

Nutrition and maternal mortality in the developing world¹⁻³

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ABSTRACT This review relates nutritional status to pregnancy-related death in the developing world, where maternal mortality rates are typically ≥ 100 -fold higher than rates in the industrialized countries. For 3 of the central causes of maternal mortality (ie, induced abortion, puerperal infection, and pregnancy-induced hypertension), knowledge of the contribution of nutrition is too scanty for programmatic application. Hemorrhage (including, for this discussion, anemia) and obstructed labor are different. The risk of death is greatly increased with severe anemia (Hb < 70 or 80 g/L); there is little evidence of increased risk associated with mild or moderate anemia. Current programs of universal iron supplementation are unlikely to have much effect on severe anemia. There is an urgent need to reassess how to approach anemia control in pregnant women. Obstructed labor is far more common in short women. Unfortunately, nutritional strategies for increasing adult stature are nearly nonexistent: supplemental feeding appears to have little benefit after 3 y of age and could possibly be harmful at later ages, inducing accelerated growth before puberty, earlier menarche (and possible earlier marriage), and unchanged adult stature. Deprived girls without intervention typically have late menarche, extended periods of growth, and can achieve nearly complete catch-up growth. The need for operative delivery also increases with increased fetal size. Supplementary feeding could therefore increase the risk of obstructed labor. In the absence of accessible obstetric services, primiparous women < 1.5 m in height should be excluded from supplementary feeding programs aimed at accelerating fetal growth. The knowledge base to model the risks and benefits of increased fetal size does not exist. *Am J Clin Nutr* 2000;72(suppl):212S–40S.

KEY WORDS Maternal mortality, pregnancy, developing world, nutrition, obstetric care, operative delivery, obstructed labor, toxemia of pregnancy, iron, anemia, nutrient requirements, supplementation, menarche, maternal height, fetal size, zinc, uterine rupture, maternal weight, maternal body mass index

INTRODUCTION

Pregnancy-related mortality is an enormous topic that others have studied comprehensively and well [eg, Loudon (1)]. Despite this, the contribution of nutrition has not been addressed systematically, and nutrition and public health practice are often not effectively integrated. Halfdan Mahler, then Director General of the World Health Organization (WHO), in his keynote address

at the 1987 Safe Motherhood Conference in Nairobi referred frequently to the role of malnutrition in undermining maternal well-being (2). He pointed out that more girls than boys become severely malnourished and that the cause of maternal death often has its roots in a woman's life before pregnancy—during infancy or even before her birth—when deficiencies of calcium, vitamin D, or iron begin. He noted that malnutrition may result in chronic iron deficiency anemia and death from hemorrhage, and referred to maternal depletion from pregnancies spaced too closely together. Yet nowhere in the accompanying conference conclusions is there an explicit reference to a nutritional component in proposed maternal health programs. This omission is glaring and underscores the absence of unanimity about how best to serve the nutritional needs of pregnant women. It also suggests that a next step might be to scrutinize carefully how nutrition is related to—and possibly how it affects—maternal mortality, and to identify explicit gaps in knowledge and, where knowledge is secure, to propose action.

This review will relate the woman's lifetime nutritional status and dietary intake to pregnancy-related death, focusing on nutrition during pregnancy. One of its main concerns will be whether the associations between nutrition and maternal mortality may be causal and, if they are, whether amelioration is plausible.

The analysis will be concerned primarily with the developing, rather than the industrialized, world. There is no other public health statistic in which the discrepancy in risk between the industrialized and the developing worlds is greater than that for maternal mortality. In all likelihood, this discrepancy is often much higher than the usually quoted 100- to 200-fold increased risk (3). In the developing world, the dominant causes of maternal death are those that prevailed ≥ 2 centuries ago in Europe and the United States. Sadly, although ways to reverse most of the profound differences of risk between poor and affluent women are widely understood, they are often not available. The need for intensive and widespread improvements in obstetric services in the developing world is clear. What remains unclear is the extent to which improving the nutritional status of

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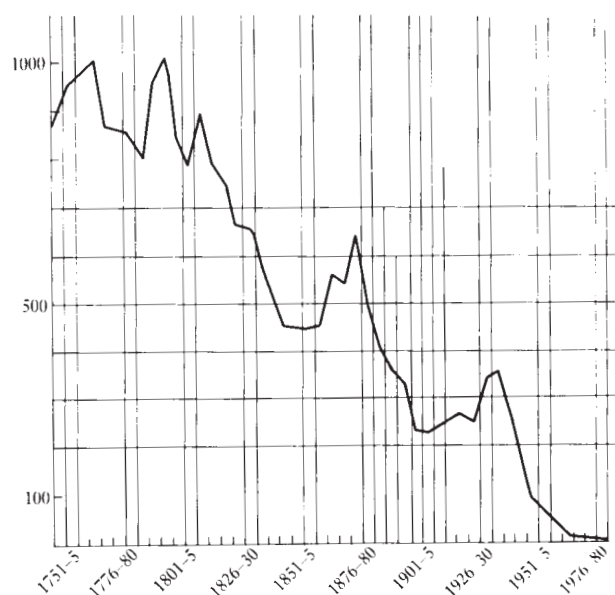


FIGURE 1. Mean annual maternal mortality ratio/100,000 live births by 5-y periods, Sweden, 1751–1989 (6). Reproduced with permission.

women, from early in their own lives through the reproductive years, is important or even essential as an adjunct to improved health services.

This review must, of necessity, make do with the data available now. It points, however, to a great need for more longitudinal, community-based studies of reproduction in the developing world, parallel to those conducted in developed countries in the past half century, such as the community studies in Aberdeen (4) or the US Collaborative Perinatal Study (5).

The paucity of comprehensive and accurate statistics makes it difficult to relate nutritional status directly to maternal death. This is a consequence of the relative infrequency and invisibility of maternal death, even at the tragically high rates prevalent in the developing world. Because of this, the review deals most often with relations between nutrition and those health conditions that are the proximal causes of maternal mortality.

Deaths during gestation do not usually result from malnutrition alone, but from conditions that may be exacerbated by poor nutrition. The 4 primary causes of maternal mortality are hemorrhage (in the intra- and postpartum periods), obstructed labor, pregnancy-induced hypertension (ie, the toxemias of pregnancy, preeclampsia, and eclampsia), and puerperal infection. This review will not address death after induced abortion, the fifth of the frequent causes of maternal death in the developing world. It is implausible that a strategy of nutritional improvement would reduce the danger from unsterile or technically inadequate abortion procedures.

A central tenet of this review is that nutrition and health services function interdependently. Setting priorities for nutrition programs, or allocating resources to support them, is illogical without interweaving these programs with health services; nutritional programs cannot confer anywhere near maximal benefits without effective health services. In fact, without such integration, they could even be dangerous. This danger could occur not only because of the diversion of resources away from essential

health services, but from direct adverse effects of dietary supplementation, as will be explained below.

HISTORICAL EPIDEMIOLOGY OF MATERNAL MORTALITY IN THE DEVELOPED WORLD

Much of this material is drawn from Loudon (1).

Historical trends

The magnitude of the challenge faced by the developing world is almost unimaginably large: in the industrialized countries, it took 250 y to reach the current low maternal mortality rates from rates similar to those in developing countries today. Some approaches to reducing maternal mortality in developing countries might be drawn from the experience of the industrialized countries.

The precipitous decrease in maternal mortality in the West did not occur evenly or gradually. Instead, maternal mortality rates followed a pattern of abrupt declines followed by plateaus, even increases, and then further abrupt declines. This ebb and flow is illustrated in **Figure 1** for Sweden from 1751 to 1980, during which time the initial ratio of maternal mortality was $\approx 1000/100,000$ live births, and the most recent ratio was $\approx 4/100,000$ live births (6).

The declines in infant and maternal mortality rates were not parallel. Shown in **Figure 2** are maternal and infant mortality ratios in the Netherlands from 1910 to 1960 (7). Infant mortality ratios fell regularly and steeply until the beginning of World War II, then rose sharply during the war, and declined after the war. In contrast, maternal mortality rates were static until the mid 1930s, when they began to fall sharply, but this decline was not affected by the war. The widespread deprivation associated with the German blockade late in the war had profound effects on infant mortality, but no obvious effect on maternal mortality. This is counterintuitive because antibiotics, the introduction of which from 1934 was concomitant with the beginning of the decline in puerperal infection, were likely to have been scarce to nonexistent during the blockade. Maternal and infant mortality rates during the 20th century until 1960 in England and Wales are shown in **Figure 3** (8). As in the Netherlands, infant mortality rates fell sharply and continuously throughout the period, whereas maternal mortality was unchanged until the 1930s and only then began to fall precipitously. The underlying reasons for the decrease in maternal mortality clearly cannot be identical to those for infant mortality because they came into play at different times and under different conditions. How they differed, and to what extent, is explored in depth by Loudon (1).

Social status and maternal mortality

Infant mortality has long been observed to have an intense social class gradient (9). Despite this, little if any gradient was observed for the association between maternal mortality and social status in England over the past century (10). The early fall in maternal mortality in Europe from the mid 18th to mid 19th centuries, such as the halving of maternal mortality rates between 1751 and 1851 in Sweden (6), may be perhaps attributed to improved social conditions. Social status, however, appears to have been only minimally related to maternal mortality in the late 19th and most of the 20th century in the European countries.

Social influences are strongly related to maternal mortality in the contemporary United States. The maternal mortality rate of

the United States in 1995 was 7.1/100000 live births (11). However, the rate among black women was 22.1/100000, >5 times the rate of 4.2/100000 live births among white women. This disparity could have been due to different social conditions, provision of obstetric care, health-related behaviors, nutritional or health status, or a combination of these factors.

Antisepsis and maternal mortality

One unequivocal cause of the decline in maternal mortality in the industrialized world was the introduction of antiseptic techniques into hospital obstetric practice. Högborg et al (12) estimated that after the obligatory introduction of antisepsis into Swedish lying-in hospitals in 1880, hospital maternal mortality ratios from sepsis declined from 2701/100000 live births in the preceding 15 y to 96/100000 births in the subsequent 15 y, a decline of 96%. The introduction of sulfonamides in the mid 1930s also had a remarkable effect on maternal mortality. Shown in **Figure 4** is the parallel, precipitous decline in death from erysipelas and maternal mortality due to puerperal fever in England and Wales that began in 1934 (1).

Other causes of maternal mortality

From the mid 1930s, as many elements in obstetric care were improving, deaths from hemorrhage and eclampsia (ie, puerperal hypertension, albuminuria, and convulsions) also declined (**Figure 5**), although not as steeply as the decrease in infection rates (1). These trends were universal throughout the industrialized world (**Figure 6**) and rates have continued to decrease (1).

Current rates of maternal mortality in developed countries

National rates of pregnancy-related deaths have fallen to extraordinarily low levels in many industrialized countries. As of 1991, mortality rates were 2/100000 live births in Ireland; 3/100000 in Australia, Belgium, Denmark, and Norway; 4/100000 in Italy and Switzerland; and 5/100000 in Canada, Germany, Greece, Spain, and Sweden, with other countries following (13).

An attempt to distinguish the impact of health services from other factors on US women

Despite low maternal mortality ratios in the surrounding community, women who were members of a small religious sect were reported to have aberrantly high maternal mortality ratios. Spence et al (14) and Kaunitz et al (15) reported the perinatal and maternal mortality rates among Faith Assembly members during 1975–1982. The Faith Assembly became active in northeastern Indiana from ≈1973. One of its tenets was that members should not receive medical care in response to health problems. Pregnant women, therefore, received no prenatal care and gave birth at home without obstetric assistance. The group had 6 maternal deaths between 1975 and 1982, resulting in a maternal mortality ratio of 872/100000 live births, ≈100 times that in the surrounding community. (Four of the deaths were from hemorrhage and 2 were from infection.) This suggests that the risk of death during reproduction among women in modern America, who, apart from medical care, were presumably living in similar social and economic conditions others living in the same area was similar to that in contemporary developing countries or in the West during the 19th century. The nutritional status of the Faith Assembly women is unknown, and the experience, although dramatic, is not conclusive in identifying which factors might have been involved in their excess risk of mortality. Nevertheless, the causes of death suggest

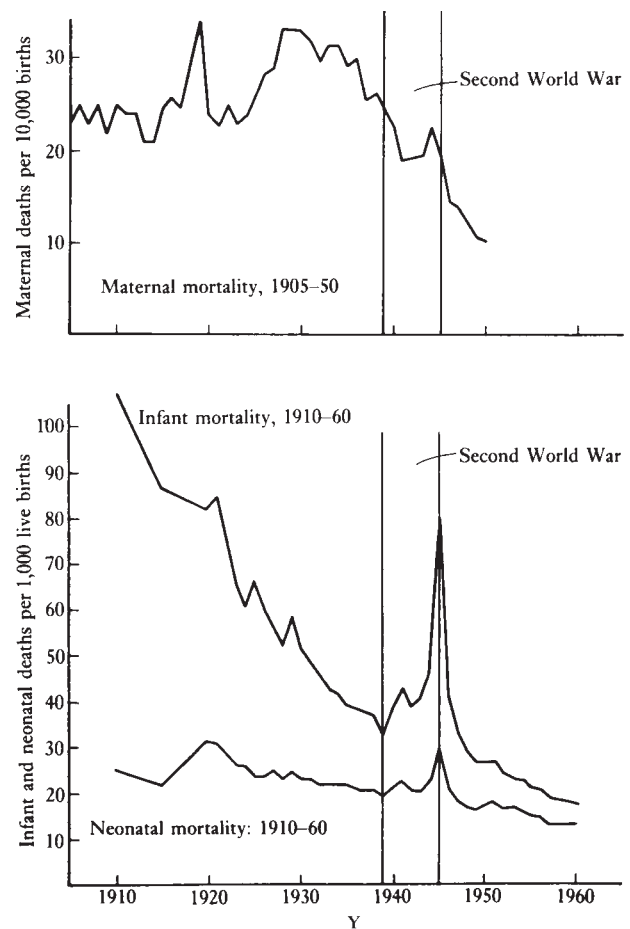


FIGURE 2. Maternal mortality ratio, 1905–1950, and infant and neonatal mortality ratios, 1910–1960, in the Netherlands (7). Reproduced by permission of Oxford Press (1).

strongly that they could have been prevented with adequate obstetric care. The increase in the risk of death among women was much greater than that among infants: the perinatal mortality rate was 2.7-fold that of surrounding communities compared with the ≈100-fold increased risk of maternal mortality.

MATERNAL MORTALITY IN THE DEVELOPING WORLD

AbouZahr and Royston (13) published an encyclopedic description of the current state of knowledge of national maternal mortality in both the developing and developed world. In addition to data on national rates, they presented an invaluable compendium of smaller and presumably more intensive—and, therefore, more reliable—community and hospital-based studies. The authors estimate that 500000 maternal deaths occur each year, of which 494000 occur in developing countries. The worldwide maternal mortality ratio is estimated to be 390/100000 live births, 30/100000 in the developed world and 450/100000 in the developing countries. Within the developing world, regional rates are as high as 660–700/100000 live births in east, middle, and west Africa, and 650/100000 live births in south Asia. Even at these high levels, the reported rates for the developing world are probably underestimated.

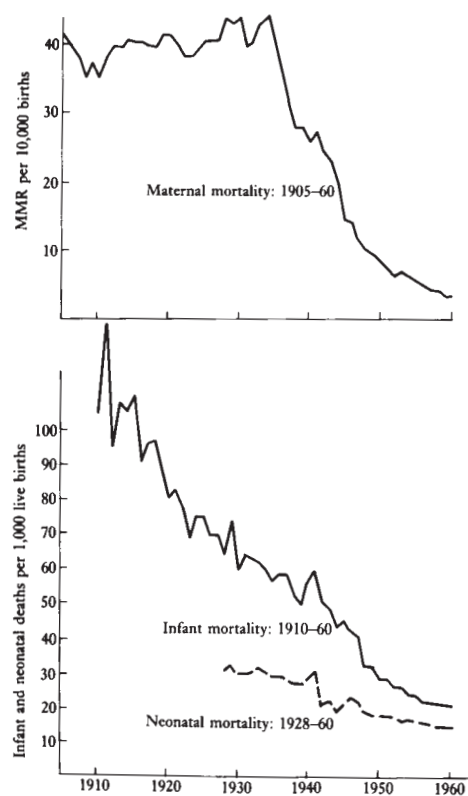


FIGURE 3. Secular trends in maternal mortality ratio (MMR), 1905–1960, infant mortality, 1910–1960, and neonatal mortality, 1928–1960 (8). Reproduced by permission Oxford University press (1).

Underestimates of maternal mortality

Much attention has been paid to the problem of accurately estimating maternal mortality in the developing world (3, 16). Despite the best intentions, these estimates are often no more than educated guesses, probably under- rather than overestimated because so many deaths are unattended and unregistered. In one area in India, only one-third of the maternal deaths were recorded in the health system (17). In another area of India, only 31% of maternal deaths had occurred in the hospital and 64% of cases had never been referred (18). In a southern district in Malawi, 56% of maternal deaths occurred outside a health facility (19). Similarly, $\approx 50\%$ of maternal deaths were unreported in a regional study in Argentina (20). Clearly, the deaths of women who never reach a hospital are usually omitted from the health statistics system. Official national statistics are, therefore, unlikely to reflect the actual severity of the problem of maternal mortality.

A paradox exists in that some thoughtful students of maternal mortality have concluded that collecting accurate counts of death is a distraction. They argue that the problem of maternal mortality is severe, knowledge exists about what should be done to correct it, and resources should not be expended to collect data that in any case are highly suspect. Graham et al (21) concluded that maternal mortality is not a feasible outcome indicator of the success of interventions.

In contrast, Moodley et al (22) reported that structural changes in the health care system would only be possible with the estab-

lishment of a common information database and if confidential inquiries were held into all maternal deaths. This opinion probably reflects that these authors are attempting to lower a maternal mortality ratio in South Africa of $\approx 150/100\,000$ live births, which is already much lower than ratios in most developing countries. Accurate counts and confidential enquiry may be the next appropriate steps in the South African context.

Clearly, there are conflicting views on the need for routine collection of data on maternal mortality. Nevertheless, it is not clear how programs can be refined and how scarce resources can be allocated without an accurate knowledge of both the extent of maternal mortality and the quantitative effect of interventions.

Reevaluation of the effect of antenatal care on maternal mortality

Some commentators have begun to question long cherished assumptions about the importance of antenatal care. Rooney (23), in a comprehensive assessment of the issue, concluded that little is known about the effectiveness of antenatal care. McDonagh (24) concluded that the evidence justifying antenatal care is weak. She cited the example of a prospective study in the Gambia that found no relation between antenatal care and maternal mortality. A subsequent publication, however, showed a more complex relation between the strengthening of primary health care and subsequent maternal mortality; maternal mortality rates did decline, but did so in both the villages with a primary health care intervention as well as in the control villages (in contrast, perinatal mortality rates decreased only in villages that received improved primary health care) (25). This suggests an effect from participating in the study, even as a control (ie, a Hawthorne effect), because of improved surveillance, heightened awareness, or better access to transport. A series of small studies reported the near disappearance of maternal death after the introduction of relatively uncomplicated health services. These include the experience of the MRC-Dunn Nutrition Unit in the Gambia (26) and a pilot program in the rural areas around the city of Fortaleza in northeastern Brazil (27). One of the best known intervention programs was the controlled trial in Bangladesh that introduced improved community-based midwifery services in the Matlab region (28). Maine et al (29), however, have disputed that the decline in maternal mortality rates in Matlab was due to improved primary care services and attribute the rates to improved access to hospital perinatal services.

The most remarkable localized effort to reduce maternal mortality was probably the Frontier Nursing Service in rural Kentucky, which began in 1925 (1). Only 9 maternal deaths from direct obstetric causes were recorded among $>12\,000$ deliveries between 1925 and 1965. In the early years of the Frontier Nursing Service, the mortality rates were ≈ 10 times lower than those in surrounding affluent communities. Which elements of the program were most important and whether they can be replicated remains uncertain, but this experience is a beacon for those who aspire to create good maternal health services under difficult conditions.

Maternal mortality and national social and environmental factors

Only one study was found on cross-national social indices and maternal mortality. Hertz et al (30) related national social and environmental indices, including several nutritional ones, to reported rates of maternal mortality, infant mortality, and life

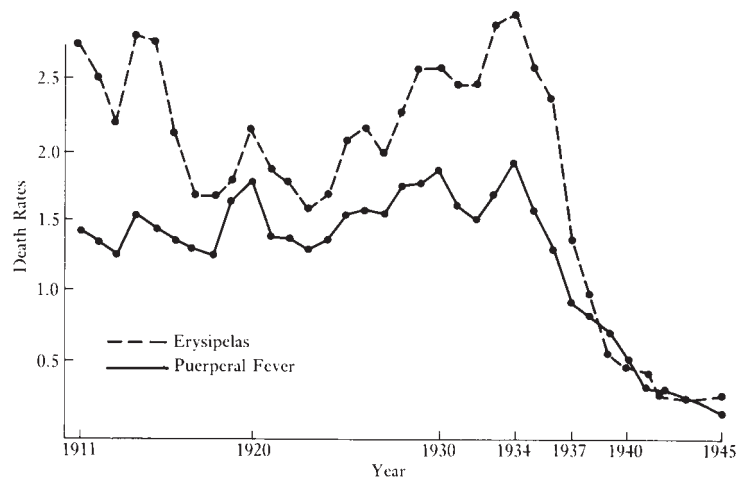


FIGURE 4. Erysipelas mortality ratio/100 000 people of all ages and maternal mortality ratio/1000 births due to puerperal fever, England and Wales, 1911–1945 (1). Reproduced by permission of Oxford University Press.

expectancy. Their tentative conclusions were that the indices differed among the 3 endpoints studied. The published regression model for maternal mortality included 3 nutritional variables that were significant; the model was apparently overdetermined, however, this was due to one variable in the regression model being mislabeled. The senior author has since clarified this error (JR Hebert, personal communication, 1999). The corrected final model showed that maternal mortality was positively and significantly related to the percentage of households with sanitation and total energy intakes, but negatively (and almost significantly, $P = 0.07$) associated with the residual of total fat intakes. This negative relation with energy derived from fat probably reflects that the latter was relatively expensive and thus may have been an index of affluence as much as of nutrition. National numbers of medical personnel, hospital beds, households with safe water, and literacy were not significantly related to maternal mortality.

Economic disparity, structural adjustment, and maternal health

Evans (31), reporting on a lecture by Professor Kelsey Harrison, indicated that the gulf between the richest and poorest countries' gross national product per capita increased from 8-fold in 1950 to nearly 30-fold in 1995. Although 24 countries were categorized as poor in 1950, in 1995 there were 47, of which 29 were in sub-Saharan Africa. The disparity in health between rich and poor countries was starkly reflected by the lifetime chance of a woman dying during pregnancy: 1 in 17 000 in Italy compared with 1 in 7 in Mali. Harrison stated that the cost of an uncomplicated cesarean delivery in the area where he worked in Nigeria was \$274. This was an average 9-mo salary, and those who needed the operation but could not afford to pay, died.

The conditions devised by the World Bank or the International Monetary Fund so that developing countries can receive loans typically require reduced government spending, usually leading to lower social expenditures, ie, health care expenditures, public education, and the education of women. This is likely to affect health adversely, both from reduced health services and from continued illiteracy; there is a close association between maternal literacy and health outcomes (32). Thus, these

organizations, which represent the world community, although doing some well-motivated work to improve public health and nutrition, are also implementing other policies that are almost surely making population health and nutrition status worse, at least in the short run.

Effect of maternal death on surviving children

In their study of maternal mortality in Sweden in the 19th century, Högberg and Broström (33) found that 68% of infants born alive to dying mothers did not survive. Even more striking, siblings aged <1 y at the time of the mother's death had only a 3% chance of surviving to age 5 y. Similarly, siblings between ages 1 and 5 y had only a 13% chance of surviving to the same age. Although the effect in the contemporary developing world may not be this severe, the death of a mother is likely to be followed by the death of $\approx 50\%$ of her children under the age of 5 y (34). Although some of these children may die of causes shared with their mothers (eg, starvation or AIDS), most will die directly or indirectly from the lack of maternal care.

ANEMIA AND MATERNAL MORTALITY

Current concepts of the relationship between anemia and maternal mortality

The problem of anemia during pregnancy, especially in the developing world, has received much attention during recent decades (35–40). 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. These reviews unanimously concluded that iron deficiency anemia during pregnancy is common, that it incurs severe adverse consequences, and, therefore, that aggressive iron supplementation during pregnancy is necessary, particularly in the developing world. For example, Viteri (39) 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 500 000 maternal deaths/y. A high-level international group recently concluded that high prevalence rates for iron deficiency anemia in many developing countries constitute a public health

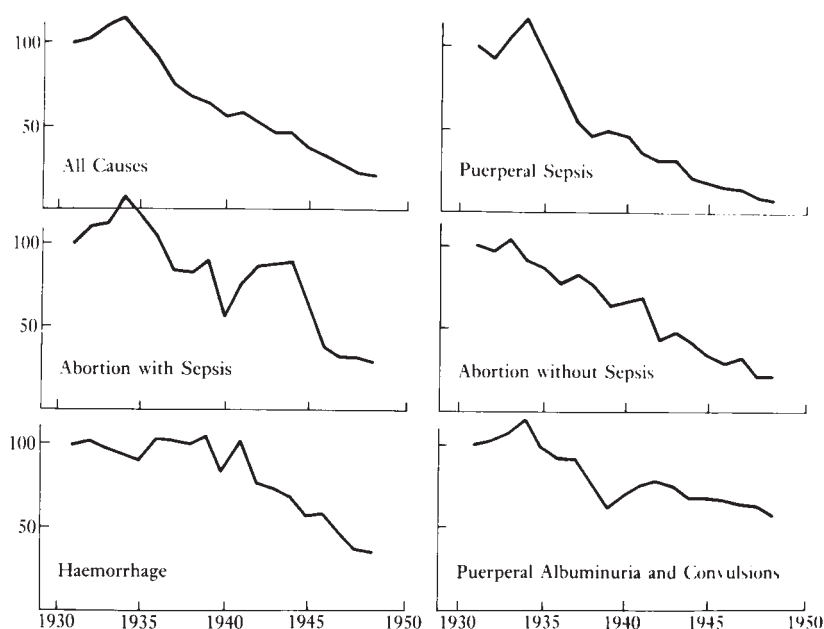


FIGURE 5. Trends in maternal mortality ratios by cause, England and Wales, 1931–1950 (1). Reproduced by permission of Oxford University Press.

emergency equivalent to epidemics of infectious disease and have more lasting adverse consequences for survivors; the group recommended that the evidence of the role of maternal anemia on maternal mortality and other pregnancy outcomes be widely disseminated to assist in program advocacy (41).

The assumption at the onset of this review was that the knowledge base underlying this apparent consensus would be confirmed and the paucity of examples of improved health following anemia treatment and prevention would be due primarily to the failure to carry out program protocols adequately. In other words, although the consequences and the prevention and cure of anemia would be straightforward, the implementation of programs to lower iron deficiency would be problematic. This has turned out not to be true. Upon careful review, the underlying basis for the consensus is clearly far from secure. The rest of this section explores why current policies to lower 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.

A series of linked assumptions underlie current thinking about the effect of maternal anemia on maternal mortality (listed below in the section “Responding to severe anemia during pregnancy”). None of the assumptions, however, is securely supported by the available evidence as presented below. This does not imply that increasing maternal survival by preventing and treating anemia, particularly severe anemia, may not be possible. Rather it reveals crucial gaps in knowledge about whether—and how—this might best be done.

Methodologic problems relating anemia to maternal mortality

The literature on anemia during pregnancy is extensive, but the available data on the association between anemia and maternal survival are limited. A few key studies are repeatedly referred to, usually in passing and uncritically, and discussion quickly moves onto other issues. It has been chastening to scru-

tinize the basic data on which the relation of anemia to maternal mortality is usually posited.

Ideally, to determine the relation between anemia and subsequent mortality, hemoglobin concentration and other hematologic and biochemical indexes of anemia should be measured prospectively before pregnancy. This would avoid confusion resulting from the hemodilution of pregnancy. Because anemia is defined by hemoglobin concentration, rates of anemia during pregnancy are much higher than those that occur during the non-pregnant state. Risk estimates calculated from hemoglobin concentrations measured before pregnancy would be better indicators of the need for prophylaxis or treatment (42). Measurements would be made in a representative population and women would be followed to the end of pregnancy. Pregnancy outcomes would be related to the rate and etiology of anemia, whether prophylaxis and treatment were received, and the extent to which anemia was corrected. Ideally, treatment would be double blinded (ie, assigned randomly with both recipients and observers unaware of treatment assignment). Unfortunately, no investigation has come close to such methodologic rigor.

Few studies even relate hemoglobin concentrations measured prospectively during pregnancy, usually at unspecified stages of gestation, to maternal mortality. Only one study reported clearly that hemoglobin concentration measurements had been recorded in early pregnancy (43), and all of the studies but one were in hospital populations. Although the hope that prepregnancy hematologic status can be related to subsequent risk during pregnancy may be utopian, the uncertainty of inference drawn from hemoglobin concentrations measured at the time of delivery cannot be overemphasized. Hemoglobin concentration measurements at delivery are confounded in at least 4 ways: by the hemodilution of pregnancy, the physiologic rise in hemoglobin concentration in the third-trimester, concurrent illness (especially hemorrhage or infections that may have been the reasons for coming to the hospital; the most important confounder), and the unrepresentativeness of the women (a flaw common to all

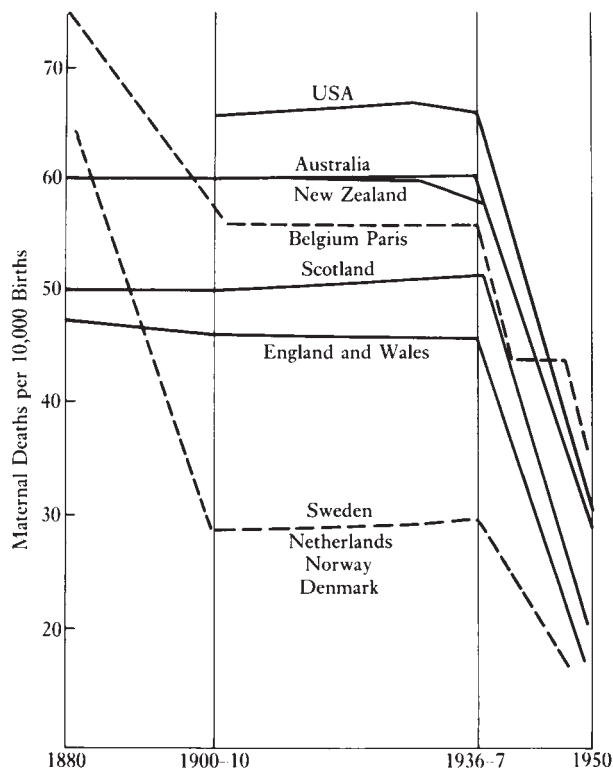


FIGURE 6. Trends in maternal mortality in various countries, 1889–1950 (1). Reproduced by permission of Oxford University Press.

studies on patients first encountered at confinement). Population rates of observed outcomes cannot be inferred from women enrolled at confinement because the referent population (those who are cared for in hospitals on an unbooked or emergency basis) can rarely be described or quantified.

The plea for representativeness in such studies may seem to be a methodologic nicety—epidemiologic prissiness—but it is a crucial issue. Women who arrive at a hospital only at the time of birth rarely do so because of disinterest or laziness. Quite the contrary: they typically go to the hospital because they are very sick and often do so after an arduous and unsettling journey. 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. This is especially true because hemoglobin concentration at confinement is likely to be measured because of bleeding and may have been the reason for the transfer to the hospital in the first place. Most studies have correlated hemoglobin concentrations in moribund women entering the hospital with their subsequent death, which does not provide an adequate basis on which to decide how anemia affects maternal survival. Furthermore, 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. Fullerton and Turner (55), in Ibadan, Nigeria, reported that there were no cases of cardiac failure and no maternal deaths when hematocrit was >0.13. The death rate among severely anemic women (hematocrit <0.14) decreased from 20% to <3% by using

exchange transfusion. Yet this patently inadequate set of studies is used as the basis for prophylaxis and treatment programs.

Drawing conclusions from the proportion of all deaths attributed to anemia rather than to the risk of death given anemia only adds to the confusion. Ross and Thomas (44), in their review of maternal anemia and mortality, used the proportion of all maternal deaths attributed to anemia as their central index. Their analyses were typically based on hospital series data. Such attribution can be highly subjective and is likely to vary widely. Moreover, estimating whether and to what extent the risk of death was increased in anemic women, using this approach, is not possible because the risk of death from anemia cannot be estimated by considering only those who died. With so many uncertainties, it is hardly surprising that the percentage of maternal deaths attributed to anemia, or in which anemia was considered a contributing factor, 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 (39)]. Stokoe (45), 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 variable than those suggested by Ross and Thomas (44).

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.

A cohort approach is needed to estimate the risk of death from anemia: comparison of mortality rates between groups of pregnant women with and without anemia. If the same proportion of women who die have anemia with the same degree of severity as surviving women, anemia cannot logically be implicated as a contributory cause of death. (Even the few reports from which relative risk of death associated with anemia can be calculated, rarely, if ever, specify the causes of anemia or the effect of therapy.)

Studies relating anemia to maternal mortality

All studies relating anemia to maternal mortality from which relative risks could be calculated are presented in **Table 1**. Llewellyn-Jones (46) presented one of the rare reports that is probably entirely prospective, although he makes no explicit statement that all the hemoglobin concentration measurements were done before confinement. He described 73 048 women delivered at the maternity hospital in Kuala Lumpur between 1953 and 1962, of whom 2250 (3.1%) had severe anemia, with initial hemoglobin concentrations <66 g/L. The maternal mortality ratio for those with severe anemia was 1556/100 000 live births ($n = 35$) compared with 350/100 000 live births ($n = 248$) for (presumably) all the other women, a relative risk of 4.4.

There are vexing and important uncertainties in this report. Whether all hemoglobin concentrations were measured before term is not clear and no data were presented on the specific out-

TABLE 1

All studies of severe anemia and maternal mortality for which relative risk (RR) could be calculated

Study	Site and subjects	Level of anemia	RR
Llewelyn-Jones ¹ (46)	Hospital, Kuala Lumpur (<i>n</i> = 73 048 total, 2250 anemic)	Severe	4.4
Harrison ² (47)	Hospital, Zaria, Nigeria (<i>n</i> = 12 262 total, 760 anemic)	Uncertain	3.84
Harrison (48)	Hospital, Zaria, Nigeria (<i>n</i> = 5178 total, 258 anemic)	Very severe (Hct ³ <0.14)	20.0
		Severe (0.14–0.25)	3.4
		Moderate (>0.25–0.29)	0
Harrison and Rossiter ⁴ (49)	Hospital, Zaria, Nigeria (<i>n</i> = 1777 total)	Very severe (Hct <0.14)	1.34
		Severe (0.14–0.24)	1.05
		Moderate (0.25–0.29)	0.75
		Polycythemia (≥0.45)	3.3
Chi et al ⁵ (50)	12 teaching hospitals Indonesia, (<i>n</i> = 36 062 total)	Severe and moderate	Urban 2.1
		Severe and moderate	Rural 5.9
Thonneau et al ⁶ (51)	Hospital, Conakry, Guinea, case control study (<i>n</i> = 102 deaths, 338 controls)	Uncertain	2.1
Diallo et al ⁷ (52)	Hospital, Conakry, Guinea (<i>n</i> = 13 191 total, 1408 anemic)	All	2.8(?)
Sarin (53)	Hospital, Punjab (<i>n</i> = 35 565 total, 8348 moderately anemic, 19 946 severely anemic)	Severe (Hb <70 g/L)	3.13
		Moderate and mild (Hb 70–109 g/L)	1.64
McDermott et al ⁸ (54)	Malawi, prospective (<i>n</i> = 3740 total, 233 anemic)	Severe	5.9 ⁹

¹ Anemia = hemoglobin (Hb) ≤65 g/L, all subjects hospitalized; parenteral iron given (no data on effect); no data on when Hb measured.² Level of anemia not specified; odds ratio calculated from author's data.³ Hct, hematocrit.⁴ Unbooked women who presented at the hospital for the first time at delivery; Hct at delivery; 24% of women had Hct measured.⁵ Anemia = Hb ≤90 g/L; 92% of deaths admitted as emergencies, 37% of deaths moribund. Numbers of anemic women not given.⁶ Anemia not defined.⁷ Anemia = Hb ≤110 g/L, most subjects had severe anemia; authors' data inconsistent and calculated RR therefore uncertain.⁸ Anemia = Hct <0.25. If positive for HIV, then RR = 9.8 for sum of maternal plus postmaternal mortality, and RR = 30.8 for postmaternal mortality only.⁹ Sum of maternal and postmaternal mortality (postmaternal mortality only, RR = 9.9).

come for women with moderate anemia (hemoglobin concentrations >66 g/L). To infer that their outcomes were not remarkable, ie, that moderate anemia did not confer any increased risk of mortality, seems both reasonable and logical because the author did not report otherwise. Nevertheless, interpreting omitted results is risky, albeit probably unavoidable here. It would also be of great value to know whether treatment of anemia conferred any benefit. The author stated that all women with hemoglobin concentrations of <66 g/L were admitted to the hospital. They received 2500 mg parenteral iron if, after intensive investigation, iron treatment was warranted. If administered early enough in gestation, such an aggressive treatment regimen should have eliminated iron deficiency as a cause of severe anemia. No data, however, were presented describing the effect of treatment for anemia, either on hemoglobin concentrations or on rates of maternal death. It is also discouraging that the causes of excess death among severely anemic women, whether from greater risk of shock after hemorrhage, toxemia, or another cause, were not presented. What can be concluded from this report is that even with skilled and intensive antenatal and perinatal care, severe anemia (probably measured prospectively and treated competently, including aggressive response to iron deficiency) was associated with a 4.4-fold increased risk of maternal death. What remains unresolved is the extent to which aggressive treatment of iron deficiency eradicated anemia; whether effective treatment of anemia modified maternal, fetal, and infant outcomes; and whether the presumably more numerous population of women with moderate anemia were at greater risk of death than the nonanemic population. Finally, the applicability of this experience to the rest of the developing world is uncertain because this

population received specialized obstetric attention, including prenatal care, operative obstetrics, and access to a blood bank. The increased risk of death with severe anemia might be far greater for women without access to this level of health care.

Harrison (47) presented data suggesting that the percentage of anemia in 12 262 mothers delivered in Zaria, Nigeria, was 6.1%, whereas that in mothers who died was 4.7%. The anemia criterion was not defined. Inferring from the author's data, it appears more likely that there were 36 deaths among the 760 anemic women, a ratio of 4.7%, and 142 deaths in the 11 699 other women, or a ratio of 1.2% and a relative risk of 3.9.

In another publication from the same hospital, Harrison (48) presented the relation between hematocrit and maternal death for 5178 singleton births in 1976. Whether the hematocrit was measured before term was not specified. In this series, the maternal death rate was 20% (5/25) with a hematocrit <0.14, 3% (3/90) with hematocrit between 0.15 and 0.25, and zero (0/143) with hematocrit between 0.25 (equivalent, approximately, to a hemoglobin concentration of 80 g/L) and 0.29. Thus, maternal death was extremely common with very severe anemia and common with severe anemia, but nonexistent with moderate anemia. This is only 1 of 2 reports explicitly reporting the risk of maternal mortality associated with moderate anemia.

Harrison and Rossiter (49), also in Zaria, Nigeria, observed maternal mortality ratios of 370/100 000 live births for patients registered for prenatal care (booked) and 2860/100 000 live births for patients who presented at the hospital for the first time at delivery (unbooked). The 19 deaths among the booked patients were not arrayed by hematocrit. Only 22% of the unbooked survivors and 55% of those who died had hematocrit measured.

TABLE 2Maternal mortality per 100 births for unbooked women delivered at Zaria Hospital, by hematocrit at delivery¹

	Hematocrit at delivery								Total (n = 1777)
	≤0.14 (n = 122)	0.15–0.20 (n = 185)	0.20–0.25 (n = 241)	0.25–0.30 (n = 331)	0.30–0.35 (n = 346)	0.35–0.40 (n = 346)	0.40–0.45 (n = 170)	≥0.45 (n = 36)	
Hemorrhage									
Antepartum	2.9	10.0	3.1	8.5	6.7	16.7	0	0	6.5
Postpartum	6.7	5.3	16.1	9.3	15.0	4.0	0	—	12.6
All deaths	9.0	5.4	8.3	4.2	5.5	6.9	8.8	22.2	6.8

¹Unbooked women presented at the hospital for the first time at delivery. From reference (49), extracted from authors' results. Analysis presumably limited to the minority of women with hematocrit values.

Hematocrit values for the 219 unbooked women who died are compared with those of unbooked survivors in **Table 2**. Presumably, the women's hematocrits were not measured until they arrived at the hospital, and women with antepartum hemorrhage were not excluded. Although there was no clear relation between low hematocrit at delivery and either total mortality or mortality associated with antepartum or postpartum hemorrhage, high hematocrit was associated with high mortality. This does not, however, preclude the possibility that anemia might have been associated with high mortality; a relation could have been masked by the incompleteness of these data. The inference that can be drawn from these results is limited for 5 reasons: 1) The hematocrit of only a small number of women was measured, and these women were almost certainly, on average, sicker than women whose hematocrit was not measured. Because hematocrit was not measured universally, presumably measurement would have been far more likely when clinically indicated (ie, in the presence of anemia and when transfusion might be contemplated). 2) The at-risk population from which these women were drawn is unknown; inferring rates of anemia and estimating risks of death in the larger population is, therefore, very uncertain. 3) Hematocrit at hospital entry for delivery may have had a weak relation with hematocrit earlier in pregnancy. 4) The causes and duration of anemia in these women are unknown. 5) Iron deficiency was stated to be an unusual cause of anemia in this region.

Chi et al (50) studied 108 maternal deaths between 1977 and 1980 that had adequate records (out of a total of 135) at 12 teaching hospitals in Indonesia. Anemia was defined as a hemoglobin concentration ≤90 g/L at confinement. The death ratio among anemic urban women was 388/100000 live births compared with 184/100000 live births for the nonanemic women, a relative risk of 2.1. For rural women, the mortality ratios were 1348/100000 live births and 228/100000 live births, respectively, a relative risk of 5.9. All but 9 of the 108 deaths were emergency admissions and 40 were among women who were moribund at admission. Estimating population death rates is not only impossible, because the background populations from which these women were drawn are unknown, but the implications of hemoglobin measured at admission for women who were very sick and often in shock, are uncertain. Death ratios were not presented for women with hemoglobin concentrations between 90 and 110 g/L. The much higher risk of death associated with anemia for rural women is provocative and consistent with anemia being far more dangerous when access to obstetric care is limited; women who need obstetric services most are least likely to have access to them. These data strongly suggest the interdependence between nutritional status and health services in affecting pregnancy outcome.

Thonneau et al (51) carried out a case-control study of 102 maternal deaths and 338 control women who delivered between July 1, 1989, and June 30, 1990, in Conakry, Guinea. The relative risk of death if anemia was present was 2.1 (95% CI: 1.1, 4.1). However, anemia was not defined, hemoglobin concentrations were not given, and is it not clear whether hemoglobin was measured prospectively.

In western Kenya, Zucker et al (56) observed 6 deaths among 73 severely anemic pregnant women with hemoglobin concentrations <60 g/L at admission, a death rate of 8.2%. The hospital apparently provided medical but not obstetric services. Of the 279 women in the reference group who were hospitalized but who did not have severe anemia, 177 of whom were pregnant, only 4 died. No results were presented for anemic pregnant women with hemoglobin concentrations >60 g/L, and these admissions were presumably a mix of both pregnant and nonpregnant women with either severe medical or obstetric problems. Neither death rates nor relative risks of death with severe anemia during pregnancy can be calculated because of the indeterminate reference population. Nevertheless, the very high death rate among the severely anemic is striking.

Diallo et al (52), in a prospective hospital study in Conakry, Guinea, observed a maternal mortality ratio of 852/100000 live births for the 10.7% of women who were anemic. Anemia was defined as <110 g/L hemoglobin. They stated in their summary that these 12 deaths represented 65% of all maternal deaths but, in the text, a value of 25% was given, which appears more plausible. If the latter value was correct, by comparing anemic with nonanemic women, the relative risk of death can be calculated as 2.8. From the data presented, it is not possible to estimate whether there were different death ratios for severe and moderate anemia. This population of hospitalized women served as an unrepresentative sample in which to study anemic women compared with nonanemic women, as reflected by the high frequency of severe anemia: 56% of all women with anemia had hemoglobin concentrations <80 g/L; only 44% had concentrations between 80 and 110 g/L, the reverse of what would be expected in the general population. Thus, this subset of women cared for in the hospital was skewed to the very sick.

Sarin (53) reported on maternal mortality in a hospital series (as well as a population survey of the prevalence of anemia during pregnancy) in Punjab State, India. The author related maternal mortality to hemoglobin concentrations measured at admission for delivery. For nonanemic women (n = 38), the maternal mortality ratio was 566/100000 live births, for mildly anemic women (n = 184) it was 927/100000, and for severely anemic women (n = 117) it was 1769/100000. These cross-sectional

TABLE 3
Estimated prevalence of anemia in women (≈ 1988)¹

Region	Women with Hb concentrations below average		
	Pregnant	Nonpregnant	All
	<i>n</i> (%)		
World	58 270 (51)	399 250 (35)	457 520 (37)
Developing countries	55 750 (56)	363 800 (43)	419 550 (44)
Developed countries ¹	2 520 (18)	35 460 (12)	37 970 (13)
Africa	11 450 (52)	47 940 (42)	59 400 (44)
Eastern	3 380 (47)	13 540 (41)	16 920 (42)
Middle	1 290 (54)	5 330 (43)	6 620 (45)
Northern	2 240 (53)	11 450 (43)	13 690 (45)
Southern	380 (35)	2 500 (30)	2 880 (30)
Western	4 170 (56)	15 120 (47)	19 290 (48)
Asia ²	40 140 (60)	294 960 (44)	335 100 (45)
Eastern ²	7 290 (37)	105 760 (33)	113 060 (33)
Southeastern	6 300 (63)	47 230 (49)	53 530 (50)
Southern	24 760 (75)	133 180 (58)	157 940 (60)
Western	1 790 (50)	8 790 (36)	10 570 (38)
Latin America	4 030 (39)	28 640 (30)	32 670 (31)
Caribbean	340 (52)	2 790 (36)	3 130 (37)
Central	1 210 (42)	9 550 (39)	10 760 (39)
South	2 480 (37)	16 310 (25)	18 790 (26)
Northern America	570 (17)	7 050 (10)	7 620 (11)
Europe	920 (17)	12 100 (10)	13 020 (11)
Oceania ²	130 (71)	780 (66)	910 (67)
USSR ³	640 (15)	7 770 (12)	8 420 (12)

¹From reference 42.

²Japan, Australia, and New Zealand were excluded from the regional estimates but are included in the total for developed countries. Figures may not add up because of rounding.

³Data collected before recent political changes. USSR: former Union of Soviet Socialist Republics.

hospital-based data at delivery and those of Harrison (48) are the only data available that explicitly present the mortality risk associated with moderate anemia. The results of the 2 studies, however, are contradictory. Nevertheless, whether there was increased risk of mortality associated with moderate anemia, by far the highest risk of excess mortality was in the severely anemic.

The recent study of McDermott et al (54) in Malawi, which followed a cohort of 3740 pregnant women prospectively, is extremely important. Hematocrit concentrations and HIV antibodies were assessed. Of the 6.2% of women with hematocrit concentrations <0.25 , the odds ratio for maternal death combined with death 3–10 mo after delivery was 5.9, and was 9.9 for later death alone. Among HIV-positive women, the odds ratios were 9.8 and 30.8, respectively, for the 2 time periods. The death rate for the 13.2% of women who had a hematocrit concentration between 0.25 and 0.29 was not reported and was, presumably, not raised significantly. In this population, severe anemia was profoundly related to maternal death, but mild-to-moderate anemia was probably unrelated. The role of nutrition was likely to be smaller than other factors, such as HIV infection, in the causation of both anemia and maternal death.

Conclusion

On the basis of the fragmentary evidence available, it seems reasonable to assume that the risk of maternal mortality is greatly increased with severe anemia. The data available only confirm an associative—not a causal—relationship. Nevertheless, the strength of this relationship makes it appropriate to pre-

sume that it is causal, all the while trying to collect more definitive data. From available evidence, it seems appropriate to take immediate action to correct severe anemia during pregnancy, with the understanding that there is a profound need to simultaneously examine key questions about the relationship between anemia and maternal mortality. The most urgent and most difficult of these questions is whether intervention during pregnancy can be shown to affect death rates.

The evidence of a relationship between maternal death and moderate anemia, however, is both scanty and contradictory. Until further data are available, it appears that moderate concentrations of anemia are probably best considered unrelated to excess maternal mortality, and correcting moderate anemia should be given lower priority than correcting severe anemia. There is an urgent need to clarify the relations between concentration of anemia and maternal survival and pregnancy outcome, and to estimate to what extent prophylaxis and treatment modify risk of morbidity and mortality.

Prevalence of anemia

Several extensive reviews of anemia prevalence during pregnancy have been published. A World Health Organization (42) report published in 1992 on anemia prevalence in women contains an exhaustive survey and is an update of the original summary compiled by Royston (43). 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 2.52 million live in industrialized countries (Table 3). Anemia is less prevalent among nonpregnant women, but the absolute number of anemic nonpregnant women is much greater than that of anemic pregnant women. An estimated 400 million nonpregnant women are anemic worldwide, of whom $>90\%$ are in the developing world. The most severely affected area is south Asia, where $\approx 75\%$ of women are anemic during pregnancy as are 58% of nonpregnant women. Anemia prevalence is also high in Southeast Asia, Africa (except southern Africa), and the Caribbean. The review by Sloan et al (57) summarizes all the reports on the rates of anemia from developing countries, published in refereed journals or national or regional reports between 1979 and the time of their review.

Prevalence of severe anemia

Unfortunately, no available reviews summarize the prevalence of severe anemia. With some exceptions, rates of severe anemia are much lower than those of moderate anemia. The exceptions include India, where there are extremely high rates of severe anemia among pregnant women. For instance, in a survey in Gujarat State, the prevalence of severe anemia (hemoglobin <80 g/L) rose from 23% in the first trimester to 30% in the third trimester (for all cases of anemia, the rates were 86% and 93%, respectively). The parallel rates of severe anemia in Maharashtra State were 32% and a remarkable 47% in the first and third trimesters of pregnancy, and 68% and 94% for all cases of anemia, respectively (58). In another study, in Punjab State, 86% of pregnant women were anemic and 58% had hemoglobin concentrations <70 g/L (55). This very high rate may have partly been a function of the bias associated with the decision to use the lowest recorded hemoglobin value for the analysis. In contrast, a recent survey of urban Indian women showed no women with hemoglobin concentrations <80 g/L (59). In an area of Papua New Guinea endemic for malaria, Brabin et al (60) found that

44% of primigravidae and 29% of multigravidae had hemoglobin concentrations <80 g/L in the third-trimester.

Typically, even in the developing world, rates of severe anemia have been much lower than rates of mild and moderate anemia. In rural Zaire, Jackson et al (61) found that although 72% of women attending an antenatal clinic had anemia, only 3.7% had hemoglobin concentrations <70 g/L. Zucker et al (56) observed that 6% of pregnant women in western Kenya had hemoglobin concentrations <60 g/L. Gyssens and Meheus (62), in Niger, found that 46.7% of women at their first antenatal clinic attendance had hemoglobin concentrations <110 g/L, but only 1.9% of the women had concentrations <70 g/L. In Mozambique, Liljestrand et al (63) found that 58% of pregnant women had hemoglobin concentrations <110 g/L, but that only ≈10% of the women had values <90 g/L. Bergsjø et al (64) found that 74.5% of women in Moshi, Tanzania, had hemoglobin concentrations <110 g/L, but only 7% of the women had concentrations <70 g/L. Thus, although anemia is extremely common in poor, pregnant Third World women, the reported rates of severe anemia are, with exceptions such as these reports from rural south Asia or Papua New Guinea, no more than ≈10%.

Etiology, prevention, and treatment of anemia

Etiology of anemia

Anemia has multiple causes among Third World women, which are often concurrent, especially if the anemia is severe. In any one area there may be a mix of a deficiency of dietary iron (from low bioavailability and less often from low intakes; low iron bioavailability is usually caused by dietary phytate or other dietary iron absorption inhibitors, including tannins in tea, and malabsorption syndromes such as sprue); folate and vitamin B-12 deficiency; intestinal bleeding caused by hookworm or other parasites; vaginal bleeding; malaria, particularly in primigravid or young women; hemoglobinopathies such as sickle cell disease and thalassemia; and concurrent infections, especially HIV. For example, Harrison and Ibeziako (65) noted that in their area of Nigeria, red cell hemolysis that was indirectly due to *Plasmodium falciparum* infection was the main etiologic factor of anemia, but that folate deficiency and hemoglobinopathies were also found; iron deficiency was rare. Fleming (66) noted that among 248 consecutive admissions of anemia during pregnancy or the puerperium in Ibadan, Nigeria, only 2 patients were iron deficient and both had heavy hookworm infestation. In all the other patients, the anemia was due to *P. falciparum*, folate deficiency, hemorrhage, hemoglobinopathies, and various miscellaneous other causes. Ratten and Beischer (67) found that 34% of the 202 pregnant women with hemoglobin concentrations <82 g/L in Melbourne had β-thalassemia. Melbourne has many immigrants from Mediterranean countries whose populations have high rates of the genetic trait for thalassemia.

Brabin et al (60) found that malaria prophylaxis was important for controlling anemia in Papua New Guinea. Atukorala et al (68) found in an observational study in pregnant tea plantation workers in Sri Lanka that among women supplemented with iron and folate, only those who also received anthelmintic treatment had increased hemoglobin and serum ferritin concentrations. Olukoya and Abidoye (69) found that hemoglobin concentrations in pregnant women in Lagos, Nigeria, were significantly lower if the women carried intestinal parasites. Other infections are also important causes of anemia, and HIV infection has

become the most notorious problem in the developing world (54). Thus, the causes of anemia vary with dietary practices, infectious disease and parasite burdens, genetic factors, and socioeconomic status.

Interrelationships between iron and other nutrients

Grindulis et al (70) found a strong relation between iron and vitamin D nutrition for Asian toddlers in England. Mejia and Arroyave (71) found that vitamin A fortification in Guatemala was associated with increased transferrin saturation and serum ferritin concentrations. Suharno et al (72) found that although 68% of anemic pregnant Indonesian women responded to iron supplements alone, 97% responded to a combination of iron and vitamin A.

Prevention: effect of iron supplementation during pregnancy in community-based programs

Sloan et al (57), Yip (73), and Cook and Reddy (74) commented on the discrepancy between the results of clinical trials and population-based iron supplementation programs. They noted that clinical trials have repeatedly shown that iron supplementation increases iron stores and hemoglobin concentrations in pregnancy. In contrast, there is no convincing evidence that community-wide or population-based iron supplementation programs have had much, if any, demonstrable effect on either iron stores or, more importantly, other indexes of maternal or perinatal health. This failure of community programs to reduce the prevalence of anemia may be due to many factors, including low compliance, administrative inefficiency, or the use of iron to prevent or treat anemia that is only partially due to iron deficiency.

The Indian Council of Medical Research (75) evaluated the Indian national program of anemia prophylaxis with iron and folate supplements. This evaluation, whatever its limitations, is important because India has more severely anemic women than any other country. The report presents the distribution of hemoglobin concentrations by the number of iron tablets received by pregnant women and the results were interpreted as showing no significant effect of iron therapy on severe anemia (hemoglobin concentration <75 g/L). However, on reanalysis, the data show that there was a highly significant association between ingestion of iron supplements and the prevalence of severe anemia. The frequency of severe anemia was 22.7% in those women who received any tablets compared with 26.3% in those women who did not. The effect, however, was observed at an improbably low intake of as few as 15 tablets for the entire pregnancy. Only one-fifth of the women received tablets, which is a clear indication of program insufficiency. Although highly significant statistically, the small effect on the rates of anemia and the low rate of receipt of iron tablets are discouraging.

Sloan et al (57) did a meta-analysis on 24 randomized trials published between 1966 and 1989 that met their criteria for adequate study design. Nine of the 24 studies on the effects of iron supplementation during pregnancy were from developing countries. The findings are provocative. On average, the increase in hemoglobin concentration was only 2 g/L greater in subjects who received a traditional dose of ≤60 mg Fe/d than in control subjects who received a placebo. An appreciably greater effect was observed, however, with increasing doses of iron. The mean hemoglobin response was 16 g/L greater than that of the control subjects with a dose of ≥120 mg Fe/d (**Table 4**). These findings have 4 implications for anemia prevention programs: 1) The results appear to undermine the likelihood that less-than-daily

TABLE 4
Meta-analysis of trials of iron supplementation during pregnancy¹

Daily dose of elemental iron or mean initial Hb concentration and effect	Mean change compared with control subjects (g/L)
Daily dose (mg Fe/d) ²	
≤60	2 (-17 to 11)
61-90	10 (6-15)
91-120	12 (6-22)
>120	16 (9-26)
Mean initial Hb (g/L) ³	
≤100	10 (2-17)
<110	13 (-3 to 25)
<120	5 (-12 to 12)
≥120	— (—)

¹Range in parentheses. Hb, hemoglobin. From reference 57.

²All countries.

³Developing countries only.

supplementation will be optimal. Possibly those who were prescribed ≥120 mg Fe/d took less than that but still consumed enough to make a measurable difference in hemoglobin concentrations, whereas low compliance among those given ≤60 mg Fe/d could have led to negligible change. 2) Tolerance to oral iron decreases with increasing dose and, with the observed need for high doses, there is clearly a narrow therapeutic window between an effective and a tolerable dose. 3) There was a strong inverse association between the initial group mean hemoglobin concentration and the average response to therapy (Table 4). In the few developing country studies in which the initial mean hemoglobin concentration was relatively high (110-119 g/L), iron treatment led to an average increment of hemoglobin concentration of only 5 g/L compared with that of control subjects. This increase was one-half or less the effect of iron in studies in which the initial mean hemoglobin concentrations were lower. 4) When mean hemoglobin concentrations were lowest (<100 g/L), the effect of the intervention was less than that in the trials in which the initial mean hemoglobin concentrations were between 100 and 109 g/L (mean hemoglobin increase was 10 g/L compared with 13 g/L more than control values, respectively). This may have been a chance finding, but, without alternative data, it needs to be addressed with utmost seriousness. From what is known about the physiology of iron absorption, the opposite trend would be expected—with lower hemoglobin concentrations and presumably more severe iron deficiency, iron absorption should be increased. One explanation for this anomaly may be that in populations with lower hemoglobin concentrations, anemia was less often due to iron deficiency alone and, therefore, less responsive to iron or iron-folate therapy alone.

Without knowledge of both the causes of anemia and the magnitude of the response to iron supplementation of women with low initial hemoglobin concentrations, planning and testing intervention programs to ameliorate severe anemia will be difficult. Such estimates must be made in studies that include untreated or differently treated comparable groups to control for the effects of both physiologic and measurement regressions to the mean and for the physiologic changes of hemoglobin concentration over the course of pregnancy. Regression to the mean has the effect that even with no intervention, those with the lowest measured values will have the greatest real and apparent increases in hemoglobin concentration upon remeasurement. The authors of the trials

reviewed by Sloan et al (57) and those of subsequent trials should be requested to reanalyze their results, stratifying outcome by initial hemoglobin concentration or, even better, sharing their original data, thereby saving valuable time, effort, and resources. A rational policy to ameliorate the effects of severe anemia in pregnancy is probably impossible without this information and it could save years of work to learn from extant data rather than having to repeat such studies.

Treatment: frequency of iron prophylaxis

Several reports state that weekly iron supplementation is as—or nearly as—effective in raising or maintaining hemoglobin concentrations during pregnancy as is daily supplementation. However, in their trial that showed 120 mg Fe/wk was as successful as 60 or 120 mg Fe/d in preventing third-trimester anemia, Liu et al (76) did not include women with initial hemoglobin concentrations <80 g/L for legitimate ethical reasons. The same research team showed that weekly doses of 60 mg/Fe for non-pregnant women without anemia were effective in preventing anemia (77). Ridwan et al (78) found that in anemic women (hemoglobin concentrations <110 g/L), hemoglobin increased to approximately the same concentrations with weekly or daily iron supplementation. The increase in serum ferritin, however, was far greater with daily than with weekly supplementation. The authors did not report the results for severe anemia separately. Thus, the issue of weekly prophylaxis is not yet settled. The use of less-than-daily iron therapy for any level of anemia during pregnancy seems unlikely to become standard practice because of the results of the meta-analysis by Sloan et al (57). They found scant evidence of any effect on hemoglobin concentration even with traditional doses of 60 mg Fe/d.

The possibility of adverse pregnancy outcome with high or even normal hemoglobin concentrations or with iron supplementation

The scope of this paper precludes a comprehensive assessment of possible dangers of iron treatment other than during pregnancy. The association between high hemoglobin concentration and adverse maternal and infant outcomes, the possibility that oral iron ingestion can cause high hemoglobin concentration, and the direct evidence that iron-induced increases in hemoglobin concentration are associated with toxicity will be discussed and allusions will be made to the controversies about other possible toxicities of iron. Scrimshaw (79) has comprehensively reviewed the health effects of iron deficiency.

Iron, hemoglobin concentration, and fetal growth

Mahomed and Hytten (80) conducted a meta-analysis on the effect of routine iron, folate, or iron and folate administration during pregnancy. They concluded that supplemental iron prevents, or greatly reduces, the normal decrease in hemoglobin concentration during pregnancy, but that no clinical benefit is seen either in the pregnancy itself or in the infant, only a buildup of a woman's iron stores. On the other hand, there are hints that the reversal of the normal decrease of hemoglobin concentration and iron-induced macrocytosis may increase blood viscosity to a degree that could impair utero-placental blood flow. Compared with the concentration defined as signifying anemia, higher hemoglobin concentrations have consistently been associated with a worse prognosis for the mother and child. Harrison and Rossiter (49), in Zaria, observed that hematocrit concentrations of ≥0.45 were associated

with a marked increase in maternal mortality (Table 2), but the number of subjects was very small. Murphy et al (81) found a marked increase in the incidence of maternal hypertension, as well as increased perinatal mortality, low birth weight, and preterm birth associated with higher hemoglobin concentrations early in pregnancy. In the US Collaborative Perinatal Study, Garn et al (82, 83) found steeply increased fetal death rates in white women with a hematocrit concentration above ≈ 0.32 and black women with a hematocrit above ≈ 0.30 . The associations were not as strong for increased premature delivery and low birth weight; they occurred in white women with hematocrit values > 0.35 and in black women with hematocrit values above ≈ 0.32 . Sagen et al (84), in Norway, observed markedly lower birth weights with maternal third-trimester hemoglobin concentrations > 120 g/L, especially > 130 g/L. Steer et al (85) found, in a large area-wide study in England, a J-shaped relation between midtrimester hemoglobin concentrations and both low birth weight and preterm delivery. The optimal hemoglobin concentrations were between 96 and 105 g/L, with moderately worse outcomes at lower and slightly higher hemoglobin concentrations, and much worse outcomes with hemoglobin concentrations > 136 g/L.

There has not been much concern in the public health nutrition community about potential toxicity from iron treatment or prophylaxis during pregnancy, largely because as iron stores rise, the absorption of oral iron is usually depressed. For example, in their meta-analysis, Sloan et al (57) found that there was less response to oral iron supplementation when initial mean hemoglobin concentrations were highest. In developed countries, iron treatment induced an 8-g/L increase in hemoglobin when initial concentrations were ≥ 120 g/L, and a 10-g/L increase when initial concentrations were between 110 and 119 g/L. In developing countries, the mean increases were 5 and 13 g/L for initial hemoglobin concentrations of 110–119 and 100–109 g/L, respectively. Oral iron treatment of women with normal hemoglobin concentrations, however, has been shown to raise hemoglobin to concentrations associated with adverse pregnancy outcomes. Pritchard and Hunt (86) randomly gave either a placebo, 1000 mg intramuscular iron, or 104 mg oral iron/d to term to pregnant women near the end of their the second-trimester, including those with normal hemoglobin concentrations. They found that although only 8.2% of the subjects who received a placebo had hemoglobin concentrations ≥ 130 g/L at term, 39% of those who received intramuscular iron were at or above this concentration. Oral iron had an effect equivalent to parenteral iron: 40.5% had hemoglobin concentrations ≥ 130 g/L (Table 5). This study showed that women without overt anemia who were given either parenteral iron or oral iron supple-

ments had hemoglobin concentrations that were raised to values associated with maternal and fetal toxicity. Hemminki and Rimpelä (87) reported essentially identical results, with routine iron administration having as great an effect on third-trimester hemoglobin concentrations in women with an initial hematocrit > 0.41 , as in women whose hematocrit was < 0.36 .

The possibility of iron toxicity in pregnant women in developing countries has received almost no investigative attention. Many African or south Asian pregnant women do have high hemoglobin concentrations. For example, Jenkinson (88) found that 59% of the wives of copper workers in Zambia had initial hemoglobin concentrations ≥ 120 g/L and 17% had concentrations of ≥ 130 g/L. Most studies and the reviews collating them, including the one conducted by WHO (42), do not typically report on the proportion of women with high hemoglobin concentrations. Sloan and Jordan (89) reviewed 43 prevalence studies of hemoglobin concentration during pregnancy of women living in developing countries. Of these, studies 3 (7%) reported mean initial concentrations of hemoglobin > 130 g/L and another 17 (30%) reported mean concentrations between 120 and 130 g/L. Therefore, many women are potential candidates for adverse consequences from high hemoglobin concentrations if such effects can be induced by iron treatment. Knowing the differential response to routine iron supplementation in women with very low initial hemoglobin concentration is important. Knowing whether those women with normal or high hemoglobin concentrations could be tipped into possible high-risk status by receiving high doses of iron is also important. More important, however, is to know whether such risks are real.

The practical significance of the observations on adverse outcomes associated with high maternal hemoglobin concentrations for both the mother and the infant is unclear for 2 reasons. The adverse outcomes associated with high hemoglobin concentrations may be due to relative macrocytosis, as suggested by Mahomed and Hytten (80), or due directly to placental perfusion problems because of high red blood cell concentration. They could also have little to do with iron or red cell mass because high hemoglobin concentrations, like low concentrations, reflect not only red cell mass, but also plasma volume expansion. A high hematocrit concentration may reflect inadequate plasma volume expansion and consequent poor vascular perfusion unrelated to red cell mass.

The studies of Hemminki et al (87, 90–93) are among the few to contribute to our understanding of whether iron supplementation can cause harm by increasing hemoglobin concentrations or by causing other toxicities (discussed below). In Hemminki et al's studies, 2960 pregnant Finnish women were recruited and randomly assigned to receive either routine or selective iron

TABLE 5

Initial and final hemoglobin (Hb) concentrations (%) from second trimester to term by type of iron supplement¹

Hb concentration (g/L)	104 mg Oral Fe/d (n = 74)		1000 mg Intramuscular Fe (n = 49)		Placebo (n = 49)	
	Initial	Final	Initial	Final	Initial	Final
	%					
<100	13.5	0	12.2	0	12.2	16.3
100–109.9	39.2	9.5	53.1	4.1	44.9	30.6
110–119.9	29.7	25.7	20.4	26.5	22.4	24.5
120–129.9	13.5	24.3	12.1	30.6	16.3	20.4
≥ 130	4.1	40.5	4.1	38.8	4.1	8.2

¹From reference 86.

supplementation during pregnancy. Third-trimester hematocrit values were much higher in the routine group than in the selective supplementation group. The authors found that iron supplementation increased hematocrit values but did not influence birth weight. The relation of high hematocrit values to poor fetal growth is thus probably caused by factors other than iron. The authors reported that their results were contrary to controlled trials in pregnant women and rats that consistently reported lower birth weight in groups receiving iron, yet also reported that prior studies had included fewer subjects and that in human studies, no such differences were significant. Thus, this large study suggests a dissociation between the effect of iron supplementation on hematocrit concentrations and on birth weight. Although more women in the routinely supplemented group reported adverse side-effects from the medication, the groups were similar in regard to most other outcomes, including the incidence of infection. There were several worse outcomes in the selective supplementation group, such as an increased likelihood of a cesarean delivery or blood transfusion, which the authors thought were due to the reactions of midwives and physicians to the low hematocrit values rather than to actual need for these procedures. At 7-y follow-up, the one difference in health outcome among the children, which was an important differentiation, was that the children of mothers who received routine iron supplementation during pregnancy had significantly higher rates of hospital admission for convulsions (93).

Iron and immune function

There are immunologic deficits associated with both iron deficiency and excess iron stores. Strauss (94) reviewed the literature on iron deficiency and immune function and concluded that, although the molecular defect had not been defined, an abnormality of immune function associated with anemia could be detected by several assays measuring cell-mediated immunity and that normal function was usually restored after iron repletion. Dallman (95) reviewed the relation between iron and immune function, including the possible toxic effect of supplemental iron. He concluded that the evidence that iron deficiency caused defects in cell-mediated immunity and bacterial killing was impressive, although there was little evidence of increased morbidity from infection. He also referred to several studies of toxicity from excess iron and concluded that avoiding both too little and too much iron is best.

Prema et al (96) found significantly lower proportions of T and B lymphocytes associated with hemoglobin concentrations <80 g/L but not with moderate anemia in third-trimester Indian women without overt infection. Concentrations of immunoglobulin (Ig) G were significantly higher in severely and moderately anemic women than they were in women without anemia. IgA concentrations were also higher in the severely anemic women than they were in the nonanemic women and, although the authors stated that Ig A concentrations were also significantly higher in moderate anemia, the tabulated data raise doubts about this. Kandoi et al (97) found that stimulation indexes of lymphocytes at 0 and 24 h were abnormally low in both maternal and cord blood of women whose hemoglobin was <80 g/L. Only the 24-h cord blood stimulation index, however, was significantly low when mothers were moderately anemic. Thus, there is some evidence that severe maternal anemia is associated with immunologic abnormality in pregnancy.

Although this is a review focused on pregnancy, the results of the study by Oppenheimer et al (98) raise some serious questions.

They performed a randomized controlled trial of supplementing 478 newborn infants in Papua New Guinea with 150 mg intramuscular Fe and following them to age 1 y. Their initial hypothesis was that iron deficiency would increase susceptibility to infection, but their results were the opposite of their expectations. Although treatment with iron did lead to increased iron stores and higher hemoglobin concentrations, it was also associated with a longer postinjection stay in hospital, increased incidence of malaria and acute otitis media, and more frequent and longer hospital stays for all causes, especially respiratory infection. Risk of admission was also higher with higher birth hemoglobin concentrations, and there was an interaction such that the worst effects of prophylactic iron were in infants with the highest birth hemoglobin concentrations. Because parenteral iron therapy is given routinely to many pregnant women, it is a matter of some urgency to assess whether such toxicity is confined to infants.

Adverse metabolic effects of iron also include increased free radical production (99, 100), a possible explanation for increased rates of infection among the infants treated with iron in Papua New Guinea. Hemminki et al (101), however, found no increase in the rates of infection in mothers after iron supplementation during pregnancy.

Further possible adverse effects of iron supplementation

Zinc absorption is suppressed by concurrent oral iron intake, although this effect is probably unimportant if the source of iron is from food rather than from supplements (102). Solomons and Ruz (103), in a review of the interrelation between iron and zinc intakes, advised caution about fortification and supplementation with iron because individuals who received excessive or even sufficient amounts of iron appeared to be more susceptible to some infections than were iron-deficient individuals.

Reactivation of malaria and other latent microbial diseases such as brucellosis and tuberculosis was observed in Somalian refugees given iron supplements (104). Dissemination of amebiasis caused by *Entamoeba histolytica* was ascribed to iron overload (105). A study from Indonesia showed a trend toward slower growth rates in children receiving a daily iron supplement who were thus made iron replete than in children receiving the same supplement who remained iron-depleted (106).

Solomons and Ruz (103) concluded that these diverse considerations should raise a note of caution about how aggressively iron is added to the diet or how iron affects the internal environment of the human body. The lesson may be that when anemia is caused by iron deficiency, iron therapy is indicated, but that otherwise iron may exacerbate underlying illness or be toxic.

Such cautions about the widespread need for supplemental iron represent a minority viewpoint in the public health nutrition community. A report from a recent high-level working group on iron deficiency (41) stated the following: "Under the circumstances observed in children with kwashiorkor or Somalian refugees, parenteral or even high dose oral iron can supply iron for pathogen replication at a time when the individual is highly susceptible to infection and resulting overwhelming infection. However, in field studies of iron deficient populations, iron supplementation at levels of 60 mg for an adult or older child has always resulted in decreased morbidity from infection and the effects of iron fortification are far too low to have any adverse effect on resistance to infection." This report goes on to say that except for these special situations, down-regulation of iron is very effective even when the diet is rich in heme iron and its composition favors absorption.

This report considered the only potential toxicity from iron supplementation or treatment to be among homozygotes for the gene blocking iron absorption down-regulation, which increases susceptibility to hemochromatosis. Thus, there is radical disagreement among experts about the potential toxicity of widespread iron supplementation. These issues require further investigation.

Iron supplementation, therefore, needs to be considered in context. Has attention been paid to other causes of anemia, including infection? It is a matter of great importance to explore the issue of universal iron supplementation because material and human resources in developing countries are limited and particularly because the health of women has in the past often been a low priority.

Responding to severe anemia during pregnancy

The usual arguments for universal iron supplementation rather than selective intervention targeted to the severely anemic are that maternal anemia at all levels of severity is dangerous to the mother, fetus, and infant; treating anemia can reverse this danger; clinical screening tests for anemia have low sensitivity and specificity; assessing the causes and severity of anemia is too expensive and complex in developing countries to be routine for screening, diagnosis, or follow-up; effective action can be taken without knowing the etiology of anemia; rates of iron deficiency anemia are too high to justify selective intervention targeted to anemic women; iron (with or without folate) is too inexpensive to warrant its selective use; and universal iron supplementation at usual doses (60 mg elemental Fe/d) is effective for both mild and severely anemic women. After reviewing the evidence available, these assumptions turn out to be, at best, weakly supported.

Level of anemia

There is a consistent relation between severe anemia and increased maternal mortality. The evidence to implicate moderate anemia with excess maternal (or infant) mortality (or morbidity), however, is scanty and inconsistent. This issue urgently requires further study.

Benefit from amelioration of all levels of anemia

Although there is evidence that severe anemia is associated with increased risk of maternal mortality and poor fetal growth, there is almost no evidence that treatment of anemia at any level lowers the risk of maternal or infant mortality or morbidity. The single exception is for blood transfusion performed for incipient cardiac failure in women whose hematocrit is <0.13 (55). Further studies to determine the extent of benefit of treatment of other levels of anemia are urgently needed.

Screening for severe anemia

Although screening for moderate anemia by clinical signs was judged to be poor, the sensitivity of clinical screening for severe anemia was judged to be very good to excellent (E Dusch, unpublished working paper, 1997). Because of the high sensitivity of clinical detection of severe anemia, it is technically feasible to identify severely anemic women in the field without complex or expensive equipment. Furthermore, the relatively few severely anemic women may make practical the cost of diagnosing, treating, and following up these women at very high risk.

Impracticality of specifying the cause and level of anemia

Measuring hemoglobin concentrations and specifying the etiology and treatment of anemia in poor rural women presents

real and daunting administrative and logistic problems, especially when the women live far from medical facilities. The development of techniques to decide who needs the intervention and whether intervention has been successful or needs to be modified is a high priority.

High rates of severe anemia

Except in south Asia and Papua New Guinea, the reported rates of severe anemia do not appear to exceed 10% of pregnant women. Focusing resources on those who are most in need of treatment increases the likelihood of successful diagnosis and management, even within stringent administrative and fiscal constraints.

Safety and cost of iron treatment

Iron (and folate) prophylaxis is inexpensive; nevertheless, there is little evidence that it has been worthwhile. At the population level, few if any programs targeted to pregnant women have been effective in terms of process (amount of prescribed supplementation taken), physiology (increased iron stores), or health outcomes (improved health and well-being). Furthermore, it has not been convincingly shown that iron supplementation is free of toxicity in those who are either very iron deficient or those who are iron replete or only mildly deficient. These issues require further intensive study.

Effectiveness and safety of universal iron supplementation at usual doses

A policy of universal iron supplementation does not take into account that the causes of anemia, particularly severe anemia, are diverse and multiple and, therefore, only partially addressed with iron treatment. Moreover, the use of iron in women who are anemic for reasons other than iron deficiency may be harmful. There is an open question about the safety of iron-induced high maternal third-trimester hemoglobin concentrations for both the mother and the child. Finally, where anemia in pregnancy is caused by iron deficiency, controlled trials have shown that the doses of iron usually prescribed in programs of universal supplementation are only minimally effective in raising hemoglobin concentrations in anemic women. Few, if any, large-scale, population-based iron supplementation programs have been reported to be effective in correcting moderate—let alone severe—anemia during pregnancy.

Critically Needed Research

Research is critically needed to:

- 1) Clarify the relationship between the level and etiology of anemia and adverse outcomes for both mother and child (ie, are there adverse risks associated with mild or moderate iron deficiency anemia?).
- 2) Study the responsiveness of women with severe iron deficiency anemia to various doses of oral iron as well as the need for concurrent antibiotic, antimalarial, anthelmintic, and folate and other nutritional (eg, folate, vitamins A, C, D, etc) therapy. Study both the beneficial and adverse effects of iron supplements on rates and severity of infection in anemic women.
- 3) Estimate the effects of iron prophylaxis and treatment on maternal and rates morbidity and mortality, both adverse and beneficial.

- 4) Determine how to detect, diagnose, and treat severely anemic pregnant women.
- 5) Reanalyze past trials of iron supplementation to achieve some of these goals (eg, determine whether individuals who responded to supplementation had improved pregnancy outcomes and assess the hematologic response given initial concentration of hemoglobin).

Conclusion

The evidence is strong that severe anemia (hemoglobin concentrations <70 or 80 g/L) during pregnancy is associated with increased maternal mortality. Although further intensive research is needed, presuming that this association is causal seems reasonable at this time. Routine oral iron supplementation has not been shown to reverse severe anemia. Although there is some evidence that moderate concentrations of maternal iron deficiency anemia (hemoglobin concentrations between 70 or 80–110 g/L) are associated with adverse outcomes in infants (107), there is no evidence that routine iron supplementation during pregnancy has been of any benefit other than to increase iron stores in the mother and infant.

Supplemental iron during pregnancy may cause harm because high hemoglobin concentrations are associated with increased maternal morbidity and mortality as well as higher rates of low birth weight and premature delivery. On the other hand, the scanty data available suggest that an increased concentration of hemoglobin directly caused by iron supplementation is not associated with increased risk of adverse outcomes; this issue warrants comprehensive further investigation.

From the data available, it seems rational to make treatment programs for women with severe anemia a high priority and to evaluate the efficacy of iron prophylaxis for younger and non-pregnant women with marginal iron status. The aim would be to lower the likelihood of entering pregnancy with severe anemia. Such programs need careful evaluation to assess both their risks and their benefits.

ANEMIA AND OBSTETRIC HEMORRHAGE

Although it seems logical to assume that the lower the hemoglobin concentration, the greater the risk that obstetric hemorrhage will be fatal, I could find no data to support or refute this association. The incidence of hemorrhage appears to be minimally related to nutritional factors other than obesity. An exception was the study of MacGregor (108) in Kenya, who reported that 17 of 30 women (56.7%) with hemoglobin concentrations <74 g/L had antepartum hemorrhage compared with 51 of 164 women (31.1%) with higher hemoglobin concentrations. Stones et al (109) found obesity, placental abruption, placenta previa, multiple pregnancy, retained placenta, induced labor, episiotomy, and a birth weight of ≥ 4 kg to be significant risk factors for hemorrhage. Gilbert et al (110) found primiparity, induction of labor by amniotomy, forceps delivery, long first and second stages of labor, and the use of oxytocin, compared with combined oxytocin and ergometrine maleate as a prophylactic oxytocic, to be associated with increased risk of hemorrhage.

Postpartum hemorrhage can be treated with prostaglandins (111) and the secretion of prostaglandin is induced by suckling. The effect of suckling on prostaglandin secretion is appreciable. Two reports suggest markedly increased concentrations of

prostaglandins from immediate postpartum breast-feeding or even manual nipple stimulation (112, 113). Research is needed to find out whether the incidence and consequences of hemorrhage are decreased by the treatment of anemia.

MATERNAL NUTRITION AND OBSTRUCTED LABOR

The data relating a woman's lifetime nutritional status to obstructed labor are fragmentary and urgently need to be supplemented. The central issues are whether nutritional strategies exist that could lead to increased maternal stature and how much maternal and fetal risk is increased from nutritionally induced accelerated growth of the fetus, especially among short primiparae.

Obstructed labor has virtually been eliminated as a cause of maternal death in industrialized countries. With the development of safe and universally available operative delivery, cephalopelvic disproportion poses minimal risks to the mother and infant. This is not, however, true for most of the world's women, for whom immediate, universal access to operative obstetrics of reasonable quality does not exist. Obstructed labor, leading to a ruptured uterus or severe uterine or perineal trauma, with consequent hemorrhage, infection, and soft tissue damage such as a vesicovaginal fistula, remains one of the leading causes of maternal and infant morbidity and death in developing countries.

The relative infrequency of maternal (compared with perinatal) death and, even more, its occurrence at home and away from medical attention, makes it difficult to estimate how often it is the consequence of obstructed labor. There are few studies on obstructed labor in developing countries, but there are several studies of the frequency of operative intervention in subsets of women who reach the hospital for care. Although there are many causes for operative delivery besides obstructed labor, estimates of the effect of obstructed labor using operative delivery as a surrogate measure will be conservative; the tendency will be to underestimate this relation because the other reasons for operative delivery, such as preeclampsia and eclampsia, are most often associated with small offspring and preterm delivery.

Hospital data invariably include a disproportionate number of high-risk deliveries and, therefore, maternal and perinatal deaths. Thus, population-based frequencies or relative risks of any specific condition, including obstructed labor, cannot be accurately estimated from hospital data alone. Very young pregnant women are especially vulnerable because they are more likely to be brought to a hospital late in their clinical course when their chances of being moribund are increased. Although intimately linked, the maternal and fetal factors that contribute to obstructed labor are described separately below.

Maternal age and parity

Obstructed labor is strongly related to a woman's age and parity. Very young women and women giving birth for the first time are at much higher risk of obstructed labor, although it is far more likely that obstructed labor will lead to a ruptured uterus among multiparae. The young and the primigravid are more likely to experience both obstructed labor and subsequent morbidity, such as a vesicovaginal fistula. Kelly and Kwast (114) noted that 63% of women with a fistula experienced it after their first labor. Megafu and Ozumba (115) reported that among 145 consecutive deliveries of babies weighing ≥ 4.5 kg in Enugu, Nigeria, 90% of the multiparous women achieved

spontaneous vaginal delivery compared with only 42% of the primigravidae.

Maternal height

Many studies have related maternal height to obstructed or prolonged labor. For example, among primiparae shorter than 1.54 m in Aberdeen, the cesarean delivery rate for cephalopelvic disproportion was 4.4%, and 82% had difficult labor due to mechanical causes although no cesarean deliveries were carried out for cephalopelvic disproportion among women ≥ 1.64 m tall, and their rate of difficult labor was $<13\%$ (116). The data from developing countries are similar. In Lagos, Nigeria, the rate of cesarean delivery was 7.7% in women with a maximum height of 1.54 m and 1.6% among women 1.64 m or taller (117). Mallika (118) reported on data from Madurai, India, where the cesarean delivery rate was 40.7% for women ≤ 1.4 m tall and 0.6% for those ≥ 1.5 m in height. Everett (119), in a hospital series from Tanzania, reported a cesarean delivery rate of 10% in primigravidae <1.39 m in height but only 0.3% in those who were 1.49 m or taller. In Zaire, life-threatening fetopelvic dystocia occurred in 2% of women <1.5 m tall and in 0.1% of women above 1.6 m tall (120). Abnormal and prolonged labor occurred in 3.5% of the short women and in 0.6% of the tall women. Camilleri (121) in Malta, Aitken and Walls (122) in Sierra Leone, Adadevoh et al (123) in Ghana, Sokal et al (124) in Burkina Faso, and Tsu (125) in Zimbabwe all found similar, strong, inverse associations between operative delivery (presumably due primarily to obstructed labor) and maternal height.

Harrison et al (126) related diagnosed cephalopelvic disproportion to maternal height in women registered for prenatal care (Table 6). Because these were booked patients, who were followed prospectively, the denominators are meaningful and relative risks can be legitimately calculated. Of primigravid women shorter than 1.5 m, 20% were diagnosed with cephalopelvic disproportion, but of those who were 1.6 m or taller, only 2% were so diagnosed. This is a 10-fold difference in the rate of obstructed labor for a 10-cm difference in height. In a study of adolescent primigravidae, 40% of the 20 girls <1.54 m tall at entry into the study had operative delivery, compared with 15% of the 20 girls between 1.54 and 1.57 m tall and none of the 19 girls who were ≥ 1.58 m tall (127).

A meta-analysis conducted by the WHO reported on 16 studies relating maternal height to assisted delivery (128). Although the actual rates were not presented, a combined odds ratio of 1.6 was calculated. This can be interpreted as a 60% greater likelihood of assisted delivery among women in the lowest height quartile compared with those in the highest quartile. [This study is summarized by Kelly et al (129).]

Although shorter women are at greater risk of obstructed labor than taller women, women of the same height may have different risks across populations. For example, Ecuadoran women may be at a lower risk of obstructed labor than their short stature would predict (N Sloan, personal communication, 1997).

Because of the strong relation between height and social status, it is not clear what the effect of statistically adjusting these results for social status would be. Women with higher social status will not only typically be taller, but they will have greater access to interventive obstetrics, better prenatal care and, therefore, less need for intervention. Thus, this possible confounding of height by social status could either exaggerate or partially suppress the true relation between maternal height and obstructed labor; the effect, however, is unlikely to be large.

TABLE 6

Frequency of cephalopelvic disproportion of booked primigravidae by height¹

Maternal height (m)	Cephalopelvic disproportion
	n (%)
<1.5	166 (19.9)
1.5–1.54	315 (12.4)
1.55–1.59	323 (7.1)
≥ 1.60	260 (1.9)

¹Booked women were those registered for prenatal care. Zaria birth survey (126).

Size of pelvic outlet

Although stature is a reasonable surrogate for the size of the birth canal through the bony pelvis, the 2 are not equivalent. Adequate maternal height may mask pelvic deformity resulting from childhood rickets. Also, Moerman (130) showed that after menarche, the birth canal lags in maturity compared with height. Thus, the pelvis is smaller and less mature among girls around menarche than would be commensurate with their height, and cephalopelvic disproportion in immediately post-menarcheal teenaged girls is more likely than might be predicted from height alone. Moerman's work was carried out in a healthy Western population; because of its dependence on serial radiographs of the pelvis in girls and young women, this study is unlikely ever to be repeated, at least by using radiography. (It is possible that it could be done using sonographic techniques.) Whether strategies to increase the stature of young women have comparable effects on growth of the birth canal or the timing of the maturation of the pelvic outlet is difficult to ascertain.

Attained height and catch-up growth in nutritionally deprived women without nutritional intervention

There are 2 thoughtful reviews of growth and stunting in developing countries (131, 132). In summary, the effect of adverse environmental conditions and of their amelioration may be greatest in the first few years of life. In addition, stunting after early-life deprivation persists in some populations but almost complete catch-up growth has been reported in other populations. For example, Kulin et al (133) observed that poor, rural Kenyan children were ≈ 2 SD units shorter than relatively affluent and well-nourished urban children before puberty. Nevertheless, by age 16 y, they had experienced complete catch-up growth. This was associated with a pubertal delay of 2–3 y, which may have been causally related to the catch-up growth.

Nearly identical results were observed by Dreizen et al (134), who followed 30 markedly growth-retarded, undernourished, American infant girls and a well nourished comparison group. At the age of 12.5 y, there was a 9-cm difference in height between the 2 groups, but menarche was 24 mo later in the undernourished girls. The attained adult heights of the undernourished, growth-retarded girls were nearly identical to those of the control children, almost certainly linked to their period of growth, which was far longer than that of the control children. There are other examples of remarkable catch-up growth in deprived children in late childhood and early adulthood, such as the experience of American slaves. Steckel (135), using historical

records (albeit of uncertain accuracy), found that mean heights of female slaves through age 14 y were at the second percentile of modern standards. By age 17 y, they were at the 21.5 percentile, by age 22 y, at the 29.5 percentile, and after age 25 y, at the 34.5 percentile. These findings, however, could also partly reflect selective mortality in shorter women.

Satyanarayana et al (136) reported on a longitudinal growth study of 197 stunted girls over age 17 y who had attained menarche and had almost ceased linear growth. Those who were most growth-retarded at age 5 y remained most growth-retarded at age 18 y. There was, however, an inverse relation between the increment of growth between the ages of 5 and 18 y and height at age 5 y such that the extreme intergroup discrepancy of 14.2 cm decreased to 7.3 cm, an example of catch-up growth.

Riley (137) reported on an important longitudinal study of Bangladeshi women who were first observed in 1976–1977, when they were perimenarcheal, and then again a decade later. A strong inverse relation was found between height and age at menarche, with the tallest girls having the earliest menarche. On restudy in early adulthood, however, adult height was essentially unrelated to age at menarche. In other words, girls with late menarche grew for a longer period than girls with early menarche and achieved almost complete catch-up growth. Thus, catch-up growth in the undernourished, where it occurs, seems to be associated with delayed puberty and a much longer period of growth than in the well nourished.

Late menarche had another profound significance in Riley's population (137). For many young women, menarche was the signal for marriageability and thus exposure to pregnancy. Riley noted that smaller girls with later puberty also had later marriages; the probability of early marriage was strongly related to greater height (and weight) in late childhood.

Nutritional supplementation, acceleration of childhood stature, and attained adult height

Nutritional supplementation has been shown to accelerate the growth of stunted infants and children, but little is known about its effects on ultimate adult height. Attained adult height is a function not only of the velocity but also of the duration and timing of growth.

Although moderate amounts of data are available—albeit some of it conflicting—on nutritional rehabilitation and acceleration of linear growth, there is very little relating childhood nutritional rehabilitation to adult height. One of the best-documented studies describes the effect of prenatal and early childhood nutrition supplementation in 4 villages in Guatemala (138). Differences in adult height were related to the ages of supplement intake, whether children received a high-protein supplement (atole) or a low-protein and low-energy drink (fresco), and the incremental energy consumed from these supplements. Ultimate attained linear growth in the 2 villages receiving atole was 0.9 cm greater/y of supplementation in those who took supplements from 3 to 12 mo of age, 1.0 cm greater/y if supplementation was taken from 12 to 24 mo of age, and 0.4 cm greater/y when supplementation was taken from 24 to 36 mo of age. No association was observed between later height and supplementation from 3 through 7 y of age. Calculated on the basis of supplemental energy intakes, during the first year of life each incremental 23.9 kJ/d was associated with 9 mm of additional growth, 5 mm during the second year of life, and 3.7 mm during the third year of life. A statistically nonsignificant difference of ≈ 1 mm

in growth was found for an additional 23.9 kJ/d taken between 36 and 72 mo of age. No effect was observed on growth for supplementation taken between 72 and 84 mo of age.

Martorell et al (139) studied growth in the same Guatemalan population between ages 5 and 18–26 y. They concluded that the gain in height from 5 y to adulthood was independent of height at age 5 y; all the differences in adult height associated with the preschool nutrition supplementation were in place by age 5 y and later increments in height were independent of earlier supplementation. Although height increments from 5 y to adulthood in these poor rural Guatemalan villagers were similar to those measured in a population study in Berkeley, CA (140), supplementation was stopped in the Guatemalan study after age 7 y; thus, determining whether nutritional supplementation after that age might have led to increased adult height was not possible.

Dagnelie et al (141) observed that relatively privileged Dutch children consuming a macrobiotic diet were, on average, severely stunted. The investigators therefore counseled the parents to increase the children's fat intakes to 25–30% of total energy intake and that they be given 2–3 portions of fish/wk and plant sources of calcium and riboflavin. After counseling, 3–5-y-old children had significantly accelerated linear growth. There was also impressive acceleration of growth in 6–9-y-old girls, but not boys, with a change of 0.11 SD units per year. No data were reported on attained adult height.

Several studies have been conducted on deprived children from developing countries adopted into affluent families. Graham and Adrianzen (142) observed that stunted Peruvian children, after adoption early in life, caught up in height with the Boston reference standards. Proos et al (143–146) studied Indian girls aged between 1 and 7 y when they were adopted into Swedish families. At adoption, the children were, on average, >2 SD units shorter than National Center for Health Statistics (NCHS) means, but after adoption, their growth was markedly accelerated; just before puberty they were only 0.3 SD units shorter than NCHS means. Their adult heights, however, fell back to 1.4 SD units below NCHS means. The reason for this loss of catch-up growth was, most likely, their remarkably young average age of menarche of 11.6 y (5 of the 107 girls had reached menarche before age 9). The reported mean age of menarche for contemporary Swedish girls was 13.0 y and that for rural Indian girls was 14.4 y. Thus, linear growth was briskly accelerated in response to adoption, to the point where the adoptees were close to Western standards by puberty. Age at menarche was also markedly accelerated and the discrepancy in adult height between the Indian and Swedish girls was closer to that at the time of adoption than at puberty.

Prompt growth changes among previously deprived children after adoption, or marked improvement in social and environmental conditions, have often been observed (147–150). Few studies, however, have followed the adoptees into adulthood. What was especially important about Proos's (143–146) study of ultimate attained height was the observation that early accelerated growth after improved environmental circumstances was associated with minimal increases in attained adult height. Furthermore, if these girls had remained in or returned to south Asia around puberty, their reproductive safety would have most likely been further compromised. This is because, with earlier age at menarche, the girls would likely have been exposed to much earlier marriage and pregnancy than if they had not been adopted and better fed.

Small-scale interventions compared with wide-scale programs

Taller women have a lower risk of obstructed labor, and the central (and as of yet, unproven) strategy to increase adult women's height is nutritional intervention in infancy and early childhood (as well as improved hygiene, infection control, and improved literacy). However, even if nutritional intervention were shown to be efficacious, there still remains a wide discrepancy between the effect of small-scale nutrition studies to promote child growth and community-based programs (parallel to the problems of programmatic effects from wide-scale iron supplementation). Beaton and Ghassemi (151) in their evaluation of supplementary feeding programs in developing countries concluded that although most program evaluations claimed beneficial effects, some major ongoing programs showed no demonstrable increase in anthropometric indexes for the program as a whole; some distribution centers reported positive effects but some did not. Scrutiny of the results suggested that anthropometric improvement was surprisingly small, perhaps partly because of the relatively low levels of average net supplementation. Thus, not only have the carefully monitored small-scale studies provided uneven results but, when they are scaled-up in the field, there has been only a minimal effect, probably resulting more from administrative and behavioral constraints than from biological ones.

Even if change is biologically possible, it has been achieved unevenly, if at all, in wide-scale programmatic application. A possible exception is the Tamil Nadu Integrated Nutrition Program (152). By targeting attention to children with demonstrated growth failure, this program was reported as having achieved outstanding short-term results in affecting growth among malnourished children. A more recent evaluation is much less optimistic about outcome (153). As of yet, nothing has been reported about the long-term consequences of this intervention.

Micronutrients and female growth

One of the most provocative reports on growth change in adolescent girls was the iron and folate supplementation study of Harrison et al (127). Fifty-nine Nigerian girls ages 13–16 y who were 8–24 wk pregnant were randomly assigned to 1 of 5 groups in a double-blind format. The groups received either a placebo, antimalarial medication, or antimalarial medication with iron (60 mg Fe/d), folate (1 mg/d), or both. Supplementation did not affect birth weight, and antimalarial medication with folic acid had no effect on anemia (154). There was, however, an unexpected and dramatic response in maternal height with iron or folate. The iron-supplemented group grew, on average, 3.3 cm during pregnancy; those who received folate grew 3 cm; and those who received both iron and folate grew 2.1 cm compared with an average of 1.1 cm in the placebo group or the group who received antimalarial medication alone. The treatment groups were very small, with only 31 girls receiving any of the hematinics, and the equivalent growth response to either folate or iron is inexplicable. This accelerated linear growth was not hypothesized when the trial was designed, and accelerated growth did not appear to affect pregnancy outcomes. This research is important and needs to be both replicated and extended.

Parasitic infestation and growth

Willett et al (155) and Stephenson et al (156) found that anthelmintic therapy in preschool Tanzanian and school-age Kenyan children led to increased weight gain but to no observed changes in height. Among nutritionally rehabilitated malnour-

ished children, weight change typically precedes accelerated linear growth and it is possible that these children continued to attain increased height and weight. If, however, they experienced only increases in weight, the girls might have had the adverse outcome of earlier menarche and possibly depressed adult stature.

Micronutrient supplementation and linear growth in children

The situation of micronutrient supplementation is at least theoretically different from that of energy supplied by macronutrients. The limiting micronutrients for linear growth (eg, vitamin A, zinc, calcium, iron, and folate) are probably less likely than energy and protein supplementation to lead to fat deposition and earlier menarche. Although less likely, the possibility is real. Two studies on growth after iron supplementation in children provide results that are not reassuring. Latham et al (157) found increased weight gain after iron supplementation in anemic school children but found no effect on height. Bhatia and Seshadri (158) included both nonanemic and anemic children in their trial. With iron supplementation, they observed accelerated weight gain but no increase in linear growth in both the anemic and nonanemic children.

Prentice and Bates (159) summarized the controlled trials of zinc and calcium supplementation in growing children. Of the 6 calcium supplementation trials, only 2 had positive effects on height. Of 13 trials of zinc supplementation in normal children, 4 had no effect on weight or length, 4 had positive effects on length, 2 had positive effects on length in boys only, and 1 had an effect on length in children with initially low zinc concentrations. In 6 studies of severely malnourished children, zinc supplementation improved length significantly in only 1 study. This was a 3-mo zinc supplementation trial and the effect on length was observed only at the end of the first month and not at the end of the second and third months. One of the 3 studies that reported on sexual maturity found accelerated sexual maturity with zinc supplementation. Brown et al (160) performed a meta-analysis of zinc intervention trials to promote growth in children. They included in the analysis the 25 of 52 trials that met their quality criteria. The mean age of the 1834 children in the trials was 3.6 y (range: 0–13 y). Zinc supplementation had a greater effect on weight (0.26 SD units) than height (0.22 SD units) (both highly significant), and the effects were greatest in children who were the most zinc deficient and most growth stunted. It would be of profound interest to know the long-term effects of trial participation. At this time, the record does not strongly support initiating programs to supplement either zinc or calcium to increase childhood stature.

In a randomized supplementation trial in Indonesia, vitamin A did not affect linear growth in either boys or girls (161). In a randomized trial in the Sudan, an oral dose of 60000 μ g retinol equivalents of vitamin A at 6-mo intervals did not affect growth (162). However, in the observational component of the study, children in the highest quintile of dietary vitamin A intake (measured by 24-h recall) were taller and heavier than children in the lowest quintile. Thus, there is no evidence that vitamin A supplementation had any effect on child growth. The association of better growth with a history of high dietary vitamin A intake is open to confounding by both socioeconomic and other factors associated with better diet, and the possibility that other nutrients that might affect growth are associated with a history of vitamin A intake. A large randomized trial of vitamin A and β -carotene supplementation in childbearing and lactating Nepali women reported no effect on any perinatal outcomes, but there was a suggestive effect on infant growth in the first 6 mo of life (163).

Summary: nutrition and stature

The relation between prenatal, childhood, and adolescent food intake and attained adult height requires much more study, including reanalysis of existing data sets. Clearly, greater height appears to protect against trauma during delivery, both for the pregnant woman and her offspring, particularly in situations where operative obstetric help may not be readily accessible. Adult height can be increased with increased food intakes up to age 3 y. Macronutrient supplementation among older, but still premenarcheal, girls seems to lead to short-term accelerated growth but much younger age at menarche, incomplete catch-up growth, and little if any change in adult height. No well-documented and proven interventions exist to increase adult stature after infancy, and this issue warrants intensive further study. Early pregnancy may independently contribute to shortening further the period of linear growth after menarche and may lead to shorter attained stature. In addition, early menarche may increase the likelihood of earlier marriage and thus exposure to the risks of pregnancy.

Cephalopelvic disproportion, operative delivery, and fetal size

That this simple relation has not been reported more frequently is remarkable and, on reflection, lamentable. Many data sets from hospitals in developing countries could be used for such studies. Estimates of relative risk from hospital data may be uncertain, given the bias that women with obstructed labor are more likely to go to a hospital than are those without perinatal obstetric problems. Using the case-control method, under the assumption that any particular woman with obstructed labor is as likely to go to a hospital as any other, independent of her baby's size, should produce relatively unbiased estimates of the odds ratio.

A study of anemia among pregnant teenage girls by Harrison et al (127) reported the rate of operative delivery among 24 primigravidae aged 13–16 y. Only 1 of 12 girls whose infant had a birth weight of ≤ 3.0 kg required operative delivery compared with 6 of 12 girls who delivered babies with birth weights of > 3.0 kg. The operative delivery rates by both birth weight and maternal height in 4702 primigravidae in the Zaria birth survey are shown in **Table 7** (164). The association between operative delivery rate and maternal height was, as noted above, strong. Whatever the birth weight, 23–56% of women with heights < 1.5 m, but no more than 16% of women with heights > 1.65 m, required operative delivery. The association with birth weight was equally strong. In every height stratum, the frequency of operative delivery was much higher (typically double) for a birth weight > 3.5 kg compared with lower birth weights. One-half of the women with heights < 1.5 m had operative delivery when birth weights were > 2.5 kg, and one-half of the women with heights between 1.5 and 1.54 m had operative delivery if birth weights were > 3.5 kg.

Merchant (K Merchant, unpublished report, 1991) related the probability of intrapartum cesarean delivery to maternal height and newborn head size in an urban population in Guatemala. The pattern of the results was essentially identical to those of a Nigerian population: operative delivery was much more frequent both with shorter maternal stature and larger infant head size. Among the shortest quartile of women, mothers with newborns whose head circumferences were in the smallest quartile had an incidence of intrapartum cesarean delivery of 23.9%. In contrast, women of the same height with infants in the largest head cir-

TABLE 7

Operative delivery rate by birth weight and maternal height among 4702 primigravidae, Zaria birth survey¹

Maternal height (m)	Birthweight (kg)		
	≤ 2.5	2.5–3.5	> 3.5
	%		
≤ 1.5	23	46	56
1.5–1.54	17	25	52
1.54–1.59	12	15	27
1.59–1.64	7	11	23
≥ 1.65	15	8	16

¹Rates abstracted from reference 164; totals cannot be estimated from publication because booked (women who registered for prenatal care) and unbooked (women who presented at the hospital for the first time at delivery) patients are combined.

cumference quartile had an intrapartum cesarean delivery rate of 53.2%. Among the tallest quartile of women, those with babies in the smallest head circumference quartile had a cesarean delivery rate of 11.1% compared with 29.1% of women whose infants were in the largest head circumference quartile. Thus, within the lowest and highest height strata, women with babies having the largest head circumferences were more than twice as likely to need cesarean delivery as those with babies having the smallest head circumferences. The association between cesarean delivery rate and fetal head size was also present in the 3 intermediate maternal height strata.

Adadevoh et al (123) found that birth weights of infants born to women in Ghana with cephalopelvic disproportion were, on average, 121 g greater than those of infants born to women without cephalopelvic disproportion. In Dar es Salaam, Mtimavalye et al (165) noted that the rate of cephalopelvic disproportion rose significantly during a period when birth weight increased. Unfortunately, they did not relate individual birth weight to the likelihood of operative delivery.

These few studies unanimously and clearly show a much increased need for operative delivery associated with larger baby size. Whether the increased viability associated with higher birth weight from nutritional supplementation outweighs the danger of obstructed labor to both mother and child where effective obstetric care is not readily available remains unknown.

Expected increments in birth weight associated with nutritional supplementation during pregnancy

With a few exceptions, supplementing pregnant mothers who are at risk of delivering low-birth-weight infants with foods of low or moderate protein density has generally been associated with increases in birth weight of 30–60 g (166). The potential benefit of such relatively small increments in birth weight must be weighed carefully against the increased risk of obstructed labor to both the mother and the child. Gibson (167) reviewed 7 zinc supplementation studies of pregnant women. One trial found reduced intrauterine growth retardation and another found a reduction in very early delivery (before the 33rd week of gestation) (168). Goldenberg et al (169) conducted a randomized, double-blinded, placebo-controlled zinc supplementation trial in 580 African American pregnant women with plasma zinc concentrations below the median. They found that zinc supplementation had a significant effect on birth weight and head circum-

ference, particularly for the offspring of women whose body mass index (calculated as kg/m²) was <26. If this effect of zinc supplementation on accelerated fetal growth is replicable, an intervention with zinc, like those with energy and protein, might increase the danger of obstructed labor. The data of Harrison (164) and Merchant (unpublished report, 1991) show regular increases in risk of need for operative delivery with decreased height and increased infant size at all levels of these indices. The problem is conceptually straightforward, but its solution presents many difficulties.

The benefit of a larger birth weight in situations where infant mortality is high is theoretically far less than where infant death rates are low, ie, in the developing world (170). The reasoning is that perinatal mortality is associated inversely and exponentially with birth weights up to 3.0–3.5 kg. When death rates are high, this exponential relation is far less steep than when death rates are low (ie, potentially fewer deaths are prevented by increasing birth weight if many viable normal-birth-weight infants are dying from preventable causes).

Participation by the mother in the US national feeding program for low-income pregnant women (the Women, Infants, and Children, or WIC, program) was associated with significantly increased newborn head size (166). Thus, the possibility of increased maternal feeding causing an increased risk of obstructed labor is real.

“Eating down” during pregnancy

There is a widespread belief among women in developing countries that decreased food intake during pregnancy is safer for the mother (and possibly the child) because a smaller fetus will make for an easier delivery (171–173). The international public health nutrition community has often aimed to override this folk wisdom, using as a rationale the inverse relation between perinatal mortality and birth weight in developed countries. There exist, however, no data with which to estimate the tradeoffs between large and small fetal size in situations where competent obstetric care is not available. On the basis of the very small body of data available for this review, the folk wisdom about the danger of birthing large babies is justified in the absence of comprehensive obstetric care, especially for primigravidae or short women. The belief that a reduction in food intake during pregnancy contributes to the safety of the mother needs not only to be studied further but to be honored until better data become available.

Summary: fetal size and obstructed labor

Infant survival is more likely with term rather than preterm delivery. The evidence that intrauterine growth retardation among term infants has nearly as severe immediate consequences as does preterm delivery, however, is weak. Unless access to operative obstetrics is good, large babies are far more likely to traumatize the mother and to be traumatized themselves. Where sophisticated obstetric services are not available, accelerated intrauterine growth should be promoted only with great caution. This applies to nutrition interventions including protein-energy or zinc supplementation. Until proven safe, macronutrient supplementation for primigravidae <1.5 m tall should not be offered. If energy supplementation programs are integrated with adequate obstetric care, the situation becomes radically different. These issues need further inquiry.

NUTRITION AND TOXEMIA OF PREGNANCY

Relationship between toxemia of pregnancy and maternal mortality

Maternal death from bacterial infection, hemorrhage, and obstructed labor has been nearly eradicated in the industrialized countries; preeclampsia, a syndrome of hypertension and proteinuria, and eclampsia (preeclampsia with grand mal convulsions) are now the most common causes of maternal mortality (174–176). Still, maternal death associated with hypertensive disorders of pregnancy remains far more common in the developing world than in the developed world (177, 178). The physiology of toxemia syndromes is complex (179). Although the causes of preeclampsia and eclampsia have remained elusive, several factors potentially amenable to intervention, including nutrition, have been proposed.

Parity and age

Pregnancy-induced hypertension and eclampsia are far more common in first pregnancies than in subsequent ones. The relation to age is complex (180). Most cases of hypertension and eclampsia appear in young women because most primiparae are young. Among primiparae, there is a U-shaped relation between incidence and age, with far higher rates in older women than in women between the ages of 20 and 30 y. Teenagers appear to have a minimally higher risk of hypertension and eclampsia than do women in their 20s. There is also an increase in risk with increasing age among multiparae.

Race and social status

Although rates of eclampsia and preeclampsia are higher in blacks than in whites living in industrialized countries (180), the incidence of these conditions appears to vary little by social class within ethnic groups (181, 182). In contrast, social class is clearly related to perinatal outcomes of preeclamptic pregnancies (183). The absence of a relation between incidence and social class is inconsistent with a nutritional or dietary cause of preeclampsia and eclampsia.

Seasonality

The extreme geographic variability in toxemia syndromes (184) and their relation to season (185, 186) suggest that extrinsic factors may play a large role in their etiology. Agobe et al (186) reported that in Lagos, Nigeria, the eclampsia rate was between 13.5 and 16 cases/1000 hospital deliveries in the wet months of June to August. This rate, however, decreased to as low as 4 in January, during the dry season. In Ghana, Obed et al (185) observed peak rates of eclampsia of 23 and 30 cases/1000 deliveries during June and July, respectively. This rate decreased to as low as 5/1000 deliveries during some dry months. This remarkable variability can only be from extrinsic causes, probably either nutritional or infectious. In a study in Dakar, Senegal, Sartelet et al (187) found a strong relation between malarial infection during pregnancy and preeclampsia, which could help to explain some seasonal variability of the syndrome.

Micronutrients and preeclampsia

The search for nutritional factors associated with preeclampsia is hindered by the lack of data. The review by Green (188) covers this material through the 1980s. Many nutritional factors have been suggested as possible causes of preeclampsia and eclampsia, and there have been many attempts at prevention using dietary or

nutritional interventions. No dietary interventions have had much, if any, effect. Many nutrients, including thiamine (189) and sodium chloride (190), were either not proven to be consistently related or were not studied thoroughly enough to be nominated for programmatic testing and application. Calcium, zinc, and magnesium are 3 micronutrients that seemed very promising, although their roles in preventing preeclampsia and eclampsia are now uncertain, as described below.

Calcium

The effects of calcium supplementation on pregnancy-induced hypertension and preeclampsia were described in 2 meta-analyses (191, 192). Hamet (193) also performed an extensive review that related calcium to hypertension in general. Of the 14 randomized trials of calcium supplementation during pregnancy reviewed by Bucher et al (192), 13 reported amounts of supplemental calcium. Eleven of these studies gave 1500 or 2000 mg elemental Ca/d and the other 2 provided 375 mg Ca/d and 1000 mg Ca/d. The effect of calcium supplementation was consistent for both the incidence of preeclampsia and hypertension. The pooled estimate of relative risk for preeclampsia was 0.38, and for hypertension, 0.30, both highly significant. The authors of the review raised the question of whether calcium could reduce the rate of mild preeclampsia and not reduce the morbidity associated with severe preeclampsia and eclampsia: they speculated that calcium supplementation might reduce the incidence of only relatively mild preeclampsia that, had it occurred, would not have led to serious disease. They also pointed out that supplementation studies do not show whether dietary modification to increase calcium intakes would have a comparable effect. As in so many situations where trials have used similar or identical amounts and types of supplementation, it is unknown whether lower doses of supplemental calcium might have achieved comparable results.

These findings were encouraging and strongly suggested that calcium supplements might lower the incidence of one of the main causes of maternal morbidity and mortality. This optimism has now been considerably dampened with the results of the large multicenter Trial of Calcium for Preeclampsia Prevention (194–196). In this trial, 4589 pregnant nulliparae between 13 and 21 wk gestation from 5 US university centers were randomly assigned to receive 2000 mg elemental Ca or a placebo daily. Calcium supplementation did not affect the rate of preeclampsia, pregnancy-associated hypertension, or perinatal outcome (including preterm delivery, intrauterine growth retardation, and perinatal death). The use of calcium supplements to prevent toxemia of pregnancy is, therefore, in limbo and there is no rationale for large-scale programmatic intervention with calcium at this time. It is likely that further research will need to be conducted in populations whose diets are more likely to be calcium deficient.

A logical next step might be to consider a trial in the developing world with various rates of calcium supplementation and with a sample size large enough for assessing the effects on both maternal and fetal morbidity. An intervention comparing dietary change with calcium supplementation should also be considered because of the possibility that under some conditions, dietary modification might be more practicable than supplementation.

Zinc

In Gibson's (167) review of 7 zinc supplementation studies of pregnant women, only one reported a reduced incidence of preg-

nancy-induced hypertension (168). Goldenberg et al (169) in their large trial of zinc supplementation during pregnancy did not report rates of pregnancy-induced hypertension.

Overall, the studies of zinc and pregnancy-induced hypertension have had inconsistent results. They have also been plagued with methodologic weaknesses, such as inferring that a concurrent association between low serum zinc concentration and hypertension was present before hypertension appeared. Decisions on whether and how to extend the work on prenatal zinc supplementation to developing countries must await the outcome of ongoing trials. Like all the interventions under scrutiny in this review, future studies and programs should not be undertaken unless good supportive obstetric care is available. Sample sizes should be large enough to test effects on pregnancy-induced hypertension as well as fetal growth and might, therefore, best be carried out in primiparous women.

Magnesium

Spasmodic contraction of umbilical and placental vasculature was observed in magnesium-deficient laboratory animals (197). Magnesium deficiency in the pregnant ewe can also cause increased blood pressure and a reduction in fetal weight and placental and renal lesions similar to those in preeclampsia. Studies on magnesium deficiency in pregnant women, however, have been inconclusive. Melles and Kiss (198) found lower rates of preeclampsia in areas with high concentrations of magnesium in the drinking water and a reduction in rates of preeclampsia with magnesium treatment. Spätling and Spätling (199), although finding fewer hospitalizations among magnesium-treated women than placebo-treated women, observed no differences in rates of preeclampsia. Sibai et al (200) found no significant differences in either systolic or diastolic blood pressure or incidence of preeclampsia associated with magnesium supplementation. It does not appear at this time that magnesium supplementation, or increased dietary intake of magnesium, can be promoted as an intervention to control preeclampsia.

Obesity; weight change; energy, protein, and fat intake; and preeclampsia

The relation between energy and protein intake, preeclampsia, and eclampsia has been debated extensively (188). A positive relation between obesity and preeclampsia was observed in several studies (200–202). There is general agreement, however, that weight gain during pregnancy is not a risk factor for preeclampsia. Rather, the weight gain of preeclampsia appears to reflect pathologic water retention that is a physiologic change associated with, but not a cause of, pregnancy-induced hypertension. Thus, the strategy to limit weight gain during pregnancy to avoid pregnancy-induced hypertension has been discredited (181).

Davies et al (203) found no associations between diet and toxemia in an observational study in Israel. Zlatnik and Burmeister (204) in the United States found that preeclampsia was not related directly to the amount of dietary protein, a finding similar to that of Chaudhuri (205).

Sattar et al (206) reviewed the underlying potential pathogenic roles of lipoprotein and fatty acid metabolisms in preeclampsia. Unfortunately, the results of studies in humans have been mixed. Olsen and Secher (207) found a possible protective effect of low doses of fish oil on preeclampsia. A more recent trial by Onwude et al (208) found no relation between fish

oil supplementation and any pregnancy outcome in women at high risk of developing pregnancy-induced hypertension. This inconsistency is discouraging because of the strong association in an observational study between low amounts of erythrocyte $n-3$ fatty acids and preeclampsia (209).

Other nutritional factors

Other nutritional factors implicated in toxemia of pregnancy include dietary fiber (210, 211) and leisure-time physical activity (212). The tenuousness of these associations with pregnancy toxemia is such that none has progressed beyond speculation.

MATERNAL NUTRITION AND PUERPERAL INFECTION

Deaths from puerperal infection, once a common cause of maternal mortality, are now rare in the industrialized world (213). The situation in the developing world, however, remains dire. For instance, maternal tetanus alone causes between 15000 and 30000 maternal deaths/y (214). There are reports of some changes in immune status associated with severe iron deficiency (hemoglobin <80 g/L) (94). Despite this, as Viteri (39) stated, "The lack of information on the impact of anemia and/or iron deficiency on rates of severity of different infections during pregnancy is appalling." So appalling that, at this time, although major research initiatives relating various indices of malnutrition to the incidence and severity of infection would be very valuable, this issue is nowhere near programmatic application.

West et al (215) recently completed an important trial in Nepal. Two hundred seventy communities were randomly allocated to 1 of 3 groups, and all women of reproductive age in each community were given a placebo, 7000 μ g vitamin A, or 42 mg β -carotene/wk for 3 y. Among the several predicated outcomes, the only noteworthy effects were on maternal mortality. Overall, the study found a dramatically lower maternal death rate in supplemented than in unsupplemented women (relative risk: 0.56 through 12 wk postpartum; 95% CI: 0.37, 0.84). Nevertheless, there remain several uncertainties with this study, including the different outcomes for the 2 different interventions, the results of serum studies, and—most importantly—the results of the verbal autopsies, historical attempts to ascertain cause of death. The lowering of the maternal death rate was greater for β -carotene (relative risk: 0.51) than for vitamin A (relative risk: 0.60). Serum retinol and β -carotene values were estimated in a subsample of women (these results were presented at a scientific conference but were not included in the publication). It appeared that there were only minimal effects on serum retinol concentrations from β -carotene supplementation and that the biochemical profiles of the 2 treatment groups were quite different, findings that were both inconsistent with the hypothesis that the effect in both groups was mediated by retinol concentrations. Although these results are somewhat confusing, the results of the verbal autopsies are disquieting. The authors anticipated that vitamin A would be shown to reduce the risk of death from severe infection. In fact, the relative risk of death from infection in women who received vitamin A was 0.94 (95% CI: 0.42, 2.05) and 0.60 (95% CI: 0.24, 1.51) for β -carotene; thus, the hypothesized effect of vitamin A did not occur. There was also no difference in death from hemorrhage, with the relative risks for all obstetric causes of death (including hemorrhage, eclampsia, shock, and obstructed labor) being 0.88 and 0.56 for vitamin A and β -carotene, respectively (neither significant). Thus, vitamin A had a negligible effect on any of the

biologically coherent causes of death. The supplements did succeed in dramatically reducing maternal mortality from deaths because of injury (eg, burns, drowning, snakebite, and hanging), with a combined relative risk of 0.10, and from miscellaneous causes of death, which included a combination of "uncertain," "no information," asthma, leukemia, and anemia (only one case). For this group, the relative risk for both groups combined was 0.26 (CI: 0.09, 0.73).

The findings from the Nepal study do not provide an adequate basis on which to move forward to programmatic application and certainly should not foreclose further research. These nutrients need further testing, preferably in an area with at least rudimentary obstetric services. The meaning of an intervention that lowered maternal death ratios in a population where the background maternal mortality ratio was 759/100000 live births (the placebo group) is open to question. A first priority would be to offer obstetric care to lower this terrible risk and then to judge what the incremental benefit might be from supplementation with these nutrients. It is impossible from the results of this trial to predict what the effects of vitamin A or β -carotene supplementation would be at the lower levels of maternal mortality after health care has been improved.

Interrelationships between health care and infection

As with all causes of maternal mortality, the effect of any nutritional intervention on rates of infection will depend on the quality of health care that is available. Simple lessons learned long ago may need to be relearned. Cronin et al (216) conducted a carefully structured observational study of midwives and obstetric nurses in Ghana in which they surveyed selected infection control practices related to childbirth. They concluded that most personnel did not practice basic rules of asepsis, including frequent breaks in technique, inadequate sterilization and disinfection, and repeated exposure to large amounts of blood and vaginal secretions. Medical supplies were limited and, when available, were not always used appropriately. Thus, without concurrent attention to both the availability and quality of health services, attempts to lower the rate and severity of infection by nutritional interventions alone would certainly not achieve much in the way of benefit.

Conclusion

Although the relation between nutrition and immunity has received much attention recently, a strategy of nutritional intervention aimed at decreasing the incidence or severity of maternal infection cannot be justified at this time.

This review has only dealt peripherally with perinatal problems, but the most promising preventable cause of preterm labor is probably chorioamniitis and other reproductive tract infections (217). Any studies on the relations between such infections, which are often sexually transmitted, and nutritional status need to take into account the effect of similar concomitant causes of reproductive problems for both the mother and the infant.

CONCLUSIONS

Maternal mortality is a problem of utmost importance. It is devastating whenever it occurs, and rates in the developing world are 100- to 200-fold those in industrialized countries. That this is true, despite secure knowledge about the principles of prevention, is not only a human tragedy but an indictment of world priorities.

Past efforts to lower maternal mortality rates through nutritional strategies have fallen victim to the usual culprits. These include

lack of resources, lack of interest in women's health by those who control resources, and the low status of women throughout much of the developing world. Another embarrassing factor about which little is said also stands in the way of coherent policy and programs: the knowledge base upon which many programs have been proposed or created is inadequate. Nutrition programs have been actively promoted to reduce maternal mortality when it is not at all clear whether they will have any but minimal effects. Such programs are often based on incomplete or contradictory knowledge and frequently are not field-tested before being widely disseminated. It seems there is often an underlying assumption that nutrition programs could not possibly have any adverse consequences on the health of women, which is not true. Even if they have no adverse biological effects (and even these cannot be ruled out), these programs can divert resources from initiatives that might have succeeded better and can raise expectations too high, disappointing both donors and recipients and undermining the future credibility of public health nutrition.

Certainly, the amelioration of malnutrition can greatly benefit women and their children and families. What remains unclear, however, is what the highest priorities are and how to formulate them. The public health nutrition community needs to assess its ignorance forthrightly and confront policymakers and funding agencies with the reality that lowering maternal mortality and significantly improving maternal and child health will require far better information than is now available. Moreover, gathering such information will require resources and time. Further, priorities should be set and strategies chosen with the full participation of the women and families whom these efforts are meant to help, not just by the researchers, health institutions, and governments.

A second overarching administrative reality is that in the developing world, nutrition programs are often dissociated from health programs. Even at the experimental level, several massive trials have tested specific nutrients without attention to the inadequacy of the available health and obstetric services. It is nearly certain that the adjunctive role of nutrition in lowering maternal mortality and improving maternal and child health will be minimal and marginal unless incorporated into existing and improved health care delivery. Such trials are likely to confer much less benefit than they would have had they been integrated with the health services. In practical terms, any effects observed in the absence of adequate health care cannot be assumed to be applicable once baseline rates of mortality have been lowered after the establishment of effective health care. This shortfall has a moral as well as a practical dimension: Is it ultimately important whether massive death rates were slightly lowered while provision of decent health care was neglected? The studies would almost surely be different if the poor people, who are the subjects, could express their own priorities.

For 3 of the 5 central causes of maternal mortality (except as possibly influenced by anemia, as discussed below), the knowledge base for the contribution of nutrition to maternal survival is too weak for any widespread, systemic programmatic application at this time. These 3 causes are induced abortion, puerperal infection, and pregnancy-induced hypertension (preeclampsia and eclampsia). The situation for the other 2 major causes of maternal mortality, namely hemorrhage (including, for this discussion, anemia) and obstructed labor, is very different. Large-scale nutritional programs to prevent and manage both anemia and intrauterine growth retardation, with major investments of resources, are now ongoing in the field and far more programs are being urged to the world com-

munity. The question is whether these programs, well-intentioned as they assuredly are, are even close to being as effective as they are promoted to be. If they are not, what still needs to be learned before the programs can be revised or refined?

Anemia

Almost every published study has found greatly increased maternal mortality among severely anemic women, but no study has addressed whether mortality is lowered by treatment of anemia (other than transfusion therapy for very severe anemia). Of the 2 available studies that relate moderate concentrations of anemia to mortality, one found moderately increased maternal mortality (53) and the other found no increase (48). Moreover, most publications omit data on the severity or etiology of anemia and do not discuss whether intervention was successful. Except for a recent study from Bangladesh, which reported markedly lower community rates of anemia after a program of routine iron supplementation during pregnancy and the postpartum period (218), evidence that these programs have conferred much, if any, benefit at process (amount of supplementation) or physiologic levels (iron stores increased) is scanty. Further, no studies show improved public health outcome (ie, lowered maternal morbidity and mortality, improved fetal growth, or lowered perinatal and infant mortality).

In nearly all populations, there are far more mildly or moderately anemic women than severely anemic women. Current nutrition programs to combat anemia during pregnancy in the developing world address all severities of anemia (ie, mild, moderate, and severe), paying only scant special attention to the severely anemic woman. Furthermore, iron supplementation programs seldom attempt to specify etiology or level of anemia, and severe anemia is likely due to complex, multiple causes. Programs usually distribute supplements universally in amounts that are not tailored to individual need and typically do not test whether therapy has been successful nor modify the therapy if it is not. Thus, the problem of severe anemia, as a medical and obstetric emergency, is not being directly nor appropriately addressed.

The next steps for the public health community seem relatively straightforward. First, the relationship between level and type of anemia and pregnancy-related morbidity and mortality needs to be clarified. Second, mechanisms for contending with those forms and levels of anemia associated with increased risk of death must be developed in carefully designed and monitored small-scale studies. Third, after successful strategies are developed in relatively small-scale studies, these need to be tested and refined at the population level, and those strategies that prove valuable need to be made available to all women whom they might help, all the while taking into account possible adverse consequences of intervention. These challenges imply changes in current approaches. Screening and follow-up become obligatory, with monitoring to judge whether treatment has been successful and whether action needs to be taken to modify such treatment accordingly.


The pathways by which severe anemia increases risk of death also need to be better understood. Right now, no data are available to address the widely held assumption that severely anemic women are more susceptible to death from exsanguinating hemorrhage. Quite possibly, severe anemia may also impair the muscular strength needed for labor or it may increase susceptibility to infection. Investigation of these issues is possible, albeit difficult. Public health nutritionists must be honest in confronting their ignorance and resolute in correcting these

massive uncertainties.

Obstructed labor

The risk of obstructed labor is closely related to physical size, ie, growth of both the mother and the fetus. Obstructed labor is far more common with short stature and in first births, possibly related to the lag in maturation of the pelvic outlet compared with the stature of young mothers. Unfortunately, nutritional strategies for increasing adult stature are nearly nonexistent. Supplemental feeding appears to have little benefit after age 3 y and there is evidence that improved nutrition and environmental conditions among short Third World girls have mixed benefits on reproductive health. For instance, young Indian girls adopted by Swedish families had rapidly accelerated growth in height before puberty, markedly earlier menarche (potentially exposing them to earlier marriage), and ultimate adult stature that was not much greater than might have been expected before adoption. In contrast, deprived girls without any special intervention have been observed to have late menarche and, therefore, greatly extended periods of growth, and have achieved nearly complete catch-up growth compared with relatively affluent control subjects. Whether supplementation or increased feeding after infancy is safe, in terms of precipitation of early menarche, or effective, in terms of increasing ultimate adult height, cannot now be predicted. This issue is probably not amenable to controlled clinical trials and warrants a careful reinvestigation of past intervention studies and important quasi-experiments.

The same knowledge gaps exist for micronutrient interventions. Iron and zinc supplementation of deficient populations may lead to weight increases, but few data are available on ultimate height change. This is another issue where follow-up of past intervention studies could be of enormous value.

Published research on the association between fetal size and obstructed labor is scanty, but results of the few existing studies are consistent with the universal clinical understanding that the need for operative delivery increases sharply with increased fetal size. This applies not only to macrosomic newborns, but also to those of moderate size; the risk of obstructed labor of infants whose birth weight is 3.0 or 3.5 kg is much higher than at 2.5 kg or lower and is especially severe in women shorter than 1.5 m. The problem is exacerbated in young and primiparous mothers. Many supplementary feeding programs currently exist to increase fetal size, particularly for thin women. Most of these programs identify participants on the basis of criteria independent of the woman's height, such as the body mass index (wt/ht²). This review shows that this strategy may increase the risk of obstructed labor, with consequent trauma and possible death of both the mother and child. All primiparous women shorter than 1.5 m should be excluded from protein-energy and other supplementary feeding programs aimed at accelerating fetal growth until these issues are better understood, or unless there is reasonable confidence that these short and vulnerable young women will have access to effective operative obstetric care. The knowledge base necessary to model the competing risks between the benefits and dangers of increased fetal size does not now exist. Until it does, protein-energy supplementary feeding programs in developing countries should be conservative to maximize the possibility that their benefits outweigh their risks. 

REFERENCES

- Loudon I. Death in childbirth: an international study of maternal care and maternal mortality, 1800–1950. Oxford, United Kingdom: Clarendon Press, 1992.
- Mahler H. The safe motherhood initiative: a call to action. *Lancet* 1987;1:668–70.
- World Health Organization and UNICEF. Revised 1990 estimates of maternal mortality: a new approach by World Health Organization & UNICEF. Geneva: World Health Organization, 1996.
- Barron SL, Thomson AM, eds. *Obstetrical epidemiology*. London: Academic Press, 1983.
- Niswander KR, Gordon M. *The women and their pregnancies: the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke*. Saunders, PA: National Institute of Neurological Diseases and Stroke, 1972.
- Högberg U. *Maternal mortality in Sweden*. Umeå University Medical Dissertations, NS516. Umeå University, Umeå, Sweden, 1985.
- Statistics Netherlands. 1899–1979 Tachtig jaren statistiek in tijdreeksen. (Eighty years of statistics in time sequences.) The Hague: Statistics Netherlands, 1979 (in Dutch).
- MacFarlane A, Mugford M. *Birth counts: statistics of pregnancy and childbirth*. Vol 2. London: Her Majesty's Stationery Office, 1984: 489.
- Butler NR, Alberman ED, eds. *Perinatal problems*. Edinburgh: E&S Livingstone Ltd, 1969.
- Loudon I. Obstetric care, social class, and maternal mortality. *Br Med J* 1986;293:606–8.
- Anderson RN, Kochanek KD, Murphy SL. Report of final mortality statistics. *Mon Vital Stat Rep* 1997;45(suppl).
- Högberg U, Wall S, Broström G. The impact of early medical technology on maternal mortality in late 19th century Sweden. *Int J Gynaecol Obstet* 1986;24:251–61.
- AbouZahr C, Royston E. *Maternal mortality: a global fact book*. Geneva: World Health Organization, 1991.
- Spence C, Danielson TS, Kaunitz AM. The Faith Assembly: a study of perinatal and maternal mortality. *Indiana Med* 1984;77: 180–3.
- Kaunitz AM, Spence C, Danielson TS, et al. Perinatal and maternal mortality in religious group avoiding obstetric care. *Am J Obstet Gynecol* 1984;150:826–31.
- AbouZahr C, Wardlaw T, Stanton C, Hill K. Maternal mortality. *World Health Stat Q* 1996;49:77–87.
- Bhatia J. Levels and causes of maternal mortality in southern India. *Stud Fam Plann* 1993;24:310–8.
- Turman T, AbouZahr C, Koblinsky M, eds. *Reproductive health: the mothercare experience*. *Int J Gynaecol Obstet* 1995;48(suppl): 1–137.
- Chiphangwi JD, Zamaere TP, Graham WJ, et al. Maternal mortality in the Thyolo district of southern Malawi. *East Afr Med J* 1992;69: 675–9.
- Szmoisz S, Vuegen SE, Plaza AS, et al. Argentina: risk factors and maternal mortality in La Matanza, Province of Buenos Aires, 1990. *World Health Stat Q* 1995;48:4–7.
- Graham WJ, Filippi VGA, Ronsmans C. Demonstrating programme impact on maternal mortality. *Health Policy Plan* 1996;11:16–20.
- Moodley D, Payne AJ, Moodley J. Maternal mortality in Kwazulu/Natal: need for an information database system and confidential enquiry into maternal deaths in developing countries. *Trop Doct* 1996;26:50–4.
- Rooney C. Antenatal care and maternal health: how effective is it? A review of the evidence Geneva: World Health Organization, 1992.(WHO/MSM/92.4.)
- McDonagh M. Is antenatal care effective in reducing maternal morbidity and mortality? *Health Policy Plan* 1996;11:1–15.
- Greenwood AM, Bradley AK, Byass P, et al. Evaluation of a primary health care programme in The Gambia. I. The impact of trained traditional birth attendants on the outcome of pregnancy. *J Trop Med Hyg* 1990;93:58–66.
- Lamb WH, Foord FA, Lamb CMB, Whitehead RG. Changes in maternal and child mortality rates in three isolated Gambian villages over ten years. *Lancet* 1984;2:912–4.

27. Araujo G, Araujo L, Janowitz B, et al. Improving obstetric care in Northeast Brazil. *PAHO Bull* 1983;17:233–42.
28. Fauveau V, Stewart K, Khan SA, Chakraborty J. Effect on mortality of community-based maternity-care programme in rural Bangladesh. *Lancet* 1991;338:1183–6.
29. Maine D, Akalin MZ, Chakraborty J, et al. Why did maternal mortality decline in Matlab? *Stud Fam Plann* 1996;27:179–87.
30. Hertz E, Hebert JR, Landon J. Social and environmental factors and life expectancy, infant mortality, and maternal mortality rates: results of a cross-national comparison. *Soc Sci Med* 1994;39:105–14.
31. Evans J. SAPping maternal health. *Lancet* 1995;346:1046.
32. Foege WH, Henderson DA. Selective primary health care. *XXV management priorities*. *Rev Infect Dis* 1986;8:46–74.
33. Högberg U, Broström G. The demography of maternal mortality—seven Swedish parishes in the 19th century. *Int J Gynaecol Obstet* 1985;23:489–97.
34. Measham A, Gillespie S. Implementation completion report: second Tamil Nadu Integrated Nutrition Project. Washington, DC: World Bank, 1998:159–84.
35. Kitay DZ, Harbort RA. Iron and folic acid deficiency in pregnancy. *Clin Perinatol* 1975;2:255–73.
36. Bothwell T, Charlton R. Iron deficiency in women. Washington, DC: International Nutritional Anemia Consultative Group (INACG), 1981.
37. Fleming AF. The blood. In: Parry EHO, ed. *Principles of medicine in Africa*. 2nd ed. Oxford, United Kingdom: Oxford University Press, 1984:705–60.
38. Levin H, Pollitt E, Galloway R, McGuire J. Micronutrient deficiency disorders. In: Jamison D, Mosley H, Measham A, Bobadilla JL, eds. *Disease control priorities in developing countries*. London: Oxford University Press, 1993:421–51.
39. Viteri FE. The consequences of iron deficiency and anemia in pregnancy. *Adv Exp Med Biol* 1994;352:127–39.
40. Gillespie S. Improving adolescent and maternal nutrition: an overview of benefits and options. New York: UNICEF, 1997. (Nutrition series, no. 97–002.)
41. UN ACC/Subcommittee on Nutrition. 24th session. Report of the working group on iron deficiency. Geneva: ACC/SCN, 1997.
42. World Health Organization. The prevalence of anaemia in women: a tabulation of available information. 2nd ed. Geneva: World Health Organization, 1992. (WHO/MCH/MSM/92.2.)
43. Royston E. The prevalence of nutritional anaemia in women in developing countries: a critical review of available information. *World Health Stat Q* 1982;35:52–91.
44. Ross JS, Thomas EL. Iron deficiency anemia and maternal mortality. Profiles 3. Working Notes Series no. 3. Washington, DC: Academy for Educational Development, 1996.
45. Stokoe U. Determinants of maternal mortality in the developing world. *Aust N Z J Obstet Gynaecol* 1991;31:1–8.
46. Llewelyn-Jones D. Severe anaemia in pregnancy as seen in Kuala Lumpur. *Aust N Z J Obstet Gynaecol* 1965;5:191–7.
47. Harrison KA. Approaches to reducing maternal and perinatal mortality in Africa. In: Philpott RH, ed. *Maternity services in the developing world: what the community needs*. Proceedings of the Seventh Study Group of the Royal College of Obstetricians and Gynaecologists, September. London: Royal College of Obstetricians and Gynaecologists, 1979:52–69.
48. Harrison KA. Anaemia, malaria and sickle cell disease. *Clin Obstet Gynaecol* 1982;9:445–77.
49. Harrison KA, Rossiter CE. Maternal mortality. *Br J Obstet Gynaecol* 1985;92(suppl):100–15.
50. Chi I, Agoestina T, Harbin J. Maternal mortality at twelve teaching hospitals in Indonesia: an epidemiologic analysis. *Int J Gynaecol Obstet* 1981;19:259–66.
51. Thonneau P, Toure B, Cantrelle P, et al. Risk factors for maternal mortality: results of a case-control study conducted in Conakry (Guinea). *Int J Gynaecol Obstet* 1992;39:87–92.
52. Diallo MS, Diallo TS, Diallo FB, et al. Anemie et grossesse. Etude epidemiologique, clinique et pronostique a la clinique universitaire de l'hospital Ignace Deen, Conakry (Guinee). [Anemia and pregnancy: epidemiologic, clinical and prognostic study at the university clinic of the Ignace Deen Hospital, Conakry (Guinea).] *Rev Fr Gynecol Obstet* 1995;90:128–141 (in French).
53. Sarin AR. Severe anemia of pregnancy, recent experience. *Int J Gynaecol Obstet* 1995;50(suppl):S43–9.
54. McDermott JM, Slutsker L, Steketee RW, Wirima JJ, Breman JG, Heymann DL. Prospective assessment of mortality among a cohort of pregnant women in rural Malawi. *Am J Trop Med Hyg* 1996;55:66–70.
55. Fullerton WT, Turner AG. Exchange transfusion in treatment of severe anaemia in pregnancy. *Lancet* 1962;1:75–8.
56. Zucker JR, Lackritz EM, Ruebush TK, et al. Anaemia, blood transfusion practices, HIV and mortality among women of reproductive age in western Kenya. *Trans R Soc Trop Med Hyg* 1994;88:173–6.
57. Sloan NL, Jordan EA, Winikoff B. Does iron supplementation make a difference? Arlington, VA: John Snow, Inc, 1992. (MotherCare Working Paper no. 15.)
58. Anderson MA. The relationship between maternal nutrition and child growth in rural India. PHD dissertation. Tufts University, Boston, 1989.
59. Brabin L, Nicholas S, Gogate A, Gogate S, Karande A. High prevalence of anaemia among women in Mumbai, India. *Food Nutr Bull* 1998;19:205–9.
60. Brabin BJ, Ginny M, Sapau J, et al. Consequences of maternal anaemia on outcome of pregnancy in a malaria endemic area in Papua New Guinea. *Ann Trop Med Parasitol* 1990;84:11–24.
61. Jackson DJ, Klee EB, Green SDR, et al. Severe anaemia in pregnancy: a problem of primigravidae in rural Zaire. *Trans R Soc Trop Med Hyg* 1991;85:829–32.
62. Gyssens IC, Meheus AZ. Anemia of pregnancy in Niger, West Africa: a prevalence study. *Ann Soc Belg Med Trop* 1986;66:257–64.
63. Liljestrand J, Bergström S, Birgegård G. Anaemia of pregnancy in Mozambique. *Trans R Soc Trop Med Hyg* 1986;80:249–55.
64. Bergsjø P, Seha AM, Ole-King'ori O. Hemoglobin concentration in pregnant women: experience from Moshi, Tanzania. *Acta Obstet Gynecol Scand* 1996;75:241–4.
65. Harrison KA, Ibeziako PA. Maternal anaemia and foetal birth-weight. *J Obstet Gynaecol Br Commonw* 1973;80:798–804.
66. Fleming AF. Iron status of anaemic pregnant Nigerians. *J Obstet Gynaecol Br Commonw* 1969;76:1013–7.
67. Ratten BJ, Beischer NA. The significance of anaemia in an obstetric population in Australia. *J Obstet Gynaecol Br Commonw* 1972;79:228–37.
68. Atukorala TM, de Silva LD, Dechering WH, Dassenaeike TS, Perera RS. Evaluation of effectiveness of iron-folate supplementation and anthelmintic therapy against anemia in pregnancy—a study in the plantation sector of Sri Lanka. *Am J Clin Nutr* 1994;60:286–92.
69. Olukoya AA, Abidoye RO. A study of intestinal parasites in antenatal clinic patients in Lagos. *Health Hyg* 1991;12:176–9.
70. Grindulis H, Scott PH, Belton NR, Wharton BA. Combined deficiency of iron and vitamin D in Asian toddlers. *Arch Dis Child* 1986;61:843–8.
71. Mejia LA, Arroyave G. The effect of vitamin A fortification of sugar on iron metabolism in preschool children in Guatemala. *Am J Clin Nutr* 1982;36:87–93.
72. Suharno D, West CE, Muhilal, Karyadi D, Hautvast JG. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993;342:1325–8.
73. Yip R. Iron supplementation during pregnancy: is it effective? *Am J Clin Nutr* 1996;63:853–5.
74. Cook JD, Reddy MB. Efficacy of weekly compared with daily iron supplementation. *Am J Clin Nutr* 1995;62:117–20.
75. Indian Council of Medical Research Task Force. Evaluation of the

- national nutritional anaemia prophylaxis programme. New Delhi: Indian Council of Medical Research, 1989.
76. Liu X-N, Yang W, Zhang HY, et al. Weekly iron supplementation is effective and safe in pregnant women. *FASEB J* 1995;5658:A975 (abstr).
 77. Viteri F. Weekly compared with daily iron supplementation. *Am J Clin Nutr* 1996;63:610-2.
 78. Ridwan E, Schultink W, Dillon D, Gross R. Effects of weekly iron supplementation on pregnant Indonesian women are similar to those of daily supplementation. *Am J Clin Nutr* 1996;63:884-90.
 79. Scrimshaw NS. Functional significance of iron deficiency. In: Enwonwu CO, ed. *Functional significance of iron deficiency. Annual Nutrition Workshop Series. Vol 3.* Nashville, TN: Center for Nutrition, Meharry Medical College, 1990:1-13.
 80. Mahomed K, Hytten F. Iron and folate supplementation in pregnancy. In: Chalmers I, Enkin M, Keirse MNJC, eds. *Effective care in pregnancy and childbirth.* London: Oxford University Press, 1989:301-18.
 81. Murphy JF, O'Riordan J, Newcombe RG, et al. Relation of haemoglobin levels in first and second trimester to outcome of pregnancy. *Lancet* 1986;1:992-5.
 82. Garn SM, Keating MT, Falkner F. Hematological status and pregnancy outcomes. *Am J Clin Nutr* 1981;34:115-7.
 83. Garn SM, Ridella SA, Petzold AS, Falkner F. Maternal hematologic levels and pregnancy outcomes. *Semin Perinatol* 1981;5:155-62.
 84. Sagen N, Nilsen ST, Kim HC, Bergsj P, Koller O. Maternal hemoglobin concentration is closely related to birth weight in normal pregnancies. *Acta Obstet Gynecol Scand* 1984;63:245-8.
 85. Steer P, Alam MA, Wadsworth J, Welch A. Relation between maternal haemoglobin concentration and birth weight in different ethnic groups. *BMJ* 1995;310:489-91.
 86. Pritchard JA, Hunt CF. A comparison of the hematologic responses following the routine prenatal administration of intramuscular and oral iron. *Surg Gynecol Obstet* 1958;106:516-8.
 87. Hemminki E, Rimpelä U. Iron supplementation, maternal packed cell volume, and fetal growth. *Arch Dis Child* 1991;66:422-5.
 88. Jenkinson D. Single-dose intramuscular iron dextran in pregnancy for anaemia prevention in urban Zambia. *J Trop Med Hyg* 1984;87:71-4.
 89. Sloan NL, Jordan E. Prevalence of maternal anemia in developing countries. Arlington, VA: John Snow, Inc, 1992. (MotherCare Working Paper no. 7B.)
 90. Hemminki E, Uski A, Koponen P, Rimpelä U. Iron supplementation during pregnancy—experiences of a randomized trial relying on health service personnel. *Control Clin Trials* 1989;10:290-8.
 91. Hemminki E, Nemet K, Horvath M, et al. Impact of iron fortification of milk formulas on infants growth and health. *Nutr Res* 1995;15:491-503.
 92. Hemminki E, Rimpelä U. A randomized comparison of routine versus selective iron supplementation during pregnancy. *J Am Coll Nutr* 1991;10:3-10.
 93. Hemminki E, Meriläinen J. Long-term follow-up of mothers and their infants in a randomized trial on iron prophylaxis during pregnancy. *Am J Obstet Gynecol* 1995;173:205-9.
 94. Strauss RG. Iron deficiency, infections, and immune function: a reassessment. *Am J Clin Nutr* 1978;31:660-6.
 95. Dallman PR. Iron deficiency and the immune response. *Am J Clin Nutr* 1987;46:329-34.
 96. Prema K, Ramakakshmi BA, Madhavapeddi R, Babu S. Immune status of anaemic pregnant women. *Br J Obstet Gynaecol* 1982;89:222-5.
 97. Kandoi A, Bhatia BD, Pandey S, Sen PC, Satya K. Cellular immunity status in anaemia in pregnancy. *Indian J Med Res* 1991;94:11-5.
 98. Oppenheimer SJ, Macfarlane SBJ, Moody JB, Bunari O, Hendrickse RG. Effect of iron prophylaxis on morbidity due to infectious disease: report on clinical studies in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1986;80:596-602.
 99. Halliwell B, Gutteridge J. *Free radicals in biology and medicine.* London: Oxford University Press, 1991:33-8.
 100. Wu W-H, Meydani M, Meydani SN, Burkland PM, Blumberg JB, Munro HN. Effect of dietary iron overload on lipid peroxidation, prostaglandin synthesis and lymphocyte proliferation in young and old rats. *J Nutr* 1990;120:280-9.
 101. Hemminki E, Rimpelä U, Ylä-Outinen A. Iron prophylaxis during pregnancy and infections. *Int J Vitam Nutr Res* 1991;61:370-1.
 102. Fairweather-Tait S. Iron-zinc and calcium-iron interaction in relation to zinc and iron absorption. *Proc Nutr Soc* 1995;54:465-73.
 103. Solomons NW, Ruz M. Zinc and iron interaction: concepts and perspectives in the developing world. *Nutr Res* 1997;17:177-85.
 104. Murray MJ, Murray AB, Murray MB, Murray CJ. The adverse effect of iron repletion on the course of certain infections. *Br Med J* 1978;2:1113-5.
 105. Elsdon-Dew R. Endemic fulminant amebic dysentery. *Am J Trop Med Hyg* 1949;29:337-40.
 106. Idjradinata P, Watkins WE, Pollitt E. Adverse effects of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994;343:1252-4.
 107. Scholl TO, Hediger ML, Fischer RL, Scheerer JW. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *Am J Clin Nutr* 1992;55:985-8.
 108. MacGregor MW. Maternal anaemia as a factor in prematurity and perinatal mortality. *Scott Med J* 1963;8:134-40.
 109. Stones RW, Paterson CM, Saunders NJ. Risk factors for major obstetric haemorrhage. *Eur J Obstet Gynecol Reprod Biol* 1993;48:15-8.
 110. Gilbert L, Porter W, Brown VA. Postpartum haemorrhage—a continuing problem. *Br J Obstet Gynaecol* 1987;94:67-71.
 111. Hayashi RHJ. The role of prostaglandins in the treatment of postpartum haemorrhage. *J Obstet Gynaecol* 1990;10(suppl):S21-4.
 112. Chua S, Arulkumaran S, Lim I, et al. Influence of breast-feeding and nipple stimulation on postpartum uterine activity. *Br J Obstet Gynaecol* 1994;101:804-5.
 113. Irons DV, Sriskandabalan P, Bullough CHW. A simple alternative to parenteral oxytocics for the third stage of labour. *Int J Gynaecol Obstet* 1994;46:15-21.
 114. Kelly J, Kwast BE. Obstetric vesicovaginal fistulas: evaluation of failed repairs. *Int Urogynecol J* 1993;4:271-3.
 115. Megafu U, Ozumba BC. Obstetric complications of macrosomic babies in African women. *Int J Gynaecol Obstet* 1988;26:197-202.
 116. Thomson AM. Maternal stature and reproductive efficiency. *Eugen Rev* 1959;51:157-62.
 117. Akingba JB. Outcome of pregnancy in short Nigerians. *J Nigerian Med Assoc* 1971;1:52-7.
 118. Mallika PE. Maternal height and reproductive performance. *J Obstet Gynaecol India* 1974;24:36-40.
 119. Everett VJ. The relation between maternal height and cephalopelvic disproportion in Dar es Salaam. *E Afr Med J* 1975;52(5):251-6.
 120. Kasongo Project Team. Antenatal screening for fetopelvic dystocias: a cost-effectiveness approach to the choice of simple indicators for use by auxiliary personnel. *J Trop Med Hyg* 1984;87:173-83.
 121. Camilleri AP. The obstetric significance of short stature. *Eur J Obstet Gynecol Reprod Biol* 1981;12:347-56.
 122. Aitken IW, Walls B. Maternal height and cephalopelvic disproportion in Sierra Leone. *Trop Doct* 1986;16:132-4.
 123. Adadevoh SWK, Hobbs C, Elkins TE. The relation of the true conjugate to maternal height and obstetric performance in Ghanaians. *Int J Gynaecol Obstet* 1989;28:243-51.
 124. Sokal D, Sawadogo L, Adjibade A. Operations Research Team. Short stature and cephalopelvic disproportion in Burkina Faso, West Africa. *Int J Gynaecol Obstet* 1991;35:347-50.
 125. Tsu VD. Maternal height and age: risk factors for cephalopelvic disproportion in Zimbabwe. *Int J Epidemiol* 1992;21:941-7.
 126. Harrison KA, Rossiter CE, Chong H. Relations between maternal height, fetal birth weight and cephalopelvic disproportion suggest

- that young Nigerian primigravidae grow during pregnancy. *Br J Obstet Gynaecol* 1985;92(suppl):40–8.
127. Harrison KA, Fleming AF, Briggs ND, Rossiter CE. Growth during pregnancy in Nigerian teenage primigravidae. *Br J Obstet Gynaecol* 1985;92(suppl):32–9.
 128. World Health Organization. Maternal anthropometry and pregnancy outcomes. A World Health Organization collaborative study. *Bull World Health Organ* 1995;73(suppl):1–98.
 129. Kelly A, Kevany J, de Onis M, Shah PM. A World Health Organization collaborative study of maternal anthropometry and pregnancy outcomes. *Int J Gynaecol Obstet* 1996;53:219–33.
 130. Moerman M. Growth of the birth canal in adolescent girls. *Am J Obstet Gynecol* 1982;143:528–32.
 131. Martorell R, Kettel Khan L, Schroeder DG. Reversibility of stunting: epidemiologic findings in children from developing countries. *Eur J Clin Nutr* 1994;48(suppl):S45–57.
 132. Golden MHN. Is complete catch-up possible for stunted malnourished children? *Eur J Clin Nutr* 1994;48(suppl):S58–71.
 133. Kulin HE, Bwibo N, Mutie D, Santner SJ. The effect of chronic childhood malnutrition on pubertal growth and development. *Am J Clin Nutr* 1982;36:527–36.
 134. Dreizen S, Spirakis CN, Stone RE. A comparison of skeletal growth and maturation in undernourished and well-nourished girls before and after menarche. *J Pediatr* 1967;70:256–63.
 135. Steckel RH. Growth depression and recovery: the remarkable case of American slaves. *Ann Hum Biol* 1987;14:111–32.
 136. Satyanarayana K, Nadamuni Naidu A, Swaminathan MC, Narasinga Rao BS. Effect of nutritional deprivation in early childhood on later growth—a community study without intervention. *Am J Clin Nutr* 1981;34:1636–7.
 137. Riley AP. Determinants of adolescent fertility and its consequences for maternal health, with special reference to rural Bangladesh. *Ann N Y Acad Sci* 1994;709:87–100.
 138. Schroeder DG, Martorell R, Rivera JA, et al. Age differences in the impact of nutritional supplementation on growth. *J Nutr* 1995;125:1051S–9S.
 139. Martorell R, Rivera J, Kaplowitz H. Consequences of stunting in early childhood for adult body size in rural Guatemala. *Ann Nestle [Fr]* 1990;48:85–92.
 140. Tuddenham, RD, Snyder MM. Physical growth of Californian boys and girls from birth to eighteen years. University of California publications in child development. Berkeley, CA: University of California Press, 1954:183–364.
 141. Dagnelie PC, van Dusseldorp M, van Staveren WA, Hautvast JGAJ. Effects of macrobiotic diets on linear growth in infants and children until 10 y of age. *Eur J Clin Nutr* 1994;48(suppl):S103–12.
 142. Graham CG, Adrianzen B. Late catch-up growth after severe infantile malnutrition. *Johns Hopkins Med J* 1972;131:204–11.
 143. Proos LA, Hofvander Y, Tuvemo T. Menarcheal age and growth pattern of Indian girls adopted in Sweden. I. Menarcheal age. *Acta Paediatr Scand* 1991;80:852–8.
 144. Proos LA, Hofvander Y, Tuvemo T. Menarcheal age and growth pattern of Indian girls adopted in Sweden. II. Catch-up growth and final height. *Indian J Pediatr* 1991;58:105–14.
 145. Proos LA, Hofvander Y, Wennqvist K, Tuvemo T. A longitudinal study on anthropometric and clinical development of Indian children adopted in Sweden. II. Growth, morbidity and development during two years after arrival in Sweden. In: Proos LA, ed. Growth and development Indian children adopted in Sweden. Vol 5. Uppsala, Sweden: Lindbergs Grafiska HB, 1992:1–18.
 146. Proos LA. Anthropometry in adolescence—secular trends, adoption, ethnic and environmental differences. *Horm Res* 1993;39(suppl):18–24.
 147. Winick M, Meyer KK, Harris RC. Malnutrition and environmental enrichment by early adoption. *Science* 1975;190:1173–5.
 148. Lien NM, Meyer KK, Winick M. Early malnutrition and “late” adoption: a study of their effects on the development of Korean orphans adopted into American families. *Am J Clin Nutr* 1977;30:1734–9.
 149. Schumacher LB, Pawson LG, Kretchmer N. Growth of immigrant children in the newcomer schools of San Francisco. *Pediatrics* 1987;80:861–8.
 150. Yip R, Scanlon K, Trowbridge F. Improving growth status of Asian refugee children in the United States. *JAMA* 1992;267:937–40.
 151. Beaton GH, Ghassemi H. Supplementary feeding programs for young children in developing countries. *Am J Clin Nutr* 1982;35:863–916.
 152. Balachander J. Tamil Nadu’s successful nutrition effort. In: Rohde J, Chatterjee M, Morley D, eds. Reaching health for all. Bombay, India: Oxford University Press, 1993.
 153. Meacham A, Gillespie S. Implementation completion report, India: second Tamil Nadu Integrated Nutrition Project [Credit 2158-IN]. World Bank: Health, Population and Nutrition Unit, South Asia Region, 1998.
 154. Fleming AF, Ghatoura GBS, Harrison KA, et al. The prevention of anaemia in pregnancy in primigravidae in the Guinea savannah of Nigeria. *Ann Trop Med Parasitol* 1986;80:211–33.
 155. Willett WC, Kilama WL, Kihamia CM. Ascariis and growth rates: a randomized trial of treatment. *Am J Public Health* 1979;69:987–91.
 156. Stephenson LS, Latham MC, Adams EJ, Kinoti SN, Pertet A. Weight gain of Kenyan school children infected with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* is improved following once- or twice-yearly treatment with albendazole. *J Nutr* 1993;123:656–65.
 157. Latham MC, Stephenson LS, Kinoti SN, et al. Improvements in growth following iron supplementation in young Kenyan school children. *Nutrition* 1990;6:159–65.
 158. Bhatia D, Seshadri S. Growth performance in anaemia and following iron supplementation. *Indian Pediatr* 1993;30:195–200.
 159. Prentice A, Bates CJ. Adequacy of dietary mineral supply for human bone growth and mineralisation. *Eur J Clin Nutr* 1994;48(suppl):S161–77.
 160. Brown KH, Peerson JM, Allen LH. Effect of zinc supplementation on children’s growth: a meta analysis of intervention trials. In: Sandström B, Walther P, eds. Trace elements, growth and development: role of trace elements for health promotion and disease prevention. *Bibl Nutr Dieta* 1998;54:76–83.
 161. West KP Jr, Djunaedi E, Pandiji A, Kusdiono, Tarwotjo I, Sommer A. Vitamin A supplementation and growth: a randomized community trial. *Am J Clin Nutr* 1988;48:1257–64.
 162. Fawzi WW, Herrera MG, Willett WC, Nestel P, El Amin A, Mohamed KA. Dietary vitamin A intake in relation to child growth. *Epidemiology* 1997;8:402–7.
 163. Dreyfuss ML, West KP Jr, Katz J, et al. Effects of maternal vitamin A or β -carotene supplementation in intrauterine/neonatal and early infant growth in Nepal. XVII IVACG Meeting. Washington, DC: International Vitamin A Consultative Group, 1997:104 (abstr).
 164. Harrison KA. Predicting trends in operative delivery for cephalopelvic disproportion in Africa. *Lancet* 1990;335:861–2.
 165. Mtimavalye LAR, Van der Does CD, Maathuis JB. The relationship between increasing birthweight and cephalopelvic disproportion in Dar es Salaam, Tanzania. *J Obstet Gynaecol Br Commonw* 1074;81:380–2.
 166. Rush D. Effects of changes in protein and calorie intake during pregnancy on the growth of the human fetus. In: Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. London: Oxford University Press, 1989:255–80.
 167. Gibson R. Zinc nutrition in developing countries. *Nutr Res Rev* 1994;7:151–73.
 168. Hunt I, Murphy N, Cleaver A, et al. Zinc supplementation during pregnancy: effects on selected blood constituents and on progress and outcome of pregnancy in low-income women of Mexican descent. *Am J Clin Nutr* 1984;40:508–21.
 169. Goldenberg R, Tamara T, Negggers Y, et al. The effect of zinc supplementation on pregnancy outcome. *JAMA* 1995;274:463–8.
 170. Rush D. Nutrition, birthweight, and child mortality in India: the use

- of epidemiology in setting priorities. *Indian J Commonw Med* 1987; 12:61–7.
171. Mphahlele M. Dietary restriction for the prevention of disproportion and obstructed labour among the Pedi of yester-year. *S Afr Med J* 1982;61:842.
 172. Nichter M, Nichter M. The ethnophysiology and folk dietetics of pregnancy: a case study from South India. *Hum Organ* 1983;42:235–46.
 173. Brems S, Berg A. 'Eating down' during pregnancy: nutrition, obstetric and cultural considerations in the third world. Discussion paper prepared for the ACC/SCN. Washington, DC: World Bank, 1988.
 174. Redman C. Eclampsia still kills. *Br Med J* 1988;296:1209–10.
 175. Walker JJ, Leitch CR. The death of eclampsia. *Br J Hosp Med* 1994; 51:148–9.
 176. Douglas KA, Redman CWG. Eclampsia in the United Kingdom. *BMJ* 1994;309:1395–400.
 177. Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Br J Obstet Gynaecol* 1992;99:547–53.
 178. Moodley J, Daya P. Eclampsia: a continuing problem in developing countries. *Int J Gynecol Obstet* 1993;44:9–14.
 179. Brown MA. The physiology of pre-eclampsia. *Clin Exp Pharmacol Physiol* 1995;22:781–91.
 180. Davies AM. Geographical epidemiology of the toxemias of pregnancy. *Isr J Med Sci* 1971;7:751–821.
 181. Baird D, Thomson AM, Hytten F. Weight gain in preeclampsia. *Lancet* 1962;1:1297–8.
 182. Loudon I. Some historical aspects of toxemia of pregnancy: a review. *Br J Obstet Gynaecol* 1991;98:853–8.
 183. Chamberlain G, Philipp E, Howlett B, Masters K. *British births 1970. Vol 2. Obstetric care.* London: Heinemann Medical Books, 1978.
 184. World Health Organization. International Collaborative Study of Hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension in pregnancy. *Am J Obstet Gynecol* 1988;158:80–3.
 185. Obed SA, Wilson JB, Elkins TE. Eclampsia: 134 consecutive cases. *Int J Gynaecol Obstet* 1994;45:97–103.
 186. Agobe JT, Good W, Hancock KW. Meteorological relations of eclampsia in Lagos, Nigeria. *Br J Obstet Gynaecol* 1981;88:706–10.
 187. Sartelet H, Rogier C, Milko-Sartelet I, Angel G, Michel G. Malaria associated pre-eclampsia in Senegal. *Lancet* 1996;347:1121 (letter).
 188. Green J. Diet and the prevention of pre-eclampsia. In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective care in pregnancy and childbirth. Vol 1. Pregnancy, Parts 1–5.* Oxford, United Kingdom: Oxford University Press, 1989:281–300.
 189. Chaudhuri SK, Halder K, Chowdhury SR, Bagchi K. Relationship between toxemia of pregnancy and thiamine deficiency. *J Obstet Gynaecol Br Commonw* 1969;76:123–6.
 190. Schweitz LJ, Rodriguez GA, Voyevodka IL. Dietary sodium chloride in pregnant hypertensive patients: a preliminary report. *Perspect Nephrol Hypertens* 1976;5:203–6.
 191. Carroli G, Duley L, Belizan J, Villar J. Calcium supplementation during pregnancy: a systematic review of randomized controlled trials. *Br J Obstet Gynaecol* 1994;101:753–8.
 192. Bucher HC, Guyatt GH, Cook, RJ, et al. Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. *JAMA* 1996;275: 1113–7.
 193. Hamet P. The evaluation of the scientific evidence for a relationship between calcium and hypertension. *J Nutr* 1995;125(suppl): 311S–400S.
 194. Levine RJ, Esterlitz JR, Raymond EG, et al. Trial of Calcium for Preeclampsia Prevention (CPEP): rationale, design, and methods. *Control Clin Trials* 1996;17:442–69.
 195. Levine RJ, CPEP Study Group. Calcium for Preeclampsia Prevention (CPEP): a double-blind, placebo-controlled trial in healthy nulliparas. *Am J Obstet Gynecol* 1997;176:S2 (abstr).
 196. Levine RJ, Hauth JC, Curet LB. Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997;337:69–76.
 197. Altura BM, Altura BT, Carella A. Magnesium deficiency-induced spasms of umbilical vessels: relation to preeclampsia, hypertension, growth retardation. *Science* 1983;221:376–8.
 198. Melles Z, Kiss SA. Influence of the magnesium content of drinking water and of magnesium therapy on the occurrence of preeclampsia. *Magnes Res* 1992;5:277–9.
 199. Spätling L, Spätling G. Magnesium supplementation in pregnancy: a double-blind study. *Br J Obstet Gynaecol* 1988;95:120–5.
 200. Sibai BM, Gordon T, Thom E, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study: the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 1995;172:642–8.
 201. Stone JL, Lockwood CJ, Berkowitz GS, et al. Risk factors for severe preeclampsia. *Obstet Gynecol* 1994;83:357–61.
 202. Abi-Said D, Annegers JF, Combs-Cantrell D, et al. Case-control study of the risk factors for eclampsia. *Am J Epidemiol* 1995;142: 437–41.
 203. Davies AM, Poznansky R, Weiskopf P, et al. Toxemia of pregnancy in Jerusalem. II. The role of diet. *Isr J Med Sci* 1967;12:508–18.
 204. Zlatnik FJ, Burmeister LF. Dietary protein and preeclampsia. *Am J Obstet Gynecol* 1983;147:345–6.
 205. Chaudhuri SK. Relationship of protein-calorie malnutrition with toxemia of pregnancy. *Am J Obstet Gynecol* 1970;107:33–7.
 206. Sattar N, Gaw A, Packard CJ, Greer IA. Potential pathogenic roles of aberrant lipoprotein and fatty acid metabolism in pre-eclampsia. *Br J Obstet Gynaecol* 1996;103:614–20.
 207. Olsen SF, Secher NJ. A possible preventive effect of low-dose fish oil on early delivery and pre-eclampsia: indications from a 50-year old controlled trial. *Br J Nutr* 1990;64:599–609.
 208. Onwude JL, Liford RJ, Hjartardottir H, et al. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. *Br J Obstet Gynaecol* 1995;102:95–100.
 209. Williams MA, Zingheim RW, King IB, Zebelman AM. Omega-3 fatty acids in maternal erythrocytes and risk of preeclampsia. *Epidemiology* 1995;6:232–7.
 210. Hipsley EH. Dietary 'fibre' and pregnancy toxemia. *Br Med J* 1953;2:420–2.
 211. Howler JF, Hewson AD. Dietary fibre and toxemia of pregnancy. *Med J Aust* 1957;1:761–3.
 212. Marcoux S, Brisson J, Fabia J. The effect of leisure time physical activity on the risk of pre-eclampsia and gestational hypertension. *J Epidemiol Community Health* 1989;43:147–52.
 213. Sachs BP, Jewett JF, Brown DAJ, et al. Hemorrhage, infection and toxemia, and cardiac disease, 1954–1985: causes for their declining role in maternal mortality. *Am J Public Health* 1988;78:671–5.
 214. Fauveau V, Mamdani M, Steinglass R, Koblinsky M. Maternal tetanus: magnitude, epidemiology and potential control measures. *Int J Gynaecol Obstet* 1993;40:3–12.
 215. West KP Jr, Katz J, Khatry SK, et al. Low-dose vitamin A or β -carotene supplementation reduces pregnancy-related mortality: a double-masked, randomized, controlled community trial in Nepal. *Br Med J* 1999;318:570–5.
 216. Cronin WA, Quansah MG, Larson E. Obstetric infection control in a developing country. *J Obstet Gynecol Neonatal Nurs* 1993;22:137–44.
 217. Goldenberg RL, Andrews WW. Intrauterine infection and why preterm prevention programs have failed. *Am J Public Health* 1996;86:781–3.
 218. Stoltzfus RJ, Chakraborty J, Rice A, de la Briere B, de Francisco A. Plausible evidence of effectiveness of an iron-supplementation pro-