Maternal Nutrition and Prevention of Oral Clefts

Deepa Agarwal*, Gopalan T.R**

**PhD Research Scholar, Department of Clinical Nutrition, **Professor of Surgery, Course Chairman, Department of Clinical Nutrition, Sri Ramachandra University, Chennai, India*

Each year among 135 million new births in the world, about 3% are affected with major structural birth defects, called *congenital abnormalities* (CAs).[1] At present the total group of CAs is the major cause of infant mortality and disabilities among children in the industrialized countries. Therefore, the prevention of CAs is an extremely important public health issue. Oral Facial Clefts (OFCs) are among the most common birth defects with varying birth prevalence rates among populations, gender, and geographic region, occurring in 1-2/1000 live births.[2] Its pathogenesis is multifactorial in that both genetic and lifestyle aspects such as nutrition are involved.

Inadequate maternal nutrition during pregnancy has been suspected as a cause of oral clefts in humans since at least the early 1900s. In this respect, it is important to address that during pregnancy, specifically during the development of the lip and palate, the embryonic nutritional status is fully dependant on maternal food intake and metabolism. Due to increased needs, inadequate intake, decreased absorption, disturbances in embryonic transfer, or underlying genetic aberrations in the mother or embryo or both, maternal nutritional deficiencies during pregnancy may significantly affect the nutritional status of the embryo and gene expression and other developmental events in specific embryonic tissues.[3]

Nutritional intake is also related to socio economic status and the increased frequency of oral facial clefts among the offspring of less educated women emphasizes the importance of maternal nutritional status on reproductive outcome. To date, research on the association between the maternal nutritional status and oral facial cleft has focused mainly on multivitamin and folic acid supplementation.

Address for correspondence:
Deepa Agarwal, PhD Research Scholar,
Department of Clinical Nutrition,
Sri Ramachandra University, Chennai, India.
Phone number: 9940220005
Email id: deepa_24101984@rediffmail.com

DOI: ****

Neural tube defects (NTD) share similarities in the pathogenesis of oral facial clefts because both birth defects originate from disturbances in which neural crest cells are involved. Therefore, it is conceivable that nutritional factors implicated in NTD pathogenesis also apply to OFC.

At the time of conception and during the first trimester, the mother's nutritional status is important in the development of the lip and palate, as well as other craniofacial structures of the foetus. During this critical stage of development, several key nutrients have been implicated in the development of OFCs, some of which are folic acid, vitamin B_{12}, vitamin B_6, and zinc.[4] Maternal ability to maintain adequate levels of Vitamins B_6 and B_{12} and fetal ability to utilize these nutrients are also seen as a factor in the development of oral clefts. When these nutrients are not metabolized properly, errors in DNA synthesis and transcription may occur leading to CAs.

FOLIC ACID

Folate, as a one-carbon donor, is involved in the biosynthesis of purines and pyrimidines and in homocysteine remethylation producing methyl groups for methylation of DNA, which is important for gene expression.[5] The methylenetetrahydrofolate reductase (MTHFR) gene involved in the metabolism of folate is an example of OFC risk modification. The MTHFR enzyme catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, an irreversible step, which is the predominant form of folate and the methyl donor for the remethylation of homocysteine into methionine (Fig. 1). Polymorphisms in MTHFR lead to increased levels of homocysteine, which has been associated with increased risk of OFCs. Humans are dependent on dietary sources of folate. Major contributors are bread, cereals, fruits, vegetables, and liver.

VITAMIN B_{12}

The only dietary sources of vitamin B_{12} for humans, other than supplements, are from animal or fortified products. Vitamin B_{12} functions as an essential coenzyme in the conversion of homocysteine into methionine. Because the

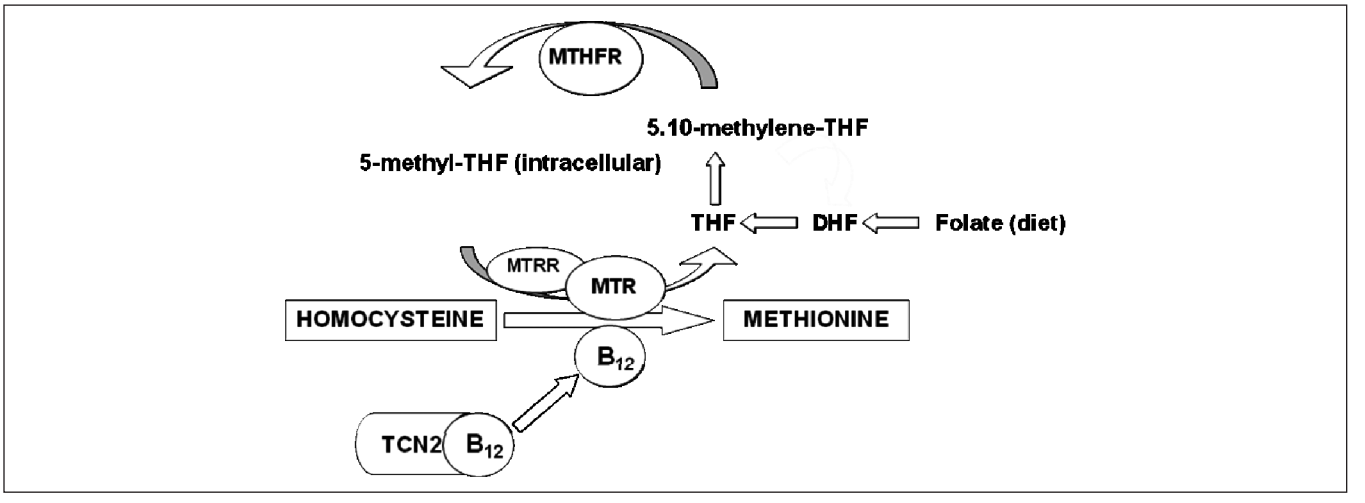

Figure 1: Remethylation of homocysteine into methionine.

formation of 5-methyl THF is irreversible, a deficiency of vitamin B_{12} traps body folate in the 5methyl form, which is known as the methylfolate hypothesis (Fig.1). This trapping leads to increased homocysteine levels and decreased methylation of DNA, which is important in the regulation of gene activity. An inadequate amount of methionine caused by lack of vitamin B_{12} decreases the availability of Sadenosyl methionine (SAM). SAM is required for methylation reactions, which are also essential for myelin maintenance and thus neural function.[6]

VITAMIN B_6

Along with vitamin B_{12}, vitamin B_6 also plays a key role in the metabolism of folate and homocysteine. Vitamin B_6 is known to protect against OFCs induced in laboratory animals by teratogens, and deficiency alone was sufficient to cause OFCs in mice. A casecontrol study in the Philippines evaluated the association between the risk for CL/P and maternal vitamin B_6 status. The study concluded that inadequate vitamin B_6 status was associated with an increased risk for CL/P. Food sources other than supplements rich in vitamin B_6 include meats, whole grain products, vegetables, some fruits, and nuts. Fortified cereals also represent a major contributor of vitamin B_6 in the diet.

ZINC

Zinc is of interest because of its role in the absorption of folate. A study in the Netherlands demonstrated that mothers of children of CL/P had lower erythrocyte zinc concentrations than control mothers. Polyglutamate hydrolase is a zinc dependant enzyme necessary for the digestion of folate in the gastrointestinal tract. In addition, zinc is involved in the conversion of 5methyltetrahydrofolate into tetrahydrofolate by the zinc dependant methionine synthase enzyme. Thus, poor zinc intake or status can diminish folate absorption. Zinc is typically associated with the protein fraction of foods. Therefore, rich sources of this nutrient are found in animal products, predominately red meats and seafood.

However, whole grains and vegetables represent good plant sources of zinc. Although single source nutrients have shown to be significant in the reduction of clefting in animal models, there have been very few studies of these associations in human studies and far fewer studies of overall diet patterns among mothers and the risk for development of OFCs in the child. Comprehensive dietary variables that are defined by the intake of many foods may show a greater effect on disease than any single nutritional component. [7] For this reason, the identification of maternal dietary patterns has become of considerable interest and has been related to cardiovascular disease, type 2 diabetes, and cancer. However, data on maternal dietary patterns and birth defects are lacking. [8]

In addition to adequate nutrition of the mother, environmental and behavioural factors such as poverty, smoking, and alcohol use have been shown to significantly increase the risk of birth defects, including OFCs .

Genetic factors are believed to account for some defects, often in combination with one or more environmental factors. A study published in the American society for nutritional sciences Journal (2004) demonstrates that the pre conceptional dietary intakes of energy and all macronutrients, vitamins, minerals and food groups were lower in mothers of OFC children compared with controls. Of particular interest is the protective effect of a higher dietary intake of vegetable, protein, fibre, ascorbic acid, iron and magnesium on OFC risk.

In conclusion, a healthy diet *rich in folate, Vitamin* B_{12}, *Vitamin* B_6, *Zinc* and periconceptional multivitamin and folic acid supplementation *(0.4–0.8 mg/day)* can reduce the *overall occurrence of CAs. Preconceptional counselling of pregnant women towards a healthier lifestyle, which includes a diet rich in plant sources and iron may be important in the prevention of nonsyndromic OFC offspring.*

REFERENCES

1. Andrew E Creizel. The primary prevention of birth defects- Multivitamin or Folic acid? International Journal of Medicine Science. 2004; 1(1):50-61.
2. Vujkovic M, Ocke MC, Spek PJ, Yazdanpanah N, Steegers EA, SteegersTheunissen RP. Maternal Western Dietary Patterns and the Risk of Developing a Cleft Lip With or Without a Cleft Palate. Obstet Gynecol. 2007; 110:378-84.
3. Krapels IPC, Rooij I, Wevers RA, Zielhuis GA, Spauwen PHM, Brussel W, Steegers- Theunissen R. Myo-inositol, glucose and zinc status as risk factors for non-syndromic cleft lip with or without cleft palate in offspring: a case-control study. Br J Obstet Gynaecol. 2004; 111:661-8.
4. Report of WHO meetings on International Collaborative Research on Craniofacial Anomalies. 5-8 November 2000, Geneva, Switzerland; 24-26 May 2001, Park City, Utah.
5. Rooij I, Ocke MC, Straatman H, Zielhuis GA, Merkus H, Steegers Theunissen R. Periconceptional folate intake by supplement and food reduces the risk of nonsyndromic cleft lip with or without cleft palate. Preventive Medicine. 2004; 39:689-94.
6. Gropper SS, Smith JL, Groff JL. Advanced Nutrition and Human Metabolism. 4th ed. Belmont, California: Wadsworth; 2005.
7. Hoffmann K, Schulz MB, Schienkiewitz A, Nothlings U, Boeing H. Application of a New Statistical Method to Derive Dietary Patterns in Nutrtional Epidemiology. Am J Epidemiol. 2004; 159:935-44.
8. Munger R. Maternal nutrition and oral clefts. In: Wyzsynski D, ed. Cleft Lip and Palate: from Origin to Treatment. New York: Oxford University Press, 2002.