THE IMPACT OF FOLIC ACID SUPPLEMENTATION ON PREGNANCY

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ABSTRACT

Folic Acid a water soluble vitamin (B9) serves as a fundamental cofactor in folate-intervened one-carbon digestion and in the epigenetic guideline of the translation of qualities that control neural tube closure. FA has increased significance in pregnant women because folate insufficiency has been connected with an assortment of clutters including birth imperfections and deformities in the improvement of neural tube closure. The folate supplementation also has beneficial role on pregnancy outcomes along with neural tube defects (NTD) reduction in women with seizures, preeclampsia, foetal development limitation and future chemical imbalance hazard. Whereas, over dosage of folic acid supplementation during pregnancy may be responsible for increased risk of cancers, severe adverse effects like heart problems, ectopic pregnancy and may also lead to miscarriage.

Keywords: Folic Acid, Neural tube defects, Pregnancy, Foetal development.

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INTRODUCTION

Folic Acid (FA) is a water-dissolvable nutrient (B9), adds to neural tube closure by improving cell expansion. Folates works as cofactors in cell division and cell support as well as in regulating the gene expression through epigenetic mechanisms [1] since 1990s, proof rose about the defensive impact of FA supplementation against the occurrence of neural tube defects (NTDs). [2, 3]. It serves as a fundamental cofactor in folate-intervened one-carbon metabolism that regulates the transcription of genes which control the neural tube closure [4] FA has increase significance in pregnant women due to its promising job in adjusting assorted clinical conditions, though folate insufficiency has been connected with an assortment of clutters including birth imperfections and deformities in the improvement of neural tube closure [5, 6, 7].

Preterm delivery contributes to the incidence of low birth weight infants. In the United States, two-thirds of infants weighing <2500 g are delivered preterm (<37 completed wk) [8] Folate supplementation may also have beneficial role on pregnancy along with NTD decrease in women with preeclampsia, fetal development limitations and future autism risk. Many studies have also shown that supplemental folate during pregnancy may cause severe adverse effects like heart problems, leukemia, and ectopic pregnancy. An inability to absorb synthetic folate may cause miscarriage. Some studies have also shown that taking supplemental folic acid past early pregnancy has no benefits, and to the contrary, may even put babies at an increased risk of developing asthma. Hence we performed this review on various studies to understand the overall adverse effects caused due to consumption of over dosage of folic acid during pregnancy. [9]

Folate synthesis

FA is key to folate-requiring one-carbon metabolism which has role in various cell responses. These include amino acid metabolism, biosynthesis of purine and pyrimidine; (the structure hinders for DNA and RNA blend), and development of essential methylating operator S-adenosyl-methionine (SAM), which is the widespread methyl contributor for DNA, histones, proteins and lipids. [10] Folate is invested in the digestive system and additionally liver and processed fundamentally to 5-methyl tetrahydrofolate (5-methylTHF) and in this manner gets polyglutamate for cell maintenance. FA devoured in braced nourishments/supplements is decreased primarily to dihydrofolate by the chemical dihydrofolate reductase in the liver lastly changes over to the tetrahydrofolate (THF), the substrate for polyglutamate synthetase. The polyglutamyl type of tetrahydrofolate (THF) framed either from FA or ordinary dietary folate is the focal folate acceptor atom in the one-carbon cycle. Next, THF is changed over to 5,10-methyleneTHF by nutrient B6 subordinate serine hydroxymethyltransferase and afterward decreased irreversibly to 5-methylTHF by
methylene tetrahydrofolate reductase (MTHFR). 5-Methyl-THF goes about as an essential methyl benefactor for the remethylation of homocysteine to methionine. Methionine is a key substrate for S-adenosylmethionine (SAM) which assumes a focal job in methylation responses catalyzed by DNA methyl transferases (DNMTs) shaping 5-methylcytosine. [11, 12, 13]

**Seizure outcomes**

FA supplementation during pregnancy may have prompt modifications in mental health bringing about changes in behaviour and at long last, 4mg FA/day prior and during growth of foetus, appears to diminish 42% of offspring’s seizure threshold. [14]

**Respiratory and unfavorably susceptible results**

In 2009, two articles that raised worries about conceivable unfriendly respiratory wellbeing results in little youngsters related with maternal utilization of folic acid enhancements during pregnancy. In Norway, Håberg et al found that folic acid enhancements in the first trimester of pregnancy somewhat expanded the danger of wheeze and lower respiratory tract infections upto ≤18 months infants related to epigenetic mechanisms. [15]. In Australia, Whitrow et al demonstrated that supplementation of folic acid enhancements in late pregnancy (30–34 weeks) was identified with an expanded danger of asthma at 3.5 yrs and of persistent asthma at 3.5 and 5.5 yrs. [16] One investigation proposes that posterity of moms that were administered with FA during the first trimester of pregnancy, had higher chances of being diagnosed with bronchiolitis compared with no FA supplementation in pregnancy. [17, 18]

**Oral clefts outcomes**

Badovinac et al audited five imminent investigations and 12 case–controls studies and presumed that taking a folic acid containing supplements during pregnancy had a defensive impact against the danger of creating oral clefts [19]. In contrast a research stated a detailed expanded danger of orofacial clefts when there was a reliable enhancement of Folic acid usage during the aetiologically significant period (weeks 0–12 post origination) [20]

**Preeclampsia outcomes**

Preeclampsia is one of the most significant and regular complications during pregnancy and one of the primary cause of maternal and fetal mortality [21].

Researchers have found that women who take high amount of folic acid from Pre-pregnancy to Mid-pregnancy may expand their risk for hazardous high blood pressure. Folic Acid with iron and Vitamin B12 assumes to have significant role in blood creation and folate deficiency can be the reason for some lethal issues such as defects in neural tube defects like anencephaly and spina bifida. [22] In the meantime, other research found that the dose of 0.4mg/day FA alone in the early pregnancy can’t prevent GHT and preeclampsia. [23]

**Heart defects outcomes**

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Congenital heart diseases (CHDs) are among the significant birth defects in babies and influence around 4 to 10 for every 1,000 live births [24]. The most grounded proof that multivitamins containing folic acid taken periconceptionally will essentially decrease the danger of inborn heart defects is upheld by information from a Hungarian RCT Fetal development. [25]

**Foetal growth and other outcomes**

A high FA portion (4mg/day) in the preconception doesn’t appear to restrict fetal development, when compared with a suggested portion of 0.4mg/day. [26] However, FA supplementation in suggested portions (0.4–0.5mg/day) can be related with expanded fetal development, and higher placental weight, bringing about higher birth weight and diminished danger of low birth weight or small for gestational age (SGA). [27]

**Metabolic syndrome outcomes**

A study in Nepal uncovered that FA supplementation during pregnancy seemed to have the best valuable impact on offspring’s kidney capacity and lower danger of metabolic disorder among the posterity. Furthermore high folate intake is additionally found to bring about huge down regulation of folate transporters in kidney, and consequently dysregulate the renal folate take-up process. [28, 29, 30].

**Conclusion:**

Folic acid which has its crucial role on pregnancy outcomes will be beneficial if taken before pregnancy and during the first trimester in prescribed doses. In later period it may be advised to make sure to avoid getting too much of folic acid. Enough folate can be obtained through food sources like cereals, legumes, dark leafy greens that usually do not carry the same risks as synthetic folate as they are metabolized differently in the body.

**REFERENCES:**

1. **G.C. Burdge, K.A. Lillycrop.** Folic acid supplementation in pregnancy: are there devils in the detail?. Br J Nutr, 108 (2012), pp. 1924-1930.

2. **N. Wald, J. Sneddon.** Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet, 338 (1991), pp. 131-137.

3. **A.E. Czeizel, I. Dudas.** Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. NEngl J Med, 327 (1992), pp. 1832-1835.

4. **Greene ND, Stanier P, Moore GE.** The emerging role of epigenetic mechanisms in the etiology of neural tubedefects. Epigenetics. 2011;6(7):875–883.

5. **Smithells RW, Sheppard S, Schorah CJ:** Vitamin deficiencies and neural tube defects. Arch Dis Child. 1976, 51: 944-950.

6. **Li D, Rozen R:** Maternal folate deficiency affects proliferation, but not apoptosis, in embryonic mouse heart. J Nutr. 2006, 136: 1774-1778.

7. **Blom HJ, Shaw GM, Den Heijer M, Finnell RH:** Neural tube defects and folate: case far from closed. Nat Rev Neurosci. 2006, 7: 724-731.
8. Ventura SJ, Martin JA, Curtin SC, Mathews TJ. Report of final natality statistics, 1995. Monthly vital statistics report. Vol 45(no. 11, suppl 2.) Hyattsville, MD: National Center for Health Statistics, 1997.

9. https://www.parents.com/pregnancy/everything-pregnancy/what-folic-acid-supplements-linked-to-health-risks-for-mom-and-baby/ accessed on May 21 2020

10. Wallingford JB, Niswander LA, Shaw GM, Finnell RH: The continuing challenge of understanding, preventing, and treating neural tube defects. Science. 2013, 339: 1222002

11. Crider KS, Yang TP, Berry RJ, Bailey LB: Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate’s role. AdvNutr. 2012, 3: 21-38.

12. Hubner RA, Houlston RS: Folate and colorectal cancer prevention. Br J Cancer. 2009, 100: 233-239.

13. Liu JJ, Ward RL: Folate and one-carbon metabolism and its impact on aberrant DNA methylation in cancer. Adv Genet. 2010, 71: 79-121.

14. F. Girotto, L. Scott, Y. Avchalumov, J. Harris, S. Iannattone, C. Drummond-Main, et al. High dose folic acid supplementation of rats alters synaptic transmission and seizure susceptibility in offspring. Sci Rep, 3 (2013), pp. 1465.

15. Håberg SE, London SJ, Stigum H, et al. Folic acid supplements in pregnancy and early childhood respiratory health. Arch Dis Child 2009; 94: 180-184.

16. Whitrow MJ, Moore VM, Rumbold AR, et al. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J Epidemiol 2009; 170: 1486–1493.

17. S.P. Veeranki, T. Gebretsadik, S.L. Dorris, E.F. Mitchell, T.V. Hartert, W.O. Cooper, et al. Association of folic acid supplementation during pregnancy and infant bronchiolitis 2014;179: 938-946.

18. S.E. Haberg, S.J. London, H. Stigum, P. Nafstad, W. Nystad. Folic acid supplements in pregnancy and early childhood respiratory health. Arch Dis Child, 94 (2009), pp. 180-184

19. Badovinac RL, Werler MM, Williams PL, et al. Folic acid-containing supplement consumption during pregnancy and risk for oral clefts: a meta-analysis. Birth Defects Res A ClinMolTeratol. 2007;79(1):8-15.

20. A.M. Rozendaal, A.J. Van Essen, G.J. TeMeerman, M.K. Bakker, J.J. Van Der Biezen, S.M. Goorhuis-Brouwer, et al. Periconceptional folic acid associated with an increased risk of oral clefts relative to non-folate related malformations in the Northern Netherlands: a population based case–control study. EurJ Epidemiol, 28 (2013), pp. 875-887.

21. Cunningham F, Gant NF, Levenok J, Glistrap LC, Hauth JC, Wenstrom KD. Williams Obstetrics. New York: McGraw-hill publisher; 2005. pp. 5-7. pp. 883–936, pp. 1042.

22. Katzung BG. In: Basic and Clinical Pharmacology. Sohrevardi SH, editor. 2006. pp. 656–9.
23. R.M. Nilsen, S.E. Vollset, S.A. Rasmussen, P.M. Ueland, A.K. Daltveit. Folic acid and multivitamin supplement use and risk of placental abruption: a population-based registry study. Am J Epidemiol, 167 (2008), pp. 867-874.

24. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth Prevalence of Congenital Heart Disease Worldwide A Systematic Review and Meta-Analysis. Journal of the American College of Cardiology. 2011;58(21):2241–7.

25. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327:1832–5.

26. G.L. Wehby, T.M. Felix, N. Goco, A. Richieri-Costa, H. Chakraborty, J. Souza, et al. High dosage folic acid supplementation, oral cleft recurrence and fetal growth. Int J Environ Res Publ Health, 10 (2013), pp. 590-605

27. S. Timmermans, V.W. Jaddoe, A. Hofman, R.P. Steegers-Theunissen, E.A. Steegers. Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: the Generation R Study. Br J Nutr, 102 (2009), pp. 777-785.

28. C.P. Stewart, P. Christian, K.J. Schulze, S.C. Leclerq, K.P. West Jr., S.K. Khatry. Antenatal micronutrient supplementation reduces metabolic syndrome in 6- to 8-year-old children in rural Nepal. J Nutr, 139 (2009), pp. 1575-1581.

29. Thakur S, Thakur SD, Wani NA, Kaur J: Reduced expression of folate transporters in kidney of a rat model of folate oversupplementation. Genes Nutr. 2014, 9: 369-374.