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Relationship between Maternal Folate Receptor Autoantibodies and the Occurrence of Neural Tube Defects in Human EmbryosTitle here

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Folate is essential to central nervous system development. Inadequate intakes of folate have been linked to higher risk of neural tube defects. Recent research has suggested that maternal Autoantibodies to folate receptors are also a risk factor for NTDs. Several studies have statistically compared maternal autoantibody concentration to the occurrence of NTDs. These studies found a significant correlation between maternal autoantibody concentration and NTDs. However, these studies did not use representative samples. The samples were either too small or country specific. To further study this hypothesis, a study should be conducted with a larger sample size and include women with diverse ethnic backgrounds.

Introduction

It is well known that folate is essential in development of the central nervous system. Folate is a B vitamin found in many green leafy vegetables among other foods. It is used as a carbon source for methylation in DNA and RNA synthesis and in cell division in human development. Inadequate intakes of folate in early pregnancy can lead to neural tube defects in the developing embryo. This issue has been addressed by implementing folate supplementation for women who are pregnant or who may become pregnant. In many countries it is mandated, or at least strongly suggested that all grain sources be fortified with folate. Folate has also a major component of all prenatal vitamins. This has made folate much more accessible. Naturally, occurring folate in vegetables and animal liver has low bioavailability, meaning that it is not absorbed in large amounts. However, folate in fortified foods has close to 100 percent bioavailability. While folate supplementation has significantly reduced the occurrence of neural tube defects, they are still a prevalent problem among newborns.

Research has shown that maternal autoantibodies may inhibit folate reception and therefore contribute to neural tube disorders. According to an article by Robert M. Cabrera et al, "…most pregnant women carrying an NTD-affected fetus do not have serum folate deficiency." Several researchers have hypothesized that maternal autoantibodies bind to folate receptors preventing folate from binding and therefore preventing folate metabolism. This would have a similar affect as folate deficiency and as such they may be risk factors for NTDs. Some studies have indicated that some of this can be offset with folate supplementation. Folate receptors are found on the surface of the cell and allow folate to pass through the cell membrane into the cell to be used. Maternal

Autoantibodies bind to the folate receptors and prevent folate from getting into the cell. However, folate supplementation may be beneficial because Folate receptors have a greater affinity to folate than to immunoglobin and therefore higher concentrations of folate overcome the Autoantibodies. To test the hypothesis that maternal Autoantibodies are risk factors in NTDs, researchers used chemical and statistical evaluations to determine the correlation of immunoglobin concentration in maternal plasma to NTD occurrence.

Recent Progress

The first step in determining maternal autoantigen concentration is collecting maternal plasma samples. One study by A.L. Boyles et al and another study by Cabrera et al took samples between the 15th and 18th week of pregnancy. Another study by S.P. Rothenberg et al took sample up to years after the pregnancy. Uniquely, this study looked at autoantibody levels in women who had already had an infant affected by NTD and the increased risk that they will have another child affected by a NTD. Slightly different methods where used to determine immunoglobin concentration in maternal plasma, but the overall procedure were the same. In each study, folate receptor was isolated, either from human placentas (Rothenberg, Cabrera) or virus expression (Boyles). These folate receptors where added to maternal plasma. The number of receptors that were blocked by immunoglobin were then determined using fluorescents in Cabrera and Boyles, and by radioactive markers by Rothenberg. The maternal autoantibody concentrations were then compared to occurrences of NTDs to determine the level of correlation.

All three studies found a significant correlation between high maternal autoantibody concentrations and incidence of NTDs. Rothenberg's study found that seven out of eleven mothers who gave birth to NTD-affected infants had high folic acid blocking levels. This is despite the fact that ten of those eleven mothers took folic acid supplements. The other two studies found similar results. All three studies concluded that maternal autoantibody concentration is a significant risk factor for NTDs.

Discussion

These studies are strong indicators that maternal Autoantibody concentration is a risk factor for NTDs. However, further research should be done. All three studies had a very small sample size. The Rothenberg study only had 12 women in the experimental group and 18 women in the control group. The Cabrera study had 29 women in the experimental group and 76 women in the control group. The Boyles study had the largest sample size with 119 women in the experimental group and 221 women in the control group. This study should be the most representative of worldwide risk. However, the Boyles study only sampled women from Norway, so the results cannot be projected on women in general.

To give greater support to the hypothesis that maternal autoantibody concentration is a risk factor for NTDs; a larger study should be conducted. This study should have a large sample size. It should also include women of diverse ethnic backgrounds to help eliminate cultural and environmental factors.

Further research may indicate a need for pretesting women for folate receptor autoantibodies before they become pregnant. The current folate intake recommendation for women who are not pregnant is 400mcg per day. Research should be done to investigate the effect of folate supplementation of autoantibody-folate receptor interaction. This may indicate that the daily intake of folate for women with higher levels of folic acid receptor autoantibodies should be higher. It is important to correct this problem before pregnancy because the embryonic neural tube develops within the first few weeks of pregnancy, before most women know that they are pregnant. Identifying women with higher levels of autoantibodies to folate receptor could further reduce the occurrence of children born with NTD's such as Spina Bifida and Anencephaly. This will in turn improve infant quality of life and increase risk of infant mortality.

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