other reasons were migration, social/religious

taboos against tablet consumption and fear of needles for withdrawl of blood.

Recent attempts to improve iron absorption and reduce the incidence of side effects have led to the discovery of a novel delayed release gastric delivery system (GDS) which consists of an orally administered hydro colloid iron capsule which is designed for the controlled release of iron. Tests conducted with this GDS capsule (Cook et al 1990, Simmons 1990) have shown reduced incidence of side effects compared to the conventional ferrous sulphate tablet although absorption of iron from GDS was twice as high as that from ferrous sulphate at the same dose level. However, until the GDS becomes more readily available at an affordable cost in the developing countries, women have to be motivated to consume the ferrous sulphate supplements. Therefore more in-depth studies are needed on the dropout rate from the iron supplementation programme and its relationship to side effects at different dose levels.

None of the controlled iron supplementation trials have reported on the positive beneficial effects experienced by the pregnant women.

Effects on Prevalence of Anemia and Rise in Hb

A series of controlled iron supplementation trials both in the developed and developing countries have been carried out in pregnant women using different dose levels, to establish the optimal level of iron required to correct anemia and to provide sufficient iron stores. These trials have all been randomized iron supplementation trials with pregnant women but differ in design and elements. The level of iron tested has ranged from 0-390 mg per day and the duration of therapy has varied from 4 - 19 weeks. The iron was provided either as a single dose or as divided doses. The additional effect of two other hemopoietic nutrients, namely, folic acid and vitamin B_{12} were examined in some of the studies. The results of these studies are summarized below.

Prevalence of anemia

Of the 14 studies of randomized iron supplementation trials that could be located only five reported on the prevalence of anemia before and after supplementation with different dose levels of iron as shown in Table 2.09 (Sood et al 1975, Aung Than Batu et al 1976, Charoenlarp et al 1988, Reddiah et al 1989, ICMR 1992). The Indian studies found a reduction in the prevalence of anemia of 18-22% with

Table 2.09 Effect of different dose levels of iron on changes in prevalence of anemia : A summary of randomized trials in pregnant women

Reference/ Duration of Therapy (weeks)	N	Level of iron (mg/day)	Prevalence of anemia		
			Initial	Final	Change
India					
Sood et al[a]	91	0	88	88	0
1975	89	30	88	70	18
10-12	91	60	88	74	14
	115	120	88	56	32
	84	240	88	56	32
Reddiah et al[b]	37	60	48	27	22
1989	37	120	46	22	24
14	36	240	56	19	37
ICMR[b]	322	60	70	48	22
1992	355	120	61	33	28
14	363	180	68	34	34
Burma					
Aung Than Batu	22	0	72	84	-12
et al 1976	30	120	72	47	25
16					
Thailand					
Charoenlarp[c]	39	0	68	74	- 6
et al 1988	38	120	65	24	41
15	41	240	73	20	53

[a] All groups received 0.5 mg folic acid and 100 mcg B_{12} daily.
[b] All groups received 0.5 mg folic acid.
[c] All groups received 5 mg folic acid except the group without iron.

60 mg iron, 24-32% with 120 mg and 34% with 180 mg iron. With 240 mg iron the level of reduction in the prevalence of anemia was found to be about the same as with 120 mg iron, showing that there may be no additional benefit in terms of reduction in prevalence of anemia by increasing the level of iron to beyond 180 mg/day.

In the studies conducted in Burma and Thailand (Aung Than Batu et al 1976, Charoenlarp et al 1988) 40-44% reduction was reported with 120 mg iron, and 35-53% with 240 mg iron.

Rise in hemoglobin

The initial and final Hb levels were studied in six of the trials and were compared with Hb levels of a group given placebo (Table 2.10) (Sood et al 1975, Aung Than Batu et al 1976, Kuizon et al 1983, Charoenlarp et al 1988, Friera 1989, Simmons 1990). All the studies showed a decrease in mean Hb after supplementation with placebo ranging from 0.1 g/dl to 0.7 g/dl. Clearly, these data indicate that pregnant women in developing countries are most likely to suffer a deterioration in their Hb levels if they are not supplemented with iron.

The rise in Hb levels with different levels of iron from these studies is summarised in Table 2.11. While 30 mg

Table 2.10 Effect of different dose levels of iron on Hb levels : A summary of randomized trials in pregnant women

Reference/ Duration of therapy (weeks)	N	Treatment		Mean Hb		
		Fe mg	Fa mg	Initial	Final	Rise
INDIA						
Sood et al[a] 1975	70	0	0.0	9.6	9.3	-0.3
10 - 12	91	0	5.0	9.6	9.4	-0.2
	89	30	5.0	9.4	10.2	0.8
	91	60	5.0	9.3	10.3	1.0
	115	120	5.0	9.6	10.8	1.2
	84	240	5.0	9.4	10.8	1.4
	107	120		9.7	10.4	0.7
Reddiah et al 1989	37	60	0.5	10.6	11.4	0.8
14 - 16	37	120	0.5	10.8	11.5	0.7
	36	240	0.5	10.8	11.4	0.6
Agarwal et al 1991	123			10.1	9.3	0.8
14	137	60	0.5	10.3	12.1	1.8
16-19	33	60	0.5	10.2	11.8	1.6
20-24	104	60	0.5	10.3	12.1	1.8
ICMR 1992	322	60	0.5	10.1	11.1	1.0
14	355	120	0.5	10.5	11.5	1.0
	363	180	0.5	10.3	11.5	1.2
BURMA						
Aung Than Batu	22	0	0	10.4	9.7	-0.7
et al 1976	19	0	10.0	10.3	9.6	-0.7
16	30	120		10.9	11.3	0.4
	25	120	10.0	10.8	11.8	0.7
Thane Toe and Thein	16	60	5.0	10.9	11.2	0.3
Than 1982	32	120	5.0	10.9	11.3	0.4
12	33	240	5.0	10.5	11.1	0.6
	18	240		10.7	11.3	0.6

[a] all groups received 100 mcg B_{12} except the group without folic acid
Fa - Folic acid

Table 2.10 (contd..)

Reference/ Duration of therapy (weeks)	N	Treatment		Mean Hb		
		Fe mg	Fa mg	Initial	Final	Rise
Charoenlarp et al 1988	40$_s$	60	5.0	10.6	11.1	0.5
	34$_s$	120	5.0	10.7	11.2	0.5
	35$_s$	240$_d$	5.0	10.6	11.1	0.5
	32$_s$	120$_d$	5.0	10.6	11.3	0.7
	36$_s$	240$_d$	5.0	10.5	11.2	0.7
	42$_u$	240	0	10.6	11.2	0.6
	46$_u$	120	5.0	10.2	10.9	0.7
	41	240	5.0	10.3	10.5	0.2
THAILAND						
Srisupandit et al 1983 6	109	60	0	11.1	11.3	0.2
	117	180	0	11.0	11.4	0.4
	113	180	5.0	11.1	11.4	0.3
12	109	60	0	11.1	11.8	0.7
	117	180	0	11.0	11.9	0.9
	103	180	5.0	11.1	11.9	0.8
Charoenlarp et al 1988 10	51$_s$	0	0	10.2	10.1	-0.1
	42$_s$	120	5.0	10.4	11.0	0.6
	47$_s$	240	5.0	10.3	11.3	1.0
	52$_m$	240	0	10.3	11.4	1.1
	54$_m$	120	5.0	10.2	11.3	1.1
	55$_u$	240	5.0	10.6	11.5	0.9
	46$_u$	120	5.0	10.2	10.9	0.7
	41	240	5.0	10.3	10.5	0.2
15	39$_s$	0	0	10.1	10.0	-0.1
	38$_s$	120	5.0	10.2	11.6	1.4
	41$_s$	240	5.0	10.4	11.7	1.3
	40$_m$	240	0	10.3	11.5	1.3
	42$_m$	120	5.0	10.4	11.6	1.2
	53	240	5.0	10.5	11.8	1.3

s supervised
u unsupervised
m monitored
d divided doses

Table 2.10 (contd..)

Reference/ Duration of therapy (weeks)	N	Treatment		Mean Hb		
		Fe mg	Fa mg	Initial	Final	Rise
PHILIPPINES						
Kuizon et al 1983	50	0	0	9.7	9.8	0.1
4	50	195	0	9.9	10.2	0.3
	50	260	0	9.9	10.3	0.4
	50	390	0	9.6	10.4	0.8
	50	260	0	9.6	10.1	0.5
	50	260	5.0	9.9	10.5	0.6
	18	240	0	10.7	11.3	0.6
12	30	0	0	9.7	10.3	0.6
	30	195	0	9.9	11.3	1.4
	32	260	0	9.9	11.0	1.1
LIBERIA						
Jackson and Latham	64	60_d	0	10.6	10.9	0.3
1982	64	180_d	0	10.0	10.5	0.5
4	64_m	180_d	5.0	9.7	10.4	0.7
	65	180	5.0	9.7	10.6	0.9
8	87	60_d	0	10.6	11.3	0.7
	100	180_d	0	10.0	11.1	1.1
	95_m	180_d	5.0	9.7	10.9	1.2
	87	180	5.0	9.7	10.9	1.2
12	30	60_d	0	10.5	11.1	0.6
	30	180_d	0	10.1	11.4	1.3
	37_m	180_d	5.0	9.7	11.0	1.3
	35	180	5.0	9.6	11.2	1.6
CAPE TOWN						
Dommisse et al	48^v	0	0	12.1	11.6	-0.5
1983	57	120	0	11.9	12.3	0.4
19-20						
ECUADOR						
Freire 1989	117	0	0	13.3	13.0	0.3
8	112	78	0	13.2	13.7	0.5

^{m} also received antimalarial treatment
^{v} group received multivitamin tablets

Table 2.10 (contd..)

Reference/ Duration of therapy (weeks)	N	Treatment		Mean Hb		
		Fe mg	Fa mg	Initial	Final	Rise
WEST INDIES						
Simmons 1990	101	0 [g]	400	10.5	10.0	-0.5
6	107	50 [g] [d]	400	9.9	10.3	0.4
	96	100 [d]	400	10.0	10.5	0.5
12	89	0 [g]	400	10.5	10.0	-0.5
	89	50 [g] [d]	400	9.9	10.8	0.9
	85	100 [d]	400	10.0	10.9	0.9
FRANCE						
Zittoun et al [c]	48	105	0	10.4	12.8	2.4
1983	72	105	0	11.7	13.5	1.8
10-12						

[g] gastric delivery system capsule
[d] divided doses
[c] all groups received 500 mg ascorbic acid

Table 2.11 Range of Hb rise with different levels of iron supplementation - a compilation from published studies

Reference	mg elemental iron/day	range of rise in Hb (g/dl)
Sood et al 1975	30	- 0.2
Sood et al 1975,Jackson and Latham 1982,Thane Toe and Thein Than 1982 Srisupandit et al 1983,Chroenlarp et al 1988,Reddiah et al 1989, Agarwal 1991,ICMR 1992.	60	0.2-1.8
Simmons 1990	100	0.51-0.84
Zittoun et al 1983	105	2.4
Sood et al 1975,1979,Aung Than Batu 1976,Thane Toe and Thein Than 1982,Dommisse 1983,Charoenlarp et al 1988,Reddiah et al 1989,ICMR 1992	120	0.3-1.4
Jackson and Latham 1982,Srisupandit 1983,ICMR 1992	180	0.3-1.6
Kuizon 1983	195	0.2-1.3
Sood et al 1975,Thane Toe and Thein Than 1982,Charoenlarp et al 1988,Reddiah et al 1989.	240	0.2-1.3
Kuizon et al 1983	260	0.5-0.99
Kuizon et al 1983	390	0.78

elemental iron per day was found to be inadequate to produce a rise in Hb, dose levels above 60 mg/day are seen to produce a rise in Hb ranging from a low of 0.2 g/dl to a high of 2.4 g/dl. Further no differences are seen in the range reported for the rise in Hb levels with different dose levels of iron viz. 60 mg, 120 mg, 180 mg and 240 mg per day which could be due to several factors such as differences in initial Hb levels, differences in duration of treatment, presence or absence of other hemopoetic nutrients single vs multiple doses and the presence or absence of supervision. Therefore further disaggregation of the results by these factors provide a clearer picture of the dose effect.

Effect of initial Hb on response to iron therapy

Four of the iron supplementation trials have reported on the rise in Hb after controlling for initial Hb by an analysis of covariance (Sood et al 1975, Jackson and Latham 1982, Charoenlarp et al 1988, ICMR 1992). These investigators reported that the rise in Hb was dependent on the dose level of iron, the increase being significant at higher levels.

Duration of therapy

The effect of varying durations (4-19 weeks) were tested by several investigators (Jackson and Latham 1982, Kuizon et al 1983, Srisupandit et al 1983, Charoenlarp et al 1988, Simmons 1990). With the same dose of iron supplementation, there was a substantial increase in Hb when the duration of supplementation was increased from 4-6 weeks to 8 weeks. Beyond eight weeks the magnitude of rise in Hb was marginal. Nevertheless, this marginal rise in Hb with longer duration of supplementation, may be sufficient to raise the Hb level of the women to the nonanemic category. Highest rise was seen to occur beyond 12 weeks of supplementation and lowest at 4-6 weeks of supplementation (Table 2.12).

Single vs divided dose

Charoenlarp et al (1988) in a Burmese population showed that 120 mg of iron in divided doses of 60 mg twice a day for 12 weeks, produced a rise in Hb of 0.66 g/dl, as against 0.55 g/dl for a single tablet of 120 mg per day. In the 240 mg dose group, there was an increase in Hb of 0.77 g/dl when two tablets were provided as 120 mg iron compared to 0.47 g/dl when a single dose was given. Thus higher dose

Table 2.12 Hemoglobin response in relation to duration of supplementation - a compilation from published studies

Reference	Dose of iron (mg)	Rise in Hb: Duration of supplementation: 4-6 weeks	8 weeks	10-12 weeks	12-15 weeks
Sood et al 1975, Jackson and Latham 1982, Thane Toe and Thein Than 1982, Srisupandit et al 1983, Charoenlarp et al 1988, Reddiah et al 1989, Agarwal 1991, ICMR 1992.	60	0.2 - 0.3	0.7	0.3-1.00	0.8 - 1.8
Sood et al 1975, Soqd et al 1979, Aung Than Batu et al 1976 Thane Toe and Thein Than 1982 Charoenlarp et al, 1988, Reddiah et al 1989, ICMR 1992	120	-	-	0.4 -1.2	0.7 - 1.0
Jackson and Latham 1982, Srisupandit 1983, ICMR 1992	180	0.3- 0.7	1.2	0.8-1.3	1.2
Sood et al 1975, Thane Toe and Thein Than 1982, Charoenlarp et al 1988, Reddiah et al 1989.	240	-	-	0.2-1.4	0.6
Kuizon et al 1983	390	0.78	-	-	-

levels of iron appear to elicit better responses if given in divided doses rather than a single dose.

Folic acid and Vitamin B_{12}

Many of the iron supplementation trials in pregnant women have included folic acid which has been given at a level of either 0.5 mg or 5 mg per day (Sood et al 1975, Aung Than Batu et al 1976, Jackson and Latham 1982, Thane Toe and Thein Than 1982, Kuizon et al 1983, Srisupandit et al 1983). Table 2.13 summarizes the results of these studies.

Table 2.13 Effect of Iron and Folic acid administration on the rise in Hb during pregnancy

Reference	Treatment		Duration	Rise in Hb
	Fe (mg)	Fa (mg)	(weeks)	g/dl
Sood et al[a]	120	5	14-16	1.2
1975	120	-		0.7
Aung Than Batu	120	10	16	0.7
1976	120	-		0.4
Jackson and Latham	180	-	12	1.3
1982	180	5		1.3
Thane Toe and Thein	240	5	12	0.6
Than 1982	240	-		0.6
Srisupandit	180	5	12	0.8
1983	180	-		0.7
Kuizon et al	260	5	4	0.6
1983	260			0.5

[a] Group received 100 mcg B_{12} daily.

Administration of folic acid alone in one of these studies (Aung Than Batu et al 1976) was shown to result in a fall in Hb of 0.7 g/dl over a 16 week period. However in the same study when folic acid was administered with iron for 16 weeks, it produced a larger rise (0.7 g/dl) in Hb than when iron was given alone (0.4 g/dl). Similar results were obtained by Sood et al (1975) in Indian pregnant women. However, other studies carried out in West Indies (Jackson and Latham 1982) and Thailand (Sirsupandit et al 1983) have shown no additional effect of folic acid on the rise in Hb due to iron therapy. These differences may find an explanation in the epidemiological finding that while folic acid deficiency is common among Indian pregnant women it is not a major etiological factor of anemia in countries like Thailand where the diets are reported to be sufficient in folic acid (Gopalan 1993).

Supervised vs unsupervised

Only two studies investigated the independent effect of supervised and unsupervised iron supplementation in the same population (Kuizon et al 1983, Charoenlarp et al 1988). Kuizon et al (1983) found that supervised consumption of iron supplements, 260 mg/d over a 4 week period, produced a rise in Hb (0.46 g/dl) that was statistically not different from the rise seen in the unsupervised group (0.49 g/dl).

With 120 mg iron for 12 weeks in Burmese women, Charoenlarp et al (1988) found that the rise in Hb was 0.55 g/dl in the supervised group compared to 0.74 g/dl in the unsupervised one. However, in the 240 mg group, women who were supervised showed a rise of 0.47 g/dl whereas the unsupervised ones showed a rise of only 0.2 g/dl. The investigators attributed this smaller rise in Hb at the higher dose level in the unsupervised group to the increased incidence of side effects. Thus it appears that supervision would be more necessary if side effects experienced are high.

In summary these supplementation trials reveal that iron therapy is chiefly responsible for the rise seen in Hb in pregnant women with only a small effect of folic acid. The Hb responses are dependent on the dose level of iron and duration of therapy and to some extent on whether iron is delivered as a single or multiple dose.

Effects on Other Hematological Indices of the Mother

Ideally iron supplementation in pregnant women should not only aim at correcting anemia by raising the Hb levels, but also build iron stores. With the advent of a reliable method for measuring serrum ferritin levels (INACG 1985) and the significant positive correlation (r= 0.83) that has been

shown to exist between stainable iron in the bone marrow and serrum ferritin levels (Bothwell et al 1979) several studies have measured the serum ferritin changes in pregnant women after therapeutic supplementation with iron. Serum ferritin level of one mcg/l is considered to represent 10 mg storage iron (INACG 1985).

Guldholt et al (1991) found that higher levels of iron, 100 mg/day given for 16 weeks prevented the drop in serum ferritin levels commonly found in pregnant women who were not supplemented or supplemented with a low dose of iron (15 mg/day). Table 2.14 lays out details of the studies in which serum ferritin levels were measured at different dose levels and duration of iron supplementation. In pregnant women supplemented with placebo or a multivitamin supplement, the level of serum ferritin was found to decrease as pregnancy advanced (Dommisse et al 1983, Charoenlarp et al 1988, Friere 1989 and Simmons 1990). A dose level of 60 mg produced an increase of only 3.9-7.6 mcg/l, whereas 120 mg and 240 mg produced an increase of 8.1-27.0 mcg/l and 8.1-25.0 mcg/l respectively (Thane Toe and Thein Than 1982, Charoenlarp et al 1988, and Reddiah et al 1989). Interestingly the mean rise in serum ferritin levels of unsupervised pregnant women supplemented with 240 mg iron was found to be the highest (43 mcg/dl) in the study by Charoenlarp et al (1988). However even with 120 mg iron

Table 2.14 Effect of different dose levels of iron on serum ferritin, serum iron and transferrin saturation in pregnant women

Reference/ Duration of Therapy (weeks)	Level of iron (mg)	Change in serum levels		
		Ferritin mcg/dl	Iron mcg/dl	TS %
India				
Sood et al (1975)[a]	0		- 3.6	- 1.9
10 - 12	30		23.5	6.5
	60	NM	33.5	8.1
	120		34.3	9.1
	240		43.5	15.1
Reddiah et al (1989)[b]	60	3.9		
14 - 16	120	8.1	NM	NM
	240	8.1		
Burma				
Aung Than Batu et al	0		- 6	
(1976)[c]	120	NM	37	NM
14 - 16				
Thane Toe and Thein	60	7.6	17.0	8.8
Than (1982)[d]	120	9.2	36.0	11.0
12	240	21.0	14.0	6.2
Charoenlarp et al[e]	0	-10.0		
(1988)	120	11.0	NM	NM
10	240	14		
15	0	- 4.0		
	120	27.0	NM	NM
	240	25.0		

[a] all groups received 0.5 mg folic acid and 100 mcg B12 daily
[b] all groups received 0.5 mg folic acid
[c] all groups received 10 mg folic acid
[d] all groups received 5 mg folic acid
[e] all groups received 5 mg folic acid except the group without iron.

NM not measured

Table 2.14 (contd..)

Reference/ Duration of Therapy (weeks)	Level of iron (mg)	Change in serum levels		
		Ferritin mcg/dl	Iron mcg/dl	TS %
Philippines				
Kuizon et al (1983)	0		-13.2	- 2.6
4	195		15.7	4.6
	260		20.5	5.6
	390	NM	19.2	5.3
12	0		- 1.0	- 2.0
	195		28.6	5.9
	260	NM	39.1	7.5
West Indies				
Simmons (1990)[f]	0	-10.6		
6	50	1.3	NM	NM
	100	2.3		
12	0	-11.2		
	50	2.1	NM	NM
	100	7.6		
Cape Town				
Dommisse et al (1983)	0	-34		-10.3
19	120	- 9.9	NM	- 1.8
Ecuador				
Freire (1989)	0	0.3	NM	- 2.5
8	78	10.8		3.1

[f] 50 mg iron group was a GDS capsule.

supplementation Dommisse et al (1983) reported a fall of 9.9 mcg/l in serum ferritin, indicating that 120 mg iron was insufficient in some individuals to prevent the depletion of body iron stores.

The positive effect of increased duration of therapy was also demonstrated by Charoenlarp et al (1988) who showed that a higher increase in serum ferritin levels was found in the 120 and 240 mg iron treatment groups when the duration of therapy was increased from 10 weeks to 15 weeks. From the point of view of building up iron stores, as shown by serum ferritin levels, 240 mg iron dose given for fifteen weeks seemed to yield the best results. Considering that it is very difficult to motivate women to consume 240 mg iron over a 12-15 week period due to the high incidence and severity of side effects, for practical programmes 120 or 180 mg appears more feasible, although producing a somewhat lower magnitude of rise in serum ferritin levels.

Table 2.14 also shows the changes in serum iron and transferrin saturation with iron therapy at different dose levels. As seen from this table there was a decrease in serum iron and transferrin saturation when pregnant women were given only placebo and an increase when iron was provided, except in the study by Dommisse et al (1983) where supplementation even with 120 mg iron resulted in a fall in

transferrin saturation. Iron treatment with higher dose levels produced a progressive increase in these parameters in Soods study (Sood et al 1975) but showed inconsistent trends in the study by Thane Toe and Thein Than (1982) and Kuizon et al (1983).

Effects on Morbidity Profile, Weight Gain and Gestational Duration of the Mother

Morbidity profile

Iron deficiency is a common finding in populations with a high incidence of infection. Two views emerge from the studies conducted on the effect of iron supplementation and immune status. Some have demonstrated that iron deficiency impairs immune response and therefore increases the susceptibility to infection, providing a rationale for iron therapy (Prema et al 1982a). On the other hand iron deficiency is also said to protect against infection, as the microorganisms do not have the conducive environment to obtain iron for metabolism, and therefore it is feared that providing iron would facilitate the growth of the organism to the detriment of the individual (Stockman 1981).

In a study of 544 pregnant women from Papua, New Guinea, 34% of whom received intravenous iron infusion. Oppenheimer et al (1986a) observed that iron treatment was

associated with perinatal malaria in primiparous but not multiparous pregnant women. In Tanzania, Byles and D'sa (1970) reported 11 cases of malaria in 917 pregnant women after parenteral iron therapy. The extrapolation of these results to the general population of pregnant women is limited by the observation that New Guinea is a malaria endemic region, and the Tanzanian study lacked a control group.

In the underprivileged population of anemic pregnant women in India, on the other hand, intramuscular injection of iron dextran (100 mg) for ten days has been shown to restore the reduced T and B lymphocytes to values similar to that seen in non-anemic pregnant women of the same gestational age (Prema et al 1982b). Prevalence of minor infective morbidities, mainly respiratory infections and diarrhoea, in the parenterally supplemented anemic women was 1.6/person. This rate was comparable for that reported for nonanemic women (1.3/day) from a similar socioeconomic background, thus indicating that iron supplements given to anemic pregnant women may be associated with improved immune status and possibly reduced morbidities.

As parenteral administration of iron has yielded divergent findings, the ACC/SCN expert committee (ACC/SCN 1989) has recommended oral iron therapy, the effect of which

on morbidities, especially at high levels, is an area that has not been investigated thoroughly.

The hypothesis that iron rich environment in the host predispose to infection raises speculations about the safety of administering high doses of iron. Considering the iron supplementation programs beamed to pregnant women both in the developed and developing countries, and suggestions to raise the level of iron, it is imperative that evaluations have to be made in terms of benefits and disadvantages related to morbidity. One of the research priorities stated by the ACC/SCN (1989) is also to evaluate iron supplementation studies in terms of immune status and response to infection. Reviews on interactions of iron and infection (Keusch and Farthing 1986, Hershko et al 1988, Oppenheimer 1989) have also emphasized the need for controlled prospective studies on iron supplementation and incidence of morbidity.

Weight gain

Correction of anemia, and improved hematological status through iron supplementation during pregnancy may influence other aspects of maternal and infant outcome, although available data are very scarce.

Monitoring of weight gain is a common procedure in most maternal health clinics in view of the relationship between birthweight of the infant and the weight gain of the mother. Weight gain in turn reflects the dietary adequacy of the mother. In industrialised countries the average weight gain is reported to be about 12.5 kg during entire pregnancy, which has been accounted for by the following components: 3.5 kg for fetal weight, 2 kg for the expansion of uterus, amniotic fluid and placenta, 1.5 kg for fluid retention, 1 kg for the mammary gland expansion and 4 kg for maternal fat deposition (Hytten and Leitch 1971).

Pregnancy weight gains reported in the developing countries are much lower than in the industrialised countries. The five country study by Durnin (1987) reported a pregnancy weight gain of 11.7 kg in Scotland, 10.5 kg in Netherlands, 8.9 kg in Thailand, 9.5 kg in the Philippnes, and only 7.3 kg in the Gambia. Studies in India have reported an average weight gain of 6-7 kg in the underprivileged pregnant women (Venkatachalam 1962, Devi and Banu 1963, Bhatt et al 1972, Shah and Shah 1972, Singh and Borkotoky 1975, Tripathi et al 1987) as against 8.0 kg in well nourished women (Tripathi et al 1987).

Accurate estimates of weight gain during pregnancy are possible only where prepregnancy weights are available.

Where prepregnancy weights are not available, either weight attained at a specific point in pregnancy or weight gain per week has been suggested as an indicator of nutritional status. Body weight values at specific gestational ages for detecting undernutrition have been suggested by Tripathi et al (1987) based on their work in Varanasi, India (45 kg at 13 w, 47 kg at 20 w, 49 kg at 25 w, 50 kg at 30 w, 51 kg at 35 w and 52 kg at 40 w). Shah and Shah (1972) suggested a cut off value of 40 kg at 20 w of gestation for detecting women who were likely to be malnourished.

Well nourished pregnant women from UK were reported to have a constant rate of weightgain in the last two trimesters of 400 g/w (Durnin 1987). Lechtig et al (1979) from Guatemala have also reported that pregnant women in their last two trimesters gained weight at a constant rate of 1.2 kg/m, which works out to be 300 g/w. These observations, that the rate of weight gain may be relatively constant in the last two trimesters makes it a useful parameter for evaluating weight gain in pregnancy based on weight measurements made at any two points in the 2nd and 3rd trimester.

Studies available on the impact of iron supplementation on weight gain characteristics in pregnancy are very few. Two studies from Coimbatore, India (Vijayalakshmi and Usha

1981, Vijayalakshmi and Shobana 1982) have reported on the weight gain in pregnant women given iron supplements. However, in one of these studies, iron (60 mg) and folic acid (0.5 mg) was provided along with supplementary food for 100 days and compared with a control group that did not receive iron and folic acid or the supplementary food. Body weight at one week postpartum was used as the pre-pregancy weight which could have underestimated the weight gain. Weight gain of the former group was reported to be 7.33 kg as against only 5.5 kg for the latter. The effect of iron-folic acid supplements per se was not separated out. Absence of any data on gestational ages of the different groups also makes interpretation difficult. In the other study (Vijayalakshmi and Shobana 1982) weight gain in pregnant women supplemented with 120 mg iron and 5 mg folic acid was reported to be 5.68 kg, compared to only 5.34 kg and 4.79 kg for those given only folic acid or the control group receiving no supplement. The difference in weight gain between the iron group and the control group was reported to be statistically significant. Once again lack of data on the study design and the gestational age at entry of the women make interpretations difficult.

Scholl et al (1992) in a prospective study of 779 women 12-29 years of age recruited from two pre-natal clinics of New Jersey (USA) reported inadequate weight gain in anemic

mothers compared to non-anemic mothers, with 60% of the subjects in both the groups receiving iron supplements. Forty percent of the women had inadequate weight gain (Butman 1982) in the anemic group compared to only 24.6% in the non anemic group . The level of iron and duration of supplementation were not indicated in this study, which makes it difficult to assess the contribution of iron supplements to the gain in weight. While weight gain data in relation to iron supplementation are scarce, an extensive study by Prema et al (1981a) have shown lower body weights in women with lower Hb levels, 43.5 kg with Hb $<$ 8.0 g/dl and 45.3 kg with Hb $>$ 11 g/dl.

Higher levels of Hb have also been shown to lead to lower weightgain. In a therapeutic trial on iron supplementation in 877 Norwegian women, Sagen et al (1984) reported different levels of weight gain for women at term ($\geq$37 weeks gestation) corresponding to their Hb levels. These women were all supplemented with 100 mg elemental iron from 16 weeks till delivery. Women with Hb levels between 9-11.9, 12-12.9 and 13-15 g/dl at term had a weightgain of 15, 14.2 and 13.1 kg respectively. Maternal weightgain in this study was found to be significantly lower with higher levels of Hb. Mitchell and Lerner (1992) found a positive correlation between the initial weight and final Hb (r =0.109) and final weight and final Hb (r=0.144) in 1058

American pregnant women supplemented with iron and folic acid (100 mg iron and 1.4 mg folate) from 12th week of pregnancy.

Gestational duration

Studies which have investigated the effect of iron supplementation on gestational duration are also very few.

Anemic and non anemic pregnant women supplemented with 105 mg elemental iron during pregnancy in France, were found to have the same mean gestational duration (Zittoun et al 1983), which was similar to the gestational duration of those who were not given any supplementation during pregnancy. Alward and Kevany (1984) made similar observations in 400 pregnant women in Dublin, that iron supplementation did not significantly affect the gestational duration of these women. However these women had a mean Hb of 12.5 g/dl which is much higher than what is found in Indian pregnant women.

In a review of 17 controlled iron supplementation trials (Hemminki and Starfield 1978), only two reported beneficial effects of mineral vitamin supplements containing iron and folic acid on the gestational duration, incidence of premature delivery and pregnancy complications. The studies referred to above have all been carried out in

affluent populations with relatively higher Hb levels compared to those reported in developing countries. The effects of iron supplementation especially as it relates to different dose levels in Indian pregnant women who have lower Hb levels need to be tested.

Effects on Birthweight, Post-natal Growth, Hemoglobin and Morbidity Profile of Infants

Birthweight

The birthweight of the infant is a potential indicator for the survival and future development. Low birthweight infants (<2500 g) are handicapped with mental, motor, and growth impairments. In India an estimated 33% (UNICEF 1994) of the infants are born with low birthweight and are at high risk of morbidity and mortality.

There is a plethora of studies in the literature that have investigated the relationship betwen Hb levels and the birthweight of the infants (Ratten and Beischer 1972, Garn et al 1981, Prema et al 1981a, Higgins et al 1982, Sagen et al 1984, Badole et al 1992, Mitchell and Lerner 1992). Higher incidence of low birthweight infants has been reported in pregnant women with low Hb levels (Prema et al 1981a, Badole et al 1992). However, studies which have investigated the effect of different levels of iron

supplementation on birthweight using a randomized experimental design are far fewer.

In a study of 418 rural pregnant women Agarwal et al (1991) reported a higher mean birthweight of 2.88 kg in women supplemented with 60 mg elemental iron and 500 mg folic acid for 100 days compared to a lower mean birthweight of 2.59 kg in infants born to women in the control group who received the supplements for only 25-30 days, at the same dose level. A higher incidence of low birthweight (37.9%) was also reported in the control group compared to the iron treated group (20.4%). These investigators also reported that when iron supplementation was initiated at an earlier gestational age (16-19 weeks) the birthweight was higher by 90 g (2.95 kg) than when it was initiated at the 20th to 24th week (2.86 kg).

The only randomized placebo controlled study, available to the investigator which tested different levels of iron supplementation during pregnancy on birthweight of infants was the WHO Collaborative study by Sood et al (1975). These investigators tested four levels of iron, 30 mg, 60 mg, 120 mg and 240 mg daily for 10-12 weeks for their various effects in pregnancy including birthweight of the infants. Of the 647 women who were supplemented, birthweights were available only for 47% of the sample. No significant

differences were found in the mean birthweight of the infants in relation to the level of iron tested.

In a study of 192 pregnant women supplemented with low (15 mg) or high level of iron (100 mg) Guldholt et al (1991) in Denmark also found no significant difference in the mean birthweights of the infants.

In the metaanalysis of determinants of birthweight by Kramer (1987), only one study on Australian women by Fleming et al (1974) was identified to be a randomized iron supplementation trial which partially met their other methodological requirements. These requirements included an appropriate definition of the population and sample, description of participation and follow up, a rigorous randomized experimental design which controlled for the effects of maternal height, pre-pregnancy weight, maternal age, socio-economic status, gestational weight gain and/or caloric intake. This study by Fleming et al (1974) found no effect of iron supplementation at 60 mg per day during pregnancy on the birthweight. But the mean Hb of these women was 12.7 g/dl and very few of the subjects may have been anemic.

There were four other studies (Ganguly et al 1972, Metcoff et al 1981, Hingson et al 1982, McLaughlin and Kevany 1982) which were correlational studies carried out in

developed countries and which met the methodological requirements partially. These studies also reported no significant effect of iron intake or hematological status on birthweight controlled for gestational duration.

The results of the meta analysis are best summarized by quoting Kramer

> 'In summary, studies that have a bearing on the impact of iron or anemia on intrauterine growth or gestational duration are particularly weak from a methodological standpoint. The few reasonably rigorous investigations do not indicate any significant effects, especially for birthweight; because none of these was carried out in a developing country, however it cannot be ruled out that iron supplementation could be beneficial in countries with a high prevalence of iron deficiency anemia'.
> (Kramer 1987, p 699)

Post-natal growth

Initially, for about 4-6 months, when infants are exclusively breastfed, maternal nutritional status contributes substantially to the growth of the infants. Studies on maternal nutritional status have shown that maternal undernutrition leads to intrauterine growth retardation and improving the mother's nutritional status improves infant birthweight (Adair and Pollitt 1985, Metcoff et al 1985, Prentice et al 1987). Kusin et al (1992) demonstrated that infants who were born to East Javan mothers supplemented with 165 Kcal/day in the last trimester

of pregnancy were heavier and taller throughout the 5 year follow-up than those infants whose mothers received only 52 Kcal/day. Significant differences in the growth rate were reported between 3-6 months of age. However practically no studies are reported in the literature which have investigated the effects of different levels of iron supplementation during pregnancy on the postnatal growth of infants.

The only studies available in the literature on the effects of iron supplementation on growth performance are related to preschool and school-aged children.

In a study on Indonesian school children supplemented with iron, Chwang Leh-chi et al (1988) showed higher rate of weight gain in iron treated children compared to the control, which was attributed to reduced morbidity and increased myeloperoxidase activity in leucocytes. Aukett et al (1986) also found that 17-19 month old anemic children supplemented with iron and ascorbic acid showed a greater rate of weight gain than the ones supplemented with ascorbic acid only. A larger percent (75%) of the iron and ascorbic acid supplemented group gained 7 g/day compared to the ascorbic acid group (48%). Bhatia and Seshadri (1993) found that 40 mg elemental iron supplementation for six months resulted in better growth and weight gain (310 g more than

the placebo group) and increased weight for height in anemic children compared to those supplemented with a placebo. Rate of weight gain per day was 5.2 g/day in the anemic iron treated group compared to 3.4 g/day in the anemic placebo group.

Hemoglobin

Iron endowment of the infant at birth is estimated to be about 75-80 mg/kg body weight with 50 mg/kg in the blood as Hb and 25 mg storage iron in the liver and body tissues (Bothwell et al 1979, INACG 1979, DeMaeyer 1989). Due to the rapid growth of the infant during this critical period a low iron intake from breastmilk (0.1-0.2 mg/dl) is often inadequate for the high iron requirements, and therefore iron stores are mobilized to supply iron for growth.

Infants already at a handicap of low birthweight are further deprived, as storage iron is directly proportional to the body weight of the infant. A full term infant with 270 mg iron needs to absorb 100 mg of iron for the whole year to maintain Hb at 11g/dl. Low birthweight infants need to assimialte even higher levels to avoid becoming anemic (Bothwell et al 1979).

During the third trimester the fetal and placental demands for iron are the greatest, and iron is transported

across a concentration gradient from the mother to the fetus. Earlier studies indicated that iron endowment of the infant was not affected by the iron status of the mother, as infants born to iron deficient mothers had Hb concentration which was not below normal at birth or 3 months (Woodruff and Bridgeforth 1953, Langkowsky 1961, Shott and Andrews 1972, Murray et al 1978).

In a randomized iron supplementation trial with different dose levels ranging from 30 mg to 240 mg iron Sood et al (1975) did not report any significant difference in the Hb of the infants at 3 months, between the placebo and iron treated groups. However, more than 50% of the iron treated pregnant women in their study were still anemic at the end of the supplementation, which may partly account for the lack of difference. Kuizon et al (1980) made similar observations in Phillipines as neither iron treatment of the mother nor the initial state prior to supplementation (anemic/non-anemic) affected the Hb of the infants significantly although infants born to iron supplemented mothers had slightly higher Hb than infants born to mothers without iron supplementation.

The existence of a linear positive correlation ($r = 0.4878$) between cord serum and placental tissue iron with maternal serum levels have been demonstrated more recently

by Singla et al (1979) which has been interpreted to mean that the fetus extracted iron in proportion to the maternal iron status. In the same study and in others anemic status of the mother was shown to be closely related to the hematologic status of the infant, iron in the cord serum, cord ferritin, and cord transferrin saturation (Barua and Foll 1960, Singla et al 1978, Agarwal et al 1983, Shenoi and Narang 1991).

In contrast Bhargava et al (1989) in a cross-sectional study did not identify any differences in the cord ferritin of anemic and non anemic groups of 95 mother infant pairs. These divergent results in the Indian studies (Agarwal et al 1983, Bhargava et al 1989) may be due to the fact that although these women were anemic (Hb $<$ 11 g/dl), the maternal ferritin levels in the studies may have varied, as there is evidence to show that maternal ferritin $<$10 mcg/l is associated with lower fetal ferritin level (Kelly et al 1978).

While an earlier study by Sturgeon (1959) did not show any effect of parenteral or oral iron during pregnancy on the iron status of infants upto 18 months of age, recently studies in India (Raman et al 1990) and Denmark (Milman et al 1987) have shown that prenatal iron supplementation with 120 mg iron or 200 mg iron produce higher ferritin levels in

infants. Thus iron supplementation during pregnancy may favour better iron stores in the infants which may in turn have an effect on growth and Hb levels post-natally, but currently these are only speculative.

Morbidity profile

The literature is notably deficient in the area of iron supplementation during pregnancy and morbidity profile of infants postnatally. However, some studies have investigated the effect of iron supplements given during infancy on the morbidity profile of the infants.

Major findings of these studies of oral or parenteral iron supplementation in term, preterm and low birthweight infants have mostly shown beneficial effects in terms of reduced incidence of infections in the iron treated groups (Salmi et al 1963, Andelman and Sered 1966, Krantman et al 1982, Reeves et al 1984, Walter 1986).

In 95 premature (birthweight 1060-2400 g) Finnish infants (Salmi et al 1963) sequentially classified into three treatment groups : Ferric choline citrate 100 mg twice a day; ferric gluconate 66.7 mg four times a day and the third receiving no medication, incidence of infection in the control group was twice that of those receiving iron medication. At six months of age the infants without iron

medication had mean Hb that was 2 g/dl lower than the infants of the other groups.

Andelman and Sered (1966) in Chicago found that in infants who did not receive reconstituted milk formula with iron, incidence of respiratory infection was significantly higher than those who received. reconstituted milk formula with iron. Although Fuerth (1972) reported that 602 full term infants in California, who were given either 30 mg of elemental iron per day, or a placebo showed no objective benefit of iron supplementation, interestingly the mothers of the iron-supplemented infants had less complaints of their children's sleep pattern, irritability during day time and illnesses, compared to the placebo group. In a randomised study of normal-term infants, Burman (1972) reported that there was a difference in the incidence of infections in infants receiving two drops of Neoferrum daily and those receiving placebo. All these studies on iron supplementation have been carried out in developed countries.

One incidence of detrimental effect of intramuscular iron dextran was reported by Oppenheimer et al (1986b) in infants at two months of age in Papua, New Guinea as it resulted in longer duration of stay in the hospital and higher incidence of respiratory illness, malaria and

pneumonia, compared to the group which received a placebo saline. In view of this oral administration of iron supplements appear to be the route of choice.

Effects on Hemoglobin and Body Weight of the Mother in the Postpartum Period

Three studies were available in the literature which investigated the effect of pre-natal iron supplementation on Hb of the women in the post-partum period. A significant difference in Hb levels at three months postpartum was reported by Sood and Coworkers (1975) in women supplemented with 240 mg iron (11.71 g/dl) compared to those given placebos (11.17). At 4-7 weeks postpartum Aung Than Batu et al (1976) reported that women supplemented with 120 mg iron and 10 mg folic acid during pregnancy had a Hb of 13.1 g/dl compared to 12.7 g/dl in those supplemented with iron alone, and 11.1 g/dl in those supplemented with placebo or folic acid. However Kuizon et al (1980) did not report any difference in Hb of anemic pregnant women supplemented either with placebo or 195 mg iron at one month postpartum. In nonanemic women those who were supplemented with iron during pregnancy had a higher Hb (12.1 g/dl) than those supplemented with placebo (11.8 g/dl), at one month post-partum.

Weight changes of the mother in the post-partum period in relation to iron supplementation during pregnancy were not available in the literature. However, studies carried out in India (NIN 1980) have made an interesting observation that weight loss of about 2 kg during the 18 months of lactation is common among the underprivileged women belonging to the poor income groups.

The Anemia Control Program in India

In view of the wide prevalence of iron deficiency anemia during pregnancy and its adverse effects, the Government of India initiated the National Nutritional Anemia Prophylaxis Program (NNAPP) in 1970. Pioneering studies conducted under the aegis of the Nutrition Society of India (1968) formed the basis for the dose level of iron to be provided to the pregnant women beneficiaries. The national program envisaged that pregnant women with Hb $\geq$ 10 g/dl would receive a daily supplementation of 60 mg iron and 500 mcg of folic acid for 100 days in the last trimester of pregnancy. Pregnant women with Hb $<$ 10 g/dl were to be placed on active anti-anemia treatment.

An evaluation of this program in 1985 (ICMR 1989) in 11 States of India revealed several lacunae in operational aspects of the programme. To start with, the coverage of the

supplements for the 5779 pregnant women surveyed was only 19.4%. For the other beneficiary groups it was even lower; 7.4% for lactating women and 1.5% for children. Part of the problem associated with poor coverage could have been due to a centralized system of delivering the tablets. Place of distribution varied from hospital to subcenter and some times to mid-day-meal centers and schools. Although home delivery of the tablets was reported in some States like Gujarat, Bihar, Andhra Pradesh, Haryana, and Uttar Pradesh, no data were available on the coverage and compliance of the pregnant women beneficiaries using this distribution outlet. These observations highlight the need to establish and evaluate an easily accessible and an alternate decentralized delivery system such as distribution in the homes of the beneficiaries.

Compliance with the iron supplement was also extremely poor as only 11.7 % of the pregnant women who were offered the supplements consumed 90 tablets, which could have been due to inadequate supply or due to insufficient follow up and counselling. Only 34.1% of 95 PHC's had 100 or more tablets available for each beneficiary woman. Monitoring of compliance by the health functionaries was reported only by 35.1% of the pregnant women. Yet another problem leading to poor compliance could have been the unsatisfactory packaging of the tablets as deterioration was found in 18.9% of the

leftover samples. More reliable estimates of compliances can be made only when coverage has been ensured which calls for further investigations.

Hemoglobin estimations on all pregnant women above 20 weeks gestation indicated that there was no difference in the prevalence of anemia in women who received or did not receive the iron supplements (87.5% vs 88.1%) which may be attributed to inadequacies not only in coverage and compliance, but also the dose level of iron. A later study by ICMR (ICMR 1992) indicated that a significant proportion of the women with a reported consumption of 90 or more tablets had a Hb level of <10 g/dl (37.8%) and 19.4% had Hb <9 g/dl. This raises questions concerning the adequacy of the currently administered dose of 60 mg iron.

Based on the above findings, an expert committee constituted by the Ministry of Health & Family Welfare and UNICEF (1989) made some recommendations to improve the NNAPP programme which are outlined below.

(1) As a majority of the pregnant women (80%) were found to be anemic it was recommended that the program be termed as Anemia Control Program' where all pregnant women are expected to receive iron folate tablets.

(2) Improved packaging of the tablets in lots of 30 in sealed polythene bags or other packaging was emphasized to facilitate distribution and to increase demand and compliance of the pregnant women.

(3) Reaching the mothers at the appropriate time with the appropriate explanation was emphasized to improve compliance which meant periodic follow up and counselling.

(4) It was recommended that the dose level of iron be increased from 60 mg to 100 mg per day for a period of 100 days. Women, who were found to be anemic by clinical observations were to be provided two doses of 100 mg iron and 0.5 mg folic acid daily for 100 days.

(5) Hb estimations, to identify women who were anemic was to be discontinued, as the facilities were lacking in many centres, and in the absence of sterile equipment, such measurement would be risky.

The expert committee emphasized the need for initiating further research, based on the above recommendations for improving the efficacy of the anemia control program.

In view of the highlights presented in this Chapter on Review of Literature, the present study was undertaken with the major goal of testing the efficacy of an improved

decentralised delivery system for distribution of iron supplements and testing the effect of different dose levels of iron on selected parameters of maternal and infant outcome.