A Review of the Benefits of Nutrient Supplements during Pregnancy: From Iron-Folic-Acid to Long-Chain Polyunsaturated Fatty Acids to Probiotics

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Abstract
This review summarizes current knowledge on the effectiveness of prenatal nutrient supplements ranging from iron-folic-acid (IFA), which is standard of care in many parts of the world, to more novel ones such as ω-3 fatty acids and probiotics in improving maternal and child health outcomes. Randomized controlled trials have shown that prenatal IFA supplements reduce the risk of anemia and iron deficiency during pregnancy and at term, but the evidence of risk reductions in low birth weight (LBW) and preterm delivery (PTD) is weak. Recent studies, however, suggest that prenatal IFA supplements may reduce child mortality. On the other hand, there is convincing evidence that multiple micronutrient supplements containing 1–2 recommended daily allowances of several vitamins and minerals are safe and reduce the risk of LBW by 19 and 17% when compared to a placebo or routine IFA. Prenatal calcium supplements (>1 g/day) have also been shown to significantly reduce the risk of pre-eclampsia and maternal death or serious morbidity by 52 and 20%, respectively. Zinc and fish oil supplements containing ω-3 fatty acids may also increase gestational age and reduce the risk of PTD, but not of LBW, in selected populations. There is, however, limited evidence to support the provision of supplements containing only vitamin A, D or antioxidants such as vitamins C and E. Although the protective effect of folic acid during the periconceptual period in reducing neural tube defects is well established, very few or no intervention trials have evaluated the independent effects of specific B vitamins (vitamins B6, B12 and folic acid), docosahexanoic acid and probiotics during pregnancy. The effects of prenatal iodine supplements in areas with mild to moderate iodine deficiency have not been examined either. Some of these nutrients may not affect outcomes such as PTD or LBW but may have long-term benefits for offspring health and development.

Introduction

Adverse pregnancy outcomes such as maternal mortality, preterm delivery (PTD) and intrauterine growth retardation remain significant public health problems especially in resource-poor environments where access to quality care and food are limited [1]. Low birth weight
Iron and Folic Acid

Iron is one of the nutrients whose requirements increase dramatically during pregnancy due to increased blood volume expansion and new tissues. Approximately 6 mg/day is needed during gestation compared to only 1.3 mg/day among nonpregnant women of reproductive age (WRA). Although iron absorption is increased, concerns have been expressed about the ability of diet alone to meet this greater demand especially in settings where iron deficiency is common in women even before they get pregnant [4]. Current recommendations for prenatal iron supplementation exist even in developed countries, where the prevalences of anemia and iron deficiency are much lower than in developing countries. For example, all women are recommended to consume a daily supplement containing 30 mg of iron during the last trimester of pregnancy in the USA and selective supplementation with higher doses may be provided earlier for women who are diagnosed as anemic or iron deficient [5]. The World Health Organization (WHO) has a universal recommendation for all pregnant women to consume a daily supplement that contains 60 mg of iron and 400 µg of folic acid, which is important for many developing countries, where anemia and iron deficiency are common [6].

In addition to the direct effects of anemia, such as fatigue and reduced work capacity, iron deficiency and anemia during pregnancy have been associated with poor birth outcomes including small for gestational age (SGA) and PTD. Most of the evidence, however, has been based on observational studies and not corroborated by findings from well-designed placebo-controlled randomized controlled trials (RCTs) [4]. In a recent systematic review, Peña-Rosas and Viteri [7] carefully evaluated the existing evidence (as of June 2009) on whether routine intake of supplements containing iron or a combination of iron and folic acid during pregnancy improves a wide range of maternal health and pregnancy outcomes. This review included a total of 49 trials (randomized and quasi-randomized) involving 23,200 pregnant women and the key conclusions were as follows.

- Women who received daily prenatal iron supplementation with or without folic acid were less likely to have iron deficiency and anemia during pregnancy and at term compared to those who received a placebo or no treatment.
- Side effects and hemoconcentration are more common in women who receive daily iron supplementation.

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<tr>
<th>Interventions with sufficient or variable evidence of effectiveness</th>
<th>Interventions for which evidence showed no or little effect</th>
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<td>Iron-folate</td>
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<td>Multiple micronutrient</td>
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<td>Iron-folate</td>
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Table 1. Effect of nutrient interventions during pregnancy on maternal and child health outcomes [3]
• There were no differences in the effects of daily and weekly supplementation on gestational anemia.
• There is no evidence of significant reduction in maternal and neonatal outcomes such as LBW, preterm birth, infection, delayed development and postpartum hemorrhage.

These findings, which are similar to an earlier review by the same authors, have led to the consideration of weekly supplementation during pregnancy as an alternate and safer approach to current practice of daily supplementation. The implications of increased hemoconcentration seen among women who consumed IFA daily are unclear, but there are practical advantages to promoting using weekly supplements in terms of reduced costs and perhaps increased compliance, which in turn may increase the cost-effectiveness. Although current recommendations for pregnant women are unlikely to change, the WHO recently made a recommendation for the provision of weekly IFA supplements to all WRA in areas where iron deficiency and anemia are significant public health problems [8]. Despite the paucity of data on the long-term benefits for maternal and child health outcomes, the expectation is that this approach would help improve the preconceptual nutritional status, which in turn would result in improved pregnancy outcomes.

It should also be noted that while the last conclusion does not support the recommendations made by Bhutta et al. [1], data on the impact of daily prenatal IFA on maternal and neonatal outcomes such as LBW are limited and there is considerable heterogeneity across studies. Only 9 (n = 6,275) out of the 49 trials included in the systematic review had data on birth size and showed a 21% reduction in the risk of LBW for those who received daily iron supplements compared to those who received no iron or placebo that was not statistically significant [risk ratio (RR) = 0.79; 95% confidence interval (CI) = 0.61–1.03]. The same was true for PTD that was based on 8 trials (n = 5,730); a 15% reduction in risk of PTD was seen among the iron-treated groups compared to placebo or no treatment, but it was not statistically significant (RR = 0.85; 95% CI = 0.67–1.09). Even fewer studies have examined maternal outcomes such as preeclampsia or mortality, indicating the need for well-designed large trials. Interestingly, the authors report that their findings for birth weight did not change when they restricted the analysis to the high-quality studies (n = 7), but it was statistically significant (RR = 0.82, 95% CI = 0.71–0.94) when the analysis was restricted to the 3 trials (n = 1,823) that had unspecified or mixed anemic status. They also found significant differences for birth length [weighted mean difference (WMD) = 0.38 cm, 95% CI = 0.10–0.65 cm], which was reported in 5 out of the 9 studies included in the birth weight analysis. The authors call for more research and the findings of several large ongoing RCTs will play an important role in confirming the effect of prenatal IFA on reducing the burden of LBW and PTD. The findings of one of these studies that was not included in the meta-analysis are described here [9]. A large double-blind RCT was conducted in rural North-West China in which villages were randomized for all pregnant women to take either daily folic acid (control), IFA or MMN with a recommended allowance of 15 vitamins and minerals. Relative to folic acid alone, prenatal IFA supplementation was associated with a 50% reduction in the risk of early PTD (<34 weeks) (RR = 0.50, 95% CI = 0.27–0.94) and a 54% reduction in the risk of early neonatal mortality (RR = 0.46, 95% CI = 0.21–0.98). There was no significant effect on LBW (RR = 0.81, 95% CI = 0.59–1.12), which was 4.5 and 5.3% in the IFA and folic-acid groups. The birth length, however, was significantly greater in the IFA group compared to the folic acid group (WMD = 0.24 cm, 95% CI = 0.02–0.46 cm). Long-term benefits of prenatal IFA supplementation have also been reported in a recent follow-up of a large cluster randomized trial in Nepal in which the efficacy of 4 different combinations of antenatal micronutrient supplements, namely folic acid only, IFA, IFA-zinc and a multivitamin-mineral supplement were compared [10]. The percentage of LBW infants was significantly lower in the group that received IFA supplements (34%) compared to the control group (43%) that received only vitamin A (RR = 0.84, 95% CI = 0.72–0.99). Although there were no differences in the prevalence of PTD or neonatal morbidity in the first 10 days of life or at 6 weeks of age [11], the offspring of women who received IFA supplements during pregnancy were less likely to die in the first 7 years of life [hazard ratio (HR) = 0.69; 95% CI = 0.49–0.99] compared to those who received a placebo [12]. These reductions in child mortality in 2 varied settings provide valuable data for improving ongoing efforts to augment antenatal care and consumption of prenatal IFA supplements. The strengths of both these studies include the large sample size, the range of outcomes examined and low loss to follow-up.

Finally, the importance of just folic acid during the periconceptual period in the prevention of neural tube defects (NTDs) is well recognized and has led to worldwide efforts to improve folic acid intakes in WRA [13]. Mandatory fortification of flour with folic acid in coun-
tries such as the USA have resulted in significant reductions in birth defects, especially NTDs [14]. However, much less is known about the importance of folic acid later in gestation. Folic acid results in megaloblastic anemia and may be associated with birth size. Christian et al. [10] found no effects of folic acid only on birth size but did find a reduced risk of mortality from birth to 7 years in the folic acid-only group compared to the placebo.

### Multiple Micronutrients

Deficiencies of MMN usually coexist in many developing countries, which led to considerable interest by researchers and implementers in evaluating the benefits of providing pregnant women with a daily MMN supplement that contains several vitamins and minerals. In an earlier meta-analysis that included 9 trials (n = 15,378 women), Haider and Bhutta [15] reported that prenatal MMN supplementation reduced the risk of LBW by 17%
studies standard IFA supplement. Although some of the early and trace elements such as iron, zinc and copper to the allowance for several vitamins (A, B complex, C, D and E) ment containing 1–2 times the recommended daily al-

Many of them compared a daily prenatal MMN supple-

ments when compared to iron, recent studies have shown otherwise [17–19]. Of particular note is the large double-blind cluster-randomised trial that was conducted in Indonesia [18]. Midwives were advised to distribute either IFA or MMN supplements (UNIMMAP supplement) in a randomized fashion to pregnant women who consumed the supplements daily up to delivery and during the first 3 months postpartum. Intention to treat analysis revealed an 18% reduction (RR = 0.82, 95% CI = 0.70–0.95) in ear-

ly infant mortality among infants born to women con-

suming MMN supplements compared to those who con-

sumed IFA supplements. Combined fetal loss and neonat-

dal deaths were also reduced by 11% (RR = 0.89, 95% CI = 0.81–1.00), with significant effects in undernourished (RR = 0.85, 95% CI = 0.73–0.98) or anemic (RR = 0.71, 95% CI = 0.58–0.87) women. This study also showed that the reductions in the risk of LBW were greatest among those infants born to women who were anemic at baseline; the overall reduction was 14% (RR = 0.86, 95% CI = 0.73–1.01) for those in the MMN group compared to the IFA group and 33% (RR = 0.67, 95% CI = 0.51–0.89) for infants of women who were anemic at enrolment. The other recent large trial was conducted in North West China [9]. This study did not find any significant differences in the risk of LBW (RR = 0.78, 95% CI = 0.56–1.08) or PTD (RR = 0.86, 95% CI = 0.64–1.14), but there were sig-

nificant increases in mean birth weight and gestational age in the MMN group compared to the folic acid-only group. There were no significant differences in perinatal mortality (stillbirths and early neonatal mortality) between the 3 groups either. The findings of these 2 recent studies [9, 18] have assuaged earlier concerns that MMN supplementation may increase infant mortality [27] and confirm the benefits of providing pregnant women with MMN supplements especially in settings where anemia and undernutrition are common. In a more recent systematic review that included the results of all the 13 MMN trials published to date, Shah et al. [28] estimated a 19% reduction in the prevalence of LBW that could be attributed to prenatal MMN in comparison to a placebo (RR = 0.81, 95% CI = 0.73–0.91). More importantly, there was a significant reduction in the risk of LBW even when prenatal MMN supplementation was compared to IFA supplementation (RR = 0.83, 95% CI = 0.74–0.93) and birth weight was significantly higher (WMD = 54 g; 95% CI = 36–72 g) among infants whose mothers were in the MMN group compared to those in the IFA group. There were, however, no differences in PTD. In summary, the evidence clearly supports the implementation of a recom-

mendation to provide MMN supplements to pregnant women especially in settings where LBW continues to be a significant public health problem.

Calcium

Hypertension is a major complication of pregnancy and several studies have evaluated the benefits of calcium supplementation in reducing the risk of pregnancy-relat-
ed hypertension and associated complications. A recent meta-analysis [29] showed that prenatal Ca supplementation (≥1 g/day) significantly reduced the risk of high blood pressure by 30% (95% CI = 14–43), preeclampsia by 52% (95% CI = 31–67) and maternal death or serious mor-

bidity by 20% (95% CI = 3–35) when compared to a pla-

cebo (12 trials; n = 15,528). There were, however, no sig-

nificant differences in the risk for PTD and still births, which were reduced by 19 and 11%, respectively. One con-

cern with the interpretation of these findings is possible publication bias. Prenatal Ca supplementation (1.5 g/day) did not significantly reduce the risk of preeclampsia (RR = 0.91, 95% CI = 0.69–1.19) in a large (n = 8,325) high-quality WHO multicenter trial that was conducted in de-
veloping country settings where calcium intakes were low [30] and included in the meta-analysis. There were, how-
ever, significant reductions in the risk of severe gestation-
al hypertension (RR = 0.71; 95% CI = 0.61–0.82), eclampsia (RR = 0.68; 95% CI = 0.48–0.97) and neonatal mortality (RR = 0.70; 95% CI = 0.56–0.88). The risk for PTD was also significantly reduced among younger women (<20 years). A recent trial conducted in India [31] has also shown significant benefits of Ca supplementation in reducing the risks of preeclampsia, high blood pressure and even preterm births. This study used a higher dose (2 g/day) and was also done among nulliparous women with low intakes of dietary Ca (~300 mg/day) similar to the WHO trial. In summary, studies conducted to date are suggestive of benefits to maternal and child health outcomes especially in settings with low Ca intakes.

**Magnesium**

There is some evidence suggesting benefits of providing magnesium during pregnancy. In a meta-analysis that included 5 trials, Makrides and Crowther [32] estimated that compared to a placebo, oral magnesium supplements before 25 weeks gestation were associated with a 27% reduction in the rate of PTD (RR = 0.73; 95% CI = 0.57–0.94; n = 2,275). Similar reductions were seen for the rate of LBW (RR = 0.70; 95% CI = 0.53–0.93; n = 1,741). All the studies were conducted in developed countries (USA, Hungary and Austria) and the authors judged only 1 study to be of high quality, raising the possibility of biased results. Of note is the lack of significant differences in mean gestational age (WMD = 0.11, 95% CI = −0.06 to 0.29 days) or birth weight (WMD = 50.8, 95% CI = −0.2 to 101.9 g) and the effects on PTD and SGA were not significant following the exclusion of a large cluster randomized trial from Hungary (n = 985). These findings suggest that there is limited high-quality evidence regarding the benefits of oral magnesium supplements during pregnancy and the value of including magnesium in routine prenatal supplements remains to be evaluated.

**Iodine**

Severe iodine deficiency has long been associated with adverse pregnancy outcomes including pregnancy loss, stillbirth and irreversible brain damage that results in cretinism. Early studies conducted in areas where severe iodine deficiency is endemic have demonstrated the benefits of providing iodine during pregnancy, primarily as injectable or oral iodized oil, in reducing the rates of endemic cretinism [33]. In contrast, little work has been done on the benefits of providing iodine supplements in women with mild to moderate iodine deficiency. A few trials have shown that iodine supplementation was effective in minimizing an increase in thyroid size during pregnancy, but none have examined outcomes such as LBW or health and development of the offspring. The other concern is related to the safety of providing iodine supplements (either alone or as part of MMN supplement) in the context of universal salt iodization, which has been a successful strategy to eliminate iodine deficiency disorders. Current WHO recommendations for pregnant women living in settings where <90% are using iodized salt and the median urinary iodine in school age children <100 µg/l indicate a single annual dose of iodized oil containing 400 mg or a daily dose of 250 µg/I as potassium iodide. Pregnant women who have received iodized oil during their current pregnancy or up to 3 months before the current pregnancy should not consume iodine supplements [33].

**Vitamin A**

Vitamin A deficiency is common during pregnancy in many developing countries and although its role in child health is well known, concerns about the safety of providing vitamin A supplements during pregnancy remain [34]. Recent interest in the role of vitamin A in reducing the risk of mother-to-child transmission (MTCT) of HIV has led to several studies primarily in Subsaharan Africa. In a recent meta-analysis, however, Kongnyuy et al. [35] found no evidence of benefit of vitamin A on the risk of MTCT of HIV (RR = 1.06, 95% CI = 0.89–1.26; n = 7,528) based on the findings of 3 trials that provided oral vitamin A daily [36–38] during pregnancy and 1 trial in Zimbabwe that provided a large single dose of oral vitamin A for the mother (400,000 IU) and newborn (50,000 IU) soon after delivery [39]. The trials conducted in South Africa [36] and Malawi [38] did not find evidence of benefit, but the trial in Tanzania [37] showed that vitamin A supplementation increased the risk of MTCT of HIV by 53% (OR = 1.53, 95% CI = 1.15–2.04) by 24 months of age and raised concerns about the safety of prenatal vitamin A supplementation in HIV-infected women. There was no evidence of effects on other pregnancy outcomes either, namely stillbirths (RR = 0.99; 95% CI = 0.68–1.43), PTD (RR = 0.88; 95% CI = 0.65–1.19), death before 24 months among live births (RR = 1.08; 95% CI = 0.91–1.29) and maternal death (RR = 0.83; 95% CI = 0.59–1.17). Interestingly, the meta-analysis showed that prenatal vitamin A...
supplementation significantly improved birth weight (WMD = 89.78 g; 95% CI = 84.73–94.83 g). Villamor et al. [40], who followed up the offspring in the Tanzania study in which prenatal vitamins and not vitamin A improved birth size [20], found that children whose mothers received prenatal multivitamins were significantly heavier at 2 years of age (459 g; 95% CI = 35–882 g) and vitamin A seemed to reduce the benefits of multivitamins on these outcomes. Finally, very few studies have evaluated the benefits of prenatal vitamin A supplements on pregnancy outcomes in other parts of the world where the prevalence of HIV is much lower but vitamin A deficiency and LBW are high. A large cluster RCT that was conducted in Nepal found dramatic reductions in maternal mortality (~40%) among the women who received a weekly supplement of either vitamin A or β-carotene compared to placebo from early pregnancy through the first 6 weeks postpartum [41]. These findings, however, were not replicated in a similar large trial that was conducted in Bangladesh [34], and the effects on other outcomes such as PTD or LBW have not been published. In summary, the evidence to date does not support the large-scale distribution of prenatal vitamin A-only supplements even in settings where vitamin A deficiency is common. This does not, however, preclude the inclusion of this important vitamin in multivitamin supplements as it could help improve maternal and neonatal health.

**Zinc**

Zinc is an important micronutrient for normal growth and development and zinc deficiency during pregnancy has been associated with pregnancy loss and poor birth outcomes [42]. Several controlled trials of prenatal zinc supplementation have been conducted with mixed findings. In a systematic review that included 17 RCTs, Mahomed et al. [43] reported that prenatal Zn supplementation resulted in a 14% reduction in preterm birth (RR = 0.86; 95% CI = 0.76–0.98 in 13 RCTs; 6,854 women) and in a small effect favoring zinc for caesarean section (4 trials with high heterogeneity). There were, however, no significant differences in LBW (RR = 1.05; 95% CI = 0.94–1.17; 11 studies of 4,941 women) or other maternal or neonatal outcomes. Although zinc supplementation during infancy has been shown to reduce child morbidity [3], the few trials that have examined maternal morbidity report mixed findings [42]. There is also some evidence that prenatal Zn supplementation may reduce infant morbidity and influence child growth and development even though the birth size is unaffected [42]. Finally, a recent case-control study found that high maternal serum levels of copper and low levels of zinc during pregnancy were positively associated with NTD in newborns [44], indicating the possible role of zinc during early pregnancy. In summary, although current findings suggest limited benefits for prenatal Zn supplementation, there may be subgroups who are likely to benefit and the recommendation made by Hess and King [42] for more research ‘to assess the benefits of the large-scale introduction of zinc supplementation during pregnancy on congenital malformations, immune functions, neurobehavior, and overall neonatal survival in countries where zinc deficiency is a problem’ is timely. The value of providing zinc in MMN supplements also needs to be evaluated in light of the potential interactions with other nutrients.

**Vitamin D**

Vitamin D is needed for the absorption and utilization of calcium, may influence fetal growth and can also influence immune function. Although there has been considerable interest in vitamin D in recent years, little is known about the value of providing vitamin D supplements during pregnancy besides being part of standard multivitamin-mineral supplements. No intervention trials evaluating the effects of prenatal supplements containing only vitamin D were identified. However, the findings of a well-designed prospective study suggest that maternal intake of vitamin D during pregnancy may be associated with preventing allergic diseases in the offspring [45]. Maternal vitamin D intakes during pregnancy were assessed using a food frequency questionnaire from food and supplements, and related to the prevalence of asthma, allergic rhinitis and atopic eczema by the age of 5 years in the offspring with HLA-DQB1-conferred susceptibility for type 1 diabetes. Maternal intake of vitamin D from food was negatively related to risk of asthma (HR = 0.80; 95% CI = 0.64–30.99) and allergic rhinitis (HR = 0.85; 95% CI = 0.75–30.97), but the consumption of vitamin D supplements alone was not associated with any outcome.

**Antioxidants**

There has been considerable interest in the benefits and risks of consuming supplements containing antioxidants, especially vitamins C and E, during pregnancy.
The key outcomes of interest concern preeclampsia and PTD. Preeclampsia is a serious complication of pregnancy which increases the risk of dying for both mother and infant and may lead to intrauterine growth retardation and premature birth. A possible contributing factor to the development of preeclampsia may be the presence of excessive amounts of chemicals called 'free radicals', which is why antioxidants, such as vitamin C, vitamin E, selenium and lycopene, may be protective as they can neutralize free radicals. PTD may also result from rupture of membranes and/or infections which may be affected by antioxidants. Based on a systematic review that included 10 RCTs (n = 6,533), Rumbold et al. [46] concluded that antioxidants during pregnancy did not reduce the risk of preeclampsia (RR = 0.73, 95% CI = 0.51–1.06) or other complications in pregnancy. The studies used varying combinations of antioxidants that were primarily vitamins; 1 study used the mineral selenium. Few trials, however, examined birth outcomes such as PTD and SGA. When antioxidants were assessed separately, there were insufficient data to be clear about whether there was any benefit or not, except for vitamins C and E. It should be noted, however, that several studies were still underway when this meta-analysis was conducted and some of the findings have been published since. Of particular interest is the recent WHO multicenter randomized trial of supplementation with vitamins C and E among pregnant women at high risk for preeclampsia in populations of low nutritional status from developing countries [47]. Pregnant women were randomized to receive 1,000 mg of vitamin C along with 400 IU of vitamin E or a placebo from 14 to 26 weeks’ gestation up to delivery and followed up for birth outcomes. The study sites included Trujillo, Peru, Nagpur, India, Cape Town, South Africa and Ho Chi Minh City, Vietnam. A total of 1,265 women were randomized to treatment; loss to follow-up was low (<2%) and compliance was 87%. No differences were seen in preeclampsia (RR = 1.0; 95% CI = 0.9–1.3), eclampsia (RR = 1.5; 95% CI = 0.3–8.9), gestational hypertension (RR = 1.2; 95% CI = 0.9–1.7) nor any other maternal outcome. Rates of LBW (RR = 0.9; 95% CI = 0.8–1.1), SGA (RR = 0.9; 95% CI = 0.8–1.1) and perinatal deaths (RR = 0.8; 95% CI = 0.6–1.2) were also unaffected. These findings clearly support the earlier conclusion that antioxidants, especially vitamins C and E, do not provide any benefits for maternal and birth outcomes.

Long-Chain Polyunsaturated Fatty Acids

There has been considerable interest in the importance of long-chain polyunsaturated fatty acids (LCPUFAs), especially the ω–3 fatty acids for fetal development. Docosahexanoic acid (DHA) in particular is an important ω–3 fatty acid which accumulates rapidly in the brain and retina during gestation and the first year of life and is an important component of neural and retinal membranes [48]. Although humans can synthesize DHA from the parent 18 carbon ω–3 fatty acid, α-linoleic acid, there have been concerns about the efficiency of this process and possible competition with ω–6 fatty acids for the same enzymes. This has led to recommendations to ensure adequate consumption of preformed DHA in the diet, especially for pregnant women and young children. Based on a review of the literature that evaluated current knowledge on the role of LCPUFAs, especially DHA in maternal and infant nutrition, it was agreed that pregnant and lactating women should aim to achieve an average daily intake of at least 200 mg of DHA [49]. These recommendations were based primarily on the findings of recent meta-analyses [50, 51] that demonstrated that the consumption of fish oils rich in ω–3 LCPUFA during pregnancy reduces the risk for early premature birth. Szwajewska et al. [51] identified 6 RCTs (n = 1,278) that compared the effects of prenatal LCPUFA supplementation with a placebo or no supplementation on pregnancy outcomes and size at birth and found that LCPUFA supplementation significantly increased the duration of pregnancy by 1.57 days (95% CI = 0.35–2.78) compared to controls among low-risk pregnancies. Interestingly, only 1 study was at low risk of bias and there was no evidence that supplementation reduced the risk of preeclampsia, PTD or LBW infants. There was a significant increase in head circumference, but the effect was small (WMD = 0.26 cm; 95% CI = 0.02–0.49 cm; n = 729) and disappeared in the sensitivity analysis. There were no significant differences in birth weight (WMD = 54 g; 95% CI = –3.1 to 111 g) in 5 RCTs (1,262 infants) and in birth length (WMD = 0.23 cm; 95% CI = –0.04 to 0.5 cm). A few trials have, however, been completed since this meta-analysis. The benefits of providing daily supplements containing fish oil (0.5 g of DHA and 0.15 g of eicosapentaenoic acid) and methyltetrahydrofolic acid (400 μg) from midgestation up to delivery was evaluated in a recent multicenter study (n = 311) in 3 European countries (Germany, Hungary and Spain). There were no differences in pregnancy outcomes and fetal development, even though fish oil significantly (p < 0.001) increased cord blood DHA and me-

thyltetrahydrofolic acid was significantly associated (p < 0.05) with increased maternal DHA (percent by weight) [52]. A key limitation is the inadequate sample size to detect significant differences in birth outcomes such as gestational age and birth weight. A recently completed large trial (n = 1,094) also failed to detect any differences in gestational age or birth size among the offspring of women who received 400 mg of algal DHA compared to placebo from midpregnancy up to delivery. There was, however, a suggestion of benefit in birth weight and head circumference in the offspring of primiparous women who received DHA compared to placebo [53]. In another meta-analysis that focused on high-risk pregnancies [50], prenatal LCPUFA supplementation did not affect the duration of gestation, birth weight or other adverse pregnancy outcomes such as pregnancy-induced hypertension or preeclampsia, but was associated with a 61% reduction (RR = 0.39; 95% CI = 0.18–0.84) in the risk of early PTD (<34 weeks); this estimate was, however, based only on 2 RCTs (n = 391). Another limitation is the heterogeneity in the treatment that varied from study to study.

Observational studies and a few intervention trials suggest that higher maternal DHA intake both in pregnancy and lactation is associated with positive infant neurodevelopmental outcomes [48]. In a large prospective study, Hibbeln et al. [54] showed that low or no maternal seafood intake during pregnancy was a risk factor for lower verbal IQ (at 8 years) and suboptimal prosocial behavior (at 7 years), fine motor skills (at 18 and 42 months), communication (at 6 and 18 months) and social development (at 30 and 42 months) scores in the offspring. More importantly, follow-up of infants born to women who participated in an RCT in Norway showed that offspring of women who received the fish oil supplements from midgestation and through the first 3 months postpartum had improved scores in mental processing tests carried out at 4 years of age compared to those born to women who received the placebo. Loss to follow-up was, however, high [55]. Another follow-up of children born to atopic Australian women who participated in an RCT also showed that children of the fish-oil-supplemented mothers achieved significantly higher scores on the eye and hand coordination test compared to the control group at 2.5 years of age [56]. In summary, very few studies have evaluated the benefits of providing only DHA and the role of the balance of fatty acid intake, i.e., ω-3:ω-6 ratio. Little is also known on the benefits of prenatal LCPUFA supplementation on subsequent infant outcomes, although a few studies suggest that changes in maternal intake of ω-3 PUFAs, especially DHA, during pregnancy are positively associated with cognitive performance later on.

**Probiotics**

There has been considerable interest in the benefits of probiotics, especially in the prevention of atopic disease and allergy in young children. In a recent review, however, Kopp et al. [57] concluded that there was insufficient evidence to recommend probiotics during pregnancy and early infancy for the prevention of atopic disease and that more research was needed to identify subgroups that may benefit from the use of selected probiotic strains. A major limitation of the studies conducted to date is the variation in the treatment and study design. Probiotics also include a wide range of different bacteriological strains and species and vary in their protective abilities. Studies also differ in the outcomes measured and the timing of the intervention which begins during pregnancy and may continue during lactation in the mother and/or neonate. Furthermore, the few studies with comparable designs have different findings. Kalliomaki et al. [58] reported a 50% reduction in the frequency of atopic dermatitis among neonates treated with *Lactobacillus rhamnosus* GG in a randomized placebo-controlled trial that followed up the children till 7 years of age, whereas Kopp et al. [57] failed to confirm these findings. Nevertheless, studies conducted to date are suggestive of benefits especially in the immunomodulatory effects in neonates. Probiotics during pregnancy may influence the composition of breastmilk and reduce the incidence of IgE-associated eczema in infancy [59]. Since probiotics have anti-infective properties, they may also play a role in preventing PTD by killing pathogens and interrupting the role of inflammation and infection in preterm labor and delivery. Several probiotic preparations containing selected strains of lactobacilli are commercially available for treating bacterial vaginosis, yeast infections and urinary tract infections in WRA and are currently recommended for the treatment of bacterial vaginosis in high-risk pregnant women. These preparations may be administered either vaginally or orally and have been shown to be effective in reducing urogenital infections. In a recent meta-analysis, Othman et al. [60] reported an 81% reduction in the risk of genital infections (RR = 0.19; 95% CI = 0.08–0.48) when probiotics were used during pregnancy (oral or local treatment), but data on PTD and complications are lacking. Only 2 trials, however, were included in their sys-

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tematic review; one enrolled women after 34 weeks of pregnancy using oral fermented milk as probiotic, while the other study utilized commercially available yogurt to be used vaginally by women diagnosed as having bacterial vaginosis in early pregnancy.

**Conclusion**

The key findings from this review that examined the benefits of providing specific nutrient supplements ranging from folic acid to LCPUFAs and even probiotics during pregnancy are summarized below.

1. IFA supplements reduce the risk of anemia at term, but the evidence of reductions in the risks of LBW and PTD remains to be confirmed. Recent data suggest potential benefits that extend beyond birth especially in resource-poor settings. The benefits of IFA supplements in areas with endemic infection such as malaria have not been examined either.

2. Multivitamin mineral supplements that provide 1–2 RDA of several key vitamins and minerals are safe during pregnancy and have the potential to reduce the burden of LBW in many developing countries where diets are suboptimal.

3. Calcium supplementation can reduce the risk of preeclampsia and perhaps PTD in selected subgroups.

4. Severe iodine deficiency has been associated with poor birth outcomes including severe mental retardation, but the benefits of iodine supplementation during pregnancy in mild to moderate iodine deficiency remain to be evaluated.

5. Zinc supplementation can reduce the risk of PTD but not LBW. The optimal dosage and inclusion with other micronutrients needs more research.

6. Prenatal LCPUFA supplementation may reduce the risk of PTD and improve cognitive performance. More studies, however, are needed to confirm the long-term benefits of prenatal LCPUFA supplementation.

7. There is limited evidence to support the provision of supplements containing only vitamin A and D or antioxidants such as vitamins C and E. Existing data provide evidence of no benefits of providing antioxidants in reducing preeclampsia or PTD. Very few or no intervention trials have evaluated the independent effects of specific B vitamins such as vitamins B₆, B₁₂ and folic acid on pregnancy outcomes, except for the protective effect of folic acid on NTDs during the periconceptual period.

8. Probiotics can reduce genital infections, but the value of using them during pregnancy to improve child health remains to be evaluated.

Considerable progress has been made in our knowledge regarding the nature of nutrient interventions that can be recommended during pregnancy to optimize maternal and child health outcomes. Efforts to improve the preconceptual maternal nutritional status combined with timely and adequate access to antenatal care and providing interventions such as MMN supplements and minerals like calcium and zinc during pregnancy for at-risk populations would help promote the health and well-being of mothers and their offspring in a cost-effective manner. More research, however, is needed for interventions such as LCPUFAs and probiotics.

**References**

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