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Folate Nutriture and Pregnancy Outcome

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Folate, one of the B-vitamins, has important roles in the biosynthesis of purines and thymidylate, metabolism of amino acids and formate oxidation. Therefore, it is essential for cell replication and it is natural to expect that adequate folate nutriture in pregnancy is important for normal growth and development of the fetus and placenta. The increased requirement of folate for pregnant women has been well recognized. The objectives of this presentation include the review of the literature on the relation between folate nutriture and pregnancy outcome and the author's own experience in studying the association between folate nutriture and fetal growth.

Clinical research in the area of folate and pregnancy can be divided into two distinctively different historical periods. In the first period (1950s to 1970s), numerous studies were carried out to investigate folate metabolism and requirement during pregnancy and to evaluate the effect of folate deficiency on pregnancy complications and fetal growth. Based on these studies, the practice of *prenatal* folic acid supplementation to prevent folate deficiency (megaloblastic anemia of pregnancy) was established in the 1960s, and this supplementation became routine in Europe and the US. This practice resulted in the dramatic reduction of pregnancy-related folate deficiency in developed countries. However, even in the early 1990s, we found that poor folate nutriture is associated with poor fetal growth in an indigent population of the Birmingham area. Thus, inadequate folate nutriture may still be a serious problem among pregnant women in a socio-economically deprived population in developed countries as well as in developing countries where prenatal folic acid supplementation is not routinely practiced.

The 1980s began the second historical period when the research focus shifted to the prevention of diseases particularly for the reduction of incidence of fetal malformations. The investigations, pioneered by Hibbard and Smithells in the mid 1960s, led to the dramatic discovery of the beneficial effect of *periconceptional* folic acid supplementation on the prevention of the recurrence of pregnancies complicated with neural-tube defects (NTDs). The results of the 1991 study conducted by the MRC Vitamin Research Group in several European countries clearly demonstrated that about 75% of NTDs can be prevented by periconceptional folic acid supplementation. Subsequent studies in the Czech Republic and China showed a similar outcome and established that increased folate intake before conception reduces the incident of these devastating malformations. Many researchers have tried to uncover the mechanistic link (s) between folic acid supplementation and NTD prevention. The studies involved the measurements of folate and homocysteine concentrations or the analysis of polymorphism of the genes coding for enzymes involved in folate-dependent one-carbon metabolism. However, a solid explanation as to why periconceptional folic acid supplementation lowers the incidence of NTDs has yet to be offered. In addition to NTDs, other malformations, such as orofacial cleft and cardiac defects, are suspected to be linked to poor folate nutriture or altered homocysteine metabolism. In response to the outcome of the above clinical trials, the US government in 1998 mandated the fortification of enriched cereal-grain products with folic acid to reduce the incidence of NTD-complicated pregnancies. However, the reduction of incidence was not as great as expected and about 19% reduction in the births of infants with NTDs during the first few years after the mandate has been reported. A few other countries have initiated or are in preparation to start the fortification of staple foods with folic acid to reduce the frequency of NTD-complicated pregnancies.