Nutrition in pregnancy: mineral and vitamin supplements[1–3]

Oladapo A Ladipo

ABSTRACT Pregnancy is associated with physiologic changes that result in increased plasma volume and red blood cells and decreased concentrations of circulating nutrient-binding proteins and micronutrients. In many developing countries, these physiologic changes can be aggravated by undernutrition, leading to micronutrient deficiency states, such as anemia, that can have disastrous consequences for both mothers and newborn infants. Multiple micronutrients are often taken by pregnant women in developed countries, but their benefits are limited, except for prophylactic folic acid taken during the periconceptional period. Women in developing countries may benefit from multiple-micronutrient prophylaxis in pregnancy, but the underlying basis and rationale for changing from supplementation with iron and folate to supplementation with multiple micronutrients has not been debated in the context of existing program objectives. There is an urgent need for this discussion so that both program effectiveness and program efficacy can be improved. *Am J Clin Nutr* 2000;72(suppl):280S–90S.

KEY WORDS Nutrition, vitamins, trace elements, minerals, pregnancy, requirements

INTRODUCTION

The demand for both energy and nutrients is increased during pregnancy (1). For well-nourished women, only a small amount of additional energy is required because the body adapts to the increased energy requirements and becomes more energy efficient through reduced physical activity and a lowered metabolic rate. Although the average-sized, well-nourished woman requires ≈10 460 kJ/d (2000 kcal/d) during the last trimester of pregnancy (2), many women in developing countries restrict their food intake during pregnancy to have smaller infants, on the premise that smaller infants will carry a lower risk of delivery complications (3). Recent evidence suggests, however, that infants who are small or disproportionate at birth have increased health risks later in life (4–6). The hypothesis is that such infants have had to adapt to a limited supply of nutrients and that in so doing their physiology and metabolism are permanently changed, although the rationale for this hypothesis has been challenged (7).

Requirements for many, but not all, micronutrients increase during pregnancy. Deficiencies can exist because of losses or malabsorption associated with disease or inadequate intakes, lack of knowledge about adequate prenatal nutrition, or dietary taboos associated with pregnancy (8), with potential adverse consequences for both mothers and newborn infants. Rush (9) notes that anemia in pregnancy and pregnancy-induced hypertension are common and thought to contribute significantly to maternal mortality and morbidity in developing countries. Maine (10), however, shows there is little evidence that nutrition plays a role in pregnancy-induced hypertension.

This paper discusses minerals and trace elements as well as fat- and water-soluble vitamins in pregnancy—their concentrations, the requirements for them, the consequences of their deficiency, and the functional effects of supplementation with them. This is followed by a discussion of issues and required action.

VITAMINS AND MINERALS

As a component of prenatal care, micronutrient supplementation might reduce maternal morbidity and mortality directly by treating a pregnancy-related illness or indirectly by lowering the risk of complications at delivery. Nevertheless, the effectiveness of supplementation programs—notably of iron and folate—has tended to focus on infant outcomes, perinatal mortality, preterm delivery, and low birth weight (11). When infant outcomes are discussed, however, a distinction needs to be made between the teratogenic effects of deficiency at periconception and deficiency in later pregnancy. The former includes folate deficiency resulting in fetal neural tube defects (12, 13) and iodine deficiency that causes cretinism (14), whereas the latter includes intrauterine growth retardation (15, 16) and other pregnancy-related and delivery complications (17–21). This distinction is important because many pregnancies in developing countries are unplanned; the use of prenatal care services, in which iron or iron and folate supplements are generally provided or prescribed, is less than optimal (22); and the cost-effectiveness of the programs promoted needs to be considered. Even in developed countries, prenatal care providers have reservations about the widespread and indiscriminate use of prophylactic minerals and vitamins because of unproven benefits in well-nourished populations, risks of teratogenicity, and side effects (23–25). These concerns need to be considered in the context of developing countries.

[1] From the Department of Obstetrics and Gynaecology, University of Wales College of Medicine, Cardiff, United Kingdom.

[2] Presented at the meeting Iron and Maternal Mortality in the Developing World, held in Washington, DC, July 6–7, 1998.

[3] Address reprint requests to OAL, Department of Obstetrics and Gynaecology, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, United Kingdom. E-mail: oladapo.ladipo@net.ntl.com.

Am J Clin Nutr 2000;72(suppl):280S–90S. Printed in USA. © 2000 American Society for Clinical Nutrition

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

Data on vitamin and mineral metabolism and requirements during pregnancy are scanty, and determining the consequences of apparently deficient or excessive intakes is not easy (1). In pregnancy, maternal metabolism is altered by hormones that mediate the redirecting of nutrients to the placenta and mammary gland as well as the transfer of nutrients to the developing infant. Kidney function changes to handle the clearance of both fetal and maternal metabolic waste, which is associated with increased urinary excretion of water-soluble vitamins (eg, folate) (2). Blood volume and composition also change; by the third trimester, blood volume increases by 35–40% over the nonpregnant state, largely because of a 45–50% expansion of plasma volume and a 15–20% expansion of red blood cell mass.

Nutrient requirements during pregnancy are usually calculated by adding an increment to the value for nonpregnant and nonlactating women that covers the cost of fetal growth and development and the associated changes in maternal tissue metabolism. This factorial approach, however, may not necessarily be correct because it does not take into account metabolic changes in absorption or excretion that may compensate for the additional nutrient requirements without the need for an increase in intake.

Minerals and trace elements

Concentrations during pregnancy

Because the expansion of red blood cell mass is proportionally less than that of plasma, some biochemical indexes for minerals and trace elements, such as hemoglobin (26), fall in parallel to red blood cell volume. Others, such as zinc (27–29), decline progressively during pregnancy, whereas magnesium shows no gestational dependence until late pregnancy, when it declines continuously (MJ Keirse, unpublished observations, 2000). Phosphorus remains constant because of maternal adaptation (30) and copper increases in pregnancy (31). Calcium absorption increases early in pregnancy. At the same time, the protein-bound fraction in serum usually declines gradually throughout pregnancy, whereas the free ionic concentration remains relatively constant (32). The homeostatic control of ionic calcium is maintained by a complex interaction of vitamin D, parathyroid hormone, and calcitonin.

Requirements

The recommended dietary allowances (RDAs) or intakes of micronutrients for adolescent girls, nonpregnant and nonlactating adult women, and pregnant women in their third trimester taken from the National Research Council (NRC) (34), the Institute of Medicine (IOM) (34, 35), and the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) (37–41) are shown in **Table 1**. The percentage increase in dietary intakes for pregnant adults over nonreproducing women is also shown. The latter is based on the FAO/WHO values because these are the values used in most developing countries. The US data are presented for comparative purposes, with the IOM data being the most recent. In the absence of IOM values, NRC values continue to be used.

The RDA for calcium increases 122–167% during pregnancy over that for nonpregnant, nonlactating adult women, primarily for fetal skeletal development. The IOM (34) notes that no evidence exists to justify increasing the RDA for either phosphorus or magnesium above that for the nonpregnant state. The additional requirements for iron during pregnancy are described by Bothwell (26). The FAO/WHO disaggregates the recommended dietary intakes based on the bioavailability of dietary iron and, as shown in Table 1, the range increases between 187% and 407% for pregnant women eating a diet with low or very low bioavailable iron, which is the situation in many developing countries. The RDA for zinc in pregnancy increases by 44%, that for iodine by 33%, and that for selenium by 26% to cover fetal demands; copper requirements remain unchanged.

Deficiency

Calcium deficiency is rare in pregnancy but appears in cases of hypoparathyroidism and severe dietary inadequacy and in individuals who are unable to eat a diet rich in dairy products (41, 42). Low calcium and magnesium concentrations have been associated with hypertensive disorders of pregnancy, although a causal effect has not been shown (10; MJ Keirse, unpublished observations, 2000). Most foods contain phosphorus, and dietary deficiency is rare (33).

Iron deficiency resulting mainly from poor dietary iron bioavailability causes anemia (26) and has been associated with maternal mortality (9). Iron deficiency is known to affect immune status by reducing the delayed-type hypersensitivity reaction, graft rejection, and cytotoxic activity of phagocytes (43). A low plasma iron concentration also selectively inhibits proliferation of T_H1 and not T_H2 cells; thus, iron may be important for maintaining maternal health and reducing the risk of infection.

Few data exist on biochemical zinc deficiency in pregnant women, which is partly due to the lack of a consensus on the appropriate indicator to use (44). Low plasma zinc concentrations during pregnancy, resulting from low dietary bioavailability (31) or very high amounts of copper or iron in the diet that compete with zinc at absorption sites (45), have been associated with congenital abnormalities, abortions, intrauterine growth retardation, premature birth (46), and preeclampsia (18, 19). Zinc deficiency can also affect the immune response because it results in reductions in T cell development, thymic hormone release, and T cell functions (43).

Inadequate iodine intakes during pregnancy result in fetal loss, stillbirths, cretinism, and mental retardation of the newborn infant (14, 47). Selenium deficiency is associated with Keshan disease, which has been found in women of reproductive age in China; thus, like iodine deficiency, selenium deficiency tends to be geographically specific because of deficiencies in the soil and therefore the food chain. There is no evidence that prenatal copper deficiency has teratogenic effects in humans as has been observed in experimental animals (48). Changes in serum copper concentrations are likely to be due to pregnancy deviating from its normal course rather than to inadequate intakes (49).

Supplementation

McCarron (DA McCarron, unpublished observations, 2000) reports that calcium supplementation during pregnancy is safe. The tolerable upper intake limit (UL) is 2500 mg/d (34). Moreover, there is some evidence that in populations with low calcium intakes, supplementation may reduce pregnancy-induced hypertensive disorders and preeclampsia (J Belizan, personal communication, 1999). It may also reduce the risk of postnatal depression. No major changes in either bone mass or blood inorganic phosphorus have been reported during pregnancy (50, 51); thus, phosphorus supplementation is not recommended. Contrary to earlier thinking, the IOM (34) states there is little or no evidence relating calcium to phosphorus and that molar ratios of calcium to phosphorus have little meaning for maintaining blood calcium concentrations. The UL for phosphorus in pregnancy is 3.5 g/d.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

TABLE 1
Recommended dietary allowances and intakes for adolescent girls; nonpregnant, nonlactating women; and pregnant women[1]

Nutrient	Adolescent girls			Nonpregnant, nonlactating women			Pregnant women (3rd trimester)			Percentage increase over nonpregnant, nonlactating women: pregnant women[2]
	NRC, 15–18 y	IOM, 14–18 y	FAO/WHO, 15–19 y	NRC, 25–49 y	IOM, 19–50 y	FAO/WHO, 18–60 y	NRC	IOM	FAO/WHO	
										%
Calcium (mg)[3]	1200	1300	500–600	800	1000[4]	400–500	1200	1000[4]	1000–1200	140–150
Phosphorus (mg)	1200	1250	—	800	700	—	1200	700	—	—
Magnesium (mg)	300	360	—	280	310–320	—	320	350–360	—	—
Iron (mg)	15	—	—	15	—	—	30	—	—	—
Very low bioavailability[5]	—	—	60	—	—	59	—	—	179–299	203–407
Low bioavailability[5]	—	—	32	—	—	32	—	—	92–152	187–375
Medium bioavailability[5]	—	—	16	—	—	16	—	—	46–76	187–375
High bioavailability[5]	—	—	10	—	—	11	—	—	31–61	182–454
Zinc (mg)[6,7]	12	—	1.5	12	—	1.4	15	—	2.0	43
Iodine (μg)[6]	150	—	150	150	—	150	175	—	200	33
Selenium (μg)[6]	50	—	21.5	55	—	21.5	65	—	27	26
Copper (mg)[6]	—	—	1.15	1.5–3.0[8]	—	1.15	1.5–3.0[8]	—	1.15	0
Vitamin A (μg RE)[5]	800	—	600	800	—	500	800	—	600	20
Vitamin D (μg)[9]	10	5[4]	100	5	5[4]	2.5	10	5[4]	10	300
Vitamin E (mg α-TE)	8	—	—	8	—	—	10	—	—	—
Vitamin K (μg)	55	—	—	65	—	—	65	—	—	—
Vitamin C (mg)[9]	60	—	30	60	—	30	70	—	50	67
Thiamine (mg)[10]	1.1	1.0	0.9	1.1	1.1	0.8	1.5	1.4	0.9	12
Riboflavin (mg)[10]	1.3	1.0	1.4	1.3	1.1	1.4	1.6	1.4	1.5	7
Niacin (mg NE)[10]	15.0	14.0	11.9	15.0	14.0	11.5	17.0	18.0	12.6	10
Vitamin B-6 (mg)	1.5	1.2	—	1.6	1.3	—	2.2	1.9	—	—
Folate (μg)[5]	180	400	170	180	400	170	400	600	370–470	118–176
Vitamin B-12 (μg)[5]	2.2	2.4	1.0	2.0	2.4	1.0	2.2	2.6	1.4	40

[1] NRC, National Research Council (33); IOM, Institute of Medicine (34, 35); FAO/WHO, Food and Agriculture Organization of the United Nations/World Health Organization; RE, retinol equivalents; α-TE, α-tocopherol equivalents; NE, niacin equivalents.
[2] Percentage increase is based on the FAO/WHO values.
[3] Values in the FAO/WHO columns are from reference 36.
[4] Adequate intake.
[5] Values in the FAO/WHO columns are from reference 37.
[6] Values in the FAO/WHO columns are from reference 38.
[7] Zinc concentrations for adolescent girls and nonpregnant, nonlactating women are based on normative requirement × representative body weight.
[8] Estimated safe and adequate dietary intake.
[9] Values in the FAO/WHO columns are from reference 39.
[10] Values in the FAO/WHO columns are from reference 40.

Pregnancy-related magnesium deficiency has not been shown (52, 53) and there is no evidence in the literature that magnesium supplementation is worthwhile in either high- or low-risk pregnancies (MJ Keirse, unpublished observations, 2000). The UL for magnesium in pregnancy is the same as that for other adults, namely 350 mg/d (34).

Prophylactic iron supplementation is recommended in developing countries (54) and in the United States (49) for all pregnant women in the second and third trimesters of pregnancy; in other countries, iron supplementation is recommended only for anemic women with proven iron deficiency anemia, as in Great Britain (55), or for women with low prepregnancy iron stores, as in Canada (56). Safety issues related to iron are discussed by Yip (57).

For zinc, the IOM (49) concluded there was insufficient evidence on which to base a recommendation for routine supplementation during pregnancy. Nevertheless, the IOM recommends zinc supplementation when ≥30 mg/d of supplemental iron is taken to overcome the interaction effects. Zinc supplementation may improve pregnancy outcomes for chronically deficient pregnant women (JC King, unpublished observations, 2000). Prophylactic doses of 20–25 mg elemental zinc/d have generally been used in pregnant women in developing countries (58), and the WHO (49) set the UL at 35 mg/d.

Results of zinc supplementation trials are mixed. In US women with low plasma zinc concentrations who were at high risk of having low-birth-weight infants and whose intake of zinc was inadequate, supplementation with 25 mg Zn/d, beginning at an average of 19 wk gestation, resulted in an upward shift in the gestational age distribution and greater fetal growth (including head circumference) that was independent of gestational age (59). These findings occurred primarily in women with a body mass index (expressed as kg/m^2) <26. Although the authors conclude that their findings support the inclusion of zinc in multiple-micronutrient supplements, they note that unless the improved outcomes are also associated with decreased morbidity and

The American Journal of Clinical Nutrition
Downloaded from ajcn.nutrition.org by guest on March 20, 2016

mortality, there is no reason to be enthusiastic about the improved birth weight alone. Hakimi et al (60) reported preliminary data from an ongoing randomized, placebo-controlled trial in which pregnant women are being given a daily low dose of 20 mg zinc sulfate. Of the 680 women for whom data were available, zinc did not affect postpartum infection measured as elevated body temperature (>38°C) on at least day 1 postpartum [relative risk (RR) = 0.97; 95% CI: 0.43, 2.16]. Caulfield et al (61) showed that supplementing pregnant Peruvian women beginning at gestation week 10–24 with a prenatal supplement containing 60 mg Fe and 250 mg folate with or without 15 mg Zn improved maternal zinc status but did not raise it to concentrations found in well-nourished populations. They concluded that higher amounts of zinc may be needed.

In regions of moderate to severe iodine deficiency, pregnant women need iodized salt before or iodized oil before or during pregnancy (14, 62). This regimen reduces reproductive loss (47), morbidity, and adverse fetal outcomes (14). The WHO (49) did not set an UL for pregnancy although it cites a report saying that iodine intakes of < 100 μg/d are safe and that the UL could be as high as 200 μg/d.

Selenium supplementation should be considered in areas where Keshan disease is common (63) or where both iodine and selenium deficiency occur (64). Safe intakes of selenium have not been established for pregnant women, but that for adults is 400 μg/d (38).

Because copper deficiency has not been observed in pregnancy, there is no need for supplementation in pregnancy (49). Nevertheless, if zinc supplements are given to individuals with low copper intakes, a copper supplement should also be given to compensate for the zinc-copper interaction (33), and the IOM (49) recommends that a 2-mg copper supplement be given when a zinc supplement is used. This is the amount used in some commercial prenatal multiple-micronutrient supplements with no adverse effect. The UL for copper in pregnancy is 10 mg/d (38). Other minerals that are essential for healthy cell function include chromium, manganese, and molybdenum, but deficiencies in pregnancy are virtually unknown (33, 49).

Lipid-soluble vitamins

Concentrations during pregnancy

Blood vitamin A concentrations decline gradually in pregnancy because of hemodilution, and evidence exists that inadequate dietary vitamin A intake can also lower blood concentrations (65), although blood concentrations are difficult to interpret because they are not a good reflection of underlying status (66). The active metabolite of blood vitamin D (1,25-dihydroxycholecalciferol) increases in pregnancy whereas the inactive form (25-hydroxycholecalciferol) decreases (21). Vitamin E concentrations are known to increase during gestation, probably because of the hyperlipidemic state associated with pregnancy (67).

Requirements

The FAO/WHO RDA for vitamin A is 20% higher for pregnant women than for nonpregnant, nonlactating women (Table 1) because of the extensive cell proliferation and development of the fetus (65). Vitamin D requirements can be met if skin is exposed to sufficient sunlight, but the effectiveness of exposure to sunlight varies depending on how much skin is exposed, the duration of exposure, the latitude, the season, and skin pigmentation. Based on the FAO (68) recommendations, the dietary allowance for pregnant women increases 300% to take into account calcium deposition and bone mineralization in the fetus (32). The RDA for vitamin E intakes during pregnancy has not been established because of difficulties in determining requirements (49). The NRC (33) assumed that vitamin E is needed for fetal growth and recommends that intakes be increased by 25% in pregnancy. Sufficient data are not available for setting a specific RDA for vitamin K in pregnancy and the recommendation for nonpregnant, nonlactating women is used (33).

Deficiency

Vitamin A deficiency is widespread and occurs when the intake of dairy products and carotene-rich vegetables and fruit is limited and, occasionally, with malabsorption syndrome. Vitamin A deficiency in pregnancy is known to result in night blindness (69, 70), has been shown to increase the risk of maternal mortality (71), and is associated with premature birth, intrauterine growth retardation, low birth weight (17), and antepartum hemorrhage (72) due to abruptio placentae. Vitamin A deficiency reduces leukocyte numbers, lymphoid tissue weights, complement, T cell functions, tumor resistance, natural killer cell numbers, antigen-specific immunoglobulins G and E, and T_H2 numbers and increases interferon-γ synthesis (except in one study) (43).

Vitamin D deficiency is rare (42), but neonatal tetany, fetal rickets, and abnormal teeth development have been reported in areas where vitamin D deficiency is present (73). Deficiency does occur in populations where the women are kept in *purdah*, with limited exposure to sunlight (74). Vitamin E deficiency is rare except in malabsorption syndrome, but low concentrations have been associated with abruptio placentae in normal pregnancies (72). Vitamin K deficiency is also rare (75). Nevertheless, pregnant women taking an oral anticoagulant (eg, coumadin) are at increased risk of hemorrhage because of the antagonist effect of the anticoagulant on vitamin K (75).

Supplementation

Weekly vitamin A supplementation (7000 μg) in Nepal reduced maternal mortality by 40%, the prevalence of subclinical vitamin A deficiency by 84% (71), and the risk of night blindness by 38% (68). Vitamin A is associated with anemia (76, 77) and supplementing pregnant women in their second trimester with both vitamin A (2400 mg) and iron daily for 2 mo improved hemoglobin concentrations more so than did supplementation with iron or vitamin A alone (78). Specifically, the increase in hemoglobin was >50% greater when both nutrients were supplied and was sufficient to eliminate anemia in 97% (95% CI: 88%, 99%) of the anemic women who received both iron and vitamin A. In a study in Nepal, Stoltzfus et al (79) found that vitamin A supplementation reduced pregnancy anemia but only in women with little or no hookworm infection. In a randomized, double-blind, placebo-controlled trial in pregnant women positive for HIV in Tanzania, Fawzi et al (80) found that 1500 μg vitamin A had no significant effect on birth outcomes, which they said may have been due to poor absorption and increased requirements in HIV-infected women.

Vitamin A therapy, in the form of cod liver oil, for women with puerperal fever reduced the severity of puerperal fever and reduced maternal mortality by about two-thirds when given with the usual treatment for sepsis (81). In later studies, prophylactic cod liver oil reduced the incidence of puerperal fever (82, 83). Hakimi et al's (60) preliminary data from an ongoing, randomized,

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

placebo-controlled trial showed for the 680 women for whom data were available that the number of episodes of elevated body temperature (>38°C) on at least day 1 postpartum was reduced by 78% in women given 2400 μg vitamin A daily during pregnancy compared with the control group who received no vitamin A supplement (RR = 0.22; 95% CI: 0.08, 0.65).

Hypervitaminosis A increases the risk of fetal malformation, and supplementation should not exceed 3000 μg/d (84). Excess vitamin A also has adjuvant effects that increase lymphocyte proliferation, tumor resistance, graft rejection, and cytotoxic T cell activity, possibly by inhibiting T cell apoptosis (43).

Vitamin D supplementation is not likely needed during pregnancy except perhaps in high-risk population groups, for example, in women whose clothing limits exposure to direct sunlight and in women who live in northern latitudes with few hours of daylight. Vitamin D can be toxic to both the mother and fetus if given in large doses in pregnancy, although the intake at which this occurs is uncertain because interindividual sensitivity to excessive intakes varies (49). When used, however, daily low doses are preferable to a few large doses because the risk of toxicity is reduced. The IOM (34) concluded there are insufficient data to set a UL for vitamin D in pregnancy that is different from that for other adults (ie, 50 μg/d).

Vitamin E supplementation is not needed in pregnancy because most diets containing plant oils, fruit, and vegetables should provide an adequate supply, especially because pregnancy has no additional vitamin E requirements. Both vitamins E and K are nontoxic in adults, even at large doses (33).

Water-soluble vitamins

Concentrations during pregnancy

During pregnancy, serum vitamin C progressively decreases ≈50% (75), partly because of the extra uptake by the fetus (41) and partly because of hemodilution (85). Plasma thiamine and riboflavin concentrations also decline during pregnancy (41). Evidence suggests that serum niacin concentrations decrease during pregnancy (41), whereas urinary excretion of niacin metabolites increases. Vitamin B-6 concentrations decline during pregnancy as a physiologic adjustment secondary to increased blood volume or as a result of increased requirements for active transport across the placenta (35). Folate concentrations may decline in pregnancy as a result of decreased intestinal absorption, inadequate intake, or increased demand (86). Serum vitamin B-12 concentrations progressively decline during pregnancy, which may be independent of dietary intakes and may not represent decreased maternal stores or deficiency at the biochemical level (87). Biotin concentrations are significantly lower in pregnancy than in the nonpregnant, nonlactating state and decrease progressively throughout pregnancy (33). Pantothenic acid concentrations are thought to decline during pregnancy, returning to normal within 1 wk of delivery (88).

Requirements

The RDA for vitamin C in pregnant women is 67% higher than that for nonpregnant, nonlactating women (Table 1) to offset the losses from the mother's body pool (39). Thiamine dietary allowances are 12% higher in early pregnancy because of increased requirements associated with pregnancy and remain constant throughout (89). Riboflavin dietary allowances are 7% higher because of increased maternal and fetal tissue synthesis and a small increase in energy utilization (40). Niacin dietary allowances are 10% higher for the same reasons (40), despite a possibility that bioconversion from tryptophan may increase as a result of increased energy requirements (49). Vitamin B-6 deficiency rarely occurs; thus, the FAO/WHO has not recommended additional requirements for pregnant women but the IOM (35) has. Because vitamin B-6 is not stored in the body to any great extent and the increased need is concentrated in the second half of pregnancy, the IOM (35) has recommended that the RDA be increased by 46% to ensure sufficiency throughout pregnancy.

Besides the need for folate at periconception to prevent neural tube defects, folate dietary allowances during pregnancy increase substantially by 147% (37) to build or maintain maternal stores and to meet the needs of rapidly growing maternal and fetal tissues (35). The FAO/WHO (40) recommends a 40% increase in the vitamin B-12 dietary allowance to meet fetal demands and increased metabolic needs. No recommended daily allowances are available for biotin and pantothenic acid because of the absence of evidence of increased requirements during pregnancy (35).

Deficiency

Observational or experimental data linking water-soluble vitamins to any risk of maternal mortality are unavailable. Various studies that looked at the effect of these vitamins on hypertensive disorders are reviewed by Maine (10). Evidence that the dietary intake of vitamin C is inadequate in developing countries does not exist, but seasonal fluctuations have been reported in The Gambia (90). Lower concentrations were observed in preeclamptic women in South Africa (91), but Maine (10) concludes this is unlikely to have been due to a primary deficit. Sharma et al (92) and Clemetson and Cafaro (93) report an association between the incidence of abruptio placentae and low vitamin C concentrations but no intervention trials have been done looking at status and antepartum hemorrhage.

Thiamine deficiency is now rare but can occur where the staple food is polished rice (94). Riboflavin deficiency can occur as a result of extra demand by the fetus, cooking losses, and inadequate dietary intakes, and biochemical deficiency has been reported in pregnant women (95). Nevertheless, its clinical significance has been doubted because of the lack of evidence that a deficient state results in adverse fetal or neonatal outcomes (96).

Riboflavin deficiency affects the immune response by decreasing antibody responses, thymic weight, and circulating lymphocyte numbers (43). Tryptophan, and to a lesser extent niacin, is widely available in foodstuffs and there is no evidence that pregnancy predisposes to pellagra. Vitamin B-6 deficiency rarely occurs alone and is often associated with deficiency in several B-complex vitamins (33). Nevertheless, vitamin B-6 has been associated with preeclampsia, carbohydrate intolerance, hyperemesis gravidarum, and neurologic disease of infants (20, 21, 97, 98). Vitamin B-6 deficiency also affects immunity by reducing lymphocyte numbers and the proliferative responses to mitogen, lymphoid tissue weights, graft rejection, interleukin-2 production, delayed-type hypersensitivity reactions, and antibody responses (43).

Folate deficiency has been reported in parts of India, West Africa, and Burma (99). It is due to inadequate dietary intakes, cooking habits that exacerbate losses, food taboos, inadequate food storage, and intense erythroid hyperplasia in the bone marrow (eg, sickle cell anemia, chronic hemolytic anemia, or homozygous β-thalassemia); deficiency is associated with megaloblastic anemia, low birth weight, and potential fetal anomaly (100–102).

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

In West Africa, the frequency of megaloblastic anemia was reduced by 50% after antimalarial prophylaxis and it was completely abolished with folate supplementation (103). A specific thermolabile variant of the folate-metabolizing enzyme, 5,10-methylene tetrahydrofolate reductase, which causes decreased enzymatic activity, has been described in 5–15% of populations with low folate status (104–106). This variant increases the risk of homocysteinemia and neural tube defects, necessitating additional requirements for folate before pregnancy (104).

Vitamin B-12 deficiency is rare in pregnancy, especially where nonvegetarianism is the norm. Vitamin B-12 deficiency in association with megaloblastic anemia was reported in pregnant women in Zimbabwe and India (103, 107) and low blood concentrations were observed in Mexico (108). Strict vegetarians or individuals who lack intrinsic factor and suffer from malabsorption resulting from diseases affecting the terminal ileum can be vitamin B-12 deficient. Deficiency in pregnancy can lead to intrauterine death and possibly to adverse infant neurobehavioral development (109). Vitamin B-12 deficiency depresses phagocyte functions, delayed-type hypersensitivity responses, and T cell proliferation (43).

Supplementation

Routine use of large doses of ascorbic acid in amounts >1 g/d is not recommended (33). Prophylactic thiamine fortification of the diet or pharmaceutical supplementation is desirable to avert neonatal death where deficiency is known to exist (94). Riboflavin supplementation can improve the hematologic response to iron (95) and, where deficiency is common, supplementation is needed to restore biochemical normality (90, 110). There is no evidence of thiamine or riboflavin toxicity by oral administration and no UL has been set for either vitamin (35). The UL for niacin is 35 mg/d and that for vitamin B-6 is 100 mg/d (35).

The administration of folic acid in the periconceptional period reduces the number of births with neural tube defects by 75% (111); thus, folic acid administration is recommended as standard prenatal care by the International Nutritional Anemia Consultative Group (54). In countries where dimorphic and megaloblastic anemias are common, prophylactic medication with folic acid should be added to the routine iron medication that all pregnant mothers require (112). Except for women taking anticonvulsant drugs, who may have coexisting vitamin B-12 deficiency, there is no evidence that folate supplementation in pregnancy is unsafe (113). The UL for folate is 1000 μg/d (35). Vitamin B-12 requirements would be met by the usual dietary intake for everyone other than strict vegetarians; hence, there is no need for prophylactic therapy. No clear toxicity has been reported from daily oral intakes of vitamin B-12 in healthy individuals (35).

ISSUES AND REQUIRED ACTION

Many people in developing countries exist on monotonous cereal- or legume-based diets and have little access to animal products or a variety of fruit and vegetables. Even when such foods are available, cultural beliefs may deny pregnant women access to these foods (114), rendering them at risk of micronutrient deficiencies. Thus, malnourished pregnant women in developing countries may benefit from prophylactic micronutrient supplementation during pregnancy. Currently, iron or iron and folate supplements are distributed to pregnant women in most developing countries free of charge or at low cost by public health authorities. Nevertheless, few data show that coverage is good or that anemia prevalence rates are declining (115).

Multiple-micronutrient supplementation

Although much more needs to be done to ensure that women in need of iron and folate supplements have good access to them, multiple-micronutrient supplements are being advocated over conventional iron and folate supplements (116). Manipulating the formulation, however, simply adds to the cost of the treatment with no added benefit in efficacy except when other micronutrient deficiencies coexist (117). Moreover, an abrupt change in direction is questionable because it does not address the underlying problem of inadequate prenatal iron and folate coverage and, indeed, could divert attention and resources away from correcting existing program problems. Better data are needed to show that iron and folate supplementation is effective in reducing the prevalence of anemia, but this does not mean that existing programs should be changed. Instead, the evidence to justify changing current iron and folate supplementation practice, which includes identifying and defining the measurable outcomes, needs to be generated. This is important because the potential benefits of prophylactic prenatal supplementation in the context of developing countries include improving maternal nutritional status, which may, in turn, enhance multiple components of the immune and antioxidant defense systems, reducing pregnancy complications, and reducing the risk of some developmental and common birth defects (118).

The purpose of multiple-micronutrient supplementation during pregnancy is twofold: to improve pregnancy outcome and to improve breast-milk quality. This paper focuses on the former, specifically as it relates to maternal health and mortality. Issues related to intrauterine growth retardation, which are equally inconclusive, are reviewed by Gulmezoglu et al (15) and Ramakrishnan et al (17). Keen and Zidenberg-Cherr (118) present the evidence for the beneficial effects of vitamin-mineral supplements on neural tube defects, which they note have multiple etiologies and occur as a consequence of complex interactions among genetic, environmental (maternal), nutritional, and immunobiologic factors. The preceding section shows that data on the efficacy of single- or multiple-micronutrient supplementation are inconclusive about pregnancy outcomes except for folate and iodine, which are critical at periconception, and iron and folate supplementation in tropical areas where dimorphic and megaloblastic anemia exist. Although iron deficiency is the most common cause of nutritional anemia in the world, folate deficiency is considered as the second most common cause and often coexists with iron deficiency.

Besides efficacy, however, 4 other major concerns related to multiple-micronutrient supplementation (119) are also relevant to developing countries. First, women eating a good diet are more likely to take supplements regularly than are those at greater risk of micronutrient deficiencies. Second, the micronutrients taken may not be limiting in the diet. Third, some pharmaceutical preparations do not indicate on the package labeling how the micronutrient doses are related to the recommended daily intake. Moreover, less-informed women may take more than the recommended dose on the premise that it is advantageous to the pregnancy outcome and the newborn infant's health. Toxic effects caused by overdosing are a major concern for anyone involved in prenatal care, especially for lipid-soluble vitamins such as A and D that have limited excretion routes. Fourth,

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

other concerns are related to interactions between and among nutrients. Lonnerdal and Keen (120) classified these into 2 groups. In the first group, deficiency of one element affects the metabolism of another. Copper deficiency, for example, causes low ferroxidase activity, which induces an iron-deficiency-like anemia (121). In the second group, 2 or more trace elements share the same absorptive pathway and a high concentration of one may interfere with the absorption of the other; thus, trace element ratios are important.

Multinutrient interactions

Lonnerdal (121), in his review and summary of iron-zinc-copper interactions, notes that a high concentration of iron can interfere with zinc uptake when no dietary ligands are present (ie, in a fasting state). High iron intakes may interfere with copper absorption if both are taken simultaneously, even when the differences in iron-copper ratios are relatively small. Modest increases in zinc intakes can also affect copper absorption, even with small changes in the ratio. Lonnerdal (121) concluded that these interactions are more likely to occur when the elements are given as a supplement, and that the outcomes can vary greatly depending on whether they are taken with or without a meal. He also notes potential negative effects. For example, modest amounts of zinc may have a positive effect on immune function but higher amounts can interfere with copper and iron absorption, which in turn can adversely affect immune function.

Other micronutrients also interact. For example, some studies found that high plasma folate concentrations decreased the absorption of zinc when zinc intake was low and that a mutual inhibition between folic acid and zinc occurs at the site of intestinal transport (122–124), whereas another study did not find this (125). Selenium and vitamin E interact with each other, and each potentiates the effect of the other (126).

Babior et al (127) looked at iron absorption after supplementation with high amounts of calcium and magnesium. First-trimester iron absorption was lower in fasting pregnant women after they received a high-dose calcium supplement than after they received a low-dose preparation. Calcium is known to inhibit both heme- and nonheme-iron absorption, and Hallberg (128) recommends that, when needed, calcium supplements be taken separately from meals (eg, at bedtime). Ascorbic acid is known to enhance iron absorption but only when taken with meals; thus, the addition of vitamin C to iron-containing supplements to enhance iron absorption is of little value unless the supplements are taken with meals. Calcium also interacts with zinc, magnesium, and phosphorus, but there is little evidence to suggest high intakes of calcium show evidence of causing the depletion of any of these 3 other minerals or iron (34).

The issue of interactions clearly has important implications for a multiple-micronutrient supplement regimen in pregnancy, especially in vulnerable populations with low intakes. On the one hand, calcium supplementation may be important, but on the other hand, calcium should not be taken at the same time as iron; 2 separate supplements taken at different times have been suggested (116). If zinc is included with iron and folate, the supplement should be taken with meals to overcome the inhibitory effect of iron on zinc. If this is done, dietary inhibitors will affect the absorption of the nonheme iron; this can be overcome by including vitamin C, but this is expensive. At the same time, there is the unresolved issue of folate-zinc interactions. The current generally accepted recommendation is that iron and folate supplements should be taken shortly after meals to limit gastric interaction to reduce side effects (117). Clearly, there are trade-offs in terms of interactions and the number of tablets women can be expected to take regularly. For these reasons, these issues need to be discussed and agreement reached on the priority outcomes for both the mother and the fetus.

Other concerns

Another important concern is the use of coloring in micronutrient supplements. Although coloring may make the tablets more attractive, it raises safety concerns, particularly regarding children, who may consume the tablets on the premise that they are sweets and thus poison themselves (114). This issue is very important in developing countries, where commercial interests often conflict with public health needs despite regulations to control the inappropriate use of dangerous drugs (personal observations). There is also a need for proper quality assurance systems to ensure bioavailability of the nutrients in supplement preparations.

Cost of supplements

Finally, whether public health systems can bear the additional cost, or whether pregnant women will have the resources to buy multiple-micronutrient supplements, is questionable. Developing countries typically spend 4–5% of their meager gross national product on health, and ≈40% of this is allocated to buying pharmaceuticals (129). The cost of 270 iron-folate tablets, which is sufficient for preventing iron deficiency anemia in an entire pregnancy, is $0.46 (W Schultink, personal communication, 1999) or $0.27 (O Ayeni, personal communication, 1999). The former are supplied by the United Nations Children's Fund (UNICEF/UNIPAK) and include a 6% handling charge but not shipping costs, whereas the latter are available through WHO Maternal and Newborn Health/Safe Motherhood (WHO/MSM) and exclude handling and shipping costs.

Huffman et al (116) provide costs for 4 multiple-vitamin supplements sold by nonprofit agencies that vary between $0.54 and $0.81 for an entire pregnancy. Four of the 6 vitamins provide well below the FAO/WHO RDAs for pregnancy (riboflavin, 33%; niacin, 60%; vitamin C, 30%; and vitamin D, 75% of the allowances), whereas the vitamin A delivery is slightly lower than the RDAs (95% of the allowances) and the thiamine delivery is slightly higher (111% of the allowances). A well-known micronutrient pharmaceutical company has said that it could make a multiple-micronutrient supplement based on the NRC RDAs for iron, zinc, and the main water- and fat-soluble vitamins listed in Table 1 for about $0.01 each, which would cost $2.55 per pregnancy. Vitamin C accounts for ≈25% of this cost, iron and vitamin E for just over 20% each, vitamin A for just over 10%, and the rest between 1% and 5% each. The total cost, however, does not include the costs of tablet production, packaging, distribution, taxes, customs duties, marketing, and so forth (A Nilson, personal communication, 1996; 116). Through the use of data from a recent inventory of all iron-containing supplement tablets or capsules in New Delhi (130), for example, the average retail price for the 64 products was 19.3% higher than the average wholesale price (range: 15.9–28.6%) and each tablet or capsule retailed at an average cost of $0.02. Although not all these supplements would be considered appropriate for pregnant women, these values show that at average wholesale prices, supplementation throughout pregnancy in India could cost ≈$4.35.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

It is often argued that the marginal cost of adding other vitamins and minerals to iron and folate supplements is small, but this is not the issue. The issue is the total costs to the program that includes the wholesale price and the costs of packaging, transport or logistics, storage, and distribution. For a country such as India that has ≥26 million pregnant women, the budget implications are enormous: $7.02 million for the WHO/MSM iron-folate tablets, $11.96 million for the UNICEF/UNIPAK iron-folate supplements, $66.3 million for the unnamed company's product, and $113.1 million calculated by using the average wholesale price of the existing multiple-micronutrient supplements in the market. Health ministries have to make tough decisions about the way they allocate resources; thus, the scientific basis and rationale for making decisions must be unequivocal. Costs, however, do not have to be perceived to be prohibitive if the government has a basis for—and becomes committed to—controlling micronutrient deficiencies and the commercial pharmaceutical sector works in collaboration to support the government's effort.

Programmatic challenges

In addition to the economic constraints, a major programmatic challenge and concern in many developing countries is the lack of well-defined government policies on maternal health and nutrition (131). This is reflected in inadequate funding for reproductive health care programs, an uneven distribution of health centers in rural areas, chronic shortage of skilled health care personnel, logistic problems with the distribution and storage of prenatal supplements, and low morale of health care workers because of low wages and the lack of job satisfaction (132). Globally, 35% of pregnant women in the developing world do not have prenatal care, 60% do not deliver at a health facility, and 47% do not have a skilled attendant at delivery (22). Moreover, there are huge regional and subregional disparities, partly because of a lack of good access to health centers, local culture, and socioeconomic constraints. The logistic problems can be partly overcome by improving both the access to rural communities and the availability of transport to health centers. National governments could also ensure a more even distribution of well-staffed primary health care centers, where prenatal pharmaceutical supplements could be stored and distributed by traditional birth attendants and extension workers who are familiar with the terrain and their local population.

Merely providing more staff, however, will not solve the problems of delivering adequate prenatal care. In a review of 36 prenatal interventions during pregnancy, Gulmezoglu et al (15) concluded that social support, including health and nutrition education, may teach pregnant women about pregnancy-related issues but the recipients seldom take action. In other words, the interventions do not overcome the negative biological outcomes of pregnancy. The authors say that it is unclear whether this is because women do not change their behavior or because the health services are not user friendly. Poor compliance is also often stated to be an issue with prophylactic iron therapy, and Rush (9) discusses the lack of evidence for this. Low literacy levels and the frequent inability of physicians in developing countries to translate scientific ideas into local culture also results in many people not necessarily understanding either the need for or the need to take supplements (129). Sociocultural factors, too, are important to consider, especially where women do not make decisions about their own health care or where the health facility is not close by, because these can limit access to health care services (133, 134) and restrict access to nutrition and health education. Clearly, pregnant women need to be provided with information that will reduce or close their knowledge gap about the nutritional value of locally available foodstuffs, what they actually eat, and the need for prophylactic micronutrient supplements. The challenge is how to do all this effectively.

CONCLUSION

To decide which micronutrients are of greatest concern in developing countries, a more systematic and comprehensive approach is needed that will result in agreement on the objectives of prophylactic multiple-micronutrient supplementation, the criteria for identifying and setting concentrations, and the outcomes to be measured. This will require carefully reviewing the dietary intakes of both nonpregnant, nonlactating women and pregnant women; the micronutrient status of nonpregnant, nonlactating women; and the cost-effectiveness of ongoing interventions in developing countries. At the same time, discussion and agreement is needed about issues related to what motivates women to change behavior that can result in improved nutrition status—be it through improved dietary practices or the use of supplements—and this has to link in with the safety issues. The discussion should differentiate between nutrient needs and the consequences of deficiency at periconception and in pregnancy and how best to address these differing needs. The issue of whether high-risk women should be identified and, if so, how this can be done practically also should be revisited.

The need for micronutrient supplementation in pregnancy in developing countries is likely to be great because of widespread maternal malnutrition. Public health resources, however, are limited and it is inevitable that priority will be given to interventions that are both efficacious and effective. Current evidence shows that some micronutrients, such as folate and iron and iodine in population-based iodine supplementation, can reduce the risk of adverse pregnancy outcomes (135). Others, such as calcium, vitamin A, and zinc, may reduce the incidence of ill health and some life-threatening complications of pregnancy that are still common in many developing countries. Additional studies, however, are needed in different geographic regions to identify whether micronutrient supplementation in pregnancy results in functional and measurable outcomes for maternal health and survival. These studies would enable the appropriate intervention strategies to be developed, implemented, and evaluated. Such efforts will require the collaboration and commitment of government agencies, health care providers, nutritionists, research institutions, and the community.

I gratefully acknowledge the assistance of Penny Nestel and Judy Dickson in the preparation of this paper.

REFERENCES

1. Picciano MF. Pregnancy and lactation. In: Ziegler EE, Filer LJ, eds. Present knowledge in nutrition. Washington, DC: ILSI Press, 1996: 384–95.
2. Hytten FE. Nutritional physiology during pregnancy. In: Campbell DM, Gillmer DG, eds. Nutrition in pregnancy. London: Royal College of Gynaecologists, 1983:1–18.
3. Brems S, Berg A. Eating down during pregnancy: nutrition, obstetric and cultural considerations in the third world. Discussion paper prepared for the ACC/ACN. Washington, DC: World Bank, 1988.
4. Godfrey KM. Maternal regulation of fetal development and health in adult life. Eur J Obstet Gynaecol Reprod Biol 1998;78:141–50.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

5. Barker DJ. Maternal nutrition, fetal nutrition and disease in later life. Nutrition 1997;13:807–13.
6. Barker DJP. Fetal nutrition and cardiovascular disease in later life. Br Med Bull 1997;53:96–108.
7. Susser M, Levin B. Ordeals for the fetal programming hypothesis. BMJ 1999;318:855–6.
8. Gittelsohn J, Thapa M, Landman LT. Cultural factors, caloric intake and micronutrient sufficiency in rural Nepali household. Soc Sci Med 1997;44:1739–49.
9. Rush D. Nutrition and maternal mortality in the developing world. Am J Clin Nutr 2000;72(suppl):212S–40S.
10. Maine D. Role of nutrition in the prevention of toxemia. Am J Clin Nutr 2000;72(suppl):298S–300S.
11. Rooney C. Antenatal care and maternal health: how effective is it. A review of the evidence. Geneva: WHO, 1992. (WHO/MSM/92.4.)
12. Kirke PN, Daly LE, Molloy A, Weir DG, Scott JM. Maternal folate status and risk of neural tube defects. Lancet 1996;348:67–8
13. Medical Research Council Vitamin Study Groups. Prevention of neural tube defects: result of the MRC vitamin study. Lancet 1991;238:131–7.
14. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. Bull World Health Organ 1996; 74:101–8.
15. Gulmezoglu M, de Onis M, Villar J. Effectiveness of interventions to prevent or treat impaired fetal growth. Obstet Gynecol Surv 1997;52:139–49.
16. Scholl TO, Hediger ML. Anemia and iron-deficiency anemia: compilation of data on pregnancy outcome. Am J Clin Nutr 1994; 59(suppl):492S–501S.
17. Ramakrishnan U, Manjrekar R, Rivera J, Gonzalez-Cossio T, Martorell R. Micronutrients and pregnancy outcome: a review of the literature. Nutr Res 1999;19:103–59.
18. Kiiholma P, Paul R, Pakarinem P, Gronroos M. Copper and zinc in pre-eclampsia. Acta Obstet Gynecol Scand 1984;63:621–31.
19. Zimmerman AW, Dunham BS, Nichimson DJ, et al. Zinc transport in pregnancy. Am J Obstet Gynecol 1984;149:523–9.
20. Spellace WN, Buti SC, Birk SA. Vitamin B6 treatment of gestational diabetes mellitus: studies of blood glucose and plasma insulin. Am J Obstet Gynecol 1977;127:599–602.
21. Moghissi KS. Risks and benefits of nutritional supplements during pregnancy. Obstet Gynecol 1981;58:685–785.
22. World Health Organization. Coverage of maternity care: a listing of available information. 4th ed. Geneva: WHO, 1997. (WHO/RHT/MSM/96.28.)
23. Rossa FW, Wilk AL, Kelsey FO. Vitamin A congeners. Teratology 1986;33:355–64.
24. Hibbard BM. Minerals and vitamins in pregnancy. Pract Nutr 1992;1(3):1–8.
25. Department of Health. Vitamin A: women cautioned. London: Her Majesty's Stationary Office, 1990. (Press release 90/507.)
26. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. Am J Clin Nutr 2000;72(suppl):257S–64S.
27. Hunt IF, Murphy NJ, Cleaver AE, et al. Zinc supplementation during pregnancy: zinc concentration of serum and hair from low-income women of Mexican descent. Am J Clin Nutr 1983;37:572–82.
28. Jameson S. Effect of zinc deficiency in human reproduction. Acta Med Scand Suppl 1976;593:1–89.
29. Hambidge KM, Krebs NF, Jacobs MA, Favier A, Guyette L, Ikle DN. Zinc nutritional status during pregnancy: a longitudinal study. Am J Clin Nutr 1983;37:429–42.
30. Weiss M, Eisenstein Z, Ramot Y, Piptz S, Shulman A, Frenkel Y. Renal reabsorption of inorganic phosphorus in pregnancy in relation to the calciotropic hormones. Br J Obstet Gynaecol 1998;105: 195–9.
31. Tuttle S. Trace element requirements during pregnancy. In: Campbell DM, Gillmer MDG, eds. Nutrition in pregnancy. London: Royal College of Gynaecologists, 1983:47–54.
32. Pitkin RM. Calcium metabolism in pregnancy and the perinatal period: a review. Am J Obstet Gynecol 1985;151:99–109.
33. National Research Council. Recommended dietary allowances. 10th ed. Washington, DC: National Academy Press, 1989.
34. Institute of Medicine. Dietary reference intakes. Calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press, 1999.
35. Institute of Medicine. Dietary reference intakes. Thiamin, riboflavin, niacin, vitamin B-6, folate, vitamin B-12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press, 1998 (prepublication edition).
36. Food and Agriculture Organization of the United Nations. Calcium requirements. Report of a joint FAO/WHO Expert Consultation. Rome: FAO, 1962. (FAO Nutrition Meeting Report no. 30.)
37. Food and Agriculture Organization of the United Nations, World Health Organization. Requirements for vitamin A, iron, folate, and vitamin B-12. Report of a joint FAO/WHO Expert Consultation. Rome: FAO, 1988.
38. World Health Organization. Trace elements in human nutrition and heath. Geneva: WHO, 1996.
39. World Health Organization. Handbook of nutritional requirements. Geneva: WHO, 1974.
40. Food and Agriculture Organization of the United Nations, World Health Organization. Requirements of vitamin A, thiamin, riboflavin, and niacin. Report of a joint FAO/WHO Expert Group. Rome: FAO, 1985.
41. Kazzi GM, Gross CL, Bork MD, Moses D. Vitamins and minerals. In: Gleicher N, Buttin L, eds. Principles of medical therapy in pregnancy. 3rd ed. Old Tappan, NJ: Appleton and Lange, 1998:311–9.
42. Stabile I, Chard T, Grudzinskas G, eds. Clinical obstetrics and gynaecology. London: Springer, 1995:96–7.
43. Yoshida SH, Keen CL, Ansari AA, Gershwin ME. Nutrition and the immune system. In: Shils ME, Olsom JA, Shike M, Ross AC, eds. Modern nutrition in health and disease. 9th ed. Baltimore: Williams and Williams, 1999:725–50.
44. Caulfield LE, Zavaleta N, Shankar AH, Merialdi M. Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. Am J Clin Nutr 1998;68(suppl):499S–508S.
45. Sheldon WL, Aspillaga MO, Smith PA, Lind T. The effect of oral iron supplementation on zinc and magnesium levels during pregnancy. Br J Obstet Gynaecol 1985;92:892–8.
46. Jameson S. Zinc status in pregnancy: the effect of zinc therapy on perinatal mortality, prematurity and placental ablation. Ann N Y Acad Sci 1993;678:178–92.
47. Pharoah POD. Endemic cretinism in the Jimi Valley of New Guinea. PhD thesis. London University, London, 1972.
48. Taper LJ, Oliva JT, Ritchey SJ. Zinc and copper retention during pregnancy: the adequacy of prenatal diets with and without dietary supplementation. Am J Clin Nutr 1985;41:1184–9.
49. Institute of Medicine. Nutrition during pregnancy. Washington, DC: National Academy Press, 1990.
50. Sowers M, Crutchfield M, Jannausch M, Updike S, Carton G. A prospective evaluation of bone mineral change in pregnancy. Obstet Gynaecol 1996;77:741–5.
51. Frolich A, Rudricki M, Fischer-Rasmassen W, Olfsson K. Serum concentration of intact parathyroid hormone during late human pregnancy: a longitudinal study. Eur J Obstet Gynecol Reprod Biol 1991;42:85–7.
52. Husain SM, Sibley CP. Magnesium and pregnancy. Miner Electrolyte Metab 1993;19:296–307.
53. Repke JT. Calcium, magnesium, and zinc supplementation and perinatal outcome. Clin Obstet Gynecol 1991;34:262–7.
54. Stoltzfus RJ, Dreyfuss ML. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington, DC: INACG/WHO/UNICEF, 1998.
55. Hibbard BM. Iron and folate supplements during pregnancy: supplementation is valuable only in selected patients. BMJ 1988;297: 1324–6.
56. Health Canada. Nutrition for a healthy pregnancy: national guidelines for the childbearing years. Ottawa: Health Canada, 1997.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

57. Yip R. Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. Am J Clin Nutr 2000;72(suppl):272S–9S.
58. Gibson RS, Ferguson EL. Nutrition intervention strategies to combat zinc deficiency in developing countries. Nutr Res Rev 1998;11: 115–31.
59. Goldenberg RL, Tamura T, Neggers Y, et al. The effect of zinc supplementation on pregnancy outcome. JAMA 1995;274:463–8.
60. Hakimi M, Dibbley MJ, Suryono A, et al. Impact of vitamin A and zinc supplements on maternal post partum infections in rural central Java, Indonesia. Report of the XIX International Vitamin A Consultative Group Meeting. Durban, South Africa, 8–11 March, 1999. Washington, DC: ILSI Press, 1999:34.
61. Caulfield LE, Zavaleta N, Figueroa A. Adding zinc to prenatal iron and folate supplements improves maternal and neonatal zinc status in a Peruvian population. Am J Clin Nutr 1999;69:1257–63.
62. Dunn JT. Iodized oil in the treatment and prophylaxis of IDD. In: Hetzel BS, Dunn JT, Stanbury JB, eds. The prevention and control of iodine deficiency disorders. Amsterdam: Elsevier, 1987:127–34.
63. Xu GL, Wang SC, Gu BQ, et al. Further investigation on the role of selenium deficiency in the aetiology and pathogenesis of Keshan disease. Biomed Environ Sci 1997;10:316–26.
64. Kohrle J. The trace element selenium and the thyroid gland. Biochimie 1999;81:527–33.
65. Wallingford JC, Underwood BA. Vitamin A deficiency in pregnancy, lactation, and the nursing child. In: Bauernfeind JC, ed. Vitamin A deficiency and its control. New York: Academic Press, 1986:101–52.
66. Underwood BA. Maternal vitamin A status and its importance in infancy and early childhood. Am J Clin Nutr 1994;59(suppl): 517S–24S.
67. Wickens D, Wilkins MH, Lyne CJ, et al. Free radical oxidation (peroxidation) products in plasma in normal and abnormal pregnancy. Ann Clin Biochem 1981;18:158–62.
68. World Health Organization. Requirements of ascorbic acid, vitamin D, vitamin B-12, folate, and iron. World Health Organ Tech Rep Ser 1972;452.
69. Katz J, Khatry SK, West KP, et al. Night blindness is prevalent during pregnancy and lactation in rural Nepal. J Nutr 1995;125:2122–7.
70. Christian P, West KP, Khartry SK, et al. Night blindness of pregnancy in rural Nepal: nutritional and health risks. Int J Epidemiol 1998;27:231–7.
71. West KP, Katz J, Khatry SK, et al. Double blind, cluster randomized trial of low dose supplementation with vitamin A or β-carotene on mortality related to pregnancy in Nepal. Br Med J 1999;318:570–5.
72. Sharma SC, Bonnar J, Dostalova L. Comparison of blood levels of vitamin A, β-carotene, and vitamin E in abruptio placentae with normal pregnancy. Int J Vitam Nutr Res 1986;56:3–9.
73. Roberts SA, Cohen MD, Farfar JO. Antenatal factors associated with neonatal hypocalcaemia convulsions. Lancet 1973;12:809–11.
74. El-Sonbaty MR, Abdul-Ghaffar NU. Vitamin D deficiency in veiled Kuwaiti women. Eur J Clin Nutr 1996;50:315–8.
75. Drife J, MacNab G. Mineral and vitamin supplements. Clin Obstet Gynaecol 1986;13:253–67.
76. Meija LA, Chew F. Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron. Am J Clin Nutr 1988;48:595–600.
77. Bloem MW, Wedel M, Van Agtmaal EJ, Speeck AJ, Saowakontha S, Schreurs WHP. Vitamin A intervention: short term effects of a single, oral, massive dose on iron metabolism. Am J Clin Nutr 1990;51:76–9.
78. Suharno D, West CE, Muhilal, Karyadi D, Hautvast JGAJ. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. Lancet 1993;1: 1593–6.
79. Stoltzfus RJ, Dreyfuss M, Shrestha JB, Khatry SK, Schulze K, West KP. Effect of maternal vitamin A or β-carotene supplementation on iron-deficiency anemia in Nepalese pregnant women, post partum mothers, and infants. Report of the XVIII International Vitamin A Consultative Group Meeting. Cairo, Egypt, 22–26 September, 1997. Washington, DC: ILSI Press, 1998:86.
80. Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomised trial of effects of vitamin A supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. Lancet 1998;351: 1477–82.
81. Mellanby E, Green HN. Vitamin A as an anti-infective agent: its use in the treatment of puerperal septicemia. Br Med J 1929;1:984–6.
82. Green HN, Pindar D, Davis G, Mellanby E. Diet as a prophylactic agent against puerperal sepsis. Br Med J 1931;2:595–8.
83. Cameron SJ. An aid to the prevention of puerperal sepsis. Trans Edinburgh Obstet Soc 1931;52:93–103.
84. World Health Organization. Safe vitamin A dosage during pregnancy and lactation. Geneva: WHO, 1998. [WHO/NUT/98.4.]
85. Hytten FE. Nutrition. In: Hytten F, Chamberlain G, eds. Clinical physiology in obstetrics. Oxford, United Kingdom: Blackwell Scientific Publications, 1980:163–92.
86. Czeizel AB. Folic acid in the prevention of neural tube defects. J Pediatr Gastroenterol Nutr 1995;20:4–16.
87. Metz J, McGrath K, Bennett M, Hyland K, Bottinglieri T. Biochemical indices of vitamin B12 nutrition in pregnant patients with subnormal serum vitamin B12 levels. Am J Hematol 1995;48:251–5.
88. Malone JI. Vitamin passage across the placenta. Clin Perinatol 1975;2:195–307.
89. Heller S, Salkeld RM, Korner WF. Vitamin B_1 status in pregnancy. Am J Clin Nutr 1974:27:1221–4.
90. Bates CJ, Prentice AM, Paul AA. Seasonal variation in vitamin A, C, riboflavin and folate intakes and status of pregnant and lactating women in a rural Gambian community: some possible implications. Eur J Clin Nutr 1994;48:660–8.
91. Bowen RS, Mars M, Chuturgoon AA, Dutton MF, Moodley J. The response of the dietary antioxidants vitamin E and vitamin C to oxidative stress in pre-eclampsia. J Obstet Gynecol 1998;18: 9–13.
92. Sharma SC, Walzman M, Bonnar J, Molloy A. Blood ascorbic acid levels and histamine levels in patients with placental bleeding. Hum Nutr Clin Nutr 1985;39C:233–8.
93. Clemetson CAB, Cafaro V. Abruptio placentae. Int J Gynecol Obstet 1981;19:453–60.
94. Blegen SD. Postpartum congestive heart failure, beriberi heart disease. Acta Med Scand 1965;178:515–24.
95. Powers HJ. Effects of riboflavin deficiency on the handling of iron. In: Micronutrient interactions: impact on child health and nutrition. Washington, DC: ILSI Press, 1998:36–42.
96. Heller S, Salkfeld RM, Korner WF. Riboflavin status in pregnancy. Am J Clin Nutr 1974;27:1225–30.
97. Pitkin RM. Vitamins and minerals in pregnancy. Clin Perinatol 1975;2:221–32.
98. Nichols BL, Nichols VN. Nutritional physiology in pregnancy and lactation. Adv Paediatr 1983;30:473–515.
99. Sloan NL, Jordan EA, Winikoff B. Does iron supplementation make a difference? Arlington, VA: John Snow, Inc, 1992. (MotherCare Working Paper no. 15.)
100. Baker K, Thind IS, Frank O, et al. Vitamin levels in low birthweight new-born infants and their mothers. Am J Obstet Gynecol 1997;129: 521–4.
101. Qvist I, Abdulla M, Jagerstad M, et al. Iron, zinc and folate status during pregnancy and two months after delivery. Acta Obstet Gynecol Scand 1986;65:15–22.
102. Bruinse HW, Vander Berg H, Haspels AA. Maternal serum folacin levels during and after normal pregnancy. Eur J Obstet Gynecol Reprod Biol 1985;20:153–8.
103. Savage D, Gangaidz O, Lindenbaum J, et al. Vitamin B12 deficiency in the primary cause of megaloblastic anaemia in Zimbabwe. Br J Haematol 1994;86:844–50.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016

104. Kang SS, Wong PWK, Susmano A, Sorg J, Norusis M, Ruggie N. Thermolabile methylenetetrahydrofolate reductase: an inherited risk factor for coronary artery disease. Am J Hum Genet 1991;48: 536–45.
105. de Franchis R, Sebastio G, Mandato C, Andria G, Mastroiacovo P. Spina bifida 677T- (mutation) and role of folate. Lancet 1995;345: 1703 (letter).
106. Molloy AM, Daly S, Mills JL, et al. Thermolabile variant of 5,10 methylenetetrahydrofolate reductase associated with low red-cell folate: implication for folate intake recommendations. Lancet 1997; 349:1591–3.
107. Baker SJ, Jacob E, Rajan KT, Swaminathan SP. Vitamin B12 deficiency in pregnancy and puerperium. Br Med J 1962;1: 1658–61.
108. Allen L. The nutrition CRSP: what is marginal malnutrition and does it affect human function? Nutr Rev 1993;1:255–67.
109. Shojania AM. Folic acid and vitamin B12 deficiency in pregnancy and in the neonatal period. Clin Perinatol 1984;11: 433–59.
110. Bates CJ, Prentice AM, Watkinson M, et al. Efficacy of a food supplement in correcting riboflavin deficiency in pregnant Gambian women. Hum Nutr Clin Nutr 1984;38C:363–74.
111. Department of Health, Scottish Office, Home and Health Department, Welsh Office, Department of Health and Social Services, Northern Ireland. Folic acid and the prevention of neural tube defects: report from an expert advisory group. London: Department of Health, 1992.
112. Lawson JB, Stewart D. Obstetrics and gynecology in the tropics and developing countries. London: Edward Arnold Ltd, 1970.
113. Wickramasinghe SN. Folate and B-12 deficiency and supplementation. Prescribers J 1997;37:88–95.
114. UNICEF. State of the world's children. Oxford, United Kingdom: Oxford University Press, 1998.
115. International Nutritional Anaemia Consultative Group Symposium. 12 March 1999, Durban, South Africa. Washington, DC: ILSI Press, 2000.
116. Huffman SL, Baker J, Shumann J, Zehner ER. The case for promoting multiple vitamin/mineral supplements for women of reproductive age in developing countries. Washington, DC: Linkages Project, Academy for Educational Development, 1998.
117. Smith AG. Prescribing iron. Prescribers J 1997;37:82–7.
118. Keen CL, Zidenberg-Cherr S. Should vitamin-mineral supplements be recommended for all women with childbearing potential? Am J Clin Nutr 1994;59(suppl):532S–9S.
119. Truswell S. Who should take vitamin supplements? BMJ 1990;301: 135–6.
120. Lonnerdal B, Keen CL. Trace element absorption in infants: potentials and limitations. In: Clarkson TW, Nordberg GF, Sager PR, eds. Reproductive and developmental toxicity of metals. New York: Plenum Press, 1983:759–76.
121. Lonnerdal B. Iron-zinc-copper interactions. In: Micronutrient interactions: impact on child health and nutrition. Washington, DC: ILSI Press, 1996:3–10.
122. Simmer K, Iles CA, James C, Thompson RPH. Are iron-folate supplements harmful? Am J Clin Nutr 1987;45:122–5.
123. Ghishan FK, Said HM, Wilson PC, Murrell JE, Greene HC. Intestinal transport of zinc and folic acid: a mutual inhibitory effect. Am J Clin Nutr 1986;43:258–62.
124. Milne DB, Canfield WK, Mahalko JR, Sandstead HH. Effect of oral folic acid supplements on zinc, copper, and iron absorption and excretion. Am J Clin Nutr 1984;39:535–9.
125. Tamura T, Goldenburg RL, Freeberg LE, Cliver SP, Cutter GR, Hoffman HJ. Maternal serum folate and zinc concentrations and their relationships to pregnancy outcome. Am J Clin Nutr 1992;56: 365–70.
126. Mervyn L, ed. Dictionary of minerals. Wellingborough, NY: Thorsons Publishing, 1985:173–7.
127. Babior BM, Peters WA, Briden PM, Cetrulo CL. Pregnant women's absorption of iron from prenatal supplements. J Reprod Med 1985;30:355–7.
128. Hallberg L. Does calcium interfere with iron absorption? Am J Clin Nutr 1998;68:3–4 (editorial).
129. Homedes N, Ugalde A. Patients' compliance and medical treatments in the third world. What do we know? Health Policy Plan 1993;8: 291–314.
130. Sharon M. Commercial micronutrient supplements and fortified food in India. Washington, DC: USAID/OMNI, 1998.
131. Leslie J. Women's nutrition: the key to improving family health in developing countries. Health Policy Plan 1991;6:1–19.
132. Ladipo OA. Opportunities and constraints for reproductive health research in developing countries. In: Van Look PF, Perez-Palacios G, eds. Contraceptive research and development, 1984–1994: the road from Mexico City to Cairo and beyond. New Delhi: Oxford University Press, 1995:489–500.
133. Wall LL. Dead mothers and injured wives: the social context of maternal morbidity and mortality among the Hausa of northern Nigeria. Stud Fam Plann 1998;29:341–59.
134. McCarthy J, Maine D. A framework for analyzing the determinants of maternal mortality. Stud Fam Plann 1992;23:23–33.
135. World Health Organization. The WHO reproductive health library. No 2. Geneva: WHO, 1999 (CD-ROM). (WHO/RHR/RHL/2/99.)

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on March 20, 2016