Severe Anemia in Pregnancy

Report of a workshop held at the Institute of Child and Mother Health in Dhaka, Bangladesh

Edited by Erick Boy Gallego

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The Micronutrient Initiative

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PART I

Introduction

THE PURPOSE

In recognition that women with severe anemia account for a disproportionately large number of acute medical problems and deaths, this workshop brought together interested parties representing some of the best knowledge and experience in South Asia to examine the data on anemia and maternal mortality and to discuss the development of a mechanism to identify and treat women at high risk. In making recommendations for greater efficacy and effectiveness of interventions, workshop participants were careful not to compromise or otherwise replace the existing focus on treating women with mild or moderate anemia, because these women too are at risk (or at least there is insufficient evidence to show that they are not at risk), except when there is clear evidence to the contrary.

The recommendations from this workshop could have far-reaching implications within and beyond the South Asian region and have been framed in a manner that should be directly useful to policymakers and program planners as they strengthen and expand programs, since the information needed by policymakers does not flow automatically from scientific consensus and technological feasibility. We need to build bridges between those who have done the science and developed the technology, those who deliver the services, and those with the power to make the political and financial decisions. Questions of cost, effectiveness, benefits and risk in relation to gains, and performance of the technology within the environmental, socioeconomic, and cultural context of the target population, as well as the identification of the intended beneficiaries, their needs, and their social and economic circumstances, all enter into the agenda

for policy formulation. This workshop addressed in part the last of these topics: the identification of the intended beneficiaries of new programs to prevent and treat severe anemia.

THE PROBLEM

The latest statement on iron deficiency from the UN ACC/SCN (1997) describes the problem of anemia as "a public health emergency fully equivalent to epidemics of infectious diseases." The workshop participants were aware that the elimination of anemia could do more than any other single measure to achieve the goals of development, because anemia affects not only women of childbearing age, but males and females of all age groups. Furthermore, the huge toll that this problem takes in economic terms is becoming increasingly evident. A recent Micronutrient Initiative study (Ross and Horton 1998) revealed that in South Asia alone, economic losses attributable to iron deficiency amount to more than US$5 billion annually, which is 1% to 2% of the gross domestic product of many countries in the region. Despite being the most widespread of all nutritional deficiencies, iron deficiency is the most neglected, and it constitutes a real brake on human development.

THE CHALLENGE

All analyses of trends in the prevalence of anemia from the 1970s to the 1990s have failed to show any significant improvement, and progress in eliminating anemia compares poorly with progress in eliminating iodine deficiency disorder and vitamin A deficiency over the same period (MI and INF 1998). The problem is compounded by the fact that iron supplementation during pregnancy, lactation, and early childhood is effective in eliminating iron deficiency anemia under controlled and supervised conditions, yet under field conditions its effectiveness in most developing countries has been unimpressive (Viteri 1998). As a result, progress in reducing levels of iron deficiency anemia in women and children relative to the modest goal set at the 1990 World Summit for Children (a reduction by one-third of 1990 levels) is bound to be disappointing unless we act now. The challenge is to approach the problem both creatively and strategically.

The question is whether severe anemia can be identified and treated before and during pregnancy as a means to reduce maternal mortality. The problem is

compounded if conventional wisdom is challenged by asking whether there is enough evidence to conclude that maternal anemia is caused predominantly by dietary iron deficiency and whether universal iron supplementation is the appropriate way to treat all levels of anemia during pregnancy.

THE POSSIBLE COMPLEMENTARY SOLUTIONS

The workshop participants recognize the complex causes of the problem and its interrelationship with diet and disease. We also know that there is no single intervention to be universally advocated. Deciding which of an array of possibilities to undertake is not an "either–or" situation, but an "and–and" one. Supplementation for at-risk groups, fortification, dietary modification, control of parasitic diseases, and education of policymakers, professionals, and the public all have their places. The relative prerequisites, costs, constraints, and opportunities of these approaches must all be explored in any given situation to determine the appropriate mix of interventions.

THE ISSUES

There are four fundamental issues relating to the efficacy and effectiveness of iron supplementation (in some form) in safely improving iron status. Although these issues must be considered in the context of pregnancy and maternal outcomes, they should also be viewed in a broader context.

- Multiple integrated interventions: Integrated interventions could mutually reinforce one another. For instance, the focus on supplementation can benefit from and be reinforced by greater attention to other approaches, such as fortification and dietary diversification. Both supplementation and fortification could be used to improve iron status before pregnancy.
- Operational effectiveness: In the broader context, technological problems are not nearly as serious as operational ones related to making programs work in the communities where iron-deficient people live. Issues of supply and logistics, the motivation and training of health-care providers, communications and community participation, and partnership-building across a wide spectrum of players (public and private) are all equally important in ensuring the effectiveness and sustainability of efforts to eliminate iron deficiency and anemia in large populations. Many of these needs interact and are mutually reinforcing.

- All age groups at risk: We also need to look at iron deficiency anemia throughout the human life cycle and make consistent recommendations for its elimination, given that interventions could have longitudinal and longer-term impacts from infancy to childhood to adolescence and pregnancy. For instance, to effect a reduction in maternal anemia, iron status must be improved well before pregnancy.
- Beyond iron: In developing countries, iron is not the only nutrient lacking from the diet. Recent evidence that vitamin A, β-carotene, and zinc can help reduce maternal morbidity and mortality gives reason to consider developing an approach to combat the whole spectrum of micronutrient deficiencies (Jameson 1993; Caulfield et al. 1999; Coutsoudis et al. 1999; Shankar et al. 1999; West et al. 1999). This approach would further improve the cost-effectiveness of supplementation or fortification.

PART II

Reviewing the evidence

The following section presents analyses of the association between anemia and maternal mortality (presented during the workshop by David Rush), the implications of the accepted definition of anemia (presented by George Beaton), and epidemiologic data on the prevalence of anemia and the programs to address this problem now in place in India and Bangladesh (presented by Faruk Ahmed, Subadra Seshadri, and Kamala Krishnaswami). Discussion of these issues served as a preamble to the workshop's core deliberations on the programmatic and research implications of severe anemia and maternal mortality.

MATERNAL MORTALITY AND ANEMIA

On careful review, the underlying basis for the consensus that all forms of anemia cause maternal mortality is insecure: there are crucial gaps in the body of knowledge supporting current programs for preventing and controlling anemia. The three linked assumptions that underlie current thinking about the impact of maternal anemia on maternal mortality are stated and analyzed below.

CRITICAL ANALYSIS OF ASSUMPTION 1

The assumption: Anemia during pregnancy, in contrast to severe anemia, is related causally to maternal mortality, and treatment of anemia with iron can, in large part, reverse this risk.

With the exception of treatment by transfusion in cases of incipient cardiac failure (hematocrit < 0.13), there is no documentation that the risk of mortality is reduced by treating anemia (Fullerton and Turner 1962). However, there is a strong relationship between severe anemia and maternal death.

Table 1 presents the results of all studies of anemia during pregnancy from which relative risk of maternal mortality could be calculated. Each study had limitations. Only the most recent (McDermott et al. 1996) measured hemoglobin prospectively. None estimated whether treatment of anemia affected outcome. Only two presented data relating mild or moderate anemia to mortality rate, and these gave contradictory results. (We assume that the other reports omitted mention of mild and moderate anemia because these conditions were unrelated to increased risk of death.) Nonetheless, the relationship of maternal mortality to severe anemia (hemoglobin < 70 or 80 g/L) was remarkably consistent: severe anemia was associated with about a fourfold increase in risk of death.

On the basis of this fragmentary evidence, a reasonable working assumption is that the risk of maternal mortality increases steeply with severe anemia. Although the available data confirm only an association, not cause and effect, the strength of the association makes it appropriate to presume a causal relationship while more definitive data are sought. Thus, action to correct severe anemia should probably be taken while we struggle to better understand the problem. In contrast, the evidence for a relationship between maternal morality and moderate anemia is both scanty and contradictory. Therefore, until further data are available, moderate levels of anemia are probably best considered unrelated to excess maternal mortality, and correcting moderate anemia should be given lower priority than preventing and treating severe anemia. Research is urgently needed to clarify the relationship between level of prior anemia on one hand and maternal survival and pregnancy outcome on the other and to determine the extent to which prophylaxis and treatment modify risk of morbidity and mortality.

CRITICAL ANALYSIS OF ASSUMPTION 2

The assumption: It is unnecessary to specify the causes of anemia at an individual or population level, because maternal anemia is caused predominantly by dietary iron deficiency, and therefore iron supplementation can reverse the risk of maternal death associated with anemia.

Causes of Anemia

Anemia in poor women in developing countries has a variety of causes, which often occur in combination, especially if the anemia is severe. Thus, in any one area there may be a mix of dietary iron deficiency (due to low iron intake or low bioavailability, caused by high intake of iron binders such as phytate or tannins), folate deficiency, bleeding (vaginal or caused by hookworm or other parasites), malaria (particularly in primigravida and young women), hemoglobinopathy (e.g., sickle cell disease or thalassemia), and other concurrent infections such as HIV infection.

Table 1. Studies of severe anemia and maternal mortality for which relative risk could be calculated.

Reference	Site	Criteria for anemia	No. of subjects	No. with anemia	Relative risk (RR) of maternal mortality
Llewelyn-Jones 1965	Hospital, Kuala Lumpur, Malaysia	Hb < 65 g/L; all subjects in hospital; parenteral iron given; no data on when Hb was measured	73 048	2 250	4.4
Harrison 1979	Hospital, Zaria, Nigeria	Level of anemia not specified; odds ratio calculated from reported data	12 262	760	3.90
Chi et al. 1981	12 teaching hospitals, Indonesia	Hb < 90 g/L; 92% of women who died were admitted as emergencies, 37% of women who died were moribund at time of admission	36 062	na	Urban: 2.1 Rural: 5.9
Harrison 1982	Hospital, Zaria, Nigeria	na	5 178	258	Hct RR ≤ 0.14 20.0 0.15–0.25 3.4 0.26–0.29 0
Harrison and Rossiter 1985	Hospital, Zaria, Nigeria	na	1 777	na	Hct RR ≤ 0.14 1.34 0.15–0.24 1.05 0.25–0.29 0.75 0.30–0.44 1.00 ≥ 0.45 3.30
Thonneau et al. 1992	Hospital, Conakry, Guinea	Case-control study; anemia not defined	102 deaths; 338 controls	na	2.1
Diallo et al. 1995	Hospital, Conakry, Guinea	Hb < 110 g/L; reported data inconsistent	13 191	1 408	2.8
Sarin 1995	Hospital, Punjab, India	Moderate anemia: Hb 70–109 g/L; severe anemia: Hb < 70 g/L	35 565	1 946 moderate; 8 348 severe	3.13
McDermott et al. 1996	Rural Malawi	Prospective study; severe anemia: Hct < 0.25	3 740	233	For maternal + post-maternal mortality, 5.9; for post-maternal mortality only, 9.9

Hb = hemoglobin, na = not available, Hct = hematocrit.

Interrelationship of Iron with Other Nutrients

Iron can compete with zinc for intestinal absorption and is affected by ingestion of vitamin A. Concurrent tea intake reduces iron absorption because of the inhibitory effects of its polyphenolic substances (tannins).

Response to Community-Based Programs of Iron Supplementation During Pregnancy

Sloan et al. (1992), Cook and Reddy (1996), and Yip (1996) have commented on the discrepancy between evidence from clinical trials, which indicates the efficacy of iron supplementation in raising iron stores and hemoglobin levels during pregnancy, and the absence of any convincing evidence that community-wide or population-based programs of iron supplementation have a notable impact on iron stores or any other indices of maternal or perinatal health.

The findings of the meta-analysis of Sloan et al. (1992) are provocative. These researchers summarized data from 24 randomized trials meeting their criteria of adequate study design and publication between 1966 and 1989. Nine of these trials were from developing countries and concentrated on the effects of iron supplementation during pregnancy. On average, there was a trivial impact (increase in hemoglobin of 2 g/L relative to control) with traditional doses of up to 60 mg elemental iron daily. A strikingly similar mean difference between daily and weekly iron supplementation for pregnant women (2.47 g/L, 95% confidence interval -0.38 to 2.43 g/L) was recently reported by the Micronutrient Initiative (Beaton and McCabe 1999); the result was based on eight clinical trials in developing countries. However, in the review by Sloan et al. (1992) there was an appreciably greater impact with higher doses of iron: with an iron dose of more than 120 mg daily, the mean increase in hemoglobin was 16 g/L greater than for controls (Table 2).

Another important observation in the meta-analysis of Sloan et al. (1992) was the strong relationship between mean initial hemoglobin level and mean response to therapy for the studies conducted in developing countries (Table 2). When the initial mean hemoglobin level was relatively high (111–120 g/L), iron treatment led to only a small increment (5 g/L) in the hemoglobin concentration relative to controls. In fact, the effect of supplementation on hemoglobin level in studies with high initial mean hemoglobin was half or less than half the effect in studies with lower initial mean hemoglobin (Table 2). Another provocative finding, one of potentially great programmatic significance, is that for the lowest initial mean hemoglobin levels (< 100 g/L), the impact of intervention was less (mean increase 10 g/L more than controls) than for initial mean

Table 2. Meta-analysis of 24 randomized trials of iron supplementation in pregnancy (1966–1989).*

	Change in Hb level relative to control (g/L)	
	Mean	Range
Daily dose elemental iron (mg)		
≤ 60	2	−17 to 11
61–90	10	6 to 15
91–120	12	6 to 22
> 120	16	9 to 16
Mean initial Hb level (g/L)†		
< 100	10	2 to 17
100–110	13	−3 to 25
111–120	5	−12 to 12
> 120	—	—

Hb = hemoglobin.
*Data from Sloan et al. (1992).
†Data for studies from developing countries only.

hemoglobin levels between 100 and 110 g/L, for which the increase averaged 13 g/L more than controls. This could be a chance finding, but, in the absence of alternative data, it needs to be addressed with utmost seriousness. What we know about the physiology of iron absorption would lead us to expect the opposite trend: at lower hemoglobin levels and presumably worse iron deficiency, absorption should increase. One explanation for the anomalous finding may be that in populations with lower hemoglobin levels, anemia is less often due to iron deficiency alone and therefore may be less responsive to iron therapy.

Given both physiologic- and measurement-based regression to the mean (i.e., with no intervention, those with the lowest measured levels will, upon remeasurement, have the greatest real and apparent increases in hemoglobin level), it is essential that studies estimating hemoglobin level include untreated or differently treated comparable controls. The authors of the trials reviewed by Sloan et al. (1992), as well as those who have completed any subsequent trials, should be asked to reanalyze their results and to stratify them by initial hemoglobin level, or, even better, they should be asked to share their original data, which would save valuable time, effort, and resources. A rational policy to ameliorate the effects of severe anemia in pregnancy is probably impossible without this information, and analysis of extant data, rather than the repetition of studies to gather the necessary data, could save years of work.

The preceding discussion supports the contention that iron supplementation must be considered in context. Prior or concurrent attention to the other causes of anemia, including infection, seems obligatory. It is a matter of great urgency to explore how this can be done, given limited material and human resources in the developing world, particularly since the health of women has often been a low priority.

Brief analysis of assumption 3

The assumption: Clinical screening for anemia is insensitive.

Although screening for moderate anemia by clinical signs has been judged poor, the sensitivity of clinical screening for severe anemia has been judged very good to excellent (Gjorup et al. 1986).

Given that the sensitivity of clinical screening is high for detecting severe anemia but much lower for detecting moderate anemia, the strategies for identifying severe anemia are likely to differ considerably from those focusing on moderate anemia.

Conclusion

It is reasonably clear that maternal death is strongly associated with severe anemia, whereas moderate anemia is not likely related to excess maternal mortality. This suggests that the prevention and treatment of severe anemia deserve substantially higher priority than they have been accorded to date, particularly in South Asia. In addressing these needs, concurrent attention to causes of anemia beyond iron deficiency is imperative. Fortunately, given the high sensitivity of clinical screening for severe anemia, the ability to identify and, in turn, treat severely anemic women appears a reasonably manageable task within the South Asian context.

IMPLICATIONS OF THE DEFINITION OF ANEMIA

David Rush's presentation reflected on the foundation for action on anemia, noting that this foundation is incomplete. The accepted reference values for hemoglobin during pregnancy also relate to this foundation, having been established according to maximal hemoglobin concentrations rather than on the basis of the functional consequences of different hemoglobin concentrations. When iron needs during pregnancy are defined on a functional basis, adverse outcomes are found to be associated with very high and very low hemoglobin levels, but not

with moderate deficiency. The functional cutoff for significant clinical outcomes related to low hemoglobin levels appears to be around 70 or 80 g/L.

The current cutoff values for iron status during pregnancy were determined by the World Health Organization, which used reference mean values for women of European ancestry obtained from the Centers for Disease Control and Prevention. Levels two or more standard deviations below the mean were defined as "low." In other words, no functional criteria were considered when the reference values were established.

A functional approach to defining anemia would fundamentally change the way we think about iron programs: rather than attempting to bring all women to a hypothetical, population-based target hemoglobin level, such programs might address the functional needs of the individual. If a functional definition is used, the iron programs that we continually lament as unsuccessful may actually be effective. Table 3 presents data from three studies of pregnant women who received iron and folate supplementation. If the definition of anemia was a hemoglobin level of less than 110 g/L, more than 50% of the women in two of the studies remained anemic at the end of the study period. However, if 90 g/L represents a hemoglobin level free of adverse functional consequences, these programs may in fact have been highly effective in functional terms. In addition to the problem of definition of anemia and its impact on programs, no current programs focus on the particular problem of severe anemia.

Finally, to succeed in treating anemia during pregnancy, perhaps it is time to abandon our current criteria for the success of an iron program, i.e., achieving maximal hemoglobin levels and raising hemoglobin levels above some ultimately arbitrary level. Instead, we should focus on the "tails" of the hemoglobin distribution. We might then be able to address the clinical outcomes associated with very low as well as very high hemoglobin levels.

Table 3. Prevalence of anemia in pregnant women receiving iron and folate supplementation.*

Definition of anemia (Hb level, g/L)	Setting; prevalence of anemia (%)		
	West Java (n = 139)	Malawi (n = 216)	Maluku (n = 399)
< 110	51.1	56.9	19.5
< 100	12.2	28.2	6
< 90	0	9.3	1.3
< 70	0	0	0

Hb = hemoglobin.

*Reproduced from Beaton and McCabe (1999). All studies excluded severe anemia at baseline; groups receiving daily (60 mg) and weekly (2 × 60 mg) supplements were pooled.

PREVALENCE OF SEVERE ANEMIA IN INDIA AND BANGLADESH AND CURRENT PROGRAMS TO ADDRESS ANEMIA IN PREGNANCY

Four main conclusions can be drawn from the presentations during the workshop.

First, although overall levels of anemia in Bangladesh are very high, estimates vary widely. Prevalence data on severe anemia are almost nonexistent, so the situation concerning severe anemia is uncertain. Nonetheless, from the scanty data that are available, it appears that severe anemia during pregnancy is less frequent in Bangladesh than in India and may affect 2% to 5% of pregnant women. If these prevalence estimates, far lower than those for India and Nepal, prove accurate, it will be important to identify and understand the reasons.

Second, according to the latest national survey by the Institute of Nutrition and Food Science, dietary intake of iron in Bangladesh is only 58% of the Indian-derived recommended daily intake. In the past, reported intakes were much higher, but the food composition tables used for previous surveys overestimated the iron content of rice. In addition to these low overall intakes, nearly all iron consumed is from vegetable sources and thus of low bioavailability.

Third, a multiple-state survey carried out by the Indian Council of Medical Research in 1985/86 found that 13.1% of pregnant women were severely anemic, whereas 33.6% and 40.8% were moderately and mildly anemic, respectively. More recent national data do not exist, but the results of several large studies suggest that these rates have not declined appreciably.

Finally, treatment of severe anemia in pregnancy, in both India and Bangladesh, requires identification of the technical and financial impediments to better care of this disorder. Although both countries have policies for identifying and referring severely anemic pregnant women through the primary health-care system, implementation of these policies is inadequate, and many women receive no treatment other than iron prophylaxis, which itself is inadequately implemented.

PART III

Proceedings of the workshop

Workshop participants concurred that severe anemia is strongly associated with maternal death in South Asia and is barely addressed by current programs. Moreover, there are few data to support the effectiveness of current community-based iron prophylaxis programs. Perhaps it is time to pay special attention to severe anemia. The first step is to develop and test interventions to prevent and treat severe anemia through the primary health-care system.

PROGRAMMATIC RESPONSE FOR PREVENTING SEVERE ANEMIA

Recognizing the difficulties of treating severe anemia through the primary health-care system, one discussion group at the workshop attempted to devise schemes for preventing the condition. After presentation of their results, prevention became a major issue for the duration of the workshop. The scheme developed by the working group is presented below.

1. Targets
   - 1.1. Pregnant women
   - 1.2. Adolescent females (10–19 years of age)
     - ✦ unmarried, newly married, pregnant
     - ✦ in school, out of school
     - ✦ formal-sector employment, informal-sector employment, unemployed
   - 1.3 Newly married, nonpregnant women

2. Packages
   - 2.1 Pregnant women receive:
     - ✦ iron tablets
     - ✦ dietary advice
     - ✦ community-specific intervention based on presumed diagnosis
   - 2.2 Adolescent females receive:
     - ✦ iron tablets, drinks, or premixes
     - ✦ action-oriented public health education
     - ✦ dietary advice
     - ✦ community-specific intervention based on presumed diagnosis
   - 2.3 Newly married, nonpregnant women receive:
     - ✦ weekly iron supplement
     - ✦ counseling on eating iron-rich foods, taking iron tablets, delaying pregnancy, and other related topics
     - ✦ other services by preferential access
   - 2.4 Policymakers and senior managers are targeted to receive information, education, and communication (IEC)

3. Preventive strategy
   - 3.1 Major interventions
     - ✦ supplementation (pharmacological)
     - ✦ diet diversification
     - ✦ food fortification
     - ✦ public health measures, especially in relation to malaria, hookworm or roundworm, *Giardia*, other parasites
   - 3.2 Cross-cutting issues
     - ✦ compliance: supervised administration, education system, health system
     - ✦ captive audiences: schools, other institutions
     - ✦ logistics and supplies
     - ✦ decentralization
     - ✦ private sector involvement
     - ✦ IEC and "positioning" of severe anemia to change behaviours
     - ✦ policy (especially national)
     - ✦ private sector, nonprofit organizations, nongovernmental organizations
     - ✦ production and supply of high-quality premixes and drinks
     - ✦ marketing of low-cost supplements
     - ✦ sharing of costs of IEC
     - ✦ private practitioners

- ✦ external monitoring and evaluation of system
- ✦ training for supply and logistics
- ✦ financial resources: collaborating agencies, state government, communities (where they are willing to pay)

4. Top five things we want to know
   - 4.1. Does using different approaches for different target groups work? What are the outcomes and impacts?
   - 4.2. What is the role of the private sector in supplying and distributing supplements?
   - 4.3. Will adolescent-to-adolescent counseling work?
   - 4.4. How can schools, companies, and other institutions be used in iron supplementation programs?
   - 4.5. What is the feasibility of fortification? What are the markets for fortification? What "vehicles" can be used for fortification? Where would fortification be appropriate?

OPERATIONAL RESEARCH FOR TREATMENT OF SEVERE ANEMIA

PROPOSED TREATMENT REGIMEN FOR SEVERE ANEMIA USING THE PRIMARY HEALTH-CARE SYSTEM

Treatment of severely anemic pregnant women requires their identification and an appropriate response. The logistic and financial constraints associated with universal hemoglobin testing rule out laboratory assessment for initial identification, so clinical screening must be the foundation of any community-based response. During the workshop, a working group was charged with devising a model for treatment at the community level. The model they proposed is presented in Fig. 1.

Under this model, all pregnant women would undergo clinical screening for severe anemia at no later than 20 weeks' gestation. Those diagnosed as severely anemic, if not late in the pregnancy or presenting other complications, would receive high-dose oral supplementation with iron and folate, dietary counseling, and treatment for other possible causes of severe anemia not related to iron. The basis for the additional, non-iron treatment would depend on the woman's community and the prevalence there of related factors, such as malaria or helminth infection. Women identified as severely anemic who are late in pregnancy or who present with complications would receive hospital-based treatment.

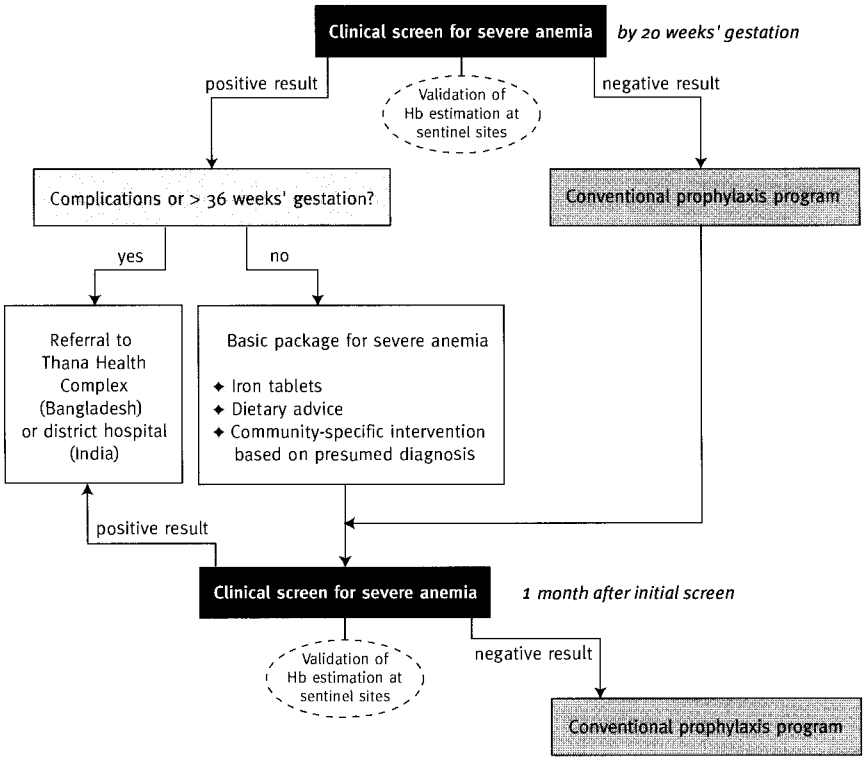

Fig. 1. Suggested model for treating severe anemia in pregnancy. Hb = hemoglobin.

Those not diagnosed as severely anemic would receive the standard iron prophylaxis currently provided in both India and Bangladesh.

One month after the initial screening, all women not referred to hospital would undergo a second clinical screening. For women identified as severely anemic during the first screening, the second screening would be a follow-up to determine response to treatment; for women not originally identified as severely anemic, the second screening would be an additional check on their status later in pregnancy. Those in whom there has been a response to treatment, as well as those never identified as severely anemic, would receive standard iron prophylaxis for the remainder of their pregnancies. Anyone identified as severely anemic at the second clinical screening would be referred to hospital.

Measuring hemoglobin level in all women would be prohibitively expensive and logistically trying for the primary health-care systems in Bangladesh and India, but it may be important for monitoring the validity of the clinical screen. One meeting participant was particularly concerned about the sensitivity of

clinical screening for monitoring efficacy of treatment and identifying mild or moderate cases of anemia. Therefore, it was suggested that sentinel sites be set up to validate the clinical estimation of iron status through regular hemoglobin measurement.

RESEARCH MODEL FOR TESTING COMMUNITY-BASED SCHEME FOR TREATMENT OF SEVERE ANEMIA

After group discussion about the proposed treatment model, another working group was given the responsibility to devise an operational research study to test the model; the study they devised is presented in Fig. 2. A primary objective for such research would be to establish whether severe anemia can effectively be reversed through activities undertaken in the primary health-care system.

Before the study, it will be necessary to determine the baseline rate of severe anemia at delivery in the study area, preferably a sentinel community where the risk of iron deficiency anemia is high. This could be accomplished through a "run-in study" of hemoglobin level (or hematocrit) for all women late in pregnancy. During the study itself, all pregnant women in the study area would be screened for severe anemia by 20 weeks' gestation and would be assigned to one of three treatment regimens: usual treatment (with monitoring) in their primary health-care system; an "enhanced" version of their local health-care system, with emphasis on training field workers to perform clinical screening for severe anemia, a standard additional treatment based on "a presumed diagnosis" related to the possible causes of severe anemia in that area (e.g., malaria or helminth infection), a guaranteed supply of iron and folate supplements, and follow-up screening 1 month after the initial assessment to evaluate response to treatment and to refer to tertiary care if needed; and training of field workers in clinical screening for severe anemia followed by referral to hospital-based care for parenteral administration of iron. Each woman entering the study would undergo a final hemoglobin measurement late in pregnancy (at approximately the same stage as for the run-in study [about 36 weeks]).

This design allows conclusions to be drawn about the reversal of severe anemia in individuals and about reductions in overall rates of severe anemia at delivery (through comparison of the rates of anemia found during the run-in study and the main study).

After intense deliberation, the group suggested that such trials should have the following characteristics.

- The number of subjects must be large enough to obtain a firm answer to the question. The aim might be to lower by at least half the national rate of

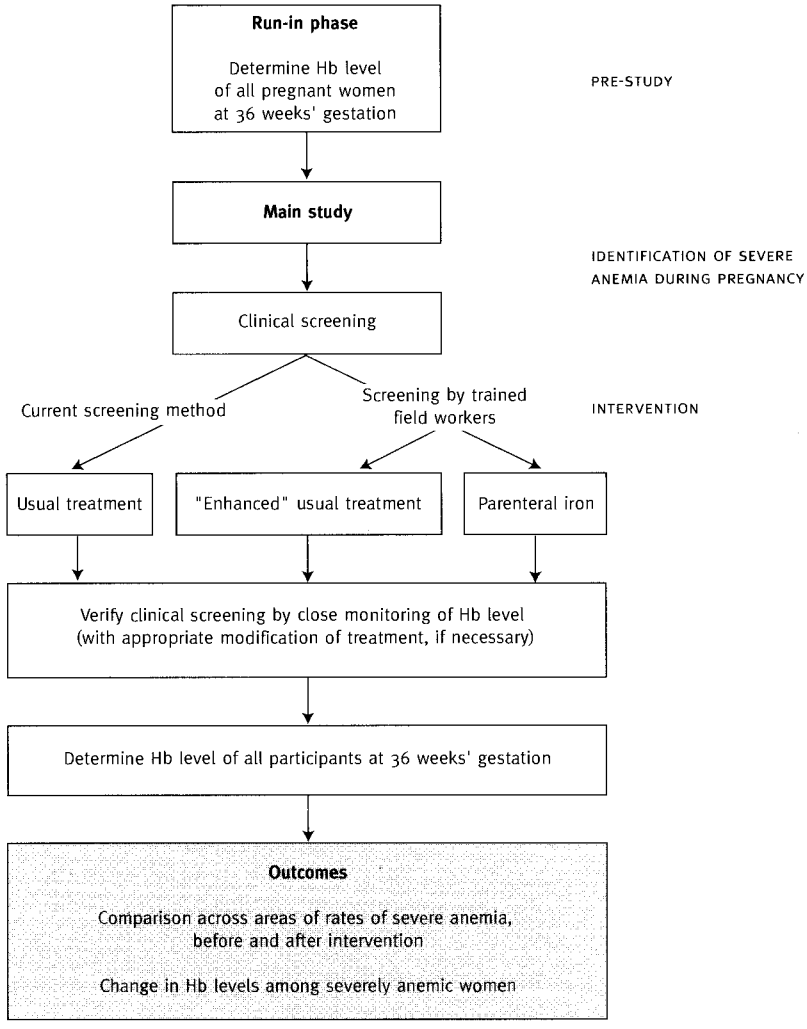

Fig. 2. Research design for testing community-based treatment of severe anemia. Hb = hemoglobin.

severe anemia (currently 13% in India). The number of participants needed is large, especially if design effects are accounted for.

✦ Considering the prohibitive cost and logistic burden of laboratory testing in a community-based intervention, clinical screening for severe anemia is almost certainly necessary and would be sensitive enough if performed in

standard, optimal ways. Training and supervision to maintain adequate sensitivity and specificity must be a priority.

- Workshop participants believed that it would not be ethically acceptable to give a placebo to women identified as severely anemic. Therefore, a randomized controlled trial at the individual level is technically impossible. (If random assignment at the individual level were done without placebo controls, there is a high likelihood that "controls" — women diagnosed and told of their condition and referred to seek treatment from available community resources — would do just that.)

- Workshop participants believed that in one arm of the trial women should be given parenteral iron (for all women who are willing to accept it). This strategy would confer several benefits: parenteral administration of iron may be the only treatment that works, and this arm would thus serve as a positive control (given that it represents the best result that oral iron could possibly achieve, bypassing issues of gastrointestinal absorption and compliance with pill-taking regimens).

- Subjects in another arm of the trial would received an enhanced version of the current treatment. The enhancements would include standardized, monitored clinical screening early in pregnancy; validation of diagnosis through measurement of hemoglobin level; and deworming and malaria prophylaxis in areas of high prevalence.

- All subjects would undergo frequent monitoring to determine response to treatment, and special attention and treatment modification would be available for those with inadequate response.

- The control arm of the trial would be the continuation, with monitoring, of current policy and activities.

The trial would be judged in two ways:

- In the run-in phase, the rate of severe anemia among all pregnant women in the study area would be estimated from hemoglobin or hematocrit measurements at a set stage in late pregnancy. During the trial, hemoglobin or hematocrit would again be measured for all pregnant women at the same stage of late gestation. Although hemoglobin or hematocrit measurement during the run-in phase may be tedious, it is the only way to feasibly determine an area-wide reduction in rates of severe anemia attributable to the

intervention, free of the effects of both physiologic- and measurement-based regression to the mean.

- In the test areas (to be defined by the researchers after the run-in phase), actual change in hemoglobin can be measured and adjusted (as well as possible) for the natural changes in hemoglobin concentration associated with pregnancy.

It would also be advisable to determine whether intensive iron treatment is associated with any dangers, such as effects on zinc absorption, on rates of pregnancy-induced hypertension, on rates of infection in mother and infant, on perinatal outcomes (birth weight and duration of gestation), and on seizures in offspring.

PART IV

Workshop conclusions

MATERNAL MORTALITY

Maternal mortality is one of the most urgent public health problems in the developing world. Rates in industrialized countries are as low as 3 or 4 per 100 000 births. Among women in many developing countries, rates are at least 100- to 200-fold higher. In the worst affected areas and taking multiple pregnancies into account, as many as 10% of all women may die in childbirth. Although both the causes (complications of induced abortion, toxemia of pregnancy, obstructed labor, and obstetric hemorrhage and infection) and the ways to prevent most cases of maternal mortality are well understood, the role of nutrition, and particularly the role of nutritional anemia, is not.

SEVERE ANEMIA IN PREGNANCY

In the developing world, severe anemia during pregnancy is associated with very high relative risk of maternal death, perhaps two- to six-fold, and severe anemia is especially common in South Asia. National surveys in India have reported a rate of severe anemia of 13% during pregnancy; if the relative risk of death is four times as high among severely anemic women as among women without severe anemia, this proportion accounts for 37.4% of maternal deaths (there is little or no evidence that moderate or mild anemia is associated with maternal mortality). Thus, three-quarters of all maternal deaths are potentially preventable by eliminating severe anemia.

ROLE OF PREVENTION AND REVERSAL OF SEVERE ANEMIA

It is therefore urgent that we determine whether preventing or reversing severe anemia during pregnancy reduces rates of maternal mortality (and morbidity). Unfortunately, there have been few or no demonstrations that severe anemia in pregnancy can be prevented or reversed, and these goals must be achieved before effects on mortality can be tested.

Given the practical difficulties in identifying and treating severe anemia in pregnancy through the primary health-care system, intervention to prevent this condition by maximizing iron stores among nonpregnant women is an attractive option. It may be necessary to combine continuous maintenance of supplemental iron with intensive, relatively short-term supplementation.

Intervention before marriage, to help unmarried girls and women achieve adequate iron stores, may reduce rates of severe anemia in pregnancy; this strategy should be tested.

Focused interventions to improve iron stores during the interval between marriage and the onset of the first pregnancy and for periods between pregnancies may reduce rates of severe anemia in pregnancy, and these strategies should also be tested. Furthermore, this approach may be more efficient than iron supplementation long before marriage.

The treatment of severe anemia, although one of the stated objectives of primary health care during pregnancy, has in reality been neglected. It is of the highest priority and deserves far greater attention, especially in South Asia, where rates of severe anemia are among the highest in the world. Women in whom severe anemia is diagnosed are likely to be highly motivated to seek and comply with treatment.

PROMOTING DEMAND AS AN ADJUNCT STRATEGY

Given the potentially high recurring costs of long-term prevention, it is important to test the ability to create demand for supplementation, as well as food fortification. This option could serve as an adjunct to supplementation by governments and private agencies, particularly for women who are mildly or moderately anemic during pregnancy.

PART V

Workshop recommendations

APPLY CURRENT KNOWLEDGE AND POLICIES

The public, health workers, and policymakers must be educated about the enormity of the problem of maternal mortality and its very strong associations with severe anemia during pregnancy. Every effort should be made to adhere with current policies to address severe anemia during pregnancy.

DEVELOP METHODS TO PREVENT AND REVERSE SEVERE ANEMIA

Although the association between severe anemia and maternal mortality is strong, a causal relationship has not been established. A strategy to give universal and immediate attention to preventing and treating severe anemia would inevitably deflect attention from current programs of universal iron and folate supplementation. Even though these programs are not explicitly limited to the treatment of mild and moderate anemia, they are unlikely to have much, if any, effect on severe anemia. Given the paucity of relevant data, it appears prudent not to promote or initiate worldwide changes in anemia control programs without first demonstrating in pilot projects that it is possible to prevent or reverse severe anemia and that such change confers benefit (i.e., results in lower maternal mortality rates). So far, such prevention or reversal has not been demonstrated even in intensive, small-scale trials. Reversal of the condition does not imply achieving hemoglobin levels defined as "normal," but rather levels around

90 g/L. It has also not been demonstrated that reversal of the condition confers health benefits, specifically by reducing maternal or infant morbidity or mortality rates.

FOCUS ON PREVENTION

The concept of prevention is appealing. Perhaps the adverse effects of severe anemia can be optimally reversed only by making changes before pregnancy occurs. It is also preferable that high doses of a potentially toxic substance — in this case, iron — be avoided during a vulnerable period such as pregnancy.

Although the prevention of anemia in early childhood is attractive in its own right, workshop participants felt that increasing iron stores in the period just before marriage and childbearing might prevent severe anemia in subsequent pregnancy. (It remains to be demonstrated that programs before marriage can indeed prevent later anemia. It will therefore be helpful, even before trials are started, to have more reliable data on the natural history of anemia and iron stores — in particular, whether and to what extent iron status earlier in life predicts later risk of anemia and the modifications to these relationships that may be caused by duration and intensity of menstrual flow, diet, disease, and parasite burden.)

The workshop participants concluded that trials of iron supplementation and other interventions to build iron stores and reverse anemia before marriage should receive high priority in an overall strategy aimed at preventing severe anemia in pregnancy.

Strategies to recruit newly married girls and women into multifaceted programs to prevent later anemia should be developed and tested. Registration for marriage, where it exists, is a possible sampling frame to identify such women. Furthermore, since newly married women are very likely to become pregnant shortly, reversal of their anemia will often exert an immediate influence on the course of the pregnancy.

Preventive efforts during the periods between pregnancies could be important. This strategy is attractive because it could be integrated with family planning programs among women who could be screened and involved in treatment as part of such activities.

CONDUCT TRIALS ON REVERSAL

Although prevention of anemia is probably desirable, there are currently millions of South Asian women entering and continuing pregnancy who are already severely anemic. Therefore, it is urgent to attempt to reverse severe anemia during pregnancy through large-scale, field-based programs. We believe that large-scale trials attempting reversal should be initiated as soon as possible, using the method presented in Part III ("Research Model for Testing Community-Based Scheme for Treatment of Severe Anemia").

DETERMINE IMPACT OF PREVENTION ON MATERNAL MORTALITY AND MORBIDITY

Many of the workshop participants are convinced that, if it becomes clear that severe anemia can be prevented or reversed, the trial or trials should be extended in duration and numbers of subjects to determine the impact of prevention or reversal on maternal mortality and morbidity and other perinatal outcomes.

Inevitably, there will be controversy about the need for such a demonstration; many will assert that the value of reversing severe anemia is self-evident and does not require a further demonstration of outcome effects.

There are several arguments for conducting such further studies:

- There will be costs associated with prevention or reversal programs. It will be easier to justify new resources or the modification of current anemia control programs if the utility for the well-being of the mother and child has been clearly demonstrated and quantitatively estimated.
- Iron is not wholly benign; it can be toxic, and the justification for its use demands an estimation of the ratio between risk and benefit.
- For any new intervention other than iron, it would be taken for granted that effectiveness and danger would have to be estimated before promotion of worldwide extension of programs. Many (but not all) of the workshop participants believe that this standard should hold for iron as well.

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Workshop participants

Faruk Ahmed
University of Dhaka
International Nutrition Foundation
Dhaka 1000
Bangladesh
email: duregstr@bangla.net [include name in subject line]

A.M.M. Anisul Awwal
BINP
7/A Paribagh
Dhaka 120
Bangladesh
email: BINP@bangla.net

George Beaton
GHB Consulting
9 Silverview Drive
Willowdale ON M2M 2B2
Canada
email: g.beaton@utoronto.ca

Sameena Chowdhury
Institute of Child and Mother Health
37/2 Eskaton Gardon Road
Dhaka 1000
Bangladesh
email: anindya@bdonline.com

Sham El-Arifeen
International Center for Diarrheal Disease Research
GPO Box 128
Dhaka 1000
Bangladesh
email: shams@icddrb.org

James Greene
500-4800 Chevy Chase Drive
Chevy Chase MD 20815
USA
email: jgreene@waterwisp.com

Carrie Hubbell
146 The Fellsway West
Medford MA 02155
USA
email: chubbell@emerald.tufts.edu

S.M. Ziauddin Hyder
BRAC
75 Mohakali C/A
Dhaka 1212
Bangladesh
email: smzia@bangla.net

Kamal Islam
UNICEF House
73, Lodi Estate
New Delhi 110003
India
email: kislam@uncdel.ernet.in

A.F.M. Iqbal Kabir
The World Bank
3A Paribagh
GPO Box 97
Dhaka 1000
Bangladesh
email: akabir@worldbank.org

George John Komba-Kona
WHO Bangladesh
GPO Box 250
Dhaka 1000
Bangladesh
tel: (880-2) 864-653
fax: (880-2) 863-247

Kamala Krishnaswami
Deputy Director
National Institute of Nutrition
PO Jamai Osmania
Hyderabad 500 007
India
email: icmrnin@ren.nic.in
nin@ap.nic.in

James Levinson
School of Nutrition, Science and Policy
Tufts University
132 Curtis Street
Medford MA 02115
USA
email: jlevinso@emerald.tufts.edu

Venkatesh Mannar
Micronutrient Initiative
250 Albert Street
Ottawa ON K1G 3H9
Canada
email: vmannar@idrc.ca

Lalit Nath
E-21 Defense Colony
New Delhi 110024
India
email: nath@doe.ernet.in

Sidharath Nirupam
Health and Nutrition
UNICEF, Gujarat
Plot Nr 70
Section 19
Gandhinagar 382022
India
email: snirupam@uncdel.ernet.in

David Rush
Human Nutrition Research Unit
Tufts University
711 Washington Street
Boston MA 02111
USA
email: drush@emerald.tufts.edu

Tom Schaetzel
Senior Program Specialist
Micronutrient Initiative, New Delhi Office
208 Jor Bagh
New Delhi 110003
India
email: tschaetzel@idrc.org.in

Subadra Seshadri
Department of Food and Nutrition
Faculty of Home Science
MS University of Baroda
Baroda 390002
India
fax: (91-265) 330-980

A.K.M. Shahabuddin
Professor of Obstetrics
Institute of Child and Mother Health
90 Kalabagan 2nd Lane
(240 Bashiruddin Road)
Kalabagan, Dhanmondi
Dhaka 1205
Bangladesh
email: abin@ncll.com

Mohammed Shajahan
National Program Officer
Micronutrient Initiative
House D2, Road 95
Gulshan
Dhaka
Bangladesh
email: mshah@bangla.net

S.M. Younus Ali
USAID/Bangladesh
US Embassy
Baridhara
Dhaka
Bangladesh
email: yali@usaid.gov

Harun K.M. Yusuf
Department of Biochemistry
University of Dhaka
Dhaka 1000
Bangladesh
email: hossaina@bangla.net

The Editor

Erick Boy Gallego is a medical doctor and holds a master's of science degree from the University of California, Davis, where he specialized in international nutrition. His work with the Micronutrient Initiative and the Instituto de Nutrición de Centro América y Panamá over the past decade has centred around the control and prevention of micronutrient deficiency, focusing on iron and iodine in Latin America and the Caribbean.

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Severe Anemia in Pregnancy

Report of a workshop held at the Institute of Child and Mother Health in Dhaka, Bangladesh

Edited by Erick Boy Gallego

The latest UN statement on iron deficiency describes the problem of anemia as "a public health emergency fully equivalent to epidemics of infectious diseases." In India, for example, fully three-quarters of maternal deaths could be prevented through the elimination of severe anemia. Furthermore, the economic toll attributable to iron deficiency in South Asia has been calculated at US $5 billion annually. It is generally agreed that the elimination of severe anemia could do more to improve human health, well-being, and quality of life in South Asia than any other single development initiative.

This publication presents the analysis and recommendations of a group of experts brought together in Dhaka, Bangladesh, to examine current data on anemia and maternal mortality and to develop a mechanism for the identification and treatment of women at high risk. It outlines salient research needs and details explicit recommendations to improve the delivery of iron supplements to target populations. The publication will be of interest to researchers, program managers, and policy-makers working in the fields of public health and nutrition in the developing world.

Erick Boy Gallego is a medical doctor and holds a master's of science degree from the University of California, Davis, where he specialized in international nutrition. His work with the Micronutrient Initiative and the Instituto de Nutrición de Centro América y Panamá over the past decade has centred around the control and prevention of micronutrient deficiency, focusing on iron and iodine in Latin America and the Caribbean.

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