

MICRONUTRIENTS AND BIRTH OUTCOME

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A growing interest is developing in maternal nutritional status as a critical factor for prenatal development. The publication of *Nutrition for a Healthy Pregnancy*, a Health and Welfare Canada initiative, identifies the increased importance placed on prenatal nutrition for maternal and fetal health¹. The physiological changes that occur during pregnancy result in a need for extra nutrients and energy to meet demands of an expanding blood supply, the growth of maternal tissues, loss of maternal tissues at birth, preparation for lactation and the growing and developing fetus. Whether diet alone can help women reach optimal nutritional status and meet the physiological changes of pregnancy has been questioned². Micronutrient supplementation may be necessary to reduce the risk of fetal complications in specific groups of women. A focus has been placed on the effect of folic acid supplementation on the incidence of neural tube defects (NTDs) in high risk and low risk women. Table 1 provides a summary of the potential effects of micronutrient deficiencies on birth outcome³.

Neural Tube Defects

Neural Tube Defects (NTDs) are congenital malformations produced during intrauterine life (third and fourth week of gestation) by improper development and closure of the neural tube, which eventually forms the central nervous system⁴. The most prevalent NTDs include spina bifida (50%), anencephaly (40%), and encephalocele. Pregnancies affected by a NTD may result in a miscarriage or stillbirth, and children born with a NTD may have mild to severe disability or die in early childhood⁴. There are approximately 400 NTD-affected births each year in Canada, which account for 1 in every 1000 births. All factors considered, 90% to 95% of cases occur in the absence of any positive personal or family history⁴.

NTDs have multiple etiologies and occur as a consequence of complex interactions involving an embryo's genetic predisposition and its response to many factors in its environment, including pH, osmotic pressure, cytokine and growth factor signals, nutrients and xenobiotics⁵. It has been postulated that a deficiency in folic acid may lead to improper DNA synthesis and abnormal cell replication during the development of the neural tube. Mildly elevated maternal plasma homocysteine levels observed in some women with NTD-affected pregnancies, suggests a potential block of the folate dependent enzyme, methionine synthase⁶. An early intervention study⁶ that evaluated subsequent pregnancies among high-risk women who had a previous affected pregnancy, demonstrated a marked reduction (86%) in the recurrence of NTDs in those who took multivitamin supplements before becoming pregnant compared with women who did not. The protective effect was attributed to the folic acid content (0.36 mg/day) of the supplement. A small randomized trial of folic acid supplementation alone (4 mg/d) provided additional evidence of a reduction (58%) in the recurrence rate of NTDs in high risk women, although the results were not statistically significant⁷.

The strongest evidence of the protective effect of folic acid provided around the time of conception in high risk pregnancies, has become available from a multi-centred randomized double-blind prevention trial, in which 1817 women were allocated at random to one of four groups – a) folic acid (4 mg), b) other vitamins (A, D, B1, B2, B6, C and nicotinamide), c) folic acid and vitamins, or d) no supplementation⁸. Folic acid was observed to have a 72% protective effect compared to the other groups on the risk of a recurrent NTD pregnancy. Periconceptional folic acid supplementation can also decrease the risk of first occurrence of NTD in low-risk pregnancies by a minimum of 40%^{9,10}.

Most studies have examined the benefits of multivitamins, with folic acid as the key nutrient. A randomized double-blind controlled trial in Hungary showed the efficacy of a multivitamin supplement, containing 0.8 mg/day of folic acid, taken at least one month before conception and during the first 12 weeks of pregnancy⁹. Six cases of NTDs occurred in the group receiving a trace-element supplement (containing copper, manganese, zinc, and low dose vitamin C), as compared with none in the vitamin supplement group (12 vitamins, including 0.8 mg of folic acid; 4 minerals; and 3 trace elements) (p=0.029). Although the focus of research has been on the role of folic acid, it remains unclear whether the beneficial effects are related to folic acid alone or as a component of a multivitamin.

Low Birth Weight and Prematurity

Low birthweight (LBW) is defined as a weight less than 2,500 g (5½ lb) while prematurity indicates a gestational age of less than 37 completed weeks at birth¹¹. LBW is associated with approximately 75% of early neonatal mortality in both Canada and the United States¹¹. In developed countries, cigarette smoking has the most direct causal impact on low birth weight and prematurity. Other important factors include poor gestational nutrition, low pre-pregnancy weight, primiparity, short stature and poverty¹². Shaw et al.¹³, conducted a 4-month study to explore whether a reduction in the risk of delivering preterm is associated with maternal periconceptional use of vitamins. Women who used vitamins containing folic acid throughout the period of the study had a smaller risk (22% and 62%, respectively) of delivering an infant before 37 weeks gestation than did those women who initiated their vitamin use in second or third month of pregnancy. This data reveals such supplements periconceptionally may reduce the risk of prematurity. Multivitamin supplementation including 0.8 mg of folic acid had no significant effect on birth weight and gestational age compared to a trace element supplementation⁹. Marginal maternal folate nutrition has the potential to impair cellular growth and replication in the fetus and/or placenta and increase the risk for preterm delivery of LBW infant¹⁴.

Zinc plays a role in growth, development and reproduction, with a critical function in protein synthesis and nucleic acid metabolism. In a randomized double-blind placebo controlled trial among

African American women who were already receiving a non-zinc containing prenatal multivitamin or mineral tablet, Goldenberg et al.¹⁵ observed an increase in birth weight after zinc supplementation in women with low plasma zinc concentrations on enrollment. These results strengthened a burgeoning hypothesis that zinc supplementation during pregnancy might be beneficial only in populations that are zinc deficient and at high risk of poor fetal growth. In contrast, a double-blind placebo controlled trial in a poor urban population of Dhaka¹⁶ demonstrated a lack of improvement in the incidence and distribution of low birth weight, prematurity, and smallness for gestational age in women supplemented with 30 mg elemental zinc during the last 2 trimesters of pregnancy. A recent systematic review of 7 published randomized controlled maternal-zinc supplementation trials¹⁷, concluded that, although there is currently insufficient evidence to support the use of routine zinc supplementation during pregnancy, a potential reduction in preterm delivery is worthy of evaluation.

Other Birth Outcomes

The well-documented reduction in NTDs associated with folic acid and/or multivitamin supplementation has prompted investigations into the potential effect of supplementation on other birth defects. These congenital malformations include, but are not exclusive to, defects of the lip and palate, heart, limbs, urinary tract, brain and pylorus muscle. An early study showed that in women who had already had one child with a cleft lip or cleft palate, those who received no vitamin supplements during subsequent pregnancies, had a recurrence rate of 6.4% compared to women who received supplements and had no recurrences¹⁸. A recent review suggested a reduction in the incidence of conotruncal cardiovascular malformations, defects of the urinary tract, congenital hypertrophic pyloric stenosis and congenital limb deficiencies with folic acid containing multivitamins or pharmacological doses of folic acid alone¹⁹. In a Hungarian randomized controlled trial of periconceptional multivitamin supplementation, the rate of pregnancies affected by major congenital abnormalities other than NTDs was lower in the group given vitamins than that in the group given trace elements (13.3 per 100 vs. 22.9 per 100; p=0.02)⁹. In a case-control study, Werler et al.²⁰ detected a reduction in the risk of cleft palates alone, limb reduction defects, and urinary defects for those women with periconceptional multivitamin supplementation. Only moderate and statistically nonsignificant reductions in risk were observed for cleft lip and palate, hydrocephaly, and pyloric stenosis, and no reductions in risk were observed for conotruncal defects or ventricular septal defects. Thus, for defects other than NTDs, it is not clear what specific nutrients or combinations of nutrients might affect risk and malformation type. One of the limitations in identifying the beneficial nutrient is due to the variety of study designs found in the literature and the definition of supplementation used between studies²⁰.

Recommended Nutrient Supplementation During Pregnancy

Additional iron is needed during pregnancy to increase the maternal red blood cell mass and to supply the growing fetus and placenta²¹. Although the Canadian Task Force on the Periodic Health Examination states that there is currently insufficient evidence to recommend for or against routine iron supplementation of all pregnant women, the Scientific Review Committee and the U.S. Institute of Medicine (IOM), recognizing that many women have insufficient iron stores to meet the needs of pregnancy, advise daily low-dose iron supplementation (30 mg) to all women in the second and third trimesters^{22,23}. When iron deficiency with anemia (Stage 3) or without anemia (Stage 2) is diagnosed, larger doses of iron supplements may be advised to improve iron status as early in the pregnancy as possible. Thus, an iron supplement is currently recommended in Canada during the second and third trimesters, on the assumption that pre-pregnancy stores are inadequate. In 1998, Health Canada concluded that in order to reduce the risk of neural tube defects, a daily multivitamin/mineral supplement containing folic acid (0.4 mg), together with the amount of folate found in a healthy diet, taken one month before and three months after conception, is an effective primary prevention strategy⁴. Women who have had a previous pregnancy affected by an NTD, should consult their physician who may prescribe a higher dose. Women taking folic acid in a multivitamin or a multivitamin/mineral supplement should be advised not to take more than 10,000 IU per day of Vitamin A as this could increase the risk of birth defects. The recommendation that all women considering pregnancy take supplemental folic acid may be an impractical strategy for a large portion of the population due to the cost of supplements. The fortification of foods with folic acid is another mode to meet the extra needs of child-bearing women. The addition of folic acid to white flour and pasta products labelled 'enriched' became mandatory as of January 1998 in Canada. A recent study determined that on the basis of dietary intakes reported by women not taking folic acid supplements, food fortification at the level suggested in the US and Canada for grain products, showed that on average only 0.13 mg of folic acid would be ingested daily²⁴. Recent data on nutrient intakes from two provincial surveys conducted in Quebec and Nova Scotia suggest that the mean folate intake for women is 0.16-0.20 mg/day²⁵. This suggests that the consumption of folic acid through dietary intake, including fortified foods, would not meet the suggested levels for non-pregnant or pregnant women in this age group. Thus, even with food fortification, women of childbearing age should be advised and given the opportunity to obtain folic acid containing supplements on a daily basis to reduce the risk of NTDs. Table 2 provides a synopsis of the recommended level of micronutrients for child-bearing and pregnant women.

Conclusions

Throughout the prenatal period women should be encouraged to follow Canada's Food Guide to Healthy Eating as this will allow for a selection of more servings of foods that provide the additional nutrients and energy required. For some groups of women, there is a significant body of evidence that micronutrient supplement use can be associated with

a reduced risk for pregnancy complications, including birth defects. Recent reports that the use of folate-containing vitamin supplements is associated with a reduction in both the occurrence and recurrence rates of NTDs suggests that women who have not yet been classified with a high-risk pregnancy (having a previous child with a birth defect) may also benefit from preconceptional vitamin-mineral supplement use.

Table 1. Potential effects of maternal micronutrient deficiencies on pregnancy outcome¹

Nutrient	Possible Deficiency Effect
Folate	NTD, Congenital Malformations
Iron	Premature birth, low infant birthweight
Iodine	Cretinism
Vitamin A	Congenital Malformations
Vitamin D	Low infant birthweight
Zinc	Congenital malformations

¹Adapted from Rolfes and DeBruyne (1990)

Table 2. Recommended level of selected micronutrients for women at two physiological stages

Status	Nutrient				
	Calcium ¹ (mg)	Vitamin D ² (IU[mg])	Folate ^{3,6} (DFE)	Vitamin B12 ⁴ (ug)	Iron ⁵ (mg)
Non-Pregnant	1,000	200[5 mg]	400	2.4	13
Pregnant					
<18	1,300	200[5 mg]	-	-	
19-50	1,000	200[5 mg]	600	2.6	
2 nd trimester					18
3 rd trimester					23

^{1,2,3,4} represent DRIs which is a collective term that includes four nutrient-based dietary reference values for every life-stage. DRIs have replaced recommended nutrient intakes (RNIs) in Canada for selected nutrients.

⁶The amount of folate is actually expressed as "dietary folate equivalents" (DFE). This unit of measure was adopted in this report for the first time to account for the difference in bioavailability between folic acid or synthetic folate, and the folate found in foods. Bioavailability means the proportion of the folate consumed that can be absorbed and used by the body.

⁵Iron values are expressed as a RNI. DRIs for iron are expected to be released in 2000.

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