

Vitamins and minerals for women: recent programs and intervention trials

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Abstract

Women's nutrition has received little attention in nutrition programming, even though clinical trials and intervention trials have suggested that dietary improvement or supplementation with several nutrients may improve their health, especially in low-income settings, the main focus of this paper. Most attention so far has focused on how improvements in maternal nutrition can improve health outcomes for infants and young children. Adequate vitamin D and calcium nutrition throughout life may reduce the risk of osteoporosis, and calcium supplementation during pregnancy may reduce preeclampsia and low birth weight. To reduce neural tube defects, additional folic acid and possibly vitamin B₁₂ need to be provided to non-deficient women before they know they are pregnant. This is best achieved by fortifying a staple food. It is unclear whether maternal vitamin A supplementation will lead to improved health outcomes for mother or child. Iron, iodine and zinc supplementation are widely needed for deficient women. Micronutrient supplementation (MMS) in place of the more common iron-folate supplements given in pregnancy in low-income countries may slightly increase birth weight, but its impact on neonatal mortality and other outcomes is unclear. More sustainable alternative approaches deserve greater research attention.

Key Words: Maternal nutrition, multimicronutrient supplementation, vitamins, minerals, low birth weight

Introduction

Nature has given women additional challenges in their role as the bearers and early nurturers of children-which in some sense act as sizable parasites. This places women more at nutritional risk, especially where fertility rates are high, as they tend to be in low-income countries. Poor nutritional status, infection, and a heavy and stressful workload all contribute to increasing a woman's risk of health problems.

Interest in women's nutrition has grown rapidly in recent years but this is mainly because of its relation to child growth, especially nutritional stunting once it was realized that this begins at birth, with most of the insult in height growth taking place in infancy. In Malawi for example, 40% of the growth stunting that occurs by three years of life has already taken place by 6 months of age [1]. Some have suggested that maternal nutrition during gestation and breastfeeding may be involved [2]. This has led to speculation that treating women with multivitamin and mineral supplements during and after pregnancy might reduce this process of stunting in infants.

Greiner suggested an alternative hypothesis, that early infant retardation in linear growth could to a great extent, be caused by the nearly universal lack of exclusive breastfeeding [3]. This is because in low income countries the foods and fluids given in the early months of life (which always displace breast milk to a large extent), even if they are adequate in energy, lack the other nutrients needed for height growth. In wealthier settings,

milk, infant formula or fortified baby foods are more commonly given, and nutritional stunting is not among the known health consequences of the failure to breast feed exclusively. Particularly important for height growth are proteins and minerals, levels of which vary quite little in breast milk, except for the soluble and often endemically deficient minerals iodine and selenium [4].

We know that suboptimal nutrient intakes among women can have an impact on health, including pregnancy outcomes, bone development, immune function, and, in the elderly, neurological function [5]. This review will examine experience in addressing women's nutrient deficiencies at public health level. Ideally, this should be done by reviewing evaluations of public health programs. However, few such programs exist and evaluations of them are rare. Thus, the main focus here will be on intervention research that has been conducted during the past decade or so in women of about 15-45 years of age. This kind of research has been conducted mainly in low-income settings.

Some indirect interventions may have the greatest influence on maternal vitamin and mineral status such as delaying the first conception in young women, increased birth spacing, extending the period of paid maternity leave for working women, and better and earlier treatment of maternal infections. And of course women will benefit from overall strategies to improve vitamin and mineral nutrition such as the Global Alliance for Improved Nutrition (GAIN)-led Ten Year Strategy for the Reduction of Vitamin and Mineral Deficiencies [6]. However, this review focuses on specific interventions or intervention research aiming

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to improve vitamin and/or mineral status among women, first for their own health and then for that of their offspring.

Nutrient deficiencies linked to public health problems in women

Calcium and vitamin D

Calcium (1,200 mg elemental Ca/d) was found to reduce all four premenstrual syndrome symptoms examined in an older clinical trial [7]. It has even been suggested that PMS may be a marker for inadequate calcium intake [8].

Calcium supplementation during pregnancy (≥ 1 g/d) appears to reduce maternal blood pressure, approximately halve the risk of pre-eclampsia, and reduce the risk of preterm birth, with no evidence of doing harm [9]. This appears to be due to correcting deficiency (suboptimal calcium intake is common in women, even in rich countries) rather than a pharmaceutical effect.

Adequate vitamin D and calcium nutrition throughout the life-course appear to reduce the risk of osteoporosis [10]. So far there is no conclusive evidence that supplementation with any other nutrients has a beneficial impact on bone health [11].

Iron

Women tend to be more susceptible to iron deficiency than men because of monthly blood losses during their reproductive years, and the 10% who lose the most (> 80 ml/mo) are most at risk [12]. Intrauterine contraceptive devices may increase monthly losses by 30-50%, though levonorgestrel-releasing intrauterine systems reduce this problem [13]. Oral contraceptives and intensive breastfeeding [14] tend to reduce maternal iron losses during reproduction.

Pregnancy and delivery are the source of the greatest iron losses and hemorrhaging during delivery is a major cause of maternal mortality, with women suffering from anemia at increased risk [15]. Iron supplementation during pregnancy can improve maternal iron status, but only if begun early enough and where adherence is high [16]. While deficiencies of several nutrients besides iron can cause anemia, and some nutrients like vitamin A are often linked to iron status, a recent review found no greater impact of a multimicronutrient supplement on iron status than supplementing with iron alone [17].

Anemia increases the risk of preterm delivery and low birth weight (LBW). But high maternal iron levels are associated with an increased risk of fetal growth restriction, preterm delivery, and preeclampsia. High iron levels cause oxidative stress and are also linked to gestational diabetes [18]. Thus in general, where infrastructure will allow it would probably be wiser to ensure that a pregnant woman is iron deficient before giving her iron supplementation during pregnancy, at least in large doses.

Vitamin A

Vitamin A policymaking has focused on providing large doses, either to young children or to women soon after delivery [19], actively reducing the attention given to alternative approaches [20]. (Giving a dose larger than 10,000 IU, less than a two-day supply, at any other time to women in the reproductive age group is considered unethical, since higher doses may be associated with birth defects in women who do not yet know they are pregnant.) While women do receive large doses soon after delivery in some countries, the purpose of this is to increase levels in their breast milk. A recent systematic analysis failed to find any other benefit [21]. One trial in Nepal found that giving pregnant women frequent small doses of vitamin A reduced maternal mortality by 44% [22]. Later trials within less vitamin A deficient populations in Bangladesh [23] and Ghana [24] failed to find any impact.

Kirkwood argues that even the Nepal study provides inconclusive evidence, and thus, there is presently inadequate support for including low-dose vitamin-A supplementation for women in safe motherhood programs [25].

Vitamin E

One older placebo controlled trial found that a daily dose of 400 IU/d for three months led to a reduction in symptoms of premenstrual syndrome [26]. Results have been inconsistent for other supplements such as large doses of vitamin B₆ and evening primrose oil.

Zinc

There is some evidence that zinc deficiency may be involved in some maternal mental health problems. In one study, 25 mg/d of zinc, along with medical treatment, improved depression more rapidly than medical treatment alone. Anorexia nervosa patients also improved more rapidly with zinc therapy [27].

Multivitamins

In one study, the use of prenatal multivitamins was found to lead to easier pregnancies (such as less morning sickness) [8].

Health problems of the fetus or child linked to maternal nutrient deficiency

Most vitamin and many mineral deficiencies in the mother, if serious enough, are likely to have any of a range of impacts on her offspring. But major attention must be placed on mortality, as well as birth defects and LBW, both major causes of infant morbidity and mortality. We begin with single nutrient interventions and then move to the major issue attracting research attention in recent years, multimicronutrient supplementation (MMS) of pregnant women.

Single nutrients

Birth defects

Some studies have found a number of apparent benefits from taking prenatal vitamins, including reductions in heart, neural tube, and other birth defects [8]. However, the focus here will be on the outcome that has been most strongly confirmed and acted on, neural tube defects. Additional folic acid needs to be provided to women at the very beginning of pregnancy to reduce the incidence of neural tube defects (recognizing that other birth defects may be affected as well). Programs to improve folate nutrition have been introduced in 40 countries, but they represent only about 10% of the neural tube defects that could be prevented [28]. In particular, advising women to take prenatal supplements is ineffective [29]. This is partly because once a woman knows she is pregnant, the neural tube has already folded, and partly because, even with encouragement, too few women take them regularly enough. Thus impact can best be accomplished through mandatory fortification of a universally consumed food. While most staple food fortification has focused on wheat (and to a lesser extent on maize), when rice is the staple food, it can be fortified at low cost with no impact on taste or appearance [30].

Recent research suggests that vitamin B₁₂ deficiency may also be involved in the causation of neural tube defects [31]. Among other arguments for combining B₁₂ with folate in fortification programs, there is some evidence that high folate combined with low B₁₂ levels in pregnant women predisposes children to insulin resistance [32].

Infant morbidity

A study in West Java found that zinc supplementation in pregnant mothers led to a decreased incidence of diarrhea but an increase in episodes of cough during the first six months of infancy. Both zinc and β -carotene appeared to have an impact on the infant immune system [33]. Prenatal zinc supplementation was also found to reduce infant diarrhea in Indonesia [33] and Peru [34].

Birthweight

Even countries with high rates of low birthweight rarely have any defined programs to reduce it [35]. At the end of the 1990s, there were no known interventions with single vitamins and minerals that would decrease rates of intrauterine growth retardation [36], but the lack of good research was noted by the investigators.

Since then a great deal of additional research on this issue has been done. With respect to single nutrients, a systematic review found good evidence that calcium supplementation at > 1 g/day during pregnancy resulted in an average 17% reduction in LBW [37]. This effect may be due both to a prolongation of gestation and an increase in fetal growth. This same review found that the impact of magnesium supplementation during pregnancy may be even greater, but sample sizes so far have been slightly too small to be certain. The review found no

significant impact of supplementation with other single nutrients on fetal growth.

However in deficient mothers, supplementation with iodine [38] and iron [39] can increase birthweight. For iodine, this is associated with neonatal survival [40] as well as IQ. One study found that zinc (with routine iron-folate) did not increase birthweight [41]. But among African American women with low levels of serum zinc at baseline, supplementation with 25 mg of zinc (in women taking non-zinc containing prenatal MMS) resulted in a 285 g increase in birthweights [42].

Iron-folate supplementation during pregnancy has sometimes been found to improve a number of developmental outcomes in young children [43], and sometimes not [44]; also, zinc has not [45].

Multimicronutrient supplementation during pregnancy

Birthweight

During the past decade, the most extensive relevant research has involved supplementation of pregnant women with multimicronutrients, including a multi-site UNICEF study using approximately the recommended daily intakes of iron, folic acid, zinc, copper, selenium, iodine, and vitamins A, B₁, B₂, B₃, B₆, B₁₂, C, D, and E. (Note that this MMS did not include calcium or magnesium and used 30 mg of iron half the dose of what is often given in iron-folic acid supplements. However, a 60 mg dose is probably higher than necessary [46].) This research has focused on relatively large and "normal" populations, rather than on patients with clinical deficiencies.

A Cochrane review of MMS during pregnancy in 2006 found that it worked better than placebo but not better than iron-folate supplementation to reduce LBW (this is already commonly the standard of care and given to the control group in most studies) [47].

Use of MMS supplementation in pregnancy modestly increased birthweight in China (42 g compared to folate and 18 g compared to iron-folate) but did not have iron's impact in reducing mortality [48]. In West Java, its supplement resulted in a non-significant 40 g increase birthweight compared to iron-folate supplementation [49]; as well as increases of 52 g in Burkina Faso [50]; 70 g in Pakistan [51]; and 67 g in Niger [52]. In Vietnam, one district (A) received iron-folate, a second (B) received MMS and a third (C) received MMS and gender training. Birthweights were 105 g higher in C and 166 g higher in B, with A having about twice the rate of LBW. At age 2 years, children in B were about 2 cm taller and those in C were 1 cm taller than those in A [53].

A meta-analysis of 12 MMS trials found that the pooled estimate of increased birthweight was 24 g compared to supplementation iron-folate alone. There was about a 10% reduction in LBW, presumably due to an equal reduction in small for gestational age births. However, there was an equally large increase in gestational age births that were excessively large [54].

It is possible that the levels of nutrients used in the MMS were too low. One study in Guinea Bissau used a supplement with 15 nutrients at either one or two RDAs [55]. Among women for whom birth weights were available (who had had fewer births and more education), one RDA, resulted in a 53 g increase in birth weight and two RDAs, a 95 g increase (the latter was somewhat lower when potential confounders were adjusted for). There was no impact on the proportion born with LBWs or on mortality.

A few such trials have also taken place in industrialized countries. A recent trial of women who commonly had micronutrient deficiencies in East London, UK, though rather seriously flawed (about half the women did not complete the trial), suggested that MMS might reduce the incidence of small for gestational age deliveries [56]. A French study (1/3 loss to follow up) among apparently healthy mothers, found that MMS (which did not include iron but added Mg and Ca) increased birthweights from 3,049 to 3,300 g and resulted in a decrease in low birthweights (<2,700 g) [57]. Maternal vitamin C levels seemed particularly important for birth weight along with zinc for birth length. In the USA, one prospective study in a low-income city for over a decade (which measured adherence to the prenatal vitamins prescribed to all participants) found substantially lower rates of preterm delivery in women who used the supplements (which contained 1 mg of folate, 25 mg zinc, 65 mg iron and 200 mg of calcium) [58]. However, there was no difference in the proportion that was small for gestational age.

Height growth

Shrimpton [59] argues that even modest reductions in LBW would substantially reduce stunting by two years of age. In one study in Vietnam, height at two years was one cm higher and rates of stunting were 8 percentage points lower (from a baseline of 29%) in two districts that received MMS compared to one that did not [53]. In France, maternal zinc supplementation alone was associated with birth length [57]. However, these studies appear to be exceptions. There was no effect of MMS on birth length in any of the 12 studies included in a meta-analysis and there was no overall impact when the data were combined [54]. Nor was such an impact seen in an MMS trial in Mexico, though in a per protocol analysis, the investigators noted that high adherence appeared more likely to lead to impact [60].

Young child morbidity

Maternal supplementation with folic acid with or without iron and zinc reduced the risk of kidney dysfunction and, to a lesser extent, metabolic syndrome among children at 6-8 y of age, however, MMS did not [61].

Neonatal mortality

In Lombok Indonesia, a large trial found that MMS through pregnancy and until 90 days after delivery reduced early infant

mortality by 18% compared to iron-folate [62], with an impact of 38% among women who were anemic at baseline. LBW was decreased by 14% and 33% respectively. In a small trial of Indian women who were both undernourished (BMI <18.5) and anemic (Hb 7-9 mg/dl), a supplement with 29 nutrients given through pregnancy resulted in substantial decreases in LBW and early neonatal morbidity [63].

In Burkina Faso [50], perinatal death was higher in the group receiving the MMS (OR: 1.78; 95% CI: 0.95, 3.32; $P < 0.07$), particularly among primiparas (OR: 3.44; 95% CI: 1.1, 10.7). Similarly, in Pakistan [51], MMS increased the neonatal mortality rate from 23.5 to 43.2 per thousand live births, though this was not statistically significant. A meta-analysis found no impact of MMS on any type of mortality [64].

Intellectual and motor function in young children

In Bangladesh, adding multiple micronutrients to food supplements for pregnant women led to better cognitive function in children at two years of age [65], although it failed to increase infant micronutrient levels, except for vitamin B₁₂ [66]. In China, MMS increased raw scores in mental development at one year but not earlier, but it did not impact psychomotor development [67]. A study in Nepal found no such impact however [43].

Experience with actual programs aimed at improving women's vitamin and mineral status

Reviewing all the research done so far, the overall impact of MMS would appear to be quite variable, often unimpressive and sometimes apparently negative. Impacts on fetal growth and on young child growth and development appear to be of small to moderate effect sizes. However, it is unclear whether there is an overall positive or negative impact on early infant mortality rates. In addition, recent data suggest MMS may be associated with an increased risk of dysfunctional labor [68].

Some authors do feel that this accumulated evidence is enough to call on WHO to recommend that pregnant women routinely be given MMS [69,70]. Presumably, this is because MMS is so much simpler to implement than alternative interventions. However, others need to be studied even though they are complex, if only because they are likely to be less risky [71]. The period should come after the reference citation. An example of an effective alternative is conditional cash transfer programs; one in Mexico increased birthweights by 127 g [72].

We do not know whether successful food-based interventions will result in similar impacts on birth weight. While it is clear that all needed micronutrients can be obtained in diversified but relatively common diets [73], food-based programs often show improved micronutrient status without concomitant impacts on maternal and child health [74]. Diet-based approaches are complex; no particular food or nutrient manufacturer benefits from them; thus there are actually very few that have been

undertaken. Bryce *et al.* [35] found that none of the largest 20 countries, in which a total 80% of global stunting takes place, have national food supplementation programs for women, though sub-national programs were found in 13 of them.

For addressing infant stunting, further attention should focus on exclusive breastfeeding. It is no doubt difficult to measure, since feeding patterns vary over time and most studies only measure current practices using a 24 hour recall [75], and exclusive breastfeeding with a duration of longer than several weeks is often rare, requiring large sample sizes. One study did examine the link and found an OR of nearly 4 for both stunting as well as wasting associated with exclusive breastfeeding for a duration of less than six months [76]. Even though one trial failed to find an impact [77], given how small the impact of MMS appears to be on early stunting, trials that examine the efficacy of efforts to increase exclusive breastfeeding in reducing infant stunting deserve more attention.

The only widely implemented vitamin or mineral program for women at national level is iron-folate supplementation during pregnancy. When maternal anemia during pregnancy is successfully corrected, it results in an average 20% decline in maternal mortality [78] and improves women's cognitive functioning [79] as well as their capacity to care for their children [80-82].

In countries where anemia levels are higher than 40% during pregnancy, it is recommended that these tablets be offered to all pregnant women [83]. In others, it is often provided only to those with anemia (cut-off points for this vary from serum hemoglobin (Hb) concentrations of 7 mg/dl to 9 mg/dl), on the assumption that much, if not most, of this is linked to iron deficiency. Iron-folate supplements are effective in clinical trials in improving status of these two nutrients during the supplementation periods (usually about 6 months, sometimes 9). A few Latin American and Asian countries have had reasonable success at implementing such programs [84]. Among others, experience in Thailand and Nicaragua suggests that iron-folate supplements can reduce maternal anemia by one-third over a ten-year period [85]. However poor access (great distance to a health facility; outages at health facilities; ineligibility of the health workers who meet the women to access the tablets and thus provide them) and to a somewhat less, but still important extent, poor adherence (side effects, rumors of side effects, and unfounded fears) have plagued these programs for decades and no clear solutions have been found, especially in the poorest countries where needs are greatest [86]. Side effects increase and adherence declines as dosage increases [87].

Methods for improving iron-folate programs exist, usually linked to community-based approaches [88,89], but do increase the cost of what is otherwise an extremely low-cost intervention. But providing iron tablets once per week to adolescents, reducing anemia from 73% to 25% in four years, cost only US \$0.36/beneficiary/year [90]. The semi-annual counseling and deworming it included may be the reason it was more successful than previous attempts to reach adolescents with weekly iron supplements

[91,92].

The use of bovine lactoferrin instead of ferrous sulfate also appears to greatly reduce the potential for side effects [93], as does the provision of riboflavin and retinol together with ferrous sulfate [94]. Even simply providing lower doses may be useful [95].

Conclusion

Why have so few other maternal nutrition programs emerged? One reason may be that the focus has been on mortality, and only iron deficiency anemia has a substantive impact. Micronutrient supplementation and adolescent and pre-pregnancy nutrition are not included in planning and budgeting for the reduction of maternal mortality [96]. In fact, there is very little normative guidance that provides prioritized advice to policy makers on what to do to improve maternal nutrition. Major attention has focused on child rather than maternal nutrition, perhaps in part due to UNICEF advocacy [59]. Nevertheless, Shrimpton believes that in many countries, the potential for scaling up community-based approaches that will benefit women's nutrition now exists [59].

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