REVIEW

ANEMIA AND MATERNAL MORTALITY IN THE DEVELOPING WORLD

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ABSTRACT
This article analyzes current knowledge of the effects of anemia and iron deficiency on maternal mortality. Current knowledge indicates that iron deficiency anemia in pregnancy is a major risk factor, and might contribute to maternal mortality in the developing world. The purpose of this article was to examine published information regarding the prevalence of anemia in the developing world, analyze its obvious causes that are well documented, as well as those that are less obvious and less well documented and its effects on pregnancy outcome and to identify current gaps in the information. Furthermore, its purpose was to paint a comprehensive and realistic picture of the present situation, and an attempt was made to propose a solution, or to at least urge researchers and concerned government personnel to take the much needed action and further exploration that the subject demands. This could be done by not neglecting the problem any further. The reviewers conclude that the weight of evidence supports the advisability of changing our priorities towards primary health care, developing a more objective research methodology, and employment of universal food fortification programs on a large scale.

INTRODUCTION
The problem of anemia especially in the developing world, has received much attention during recent decades. Anemia is defined as a hemoglobin concentration <110 g/L (<105 g/L in the second-trimester) and severe anemia as hemoglobin <70 g/L. Studies conducted during last few decades, especially indicate a significant association between anemia and pregnancy (Kitay and Harbort 1975, Bothwell and Charlton 1981, Fleming A.F., 1984, Levin et al., 1993, Viteri F.E., 1994 and Gillespie S. 1997).

Prevalence of anemia and its causes
Several extensive reviews of anemia prevalence during pregnancy have been published. A World Health Organization report published in 1992 on anemia prevalence in women contains an exhaustive survey and is an update of the original summary compiled by Royston (1982). The more recent report estimates that 58.27 million women worldwide are anemic during pregnancy, of whom, 55.75 million live in developing countries, and only 2.52 million live in industrialized countries (Rush D., 2000).

Approximately 50% of women and children in less developed countries are anemic (DeMaeyer and Adiels-Tegman, 1985), and 60% of anemic women in the world reside in South Asia (ACC/SCN, 1992).
Globally, the most common cause of anemia is believed to be iron deficiency due to inadequate dietary iron intake, physiologic demands of pregnancy and rapid growth and iron losses due to parasitic infections. However, iron deficiency is not the only cause of anemia. Other prevalent causes of anemia include malaria, chronic infections and nutritional deficiencies of vitamin A folate and vitamin B-12. The relative contributions of these causes of anemia and iron deficiency vary by sex, age and population and are not well described in many populations (Michele et al., 2000).

During pregnancy, iron requirements exceed stored iron for most women (Bothwell and Charlton, 1984). The increased need by the body for iron is due to increase in the red cell mass, iron needs of the fetus and iron losses during delivery (Bothwell and Charlton, 1984). Although hemodilution from expansion of the plasma volume leads to a “physiologic pregnancy anemia” (DeLeeuw et al., 1966), inadequate iron supply limits cell mass expansion and leads to further deterioration in iron status during pregnancy (Viteri, 1994) that may pose risks for the pregnant woman and her infant (Allen, 1997).

Hemolytic anemia, to a greater or lesser degree, is commonly seen during pregnancy in malarious areas of developing countries. The observation that severe anemia is greatly reduced in patients who have received regular malaria prophylaxis during pregnancy (Fleming et al., 1986, Gamer and Brabin, 1994, Shulman et al., 1999) indicates that it is related to chronic infection with Plasmodium falciparum malaria. It is therefore not surprising to find that the number of patients admitted with severe anemia is highest during the months after the rainy season (Fleming 1970 and Verhoeff et al., 1999).

Hemolysis as a factor in the development of megaloblastosis in folate-deficiency anemia has been demonstrated by Chanarin et al. (1959), to be a cause.

A further group of patients who contribute to these severe hemolytic anemias are those with sickle cell disease. This group accounted for <10% of all cases in Ibadan, Nigeria (Fullerton and Watson-Williams, 1962).

Another interesting aspect was investigated recently by Lisa et al. (2002). They estimated the prevalence of postpartum iron deficiency, anemia and iron deficiency anemia in the United States and compared risk of iron deficiency between women 0-24 mo postpartum (n=680) and never-pregnant women, 20-40 y old (n=587). They concluded that, more attention should be given to preventing iron deficiency among low-income women during and after pregnancy.

Very recently, immunodeficiency (HIV) has been attributed as a cause of anemia in sub-saharan African infants (Dana et al., 2002). This idea, being so recent needs to be further investigated, and HIV infection as a possible cause of anemia in females of reproductive age group needs to be further explored and evaluated.

**Risks Involved**

Severe anemia during pregnancy is associated with an increased risk of death (Llewellyn-Jones, 1965). Whereas moderate to severe anemia is associated with an increased risk of low birth weight (Gain et al., 1981 and Murphy et al., 1986) and pre-term delivery (Klebanoff et al., 1991, Scholl et al., 1992 and Zhou et al., 1998).

Iron deficiency and anemia during pregnancy are associated with lower iron stores in the fetus, which may result in iron deficiency anemia (Agarwal et al., 1983; Kaneshige 1981; MacPhail et al., 1980; Milman et al., 1987 and Puolakka et al., 1980). In several studies, iron supplementation during pregnancy resulted in greater iron stores in young infants (DeBenaze et al., 1989; Milman et al., 1994 and Preziosi et al., 1997).
The fact that anemia not only is commonly associated with pregnancy, but results in grave consequences, have also been shown by various researchers. Viteri (1994) reported that anemic pregnant women are at greater risk of death during the perinatal period and that anemia is the major contributory or sole cause of death in 20-40% of the 500000 maternal deaths.

A UN based international group recently concluded that high prevalence rates for iron deficiency anemia in many developing countries constitute a public health emergency equivalent to epidemics of infectious disease and have more lasting adverse consequences for survivors (UN ACC/SCN 1997).

This implies that, increasing maternal survival by preventing and treating anemia, particularly severe anemia, may be possible. This, in turn leads to the question as to how this might best be done. Furthermore, it appears that remedy for this problem is not difficult or complicated, but rather simple i.e., by improving general health, diet, and employing iron supplementation of pregnant and prospective pregnant women.

These studies, therefore, unanimously conclude that:

• in the developing world, iron deficiency anemia during pregnancy is common,
• the anemia is followed by severe consequences
• aggressive iron supplementation during pregnancy is necessary
• and anemia could be related to multiple micro-nutrient and vitamin deficiencies, as well as other factors.

**Current Picture**

A very comprehensive analysis was recently published by Bernard et al. (2001). According to them, the average estimates for all-cause anemia attributable mortality (both direct and indirect) were 6.37, 7.26 and 3.0% for Africa, Asia and Latin America, respectively. Case fatality rates, mainly for hospital studies, varied from <1% to >50%. The relative risk of mortality associated with moderate anemia (hemoglobin 40—80 g/L) was 1.35 [95% confidence interval (CI): 0.92-2.00] and for severe anemia (<47 g/L) was 3.51 (95% CI: 2.05-6.00). In holoendemic malarious areas with a 5% severe anemia prevalence (hemoglobin <70 g/L), it was estimated that in primigravida, there would be 9 severe-malaria anemia-related deaths and 41 non-malarial anemia-related deaths (mostly nutritional) per 100,000 live births. The iron deficiency component of these is unknown (Bernard et al., 2001).

**Anemia Alleviation Strategies: Latest Views**

Iron fortification of staple foods and condiments holds great promise for the prevention of iron deficiency (Venkatesh M. and Erick B.G., 2002). This study quotes that:

• Iron fortification of rice is being instituted in the Philippines. Initially, the rice will be produced in government-controlled rice mills and sold at low cost mainly to low-income families.
• Fortification of fish sauce in Vietnam has shown promising initial results in reducing anemia among anemic, non-pregnant female factory workers.
• Iron-fortified soya sauce has been shown to reduce anemia in initial studies in children in China, and a large-scale efficacy trial is now underway.

These examples indicate that iron fortification of staple foods and condiments holds great promise for the prevention of iron deficiency (Venkatesh M. and Erick B.G., 2002).

Pattanee Winichagoon (2002), in another recent article informs that, nutritional improvement has been implemented as an integral part of primary health care and community development in Thailand. Utilization of village health volunteers has
been a crucial feature of the program. Available data indicate that anemia rates have declined among pregnant women and preschool children, although there has been no formal evaluation of the program effect. Universal iron supplementation has been the major strategy for pregnant women. Other strategies utilized to address iron deficiency include food fortification, dietary improvement and complementary public health measures. Program obstacles have included lack of access to iron tablets by some populations and lack of understanding of the importance of anemia. Effectiveness of the intervention strategies need to be further assessed to provide further data for decision-making (Pattanee Winichagoon, 2002).

Another study conducted by Proctor & Gambol Co. concludes that, to be effective, a well-planned communications campaign should also accompany any major iron fortification program. Eradication of iron deficiency anemia can be done but requires a holistic approach that addresses multiple barriers and leverages the untapped expertise and strength of the alliance between public and private sectors (Haile Mehansho, 2002).

DISCUSSION

This review explores why current policies to decrease rates of anemia are unlikely to lower the risk of maternal mortality greatly, why there still might be appreciable benefit from more effective programs to deal with anemia, and why a great deal of further research – both basic and applied – is essential.

Our analysis showed many gaps in our knowledge about the adverse effects of maternal anemia and iron deficiency on pregnancy outcome. Such disparities include inadequate documentation of anemia’s effects on maternal mortality, morbidity, and well-being, and on infant health and development.

Likewise, the benefits of maternal iron supplementation on these outcomes are unclear, even for women who develop anemia during pregnancy. However, there is substantial evidence that maternal iron deficiency anemia increases the risk of preterm delivery and subsequent low birth weight, and accumulating information suggests an association between maternal iron status in pregnancy and the iron status of infants postpartum. Certainly, iron supplements improve the iron status of the mother during pregnancy and during the postpartum period, even in women who enter pregnancy with reasonable iron stores (Lindsay H.A., 2000).

Therefore, a methodology needs to be developed, to actually study, the association between anemia and maternal mortality. Ideally, to determine the relation between anemia and subsequent mortality, hemoglobin concentration and other hematological and biochemical indexes of anemia should be measured prospectively before and during each trimester of pregnancy, to avoid confusion resulting from the hemodilution of pregnancy. Risk estimates calculated from hemoglobin concentrations measured before pregnancy would be better indicators of the need for prophylaxis or treatment (WHO, 1992).

The reviewers of this article failed to find any study that included hemoglobin concentrations measured prospectively before and during pregnancy, and relate anemia with maternal mortality. Only one study reported clearly that hemoglobin concentration measurements had been recorded in early pregnancy (Royston E. 1982).

Females of the under-developed nations (majority of whom, are either illiterate or unaware) do not seek medical advice until very late in the third trimester, or at the time of delivery. Some seek medical help only if there is a threat to their life due to some injury or hemorrhage. These sick women are at high risk of dying. It is difficult to justify comparing survivors with those who die among women who end up in the hospital and
then imputing the results to the larger population from which they were drawn. Such comparisons are at best weak approximations and are probably very misleading (Rush D., 2000).

Most studies usually correlate hemoglobin concentrations in women entering the hospital with subsequent death, which does not provide an adequate basis on which to decide how anemia affects maternal survival.

No available studies have taken into account the effect of anemia prophylaxis or treatment, other than transfusion in the treatment of very severe anemia (<40 g/L), on the chance of dying. That is, death can be a consequence of enthusiastic (or overenthusiastic) treatment, rather than the disease itself. Drawing conclusions from the proportion of all deaths attributed to anemia rather than to the risk of death due to anemia, only adds to the confusion (Rush D., 2000).

Prospective, controlled intervention trials to examine the efficacy of iron supplementation for reducing maternal mortality will be difficult to conduct because large sample sizes are required and it is considered unethical to not treat anemic women. Another point to consider is that the risk of maternal mortality can be greatly affected by the quality of health care a woman receives.

Some isolated but recently conducted studies point to the fact that certain micronutrient deficiencies may in fact, interfere with the absorption of other nutritional substance, which, directly or indirectly affects iron metabolism adversely. For instance, zinc and vitamin A.

Some latest experts claim, food fortification programmes should be undertaken to combat the problem. We feel that, although developing countries have their aims set at many important issues, they will have to reset their top priority agenda, and, will have to include such measures on their list.

CONCLUSION

With so many uncertainties, it is hardly surprising that the percentage of maternal deaths attributed to anemia, varied widely, from as low as 1.9% to as high as 18.6% [not nearly as high as the 20-40% conveyed by Viteri (1994)]. Stokoe (1991), in a review of 16 hospital-based studies of maternal mortality in the developing world, found that the median percentage of deaths attributed to anemia was zero (9 of 16 studies). Estimates in the other 7 studies cited ranged from 3.0% to 7.5%. These were not only lower rates, but were considerably less variables than those suggested by Ross and Thomas (1996).

There are no universally accepted standards for attributing death to anemia; even if there were, they would be difficult to apply consistently from place to place and across time, especially when clinical information is incomplete, diagnostic criteria are not uniform, and data collection is not standardized. Not only is it difficult to specify the cause of death consistently and accurately, but bias in attributing cause of death is possible. A hospital could put itself in a better light by attributing death to anemia rather than to hemorrhage because the latter is more likely to be understood to reflect obstetric mismanagement (Rush D., 2000).

Hence, in view of all the presently available facts and figures, the writers sadly conclude that:

1. There is evidence that severe anemia (hemoglobin concentrations <70 or 80 g/L) during pregnancy is associated with increased maternal mortality.
2. This association is casual but reasonably serious and significant.
3. A cohort approach is needed to estimate the risk of death from anemia.
4. Data describing the effect of treatment of anemia is scant.
5. Data describing the causes of excess death among severely anemic women, whether from greater risk of shock after hemorrhage, toxemia, or another cause, is
also deficient.
6. Data available, regarding the correlation between anemia and maternal mortality is not reliable due to reasons such as flaws in methodology, and unawareness among the population of the under-developed nations.
7. The subject, therefore, needs to be investigated objectively, and only then, the true picture will evolve; on the available evidence drawing definite conclusions is not justified.
8. Anemia alleviation strategies such as wide scale food fortification programmes must be under taken on large scale and on priority bases in the developing countries.
9. Further research, possibly with larger sample population, is required to establish a working protocol.

REFERENCES

pregnancy in endemic malarious areas. 
Bull. WHO 72: 89.


