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Synthetic Folic Acid Supplementation during Pregnancy Increases the Risk of Neonatal Jaundice in Newborns

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***Abstract*—Folate is easily and naturally absorbed and utilized by the body when it is metabolized in the small intestines. On the other hand, folic acid, which was first introduced around the 1940s and added to the prenatal supplements of pregnant women, requires the presence of a specific enzyme named dihydrofolate reductase, which is relatively rare in the body especially during pregnancy. The reason why synthetic form of folic acid supplementation by pregnant women should be replaced by natural folate, is that High folic acid intake by pregnant women will mask or may cause the vitamin b12 deficiency, which is one of the leading cause of increasing serum bilirubin in the blood of neonates.**

Keywords—Neonatal Jaundice, Folic acid, Pregnancy, Vitamin B12

INTRODUCTION

A) NEONATAL JAUNDICE

Neonatal hyperbilirubinemia is a yellowing of the skin and other tissues of a newborn infant. Bilirubin levels more than 85 µmol/l will cause a jaundiced appearance in infants. In newborns, jaundice is detected by blanching the skin with pressure that is applied by a finger so that it reveals underlying skin and subcutaneous tissue.[1] Jaundiced infants have yellow discoloration of the white part of the eye, and yellowing of the face, extending down onto the chest. This disorder can make the newborn sleepy and interfere with feeding. More extreme jaundice can cause permanent brain damage from kernicterus. In newborns, the yellowish skin is first appeared in the face and as the bilirubin level rises proceeds caudal to the trunk and then to the extremities.[2] This disorder is common in infants affecting over half 50 to 60 percent of all babies in the first week of life.[3] Infants whose palms and soles are yellow, have serum bilirubin level over 255 µmol/l. Studies have shown that trained examiners assessment of levels of jaundice show moderate agreement with icterometer bilirubin measurements.[2] In newborns, jaundice tends to develop because of two factors: the breakdown of fetal hemoglobin as it is replaced with adult hemoglobin and the relatively immature metabolic pathways of the liver, which are unable to conjugate and so excrete bilirubin as quickly as an adult. This causes hyperbilirubinemia, leading to the symptoms of jaundice which is a possibility of vitamin B_{12} deficiency.

Materials and Methods

By going deeply through the biochemical process of folate absorption, chelation and physiological differences between folate and synthetic folic acid as this article mentions in the next lines, this effects in clear on pregnant women and the neonates:

1.1 Folic Acid

Vitamin B_9 is an essential nutrient that naturally occurs as folate. Folate does many important functions in the body. It plays an important role in cell growth and the formation of DNA. Low levels of folate is associated with an increased risk of several health conditions, which is Elevated homocysteine levels that have been associated

with an increased risk of heart disease and stroke[4, 5], Low folate levels in pregnant women have been linked to birth abnormalities, such as neural tube defects[6], and Poor levels of folate are also linked to increased cancer risk.[7, 8] Therefore, supplementation with folate is common. Fortifying foods with synthetic folic acid is actually mandatory in countries such as the US, Canada and Chile. The real problem is that supplements and fortified foods contain folic acid and not the natural folate.

Folate is the natural form of vitamin B_9. The active form of vitamin B_9 is known as levomefolic acid or 5-methyltetrahydrofolate which is also called 5-MTHF. In the digestive system, the majority of dietary folate is converted into 5-MTHF before entering the bloodstream.[9] However, folic acid is a synthetic form of vitamin B_9, which is known as pteroylmonoglutamic acid. It is used in supplements and added to processed food products, such as flour and breakfast cereals. For many years, folic acid was thought to be much better absorbed than natural folate. But a diet containing a variety of folate-rich foods has been shown to be almost as effective.[10] Unlike most folate, the majority of folic acid is not converted to the 5-MTHF in the digestive system. Instead, it needs to be converted in the liver.[9, 11] but this process is slow and inefficient. After taking a folic acid supplement, it takes time for the body to convert all of it to 5-MTHF.[11] Even a small dosage, like 200 to 400 mcg/day, may not be completely metabolized till the next dosage is taken. This crucial problem is even worse when fortified foods are eaten along with folic acid supplements as most pregnant women do, and the extra will remain in blood.[12, 13] Therefore, un-metabolized folic acid is usually detected in the bloodstreams of pregnant women, even in the fasted state.[14, 15, 16] This should be of concern, since high levels of un-metabolized folic acid have been associated with several health problems and the most important is the cobalamin deficiency. However, one study suggests that taking folic acid along with vitamin B_6, makes the conversion more efficient, but as the organ meat, which is high in vitamin B_6, consumption has been decreased, this should be of a concern as well.[14]

After reviewing several studies, this should be concluded that chronically elevated levels of un-metabolized folic acid, which is the result of consuming supplemental folic acid, may have adverse health effects: (a) High levels of un-metabolized folic acid have been associated with increased cancer risk. They may also speed up the growth of precancerous lesions,[17, 18, 19] and Undetected B12 deficiency.[20]

Vitamin b12 deficiency is about 40 to 50 percent worldwide that is near the epidemiology of neonatal jaundice that is 40 to 60 percent worldwide which is very impressive.[41]

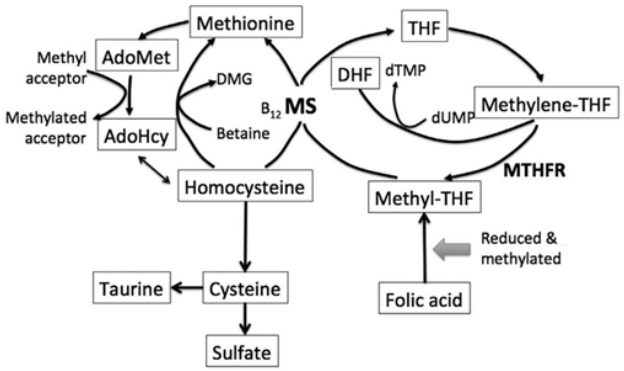

Figure (1): Simplified schematic of the methylation pathways. AdoHcy: adenosylhomocysteine; AdoMet: adenosylmethionine; DHF: dihydrofolate; DMG: dimethylglycine; MS: methionine synthase; MTHFR: methylenetetrahydrofolate reductase; THF: tetrahydrofolate. Adapted from Figure 1 in Refsum, 2001.[26]

Figure.1 demonstrates the diagram of the methylation cycle. Most notable are two important enzymes, methylene tetrahydrofolate reductase (MTHFR) and methionine synthase (MS). Defects in MTHFR have been linked to chronic fatigue syndrome, high bilirubin levels[27] and to autism.[21] These defects are a major source of folate trap, since the methyl group piles up in useless accumulations of methylene-tetrahydrofolate, while methionine synthesis cannot happen, therefore, homocysteine piles up as well. Methionine synthase is also a vulnerability point in the pathway.[22, 23] This is the reaction that converts homocysteine to methionine, after which methionine can deliver its cargo of a methyl group to all kinds of recipients. The methyl group is transferred from methyl tetrahydrofolate to methionine, however, vitamin B_{12} that is cobalamin, is an essential cofactor to catalyze the reaction. Cobalamin depends on the mineral cobalt

to function properly. Folic acid supplementation masks the symptoms of vitamin B_{12} deficiency. As a result, vitamin B12 deficiency in pregnant women which is known to increase bilirubin levels in neonates will cause neonatal jaundice in newborn babies.*[Yamada's Handbook of Gastroenterology, John Wiley & Sons Copyright]* Fortunately, there is another pathway from homocysteine to methionine where betaine serves as the source of methyl groups, and this depends on neither folate nor B_{12}. It is likely that a diet high in betaine can reduce the need for folate and B_{12}.[24]

Nitrous oxide can cause irreversible oxidation of B_{12} to an inactive form, such that levels can test as adequate even when usable levels are much too low. Nitrous oxide can arise through oxidation of ammonia, which will build up if glutamine synthase is defective. Glutamine synthase combines ammonia with glutamate to make glutamine. This process depends on manganese, a metal that glyphosate chelates, making it unavailable.[22]

Finally, homocysteine itself, the precursor to methionine, can be deficient. In fact, the bottom of the graph in Figure.1 that shows other routs homocysteine can be used should not be neglected. Sulfate, cysteine and taurine are biologically important molecules that play many roles in the body. These molecules all contain sulfur, a mineral that is widely deficient in the population.[28]

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Conflicts of Interests

There is no conflict of interests between authors of this research article.

Conclusion

From all aspects of this perspective research, folic acid supplementation during pregnancy not only leads to folate deficiency due to malabsorption of synthetic folic acid, but also causes high levels of un-metabolized pteroylmonoglutamic acid which is one of the main cause and masking of cobalamin deficiency in pregnant women. Vitamin B_{12} deficiency is a great concern since it leads to the increasing of bilirubin in neonates which cause neonatal jaundice after delivery. Many factors in prenatal nutrition can chelate folate like sulfur deficiency and high levels of glyphosate in the diet, therefore, the replacement of synthetic folic acid with natural folate may help absorption and reducing the amount of un-metabolized folic acid serum in the blood of pregnant women.

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