MANAGEMENT OF MILD ANAEMIA IN PREGNANCY

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Background information

India has the dubious distinction of having the highest anaemia rates in the world.

Anaemia in pregnancy was recognized as a major public health problem leading to high maternal morbidity and mortality, low birth-weight and high infant mortality.

Studies in the 1960 and 1970s had shown that anaemia in pregnancy was mainly due to deficiency of iron and folic acid.

The National Prophylaxis Programme for Anaemia was initiated in 1970s; this aimed at providing 60 mg of elemental iron and 500µg of folic acid supplementation during pregnancy to all pregnant women.

Over years there has been improvement in coverage under the programme, but even now coverage ranges between 15-50% in different states

In the 1980s the tardy decline in anaemia was thought to be mainly due to low coverage and compliance with oral iron-folic acid supplementation.

An ICMR evaluation showed that even in women who took the 90 tablets of IFA during pregnancy envisaged in the National Anaemia prophylaxis programme only prevented the deterioration in Hb during pregnancy but did not result in any improvement in the Hb level or the reduction in anaemia.

Taking cognisance of the finding the National Programme for Control of Anaemia was initiated in 1990.
The programme aimed at screening of all pregnant women

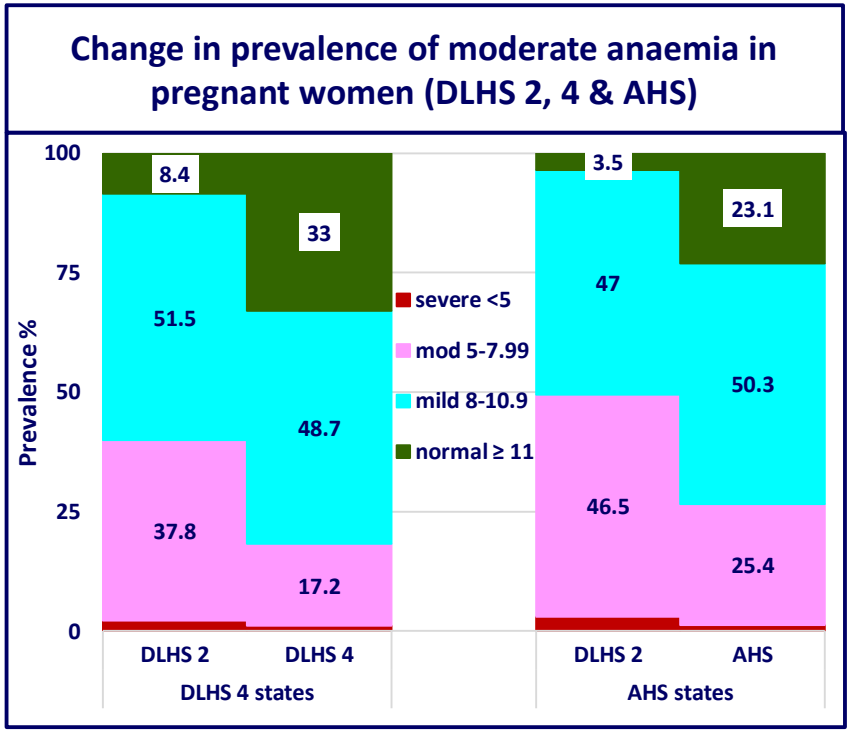
- **providing 100mg of elemental iron and 500µg of folic acid once a day to all non-anaemic pregnant women**
- **providing 100mg of elemental iron and 500µg of folic acid twice a day to all pregnant women with mild anaemia**

However screening for anaemia and providing appropriate dosage of iron and folic acid did not get operationalized mainly because of lack of facilities to accurately estimate Hb at the primary health care and community settings.

The National Iron Plus Initiative continued the strategy:

- **of screening for anaemia,**
- **providing 100mg of elemental iron and 500µg of folic acid once a day to all non-anaemic pregnant women**
- **providing 100mg of elemental iron and 500µg of folic acid twice a day to all pregnant women with mild anaemia**

Over the last decade there has been improvement in the coverage under screening for anaemia; but in most states majority of women received only 100mg of elemental iron and 500µg of folic acid



Between 2002 and 2013-14 there was some improvement in mean Hb and reduction in prevalence of anaemia.

Data from DLHS 2 (2002) and DLHS 4 & AHS (2013-14) showed that mild anaemia is the most common grade of anaemia in pregnant women.

Currently nearly 50% of all pregnant women across states have mild anaemia.

It is therefore essential to focus on successfully treating mild anaemia in pregnant women.

During the last decade studies on anaemia in pregnancy had shown that iron supplementation at 100mg level is associated with side effects in over a third of the persons consuming the tablets. Troublesome minor side effects include nausea, metallic taste in the tongue, abdominal cramps.

With increase in duration of use the proportion of persons who complain of side effects decreased. This could be due to the fact that:

- **women who experienced side effects tended to drop out or**
- **with increasing duration of use the side effects decreased.**

Unlike other segments of population, compliance and continuation rates with iron supplementation are higher in pregnant women because of the decades old nutrition education on adverse consequences of anaemia on mother-child dyad and how IFA supplement will improve Hb and obstetric outcome.

Side effects with anaemia depend partly on the dose of the iron consumed. With lower dosage the side effects decrease and compliance may improve.

Yet another reason for efforts to achieve the lowest effective dose of iron is that intestinal hurry associated with iron as well as higher hepcidin levels associated with higher dose of iron will inhibit iron absorption.

Research studies have explored the prevalence of iron, folic acid and B12 deficiencies in pregnant women with and without anaemia.

Iron deficiency is the most common nutrient deficiency in pregnant women.

In the last century folic acid deficiency ranked next to iron deficiency as the second most common micro-nutrient deficiency.

Some of the studies in the last decade has shown that folic acid deficiency is no longer widely prevalent across India.

Some of the recent investigations have highlighted the emergence of vitamin B12 deficiency as a major problem in some parts of the country.

In view of these it is important to find out whether time has come for providing vitamin B12 in addition to iron and folic acid in supplementation programme.

The two major research questions regarding treatment of mild anaemia in pregnancy are:

1. **What is the dose of iron needed to correct mild iron deficiency anaemia in pregnant women;**

2. **In addition to iron is folic acid alone sufficient or should vitamin B12 also be included in the supplementation regimen**

NFI took up two open randomized hospital based studies in pregnant women

To assess the compliance, side effects, impact of daily supplementation of:

- **two doses of ferrous sulphate containing 60 mg of elemental iron once a day vs 240mg of elemental iron per day (given as 120mg twice a day) along with**

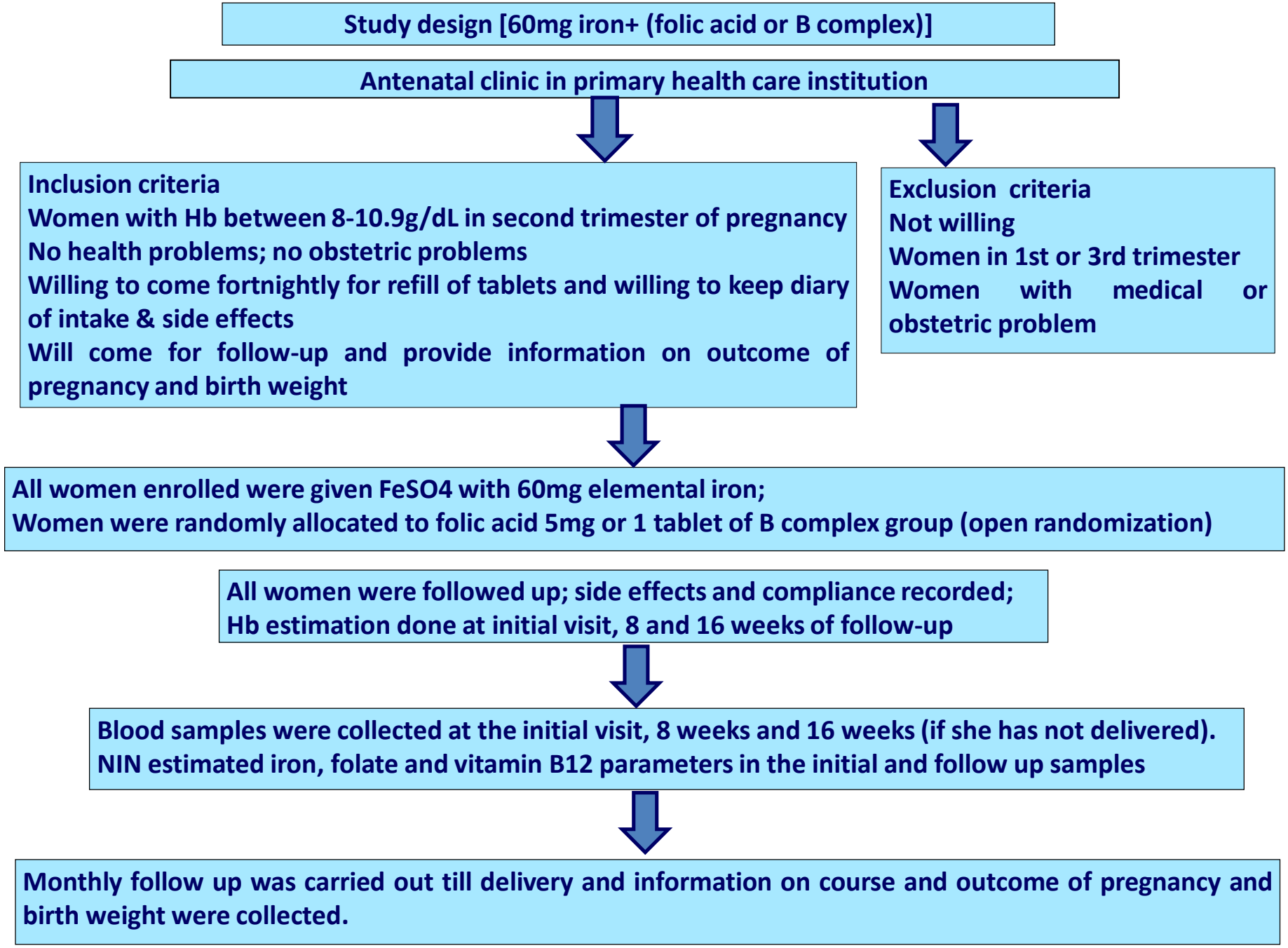
- **either only folic acid 500µg vs vitamin B complex containing both folic acid and vitamin B12**

The study design envisaged enrolment of apparently healthy pregnant women coming to antenatal clinic during the second trimester and willing to participate in the study:

- **In the first study women received 60 mg of elemental iron with either folic acid or Vitamin B complex**
- **In the second study women received 240 mg of elemental iron with either folic acid or B complex**

All women received iron tablets (either 60 mg or 240 mg) and were randomly allocated to receive either one tablet of 5 mg of folic acid or one tablet of vitamin B complex

Composition of B-complex supplement	
Thiamine mononitrate IP	10 mg
Riboflavin IP	10 mg
Pyridoxine Hydrochloride IP	3 mg
Vitamin B_{12} (as tablets 1:100) IP	150mcg
Niacinamide IP	100 mg
Calcium Pantothenate IP	50 mg
Folic Acid IP	1.5 mg
Biotin USP	100 mcg
Ascorbic acid IP (as coated)	150 mg


Study design [60mg iron+ (folic acid or B complex)]
Antenatal clinic in primary health care institution
Inclusion criteria
Women with Hb between 8-10.9g/dL in second trimester of pregnancy
No health problems; no obstetric problems
Willing to come fortnightly for refill of tablets and willing to keep diary of intake & side effects
Will come for follow-up and provide information on outcome of pregnancy and birth weight
Exclusion criteria
Not willing
Women in 1st or 3rd trimester
Women with medical or obstetric problem
All women enrolled were given FeSO4 with 60mg elemental iron;
Women were randomly allocated to folic acid 5mg or 1 tablet of B complex group (open randomization)
All women were followed up; side effects and compliance recorded;
Hb estimation done at initial visit, 8 and 16 weeks of follow-up
Blood samples were collected at the initial visit, 8 weeks and 16 weeks (if she has not delivered).
NIN estimated iron, folate and vitamin B12 parameters in the initial and follow up samples
Monthly follow up was carried out till delivery and information on course and outcome of pregnancy and birth weight were collected.

Study design [240mg iron+ (folic acid or B complex)]

Antenatal clinic in primary health care institution

Inclusion criteria
Women with Hb between 8-10.9g/dL in second trimester of pregnancy
No health problems; no obstetric problems
Willing to come fortnightly for refill of tablets and willing to keep diary of intake & side effects
Will come for follow-up and provide information on outcome of pregnancy and birth weight

Exclusion criteria
Not willing
Women in 1st or 3rd trimester
Women with medical or obstetric problem

All women enrolled were given $FeSO_4$ with 240mg elemental iron;
Women were randomly allocated to folic acid 5mg or 1 tablet of B complex group (open randomization)

All women were followed up; side effects and compliance recorded;
Hb estimation done at initial visit, 8 and 16 weeks of follow up

Blood samples were collected at the initial visit, 8 weeks and 16 weeks (if she has not delivered).
NIN estimated iron, folate and vitamin B12 parameters in the initial and follow up samples

Monthly follow-up was carried out till delivery and information on course and outcome of pregnancy and birth weight were collected.

Enrolment and follow-up 60 mg iron study			
	Enrolment	1st Follow-up	2nd follow-up
B complex	171	91	30
Folic acid	157	68	20

Enrolment and follow up of women receiving 60 or 240 mg of elemental iron with either 5 mg folic acid or vitamin B complex is shown in tables

There were no differences in enrolment and follow-up between groups

Enrolment and follow up 240 mg iron study			
	Enrolment	1st Follow-up	2nd follow-up
B complex	159	94	19
Folic acid	152	102	29

BIOCHEMICAL PROFILE OF THE PREGNANT WOMEN AT ENROLMENT

Iron, vitamin and CRP (mean±SD) in pregnant women with mild anaemia Hb 8-11 g/dL						
Hb (g/dL)	Ferritin (ng/mL)	sTfR (mg/L)	CRP (mg/L)	Hepcidin (µg/mL)	Folate (ng/mL)	Vit.B12 (pg/mL)
9.8± 0.72 (326)	17.2± 21.1 (322)	2.83± 1.50 (322)	4.31± 4.09 (321)	7.63±12.6 (324)	7.98±5.62 (322)	261.1±175.1 (321)

% inadequacy (below the cut-offs) in women with mild anaemia (baseline)								
Ferritin (ng/mL)		sTfR (mg/L)		Hepcidin (µg/mL)			CRP (mg/L)	
<12	≥12	<2.5	≥ 2.5	<8	8-18	≥ 18	<10	≥10
56.5 (182)	43.5 (140)	50.9 (164)	49.1 (158)	71.0 (230)	17.3 (56)	11.7 (38)	86.0 (276)	14 (45)

Folate (ng/mL)		Vitamin-B12 (pg/mL)	
< 3.0	≥ 3	<200	≥200
4.7 (15)	95.3 (307)	38.6 (124)	61.4 (197)

In women with mild anaemia

- about 2/3rd of had parameters suggestive of iron deficiency;
- nearly 40% had vitamin B12 deficiency;
- prevalence of folate deficiency was low (less than 5 %).
- CRP levels were high only in 14% (suggestive of inflammation)

Hb at recruitment, 1st & 2nd second follow-up (60 mg)			
	Initial	1st follow up	2nd follow up
B-Complex	9.8±0.72 (171)	11.0±0.92 (91)	11.6±0.95 (30)
Folic Acid	9.8±0.71 (157)	10.9±0.98 (68)	11.6±1.34 (20)

There was an improvement of 1.8 g/dL in 16 weeks in those who received ferrous sulphate containing 60 mg of elemental iron irrespective of whether they received vitamin B complex or Folic acid. The rise in Hb with 240 mg of elemental iron was essentially similar

The increase in Hb between initial and first, first and second follow-up was highly significant ($p<0.0001$) both in the 240 and 60 mg iron groups

There were no differences in improvement Hb levels between group receiving vitamin B complex and those receiving folic acid at enrolment, first and second follow-up irrespective of the fact whether they received 60 mg or 240 mg of elemental iron.

Hb at recruitment, 1st & 2nd second follow-up (240 mg)			
	Initial	1st follow-up	2nd follow-up
B-Complex	9.5±0.71 (159)	10.6±0.87 (102)	11.4±0.65 (26)
Folic Acid	9.6±0.71 (152)	10.6±0.84 (94)	11.2±0.75 (29)

% of non-anaemic women in 60 and 240mg iron groups receiving either folic acid 5 mg or B complex supplementation								
	60mg				240mg			
	Folic acid		B complex		Folic acid		B complex	
	No	%	No	%	No	%	No	%
Initial	157	0	171	0	152	0	159	0
8 weeks	68	50	91	58.2	94	38.3	102	36.2
16 weeks	20	70	30	70	29	69	20	73.1

Supplementation with either 60 mg or 240 mg of elemental iron resulted in significant reduction in the prevalence of anaemia by 8 weeks; by 16 weeks of supplementation over 70% of women had become non-anaemic.

There were no differences in prevalence of anaemia at 8 or 16 weeks between those who received folic acid and vitamin B complex irrespective of the fact whether they received 60 or 240mg of elemental iron supplementation.

Effect of supplementation with 60mg of elemental iron on Ferritin levels			
	Initial	8 weeks	16 weeks
B comp	20.1±27.67 (170)	30.2±54.78 (90)	26.2±23.80 (38)
Folate	15.0±14.90 (154)	28.8±16.23 (67)	25.3±20.14 (27)

There were differences in the mean ferritin levels between the four groups at enrolment. This is due to wide variations in ferritin levels in pregnant women and not statistically significant.

There was substantial statistically significant improvement in ferritin levels between enrolment and 8 weeks both in the 60 mg and 240 mg groups.

The difference in ferritin levels between 8 weeks and 16 weeks were relatively small but statistically significant both in 60 mg and 240 mg groups.

The differences in the improvement in ferritin levels from 0 to 8 weeks and 8 to 16 weeks in the 60 mg and 240 mg groups were similar and were not statistically significant.

Differences in the mean improvement in ferritin levels between Folic acid and B complex group both in the 60 and 240 mg iron groups were not statistically significant.

Effect of supplementation with 240mg of elemental iron on Ferritin levels			
	Initial	8 weeks	16 weeks
B comp	17.6±25.2 (117)	26.5±40.93 (69)	31.2±47.55 (10)
Folate	24.6±35.97 (119)	31.2±40.84 (69)	36.2±31.71 (13)

Effect of supplementation with 60mg of elemental iron on CRP levels			
	Initial	8 weeks	16 weeks
B comp	4.2±3.99 (170)	3.8±3.93 (91)	2.28±3.02 (38)
Folate	4.4±4.22 (154)	3.2±3.50 (66)	1.9±2.45 (27)

C reactive protein is considered as a good indicator of inflammation.

The differences in the mean CRP levels between the four groups at enrolment was small and not statistically significant.

There was no increase in the mean C reactive protein at 8 weeks or 16 weeks either in the 60 mg or the 240 mg groups.

The fear that higher dosage of iron will be associated with inflammation is not borne out by the data.

This may be because irrespective of the dose amount of iron absorbed was not different between the two doses.

Differences in the mean CRP levels between Folic acid and B complex group both in the 60 and 240 mg iron groups were not statistically significant at enrolment, 8 weeks and 16 weeks.

Effect of supplementation with 240mg of elemental iron on CRP levels			
	Initial	8 weeks	16 weeks
B comp	3.0±2.15 (117)	2.2±2.0 (36)	4.3±4.58 (11)
Folate	3.6±2.84 (119)	2.47±3.14 (36)	3.0±4.34 (13)

Effect of supplementation with 60mg of elemental iron on GPx levels			
	Initial	8 weeks	16 weeks
B comp	31.5±16.12 (163)	52.0±22.42 (87)	37.9±13.56 (38)
Folate	33.4±15.54 (151)	54.7±25.94 (65)	46.9±21.04 (26)

Glutathione peroxidase is considered as a good indicator of oxidative stress.

The differences in the mean Glutathione peroxidase levels between the four groups at enrolment was small and was not statistically significant.

There was an increase in the mean GPX at 8 weeks both in the 60 mg and the 240 mg groups. These differences were statistically significant.

The difference in the mean GPX at 8 weeks vs 16 weeks was not statistically significant either in the 60 mg or the 240 mg groups.

The fear that higher dosage of iron will be associated with oxidative stress is not borne out by the data.

This may be because irrespective of the dose amount of iron absorbed was not different between the two doses.

Differences in the mean GPX levels between Folic acid and B complex group both in the 60 and 240 mg iron groups were not statistically significant at enrolment, 8 weeks and 16 weeks.

Effect of supplementation with 240mg of elemental iron on GPx levels			
	Initial	8 weeks	16 weeks
B comp	35.2±12.38 (84)	48.4±14.68 (35)	40.4±18.56 (10)
Folate	35.6±11.34 (84)	47.2±12.3 (36)	52.3±9.79 (13)

SUMMARY AND CONCLUSIONS

Mild anaemia (Hb between 8.0-10.9 g/dL) was the most common grade of anaemia in pregnant women attending antenatal clinic; over 50% of women were mildly anaemic

Iron deficiency was present in over 2/3rd of the women with mild anaemia

Folic acid deficiency was seen in less than 10% of women

Vitamin B12 deficiency was seen in 38% of women

After supplementation either with 60 mg or 240 mg of elemental iron there was improvement Hb levels

There were no significant differences in the improvement in Hb between the group that received 60 mg and 240 mg

There were no differences in improvement in Hb between the groups that received folic acid or B complex with either 60 or 240 mg of iron.

By 8 weeks nearly half the women had become non-anaemic in the 60 mg group.

When supplementation was continued for 16 weeks about 70% of women became non-anaemic in both 60mg and 240 mg groups.

Following supplementation there was improvement in ferritin levels indicating improvement in iron stores. Over 50% of women became iron sufficient both in the 60 mg and 240 mg groups.

There was no increase in the mean C reactive protein at 8 weeks or 16 weeks either in the 60 mg or the 240 mg groups.

The fear that higher dosage of iron will be associated with inflammation is not borne out by the data.

There was an increase in the mean GPX at 8 weeks both in the 60 mg or the 240 mg groups. These differences were statistically significant.

The difference in the mean GPX at 8 weeks vs 16 weeks was not statistically significant either in the 60 mg or the 240 mg groups

The fear that higher dosage of iron will be associated with oxidative stress is not borne out by the data.

This may be because iron absorption in the two doses were essentially similar.

Based on the findings from these studies the Intensive National Iron Plus Initiative has recommended:

1. **Nutrition education for dietary diversity and improvement in the micro-nutrient intake**

2. **Use of iron fortified iodised salt for increase in the iron intake**

3. **Supplementation with IFA (ferrous sulphate containing 60mg of elemental iron and 500µg of folic acid) daily to non-anaemic pregnant women**

4. **Supplementation with two tablets of IFA (ferrous sulphate containing 60mg of elemental iron and 500µg of folic acid) to women with Hb between 8 and 10.9 g/dL**


Thank You