Micronutrient Supplementation During Pregnancy

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Clinical Question

What is the effect of multimicronutrient supplementation on birth outcomes in pregnant women?

Evidence-Based Answer

A multimicronutrient supplement is an oral tablet containing the recommended daily allowance of several vitamins and minerals: vitamin A, vitamin B_1, vitamin B_2, niacin, vitamin B_6, vitamin B_{12}, folic acid, vitamin C, vitamin D, vitamin E, iron, copper, selenium, and zinc. The use of multimicronutrient supplements in pregnant women reduces rates of low birth weight (by 11% to 14%) and small-for-gestational-age infants (by 9% to 17%). However, the World Health Organization does not recommend multimicronutrient supplementation because of the potential for increased neonatal mortality in some situations. (Strength of Recommendation: C, based on expert opinion and heterogeneous subgroup analyses.)

Evidence Summary

Five meta-analyses have evaluated the effects of multimicronutrient supplementation during pregnancy *(eTable A)*.

A Cochrane meta-analysis included 21 randomized controlled trials with nearly 76,000 pregnant women from developed and developing countries who were randomized to receive multimicronutrient supplements vs. iron/folate supplements. Multimicronutrient supplementation significantly decreased the number of low-birth-weight and small-for-gestational-age infants (by 11% and 13%, respectively).[1] There were no significant effects on rates of preterm birth, miscarriage, maternal mortality, perinatal mortality, stillbirth, or overall neonatal mortality (relative risk [RR] = 1.01; 95% confidence interval [CI], 0.89 to 1.2).

A large international meta-analysis found a significant reduction in the incidence of low-birth-weight and small-for-gestational-age infants whose mothers received multimicronutrient supplements (14% and 17%, respectively).[2] Another large international meta-analysis found reductions in the incidence of low-birth-weight infants, but not in small-for-gestational-age infants.[3] In both studies, overall neonatal mortality was unchanged. Two additional meta-analyses using studies from less-developed countries found reductions in small-for-gestational-age infants (9% in each), and one study evaluating low birth weight found a similar reduction (11%).[4,5]

One meta-analysis found no difference in the incidence of large-for-gestational-age infants in women who received multimicronutrient supplements (12 trials, N = 27,676; odds ratio = 1.1; 95% CI, 1.0 to 1.3).[5] Overall mortality was not changed, but subgroup analyses in three of these studies suggested that supplementation may affect neonatal mortality in some situations.[1,2,4] The Cochrane review found a decrease in neonatal mortality when supplementation was started after 20 weeks' gestation (three trials, N = 41,347; RR = 0.88; 95% CI, 0.8 to 0.97); however, the authors noted significant heterogeneity across the studies.[1] Another meta-analysis found an increased risk of neonatal death when supplementation began after the first trimester (five trials, N = 7,835; RR = 1.4; 95% CI, 1.1 to 1.8)[2]; however, this meta-analysis excluded data from a large trial (n = 31,209) that was included in the Cochrane subanalysis. A third meta-analysis found an increased risk

of neonatal mortality in studies in which more than 60% of births occurred at home (four trials, N = 11,583; RR = 1.5; 95% CI, 1.1 to 1.9).[4]

A separate meta-analysis evaluated the micronutrient intakes of pregnant women in developed countries and compared them with relevant national nutritional recommendations.[6] Sixty-two studies were included, with nearly 109,000 pregnant women. Pregnant women in the United States consumed the most micronutrients at levels above national recommendations (vitamin A, vitamin B_1, vitamin B_2, niacin, vitamin B_{12}, vitamin C, calcium, magnesium, and zinc), although intake of folate, iron, and vitamin D was below national recommendations.

Recommendations from Others

The World Health Organization recommends iron and folate supplementation in pregnant women.[7] It acknowledges that multimicronutrient supplementation reduces the risk of low birth weight, but does not recommend it for general use because of neonatal mortality data. The Centers for Disease Control and Prevention recommends multivitamin supplementation in pregnant women who do not consume an adequate diet.[8] In addition, it recommends that all women of reproductive age consume 0.4 mg of folic acid per day via fortified foods or supplements.

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eTable A. Meta-Analyses of Multimicronutrient Supplementation During Pregnancy

Year	Number of RCTs included (patients)	Control intervention	Outcomes		Comments
			Low birth weight (95% CI)	Small for gestational age (95% CI)	
2009[A1]	13 (61,705)	Placebo, or iron and folate	RR = 0.81 (0.73 to 0.91) vs. placebo RR = 0.83 (0.74 to 0.93) vs. iron and folate	No difference	—
2009[A2]	12 (27,676)	Iron and folate	RR = 0.89 (0.83 to 0.97)*	RR = 0.91 (0.84 to 0.99)*	Increased rates of small-for-gestational-age births
2011[A3]	14 (67,213)	Iron and folate	NR	RR = 0.91 (0.86 to 0.96)	Increased neonatal mortality in areas with more than 60% home births
2012[A4]	21 (75,785)	Iron and folate	RR = 0.89 (0.83 to 0.94)	RR = 0.87 (0.81 to 0.95)	Decreased neonatal mortality if started after 20 weeks' gestation
2012[A5]	16 (61,972)	Less than three micronutrients (usually iron and folate)	RR = 0.86 (0.81 to 0.91)	RR = 0.83 (0.73 to 0.95)	Increased neonatal mortality if started after first trimester

NOTE: *Multimicronutrient supplementation includes vitamin A, vitamin B_1, vitamin B_2, niacin, vitamin B_6, vitamin B_{12}, folic acid, vitamin C, vitamin D, vitamin E, iron, copper, selenium, and zinc.*

CI = confidence interval; NR = not reported; RCTs = randomized controlled trials; RR = relative risk.

**—Results reported as odds ratios, which were converted to RR assuming baseline rates of 10%.*

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