

Iron deficiency anemia in pregnancy: is intravenous iron sucrose an alternative to the oral iron-folate supplementation program in India?

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Synopsis: Intravenous iron sucrose may be the low risk solution, to eradicate Iron Deficiency

Anemia in pregnancy in India

Structured Abstract

Objectives:

To determine the current prevalence and severity of Iron Deficiency Anemia in pregnancy in rural and urban India, to prospectively document the response to an IFA supplementation program, and to pilot the response to intravenous iron-sucrose.

Patients & Methods:

We measured haemoglobin (Hb) levels in 10,000 unselected pregnant women in 4 rural centers, and in 1985 women in one urban centre. we studied the efficacy, safety and acceptability of two doses of 200mg intravenous iron sucrose as against oral iron folate

Results:

We found an IDA prevalence of 69.4% in the rural and 61.4% in the urban setting. Ninety seven (30.7%) of the women receiving oral iron showed an increase in Hb as against 64 of the 69 women (92.8%) receiving iron-sucrose, mean rise in Hb of 1.31gm/dl (sd 0.77).

Conclusions:

Thirty years of the IFA program have failed to eradicate IDA in pregnancy in India. The challenge is whether the costs and logistic difficulties posed by the use of iron sucrose on a population scale can be overcome.

INTRODUCTION

Iron deficiency anemia (IDA) remains the commonest medical disorder in pregnancy in the developing world¹⁻⁵, with the burden of disease impacting on both the mother and the newborn (and subsequent child and later adult). In India, the maternal mortality is around 350 - 450/100,000 live births, a figure similar to that found in Europe 200 years ago^{6,7}. Anemia is estimated to contribute 20 percent of all maternal deaths and nine times higher risk of perinatal mortality⁸. The odds for low birth weight are tripled, while those for preterm delivery more than doubled in association with IDA⁹. Anaemia and iron deficiency in pregnancy are associated with large placental weight and a high ratio of placental weight to birth weight (placental ratio)¹⁰, both of which are predictors of adult hypertension¹¹. In the newborn, IDA is associated with poor performance in the Bayley Mental Development Index¹². Poor mental and motor performance improves with iron therapy in iron-deficient infants at 12-18 month of age¹³. While nutritional factors may be contributory, it seems more than likely that IDA in infancy and early childhood is largely secondary to maternal iron deficiency during pregnancy. There is also evidence that infants born to women taking iron have more than double the iron reserves at 2 months of age and beyond when compared with the offspring of un-supplemented mothers. Thus to address the problem of iron deficiency in infancy and early childhood is to close the proverbial stable door after the horse has bolted. The definitive solution is to eradicate iron deficiency during pregnancy.

At face value the solution is potentially both simple and cheap. In India the National Nutritional Anaemia Control Programme (NNACP) was initiated in 1970 to provide free iron-folic acid (IFA) supplementation to all pregnant women commencing from the second trimester until 3 months of lactation. Following nearly 20 years of the IFA program the National Family Health Survey (NFHS) reported that the prevalence of IDA had dropped from the previous estimated

80-90% to 49.7% (NFHS II 1998/1999)¹⁴. In a recent (Sept 2001-April 2003) study The Healthcare and Research Association for Adolescents, Noida and the Nutrition Foundation of India, New Delhi studied women in the same districts and villages studied in NFHS-II and concluded that the prevalence and severity of anemia in rural pregnant women was much higher than that reflected in NFHS-II: 84 % prevalence, of which 9.2 % fell into the severe anemia category¹⁵. The Indian Council for Medical Research (ICMR)'s district nutrition survey data also reported similar anemia prevalence of 84.2 %, with 13.1 % being in the severe anemia category¹⁶. The most recent survey by the NFHS (NFHS-III,2005-06) has reported a rise in prevalence from 49.4% to 59.4% ¹⁷ Thus there is little doubt that the prevalence of IDA in pregnancy appears to be rising. We sought to establish the current extent of the problem by studying the prevalence and severity of IDA in rural and urban southern India. We then prospectively monitored the response to oral iron in a cohort of highly motivated pregnant women over a ten week period, and compared this to the response over four weeks in another cohort of women given just two doses of intravenous iron sucrose.

PATIENTS and METHODS

(i) Prevalence of iron deficiency anemia in pregnancy:

We recruited 10,000 unselected pregnant women in 4 rural centers and a further 1985 in one urban center between January 2006 and December 2007 and estimated their haemoglobin (Hb) at the booking visit (14-25 weeks gestation). To obtain blood samples, the tip of the index finger was cleaned with spirit and dried; a clean puncture was made with a sterile disposable needle; the first drop of free flowing blood was wiped off, and the second collected for Hb estimation, which was performed with a haemocytometer using the Shalis method^{18,19}. The Hb measurements were categorized according to criteria established by the ICMR as follows: <4g/dl = very severe anemia; 4 – 6.9 g/dl = severe anemia; 7-9.9g/dl = moderate anemia; 10-10.9g/dl = mild anemia; and ≥ 11 g/dl = non-anemic

(ii) Response to oral IFA supplementation

We prospectively studied the Hb response to oral IFA supplementation in 354 consecutive, unselected anemic (Hb less than 11g/dl) women recruited at booking (14 – 20 weeks gestation) in one urban center. Women were recruited on the basis that they were willing and motivated to adhere to a daily course of 200mg iron-folic acid supplementation for a minimum period of ten weeks, although we took no specific measures to ascertain compliance. A complete haemogram and peripheral smear were taken, and women with anemias due to causes other than IDA were excluded. We also excluded women already receiving iron supplements, or those destined to receive a blood transfusion, as well as women not willing to be participate. Prior to commencing iron therapy, all women were de-wormed with two tablets of Mebex Plus, a combination of

Pyrantyl Palomate and Mebendazole (Cipla India Pvt Ltd). Hb was estimated prior to commencing supplements and at ten weeks post treatment.

(iii) Response to intravenous iron sucrose

A cohort of 96 pregnant women from a rural center were recruited if their Hb was below 11g/dl and if they were willing to receive intravenous (iv) iron sucrose (Emcure Pharmaceuticals Ltd. Pune India) between 16 and 34 weeks gestation. We excluded women if they had a known allergy to parenteral iron, or had received a blood transfusion during this pregnancy. All participants were de-wormed as described above prior to iron therapy. The women received two doses of iv iron sucrose of 200mg per sitting, 3-5 days apart, on an outpatient basis and their Hb was estimated before and four weeks after therapy. The iron was administered after dilution with isotonic saline solution either as a bolus push over 5 minutes or a short infusion in 100ml isotonic saline over 30 minutes. No test dose was given, and any adverse reactions were monitored over an hour following the first dose of injection. We did not calculate the optimal dose of iron sucrose required by each woman based on her pre-treatment Hb: we sought to study the response to a uniform dose over a range of pre-treatment Hb's.

Ethics committee approval was not required for this study – since the use of intravenous iron sucrose in the said dosage is an accepted practice

Statistical analysis:

Data was analyzed using SPSS version 11 (Statistical Package For Social Sciences). The mean changes in Hb between the groups receiving oral iron versus iv iron sucrose were compared using the paired t-test, while the chi-square test was used to test the significance of associations with prevalence of anemia and other socio-demographic characteristics.

RESULTS

(i) Prevalence and severity of IDA in pregnancy:

Among the 10,000 rural women 6,948 (69.40%) were anemic, compared to 1,247 (61.40%) among the 1985 urban population ($p < 0.001$) [Figure 1]. The largest proportion of anemic rural women (4,352 or 43.52%) fell into the category of “moderate anemia” while the largest proportion of the urban group (688 or 35.7%) were in the “mild anemia” category. Severe anemia was found in 61 (0.61%) of the rural women, while no woman in the urban group had this degree of anemia [Table 1].

(ii) Response to oral iron-folic acid supplements

Out of the 354 women originally recruited, all had IDA but none were destined to have blood transfusions. Thirty eight women could not be reassessed at 10 weeks for a variety of reasons: (one aborted at six weeks after recruitment; five admitted that they could not continue to take the oral iron supplements because of gastric irritation; four discontinued because of constipation; and 28 did not turn up for their follow up Hb estimation at 10 weeks either because they had moved out of the city or they presented later than ten weeks). The data presented is therefore based on the remaining 316 who attended for the second Hb estimation at 10 weeks following therapy. Table 2 shows the pre- and post-treatment Hb levels. Ninety seven (30.69%) women showed a rise in Hb, the majority (40.21%) by up to a maximum of 0.5g/dl. The rest showed either no rise or even a fall in Hb [Table 2].

(iii) Response to iv iron sucrose

Follow-up Hb estimations were obtained at 4 weeks in 69 women (27 women did not attend for follow up Hb estimation). A rise of >2g/dl within 4 weeks was seen in 17.2% of these women [Table 3]. Sixty four (92.75%,) of the 69 women responded and had a mean rise in Hb of 1.31 gm/dl (sd 0.77) [Table 3].

Oral iron-folic acid versus iv iron sucrose:

The majority of women showing a rise in Hb in response to oral supplementation had a maximum rise of up to 0.5g/dl over 10 weeks, while iv iron sucrose resulted in the majority of women who responded raising their Hb by 0.6-0.9g/dl over 4 weeks ($p < 0.001$). Only 3 (3.09%) women in the oral iron group raised their Hb by ≥ 2.0 g/dl, while 11 (17.2%) in the iv iron sucrose group did so ($p < 0.001$) [Figure 2].

Adverse reactions to iv iron sucrose:

Minor adverse reactions, which included burning at the infusion site , itching, giddiness and GI symptoms like nausea and vomiting, occurred in 18.89% of the women, but there were no major adverse reactions [Figure 3].

DISCUSSION

All recent prevalence studies¹⁵⁻¹⁷ indicate that despite the IFA program, which has now been running for more than 30 years, IDA in pregnancy remains a major problem in India. Our own data corroborates this, and indeed suggests that the prevalence is rising. The evaluation by the National Nutritional Anaemia Control Programme (NNACP) in various states of India revealed that the IFA program has not achieved its objective²⁰. The Nutrition Foundation India survey in 2003 reported that in Assam 32 % of pregnant women received IFA but only 4.9 % consumed it, the equivalent figures in Madhya Pradesh being 74 % and 6.3 %¹⁵. Studies conducted by the ICMR corroborated these reports, finding that the reasons given for not consuming the tablets were nausea, constipation, causation of “heat in the body”, a belief that the baby would grow too large and cause difficult birth, and advice from elders and neighbours (ICMR 1985, 1989)^{21,22}. Thus a whole host of reasons have contributed to the failure of the IFA program including partial coverage of the population, inadequate dosing of the iron supplement, short supplies, defective absorption because of intestinal infestations, diets which contain high levels of iron chelators, problems with formulation, inadequate consumption or poor compliance by the beneficiaries, failure to replenish the stocks at the beneficiary level, and lack of effective health education and supervision.

“Best practice” dictates that women should be de-wormed prior to commencing the IFA program, and that they should be educated about the importance of taking the supplements, and exhorted to do so. Even in a controlled environment of our study in which we recruited 354 women and took all routine measures to optimize responses to iron supplementation, the Hb rise over a 10 week period was far from optimal. We encouraged, but did not seek to monitor compliance because that is not done in routine clinical practice. Neither did we seek to establish

the cause of the failure to show maximal responses to iron supplementation, as numerous studies have done this. We sought simply to establish what happens in everyday routine practice. Thus we have found that even within such a motivated group iron-folate supplementation failed to significantly raise haemoglobin levels. As indicated above, there are a whole host of reasons why the IFA program has failed, and it seems highly unlikely that these factors will ever be overcome. Initiatives beyond cosmetic changes are required if the scourge of IDA in pregnancy in India is to be overcome.

In the developed world it has long been documented that intravenous iron supplementation is highly effective in treating IDA in a variety of settings, including pregnancy. There is irrefutable evidence that compared to oral iron, iv iron sucrose results in a much more rapid resolution of IDA^{23,24}, has minimal side-effects, and because it is administered intravenously, it circumvents the problems of compliance. Unlike intravenous dextran iron, anaphylactic reactions are virtually unknown with iron sucrose. Our own small prospective cohort study shows that as little as two doses of 200mg of iv iron sucrose significantly increase Hb levels within 4 weeks, suggesting that a full-dose regimen could eradicate IDA. There were no major adverse reactions, and only a tiny minority of women experienced minor adverse reaction. All women stated that they found the treatment acceptable to them. We deliberately did not seek to calculate the optimal iron sucrose dose for each woman based on her Hb level: we simply sought to assess response to a uniform dose in all women whose Hb fell below 11g/dl, with an eye to the long term possible adoption of a single universal dose that might go a long way to eradicating IDA in pregnancy (see below). It is highly likely that responses would have been even more impressive had we administered the iron based on calculated dose requirements.

Could iv iron sucrose be the Holy Grail in the eradication of IDA in pregnancy in a setting such as India? There are huge potential, although not insurmountable, problems. Firstly, in women needing supplements most (ie those with haemoglobin levels of 8.0g/dl or less), the iron sucrose is often administered in several separate infusions, to minimize adverse reactions. Secondly, the very requirement of intravenous infusion brings in the issue of significant cost, especially when the challenge is to deliver this treatment to rural areas where the vast majority of the women needing the treatment reside. Although we did not encounter this problem in our small cohort study, nevertheless some women might find the idea of intravenous administration intimidating and or unacceptable. There are of course potential solutions to these challenges. One approach may be to investigate the potential of administering a single total dose of iron sucrose, to avoid the need for repeated hospital visits, which might compromise compliance. Costs could be reduced by administering the iron sucrose as a single bolus intravenous-push over 5 minutes, rather than giving it as an infusion, which requires a hospital bed and takes at least half an hour to accomplish. All these potential solutions require rigorous research and evaluation before they could be implemented. Oral and/or parenteral iron supplementation has failed to eradicate IDA, and cannot be said to be cost-effective. While definitive cost-effective studies for the use of iron sucrose are urgently needed, yet it is difficult to “cost” the morbidity and mortality suffered by women in the developing world as a result of iron deficiency anemia, never mind the impact on the next generation with regard to impaired motor and intellectual development associated with IDA in the newborn and child.

CONCLUSION

In India, the IFA program has failed to eradicate IDA in pregnancy, whose prevalence is rising. This is a neglected tragedy that continues to exact a heavy toll of suffering and death on women, while there are also the not-so-obvious but potentially just as devastating sequelae on the newborn and child's motor and intellectual development, and future risk of cardiovascular disease. Intravenous iron sucrose may be the solution, but rigorous research and evaluation will be required to establish its full place and potential.

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Figure 1: Prevalence Iron Deficiency Anemia

Anemia was defined as Hb less than 11 g/dl (WHO / ICMR). Among 10,000 rural ante-natal women 6,948 (69.40%) were found to be anemic, while among 1985 urban ante-natal women 1,247 (61.40%) were anemic. The difference in prevalence of anemia between rural and urban pregnant women was statistically significant ($p < 0.001$).

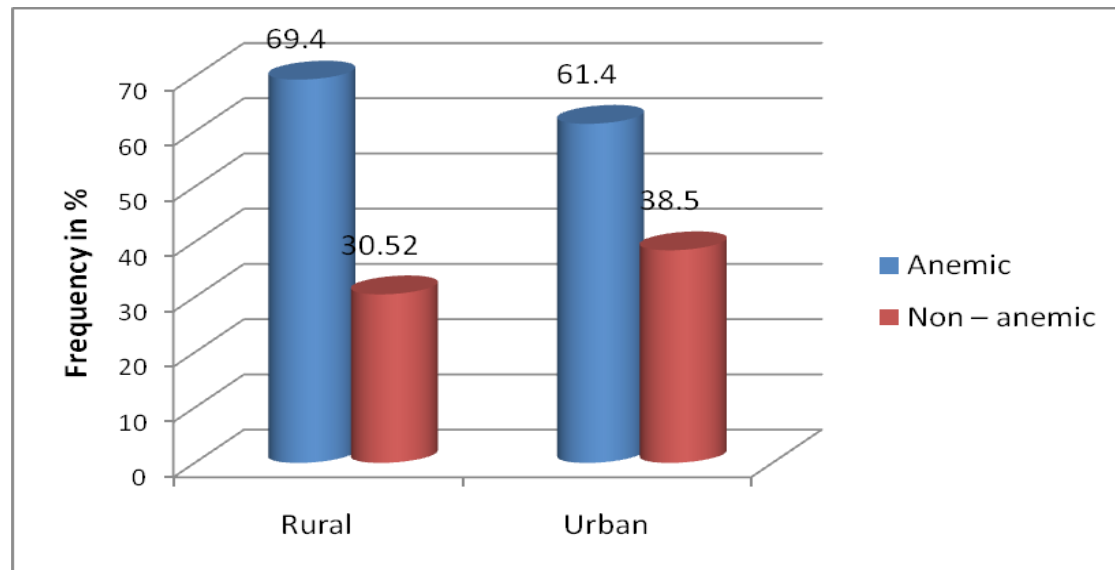


Figure 2: Response to oral iron-folate versus that to iv iron- sucrose

Among the women receiving oral iron-folate, the majority 39 (40.21%) showed an increase of Hb of up to 0.5 gm/dl, while in the iv iron sucrose group the majority of 34 (53.10%) showed a greater rise of 0.6- 0.9 gm%. Eleven (17.2%) in the iron sucrose group showed an increase in Hb of over 2.0 gm/dl while only 3 (3.09%) in the oral iron-folate group showed a similar increase.

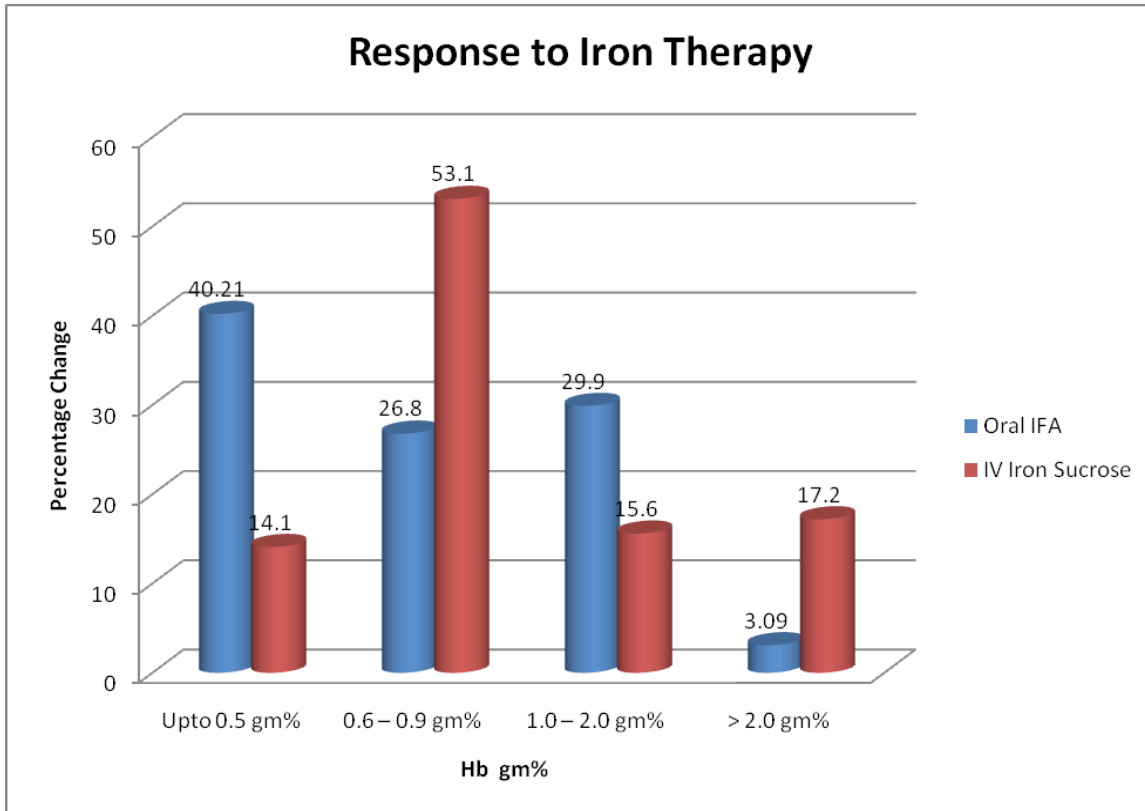


Figure 3: Frequency of adverse reactions following first dose of iv iron sucrose

Minor adverse reactions occurred in 18.89% of the women, and these included nausea, vomiting, burning at the infusion site and itching.

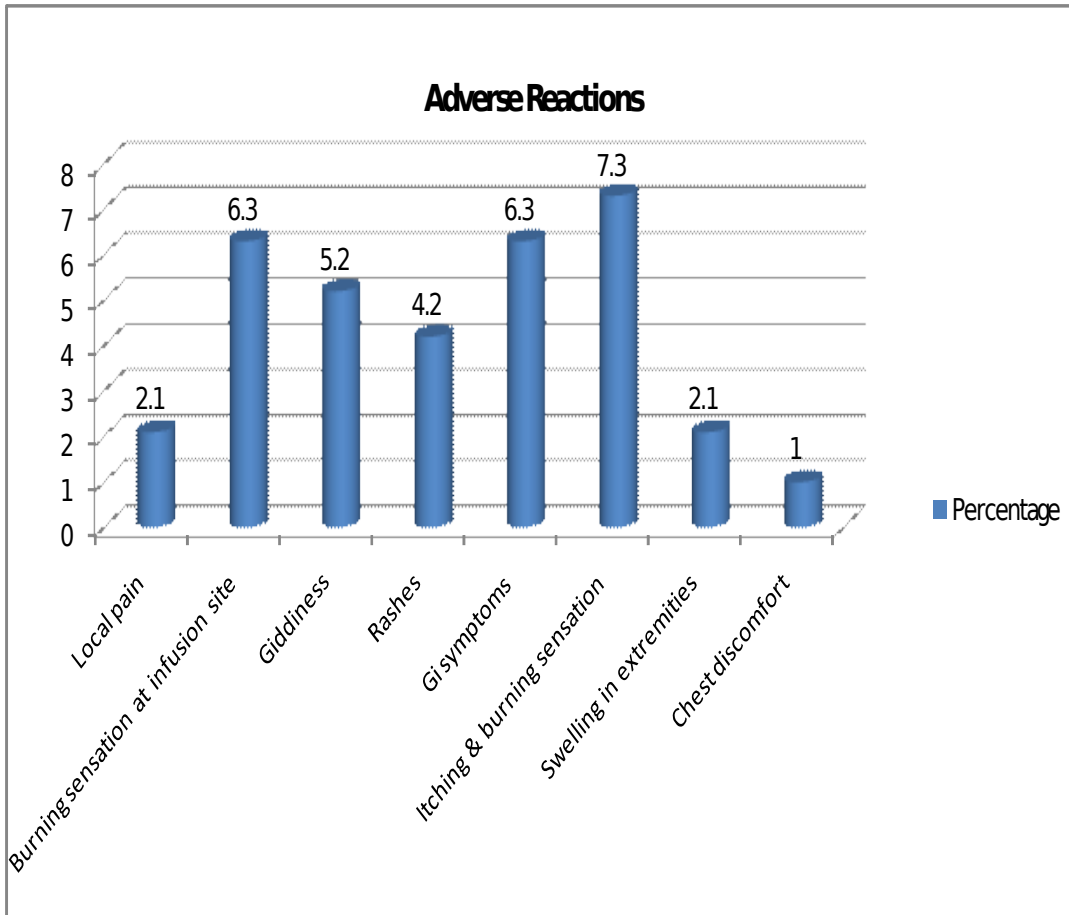


Table 1: Severity of Anemia

Anemia was categorized according to the criteria established by the Indian Council of Medical Research (ICMR) as follows: <4g/dl = very severe anemia; 4 – 6.9 g/dl = severe anemia; 7-9.9g/dl = moderate anemia; 10-10.9g/dl = mild anemia; and >11g/dl = non-anemic. The majority of anemic women (4352, or 43.52% in the rural population pregnant women had a moderate degree of anemia while the majority in the urban women (688, or 35.7%) had a mild degree of anemia.

<u>Anemia</u> <u>(Hbg/dl range)</u>	<u>Rural n=10,000</u>		<u>Urban n = 1985</u>	
	<u>(n)</u>	<u>(%)</u>	<u>(n)</u>	<u>(%)</u>
<u>Mild (10 -10.9)</u>	<u>2210</u>	<u>22.1%</u>	<u>688</u>	<u>35.7%</u>
<u>Moderate (7 – 9.9)</u>	<u>4352</u>	<u>43.52%</u>	<u>481</u>	<u>24.9%</u>
<u>Severe (4 – 6.9)</u>	<u>325</u>	<u>3.25%</u>	<u>18</u>	<u>0.9%</u>
<u>Very severe (<4)</u>	<u>61</u>	<u>0.61%</u>	<u>00</u>	<u>00%</u>
<u>Total</u>	<u>6948</u>	<u>100</u>	<u>1247</u>	<u>100</u>

Table 2: Response to oral iron-folate supplements:

Oral iron-folate was administered at 200mg once daily for 10 weeks. Hb estimations were performed before after the 10 week course of therapy. Women with unchanged Hb, or those whose Hb fell compared to pre-treatment values, were considered non-responders.

Ninety seven women (30.69%) responded to the iron-folate supplementation by showing a rise in Hb, the majority (40.21%) showing a rise of up to 0.5g/dl.

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<u>Response</u>	<u>Frequency</u>	<u>Percentage</u>
<u>Responders</u>	<u>97</u>	<u>30.69%</u>
<u>Non Responders</u>	<u>219</u>	<u>69.31%</u>
<u>Total</u>	<u>316</u>	<u>100</u>

<u>Non Responders</u>	<u>Frequency</u>	<u>Percentage</u>
<u>Decreased</u>	<u>185</u>	<u>84.47</u>
<u>Same</u>	<u>34</u>	<u>15.53</u>
<u>Total</u>	<u>219</u>	<u>100</u>

<u>Responders</u> <u>(Hb rise)</u>	<u>Frequency</u>	<u>Percentage</u>
<u>Up to 0.5 gm%</u>	<u>39</u>	<u>40.21</u>
<u>0.6 – 0.9 gm%</u>	<u>26</u>	<u>29.90</u>
<u>1.0 – 2.0 gm%</u>	<u>29</u>	<u>29.90</u>
<u>> 2.0 gm%</u>	<u>3</u>	<u>3.09</u>
<u>Total</u>	<u>97</u>	<u>100</u>

Table 3: Response to iv iron- sucrose

Two doses of iv iron sucrose (200mg each) were administered on alternate days. Hb was assessed prior to treatment, and again at 4 weeks after therapy. In the 69 women available to follow-up 92.75 % registered a rise in Hb across all ranges of anemia. 17.2 % had a rise of >2g/dl within 4 weeks.

<u>Response s</u>	<u>Frequency</u>	<u>Percentage</u>
<u>Responders</u>	<u>64</u>	<u>92.75</u>
<u>Non Responders</u>	<u>5</u>	<u>07.25</u>
<u>Total</u>	<u>69</u>	<u>100</u>

<u>Non Responders</u>	<u>Frequency</u>	<u>Percentage</u>
<u>Hb decreased</u>	<u>2</u>	<u>40</u>
<u>Hb unchanged</u>	<u>3</u>	<u>60</u>
<u>Total</u>	<u>5</u>	<u>100</u>

<u>Responders</u> <u>(Hb rise)</u>	<u>Frequency</u>	<u>Percentage</u>
<u>Up to 0.5 gm%</u>	<u>9</u>	<u>14.1</u>
<u>0.6 – 0.9 gm%</u>	<u>34</u>	<u>53.1</u>
<u>1.0 – 2.0 gm%</u>	<u>10</u>	<u>15.6</u>
<u>> 2.0 gm%</u>	<u>11</u>	<u>17.2</u>
<u>Total</u>	<u>64</u>	<u>100.0</u>