Multiple micronutrients in pregnancy and lactation: an overview[1–3]

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ABSTRACT

This overview of multiple micronutrients during pregnancy and lactation emphasizes 2 relatively neglected issues. The first is that maternal micronutrient status in the periconceptional period, and throughout pregnancy and lactation, should be viewed as a continuum; too often these 3 stages are treated and discussed separately from both a scientific and a public health perspective. Iron and vitamin B-12 are included as examples to stress how status at conception affects maternal, fetal, and infant status and health until the child is weaned. The second issue is that while most attention has been focused on a few micronutrients, for example iron and folate as discussed elsewhere in this Supplement, multiple micronutrient deficiencies occur simultaneously when diets are poor. Some of these deserve more attention as causes of poor pregnancy outcome, including other B vitamin deficiencies that result in homocysteinemia, antioxidants, vitamin D, and iodine. In lactation, maternal status or intake of the B vitamins (except folate), vitamin A, selenium and iodine strongly affect the amount of these nutrients secreted in breast milk. This can result in the infant consuming substantially less than the recommended amounts and further depleting stores that were low at birth. While the optimal mode of meeting recommended micronutrient intakes is an adequate diet, in some situations supplementation is also important. Unfortunately, information is lacking on the optimal formulation of micronutrient supplements for pregnant women, and the need to continue these supplements during lactation is not recognized in many situations where maternal and infant health could benefit. *Am J Clin Nutr* 2005;81(suppl): 1206S–12S.

KEY WORDS Pregnancy, lactation, multiple micronutrients, iron deficiency anemia, B-vitamin deficiencies, homocysteine

INTRODUCTION

Adequate maternal micronutrient status is especially critical during pregnancy and lactation. In this overview, we draw attention to micronutrient issues that are sometimes neglected in the context of pregnancy and lactation. One of these is the importance of recognizing the continuum of maternal micronutrient status from the periconceptional period through lactation, and of fetal and infant dependency on adequate maternal status through this time. Another is the fact that multiple micronutrient deficiencies are likely to be present in many situations, some of which have been insufficiently appreciated as contributors to poor pregnancy outcomes and infant development.

The main cause of multiple micronutrient deficiencies is a poor quality diet, often due to an inadequate intake of animal source foods (ASF) especially in developing countries. Women who avoid meat and/or milk in wealthier regions of the world are also at higher risk of micronutrient depletion during pregnancy and lactation. Gene polymorphisms can also cause micronutrient deficiencies through impaired absorption or altered metabolism. This usually results in suboptimal maternal status of single nutrients. One example is folate, where maternal polymorphisms may increase the risk of neural tube defects unless dietary intake of the vitamin is sufficient. In some diets high in unrefined grains and legumes the amount of nutrients consumed may be adequate, but dietary constituents, such as phytates and polyphenols, limit their absorption. Diseases such as malaria, and infection with intestinal parasites, also impair status and alter the metabolism of multiple micronutrients. Finally, in pregnancy and/or lactation, the requirements for most nutrients are higher, increasing the risk of inadequate intake.

Several micronutrient deficiencies are well established to be contributors to abnormal prenatal development and/or pregnancy outcome. These include folate, iron, and iodine deficiencies. Less well recognized for their importance are deficiencies of B-vitamins (and subsequently elevated plasma homocysteine concentrations), vitamin D, and iodine. Additional research is needed to establish adverse effects of poor maternal vitamin A and zinc status in pregnancy. Evidence is accumulating that maternal antioxidant status is important to prevent abnormal pregnancy outcomes. In lactation, maternal status of these same micronutrients (except zinc) affects their concentrations in breast milk. Little attention has been paid to the adverse consequences of micronutrient depletion on maternal health and function during this period.

IRON DEFICIENCY AND ANEMIA

The importance of adequate iron status in pregnancy is emphasized elsewhere in this Supplement. Here, iron is discussed as an example of the need for adequate maternal status of a micronutrient from conception through lactation. Though there is still some controversy concerning the optimal stage of pregnancy at which to begin iron supplementation, several studies have now shown that iron stores at conception are a strong predictor of maternal iron status and risk of anemia in later pregnancy (1, 2).

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Maternal iron deficiency early in pregnancy has been hypothesized to predict the risk of preterm delivery, based on the fact that risk of conditions such as preeclampsia and premature delivery can be predicted based on hormone concentrations established by mid-pregnancy (3, 4). Also it is very difficult to replenish depleted iron stores once pregnancy is in progress. For example, Swedish women who were not taking iron supplements had virtually no iron remaining in their bone marrow by late pregnancy, compared with 35% of those who consumed 100 mg of iron daily from 16 wk of gestation (5).

One reviewer of the evidence concluded a few years ago that there was insufficient evidence to establish causality between maternal iron status or anemia, and low birth weight or preterm delivery, due to the inadequate number of adequately designed investigations (6). One severe limitation to adequately designing iron intervention studies in pregnancy has been the exclusion of women with anemia at baseline, and/or lack of a placebo group, due to ethical concerns. Using an innovative approach to limit this problem, Cogswell et al conducted an intervention in Cleveland that provided 30 mg iron daily from <20 wk to 28 wk of gestation. A placebo group was included because women found to have a hemoglobin concentration <100 g/L or ferritin <20 μg/L at 28 wk or 38 wk of gestation were supplemented with iron (7). Iron supplementation from enrollment through 28 wk of gestation did not affect the prevalence of anemia but increased birth weight by 206 g and lowered the incidence of low birth weight infants from 17% to 4%. Preterm delivery incidence was not affected, perhaps because supplementation was not started early enough in pregnancy (4). This intervention should be replicated in other populations.

While fetal iron status has been assumed to be relatively independent of maternal status during pregnancy, it is becoming clear that maternal iron status strongly affects the iron stores of the infant at birth. In Indonesia, De Pee et al observed that, compared with a normal birth weight infant born to a mother without anemia, a similar infant born to an anemic mother had a 1.8 times greater risk of developing anemia by 3 to 5 mo of age (8). The highest prevalence of anemia at 3 to 5 mo occurred in low birth weight infants whose mothers were anemic during pregnancy, with an odds ratio of 3.7 compared with normal birth weight infants born to nonanemic mothers. A substantial number of both observational (9, 10) and iron intervention (5, 11, 12) trials support this relation between infant and maternal iron status.

Another neglected problem is that women are often iron-depleted postpartum. Even for women in the United States who were enrolled in the Women, Infants, and Children (WIC) program, postpartum anemia occurred in 27% overall and in 48% of non-Hispanic blacks. The risk of postpartum anemia was greatest in those who were anemic in pregnancy; 49% of women who were anemic in trimester 3 developed anemia postpartum compared with 21% who were nonanemic (13). Anemia postpartum is associated with increased risk of postpartum depression (14).

These examples demonstrate that steps should be taken to ensure that maternal iron status is adequate early in pregnancy, throughout pregnancy and during the postpartum period. Inadequate attention has been paid to the problem of risk of iron deficiency in infants born to iron depleted mothers and to maternal iron status postpartum.

B-VITAMIN DEFICIENCIES AND HOMOCYSTEINEMIA IN PREGNANCY

The importance of adequate maternal folate status in the periconceptional period is discussed elsewhere in this Supplement. There is increasing interest in the fact that homocysteinemia is associated with a greater risk of adverse pregnancy outcomes. Deficiencies of folate, riboflavin, vitamin B-6, or vitamin B-12 lead to elevated plasma homocysteine (Hcy) concentrations. In a retrospective study of 5883 Norwegian women and their 14 492 infants there was a strong association between current Hcy concentrations and previous adverse pregnancy outcomes (15). Women in the highest versus the lowest quartile of plasma Hcy had a history of substantially more placental abruption, still-births, very low birth weight and preterm deliveries, preeclampsia, and club-foot and neural tube defects in their offspring. In a group of 93 Spanish women and their infants, fetal cord plasma Hcy concentration and birth weight were related to maternal plasma Hcy concentration before conception and throughout pregnancy (16). Women in the highest tertile of plasma Hcy at 2 mo of pregnancy had a 3.26 times greater risk of their infant being born in the lowest weight tertile. These odds increased to a 4 times greater risk for women in the highest Hcy tertile at labor, such that their infants weighed 228 g less than those born to mothers in the low and medium Hcy tertiles.

Folic acid supplementation of women in Spain significantly enhanced the physiologic reduction in plasma Hcy that occurs during pregnancy, when the supplements were provided during the 2nd and 3rd trimesters (17). Plasma Hcy appears to respond to supplementation with folic acid up to about 500 to 600 μg of folic acid per day. In addition to poor B vitamin status, other risk factors for elevated plasma Hcy include a high intake of coffee, smoking, and no use of vitamin supplements during pregnancy (15).

More attention needs to be paid to vitamin B-12 status of women during pregnancy and lactation. It has become apparent that there is a high global prevalence of low plasma vitamin B-12 concentrations in infants, children, and adults. For example, a recent review of available data from Latin America revealed that at least 40% of individuals in all age groups studied had low plasma vitamin B-12 (18). Other reports of a high prevalence of vitamin B-12 deficiency include those from Indian adults (19), Kenyan schoolers (20), and pregnant women in Nepal (21). The cause of these low plasma vitamin B-12 concentrations is most likely low dietary intake of the vitamin. While it is commonly believed that only strict vegetarians (vegans) are at substantial risk of developing vitamin B-12 deficiency, several studies have revealed that even lacto-ovo vegetarians (22), or individuals who consume low amounts of meat (23), have lower plasma vitamin B-12 and are at greater risk of vitamin B-12 deficiency compared with omnivores. Apart from studies on folate, there are few data on the relation between the B vitamin status of pregnant women in and risk of adverse pregnancy outcomes. Urban Nepali pregnant women had a 65% prevalence of low plasma B-12, with deficiency associated with higher plasma Hcy and a doubling of risk of preeclampsia and preterm delivery (21). In poor rural pregnant Nepali women the prevalence of low erythrocyte riboflavin concentrations was 89%, of low plasma vitamin B-6, 80%, and of low plasma vitamin B-12, 49%. Riboflavin supplementation alone significantly reduced plasma Hcy, but interventions were not tested with the other B vitamins (24). Low maternal

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plasma vitamin B-12 has been reported to be associated with increased risk of very early recurrent abortion (25), neural tube defects (26), and spina bifida (27).

In summary, poor maternal B-vitamin status may be a major global cause of homocysteinemia and poor pregnancy outcomes. It has not been established how homocysteinemia affects pregnancy outcome adversely, but proposed mechanisms include: Hcy increases oxygen free radical concentrations and reduces nitrous oxide concentrations, leading to endothelial dysfunction (28); Hcy causes oxidative stress and subsequent placental ischemia; Hcy causes an inflammatory response that is cytotoxic to endothelial cells; B-vitamin deficiencies lead to hypomethylation of DNA and altered gene expression, and Hcy induces apoptosis of endothelial cells (29); birth defects may be caused by Hcy interference with the N-methyl-D-aspartate receptor system (30); or Hcy is thrombogenic (31).

OTHER MICRONUTRIENTS IN PREGNANCY

The potential adverse effect of poor vitamin A status on pregnancy outcome was demonstrated in an intervention study in a region on Nepal with endemic vitamin A deficiency (32). Supplementation of these women with approximately their recommended daily intake of vitamin A reduced maternal mortality by 40%. Supplementation with β-carotene reduced mortality by 49%. The apparent cause of the reduced mortality risk was less susceptibility to infection. This trial is currently being repeated in Bangladesh and Ghana. An additional advantage of vitamin A supplementation of pregnant women is that it can increase hemoglobin concentrations, by about 10 g/L in marginally deficient populations (26). The upper limit for retinol supplements is 3000 IU per day based on the potential for higher doses to cause teratogenic effects. β-carotene supplements have not been reported to increase risk of birth defects.

There has been much debate about the efficacy of zinc supplementation in pregnancy. Maternal zinc status was associated with birth weight in 17/41 observation studies. In 6/12 trials there were some benefits (reduction in premature delivery in 3 trials; higher birth weight in 3 trials; reduction in hypertension in 1 trial). Zinc supplementation of Peruvian women did not affect fetal dimensions, birth weight, or the incidence of preterm delivery (33). However, it did reduce fetal heart rate, and increase heart rate accelerations and variability, and fetal movements, which was interpreted to indicate better fetal development (34). In Bangladesh, maternal supplementation in pregnancy had no effect on birth weight, but reduced morbidity of low birth weight infants in the first 6 mo of life (35).

Vitamin D status of pregnant women should be of greater concern even in industrialized countries such as the United States. In the National Health and Nutrition Examination Survey (NHANES) III (1988–1994), 42% of African American women and 4% of Caucasian–non-Hispanic women in 7 states had low plasma concentrations of 25-hydroxyvitamin D (36). Low values were predicted by less intake of fortified breakfast cereals and milk, season, and no use of vitamin D supplements. Vitamin D deficiency is becoming increasingly common in adolescents. Women whose clothing covers a high proportion of their skin, or whose skin is highly pigmented, are at greater risk of vitamin D deficiency. Even moderately low plasma 25-hydroxyvitamin D concentrations observed in Parisian women at the end of winter were associated with poor fetal and infant skeletal growth and mineralization, and poor infant tooth mineralization. These biochemical and clinical signs of vitamin D deficiency were prevented by maternal supplementation with the vitamin (37).

Little attention has been paid to the potentially important issue of antioxidant nutrient status in pregnancy. Oxidative stress caused by free radicals has been implicated in many studies of the etiology of preeclampsia (38). Because ascorbic acid and vitamin E inhibit free radical formation, a double-blind randomized trial was conducted in 283 women who had either a previous history of pregnancy complications or an abnormal ultrasound (39). The supplement provided 1000 mg ascorbic acid and 400 IU vitamin E daily from week 16–22 of pregnancy, and resulted in a 76% reduction in preeclampsia, and a 21% reduction in indicators of endothelial activation and placental dysfunction.

Because even mild maternal iodine deficiency can affect fetal mental development adversely, adequate iodine status in pregnancy is critically important (40). Universal salt iodization has greatly reduced the prevalence of iodine deficiency worldwide but for various reasons, intakes of iodine are often still inadequate. Pregnancy tends to increase the appearance of clinical and biochemical symptoms of iodine deficiency in women with marginal iodine status, resulting in abnormal thyroid hormone concentrations in countries such as Belgium (40). Indeed, a recent review of the need for iodine supplementation found that the majority of women in Europe are iodine deficient during pregnancy but that many prenatal micronutrient supplements did not include iodine (41). In a recent national survey in the United States, 7% of pregnant women and 15% of women of childbearing age had low urinary iodine (42). Although signs of iodine deficiency are rare in the United States, it may be important for pregnant women who do not purchase iodized salt to ensure that their multiple micronutrient supplements contain iodine, but there is little specific information on this question.

MICRONUTRIENTS IN LACTATION

Exclusive breast-feeding is now recommended by all international agencies for the first 6 mo of life, because of the documented benefits of this feeding strategy for infant health and survival. While agencies such as the WHO emphasize the importance of paying attention to the nutritional status of the lactating woman (43), this is rarely done in practice. Maternal micronutrient deficiencies during lactation can cause a major reduction in the concentration of some of these nutrients in breast milk, with subsequent infant depletion (44). Based on a categorization of the relation between maternal status or intake of each nutrient and its effect on the nutrient concentration in breast milk, "priority" nutrients for lactating women include thiamin, riboflavin, vitamins B-6 and B-12, vitamin A, and iodine (45). This based on the fact that low maternal intake or stores reduces the amount of these nutrients in breast milk, and maternal supplementation can reverse this problem.

Our current understanding of vitamin B-12 deficiency in the perinatal period illustrates the continuum of micronutrient deficiency depletion. Recent data show a strong association between maternal and infant plasma vitamin B-12 concentrations at delivery indicating that maternal B-12 status in pregnancy affects infant status at birth (46). Poor maternal intake in lactation can lead to further infant depletion due to the low secretion of vitamin B-12 in breast milk. For example, 62% of rural Mexican women had low concentrations of vitamin B-12 in breast milk at 6 to 8 mo

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TABLE 1
Estimated percent of Adequate Intake (AI) consumed by exclusively breastfed infants in developing countries, based on reported milk nutrient concentrations[1]

	AI 0–6 mo[2]	Milk value on which AI based[3]	Possible milk value in deficient women[4]	Estimated intake by EBF infant[5]	% AI
Thiamin (mg)	0.2	0.21 mg/L	0.16 mg/L	0.12 mg	60
Riboflavin (mg)	0.3	0.35 mg/L	0.21 mg/L	0.16 mg	53
B6 (mg)	0.1	0.13 mg/L	0.10 mg/L	0.08	80
B12 (μg)	0.4	0.42 μg/L	0.13–0.36 μg/L	0.10–0.28 μg	25–55
Vitamin A (μg RE)	400	485 μg/L	290 μg/L	226 μg	56
Vitamin C (mg)	40	50 mg/L	25 mg/L	20 mg	50
Iodine (ug)	110	146 ug/L	9–32 ug/L	7–25 ug	6–23
Selenium (μg)	15	18 μg/L	10 μg/L	7.8 μg	52

[1] From Allen & Graham (43).
[2] Adequate Intake value from the Institute of Medicine's Dietary Reference Intakes, based on an assumed breast milk volume of 780 mL/d.
[3] Concentration in breast milk of well-nourished women.
[4] Based on reported breast milk concentrations in undernourished women in developing countries (43).
[5] Based on breast milk concentration in column 5 and assumed breast milk volume of 780 mL/d.

of lactation (47). In peri-urban Guatemala City, 31% of breast milk samples were low in vitamin B-12 at 3 mo postpartum (48), and 62% of infants in the same community had deficient or low vitamin B-12 concentrations in plasma at age 7 to12 mo (49). The vitamin B-12 status of these infants was inversely related to the amount of breast milk that they consumed, because those who consumed less breast milk consumed more cow's milk, which contains about 10 times more vitamin B-12 than even the breast milk of well-nourished women. Less information is available on other B-vitamins in lactation but evidence from various studies indicates that deficiencies are prevalent in some regions of the world resulting in low breast milk concentrations and inadequate infant intakes (44). Breast milk iodine concentrations are very sensitive to maternal status (50) although little is known about how improving maternal status during lactation might improve infant development; providing a high dose of iodine directly to Indonesian infants aged 6 wk reduced mortality substantially during the subsequent 4 mo (51).

The situation with vitamin A status in lactation is slightly different. Infants' liver stores of vitamin A at birth are very small even in well-nourished populations, so they are greatly dependent on dietary intake of the vitamin. Breast milk is a good source of vitamin A and clinical vitamin A deficiency is rare in breastfed infants during their first year of life, even in poor populations. The normal concentration of retinol in breast milk is about 485 μg/L but in areas of endemic vitamin A deficiency the concentrations can fall below 300 μg/L, and many infants become depleted. To prevent this situation, high dose supplements of vitamin A are provided to mothers postpartum and to infants as part of the Expanded Program in Immunization (EPI) (52). Maintaining an adequate daily supply of vitamin A in breast milk sustains infant vitamin A status better than the sporadic administration of high dose vitamin A supplements, because liver stores of the latter are typically depleted between EPI visits (53).

In contrast to B vitamins, vitamin A, and iodine, the iron content of breast milk is not affected by maternal nutritional status. The iron content of breast milk is not sufficient to maintain infant iron stores during the first year of life, but providing maternal iron supplements during lactation cannot rectify this situation. The general recommendation is therefore to provide iron supplements to infants after 6 mo of age, and after 2 mo of age in the event of preterm delivery and/or low birth weight. Concern has been raised about whether iron supplementation of infants and young children increases morbidity and mortality from infections, especially for those who are not iron deficient. Nonanemic infants who were supplemented with iron in either Sweden or Honduras had significantly more diarrheal events than a placebo group (54). Erythropoietic response to iron may be immature in young infants (55), and they may be especially sensitive to free radical formation and oxidative stress induced by iron supplements (56, 57). It may therefore be safer to provide iron to infants in foods, including fortified foods, and only if they are iron deficient or live in areas with a high prevalence of iron deficiency anemia.

In a recent review we summarized the available data on how maternal depletion affects the infant's intake of micronutrients in breast milk (44). In general, infants will consume only about half of their recommended Adequate Intake (AI) of the "priority" micronutrients if their mother is depleted (**Table 1**).

PROVISION OF MICRONUTRIENTS TO PREGNANT AND LACTATING WOMEN

There are 3 main strategies for increasing maternal intake of multiple micronutrients. The first is to improve dietary quality, which in many situations might require increasing consumption of animal source foods, fruits, and vegetables. A number of studies have reported an association between poor maternal diet and a greater risk of pregnancy complications (58). Also, the relatively few adequately designed intervention studies show that provision of micronutrient-rich foods can improve pregnancy outcome (59, 60). In some situations well-designed nutrition education programs can improve dietary quality and pregnancy outcome (61).

An easier and more common approach is to provide multiple micronutrient supplements to women on their first clinic visit. The efficacy of this approach to improving pregnancy outcome has not been studied adequately. In an observational study of low-income pregnant adolescents in New Jersey, pregnancy outcomes of those who used supplements was compared with those who did not (62). For women who started taking supplements in their first trimester, there was a substantial reduction in preterm,

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very preterm, low birth weight and very low birth weight deliveries. If supplements were started in the second trimester, a similar pattern of response was observed, although reduction in complications was somewhat less substantial. In one of the better-known studies of the effects of folic acid supplementation on recurrence of neural tube defects, one arm of the study provided 12 vitamins including folic acid, 4 minerals and 3 trace elements, while the other arm provided only 3 trace elements. The supplement that contained most micronutrients reduced neural tube defects by 90%, and birth defects by 50%, compared with the trace element supplement (63). Women in this group also had less pregnancy complications and morning sickness. When the micronutrients were consumed before pregnancy, menstrual periods were more regular, time to conception was shorter, and the rate of conception was increased by 7%. Two more recent studies compared the benefits of providing multiple micronutrients including iron compared with iron alone. In Mexico (64, 65) and Nepal (66) multiple micronutrient supplements provided 100–150% of the RDA of 15 vitamins and minerals from around 13 wk of gestation. The supplements containing multiple micronutrients were no more effective than iron in improving maternal hemoglobin at 1 mo postpartum, birth weight or gestational age, or (only studied in Nepal) mortality of the infant in the first 6 mo of life. In contrast, multiple micronutrient supplementation of HIV positive pregnant women in Tanzania reduced low birth weight by 44%, preterm delivery by 39%, and IUGR by 43% (67). Although multiple micronutrient supplementation is theoretically preferable to supplementation with iron and folic acid alone, especially in developing countries where multiple deficiencies are prevalent, more data needs to be collected to determine the advantages of different multiple micronutrient formulations for pregnant and lactating women.

CONCLUSION

Even in some industrialized countries there is strong evidence for the benefits of maternal supplementation with iron, folic acid, and vitamin D and at least in Europe, iodine. There is also some evidence that high quality diets and or multiple micronutrient supplements are beneficial for pregnant women even in industrialized countries. The reasons for inconsistent beneficial effects in the multiple micronutrient trials in developing countries is not yet clear. More efficacy trials are needed to test the benefits of neglected nutrients, such as B-vitamins, in both industrialized and developing countries.

Ideally, micronutrient deficiencies should be prevented or treated before a woman becomes pregnant. This will improve fertility and maternal health. To maximize the reduction of birth defects it is important to prevent maternal micronutrient deficiencies in the periconceptional period, but about 50% of pregnancies are unplanned even in the United States and entry to healthcare may be late. Early prevention of B-vitamin deficiencies may also be important to prevent homocysteinemia and iron depletion throughout pregnancy, and to prevent preterm delivery, which is programmed by the middle of gestation. A theoretically reasonable approach to test would be the efficacy of giving multiple micronutrient supplements once or twice a week to women capable of becoming pregnant and then possibly more frequently during pregnancy.

Finally, because micronutrient status of the lactating woman is critical for the secretion of adequate micronutrient concentrations in breast milk, and for the micronutrient status of her infant, more attention should be paid to the micronutrient status of lactating women. Provision of multiple micronutrient supplements and/or food fortification with micronutrients may be advisable for the majority of lactating women in developing countries and industrialized countries—not least to prevent their further depletion through the secretion of large amount of these micronutrients in breast milk.

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