ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Folic acid, Vitamin B_{12} and hypothyroidism in pregnancy: Review of the links.

Srilatha Bashetti[1], Bhongir Aparna Varma[2], Rajagopalan Vijayaraghavan[3], and Kumar Sai Sailesh[4]*.

[1]Assistant Professor, Department of Biochemistry, Apollo Institute of Medical sciences & Research (AIMSR), Hyderabad.
[2]Professor& HOD, Department of Biochemistry, Mediciti Institute Of Medical Sciences, Medchal, Telangana.
[3]Director Research, Saveetha Institute of Medical and Technical Sciences, Poonamalle High Road, Chennai, Tamil Nadu.
[4]Assistant Professor & HOD (I/C), Department of Physiology, Vishnu Dental College, Vishnupur, Bhimavaram, West Godavari District, Andhra Pradesh, India.

ABSTRACT

Thyroid dysfunction is most common during pregnancy. The estimated prevalence of hypothyroidism during pregnancy is to be 0.3-0.5% for overt hypothyroidism (OH) and for subclinical hypothyroidism (SCH) 2-3%. 8-14% of the women in the child-bearing age are positive for thyroid antibodies. Vitamin B12 has a key role in offspring neurodevelopment. There is an association of Vitamin B12 concentration in breast milk and in the vitamin B12concentration of infant with Vitamin B12 concentration in maternal blood. The current review was undertaken to provide detailed account of association of folic acid and vitamin B12 in pregnancy and the effect of vitamin B12 and folic acid on thyroid hormones. Understanding these associations will help to plan effective therapies for the benefit of pregnant women in general.

Keywords: Thyroid dysfunction, Vitamin B12,Folic acid, Pregnancy

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Thyroid dysfunction is most common during pregnancy. The estimated prevalence of hypothyroidism during pregnancy is to be 0.3-0.5% for overt hypothyroidism (OH) and for subclinical hypothyroidism (SCH) 2-3%. 8-14% of the women in the child-bearing age are positive for thyroid antibodies. The two main causes for hypothyroidism during pregnancy include chronic autoimmune thyroiditis and iodine deficiency [1, 2]. There is a profound influence of pregnancy on thyroid hormones. It causes the changes in thyroid hormone transport especially in TBG, effect of human chorionic gonadotropin (hCG) on the maternal thyroid, leads to the increase demands of iodine requirements. It also causes modifications in autoimmune regulations and the role of the placental deiodinase. All these events occur at different phases of gestation, leading to complex effects during delivery or postpartum. Hence, pregnancy is the testing time for the thyroid gland.

Vitamin B12 has a key role in offspring neurodevelopment. There is an association of Vitamin B12 concentration in breast milk and in the vitamin B12concentration of infant with Vitamin B12 concentration in maternal blood. Vitamin B12 cannot be synthesized in the human body. The only source of vitamin B12 is through diet (food of animal origin). The source of vitamin B12for the growing fetus is maternal vitamin B12, the transfer of maternal B12 to the offspring during pregnancy and lactation demands for excess supplementation of vitamin B12 else deficiency may occur. 3-4% of the general population shows Vitamin B12 deficiency. 12% of hypothyroid patients present with pernicious anemia especially, subjects with autoimmune hypothyroidism. Many animal studies suggested that disturbances in methylation cycle mey be one of the reasons for NTDs. Adequate methylation cycle is essential for cranial neural tube closure. Availability of methyl group is very important for many cellular functions of neuron to occur, including gene expression control and DNA methylation, nucleic acid synthesis and repair and protein metabolism. Important vitamins for methyl group transfer and availability are vitamin B6, folic acid (B9), vitamin B12 and choline. As a precaution to prevent NTD's FA supplementation is recommended during pregnancy, this is a simple intervention to greatly reduce the incidence of NTD's in offspring [3]. Certain studies suggest supplementation of folate in adults to prevent neuro degeneration [4] also helps in improvement of cognitive abilities and reduce depressive symptoms [5].

MATERIALS AND METHODS

A detailed review of published literature from Google, PubMed, and MEDLINE was performed and analyzed.

Thyroid hormones and pregnancy

Serum TBG increases noticeably few weeks after the beginning of pregnancy and around mid-gestation it reaches the plateau. Its increase is 2.5 fold higher than the initial value. This increase is in response to increased estrogen concentration which in turn causes the increased production of Thyroxine-binding globulin TBG in liver. Increased degree of scialylation of TBG gives the protein a longer half-life. Further, proportional binding of TBG to T4 promotes the stabilization of TBG.

Thyroid hormone (TH) levels increase in pregnancy. The affinity of TBG to T4 is 20 folds higher in than to T3. So, the change in total T4 is very close to the change of TBG. The molar ratio of T3/T4 does not change during pregnancy. The total T4 levels increase more rapidly between the 6^{th} and 12^{th} week of gestation. It progresses very slowly and stabilizes around mid-gestation whereas total T3 rises more progressively. This suggests that pregnancy is associated with changes in thyroid function studies and the change is significant but, reversible.

Hypothyroidism in pregnancy show defects in thyroid hormone (TH) synthesis and action leading to impaired cognitive development and increased fetal mortality[6]. As it is well studied that, TH plays very important role in development of fetal brain and nervous system, in uncontrolled hypothyroidism in pregnancy can alter the neurocognitive development of the offspring, affecting the fetal growth and brain development mainly during the first trimester [7] If hypothyroidism is untreated, may lead to increased risk of low birth weight, preeclampsia, placental abruption, perinatal mortality and miscarriage. Hypothyroidism in early or late pregnancy may increase the rate of caesarean section. Pregnancy complications are lower in SCH when compared to overt hypothyroidism.

Vitamin B12 in pregnancy and Hypothyroidism

The maternal cobalamin status is a strong predictor of vitamin B12 in breastfed infants up to at least 6 months of age [10]. Because of the transfer from mother to offspring during pregnancy and lactation, maternal requirements during this period are increased and deficiency may occur. The influence of low vitamin B12during pregnancy may have cognitive ability of children later in life. In Mexico, a study that assessed maternal diet during the trimester of pregnancy and offspring neurological development reported a decrease in cognition test score among children of mothers with a deficient intake of vitamin B12 (<2µg/ day)(Lynch et al, 2005) but, two studies conducted in India reported contradictory results found no such association between the infant cognitive abilities and maternal Vitamin B12 concentration, possibly due to differing levels of vitamin B12 among the populations.[8,9]There are many different causes that lead to vitamin B12 deficiency some of those causes include inadequate intake, altered intestinal absorption due to sluggish bowel motility, bowel wall edema, and bacterial overgrowth.

Association of folic acid and vitamin B12 in pregnancy

Inhibiters such as ethionine and cycloleucine is administrated in cultured mouse embryo during cranial neurilation showed increased NTDs but, had not lead to growth retardation and developmental delay[11]. S-Adenosyl methionine (SAM) is an active donor helps in lipid biosynthesis, protein biosynthesis and DNA methylation. It might be the altered ratio of SAM/S-adenosyl homocysteine (SAH) that may lead to decreased cellular methylation. SAH is a strong inhibitor of many methyltransferases, the enzymes essential for methylation pathway. This is proved in an animal study wherein, genomic DNA showed hypomethylation in the brain of NTD affected fetuses [14,15]corrected on the administration of methionine,stated that increase in maternal methionine reduces NTD risk [12,13]. It is established that supplementation of folate during pregnancy is very important to prevent NTDs and other growth- related problems of the fetus. It is well known that low maternal folate levels lead to NTDs and small for gestational age (SGA) infants [16]. Supplementation of folate to the women during pregnancy is common all-around the world. This had in fact, lead to the increase intake of folate beyond the requirement, before planning the pregnancy or after conception. On the other hand deficiency of vitamin B12 is commonly noticed in pregnant women, the concern in India is due to widespread vegetarianism Few studies in urban areas of South India, stated that low vitamin B12 is associated with increased risk of fetal NTDs and intrauterine growth restriction[18,19]. The study suggests the supplementation of vitamin B12 especially, to vegetarians along with folate[20]. There are certain studies showed the relation to cognitive impairment associated with high plasma folate with low vitamin B12 [21]. If a similar condition is seen during pregnancy may lead to adverse effects on the growing fetus and may continue after birth. An observational study conducted by St. John's Research and Medical institute, Banglore, India had showed that intake of high folic acid with low vitamin B12 i.e. imbalance ratio of vitamin B12 and folate may lead to adverse birth outcomes like SGA infants [22]. This study included 1838 pregnant women of South India. They examined the ratio of vitamin B12 and FA, and also noted the effects of high folate with low vitamin B12. It was observed that intake of low vitamin B12 with high folate intake during the first and second trimester, had led to an increased risk of SGA. However further certain prospective studies like controlled trial of vitamin B12 supplementation should be conducted to extensively understand the associated effects of high or low ratios of vitamin B12 and folic acid during pregnancy and to study the birth outcomes.

The adverse effects may be due to un-metabolized plasma folic acid (FA) in the presence of low vitamin B12 may lead to poor cognitive abilities in the elder people [21]. Studies with increased supplementation of folate in subjects with low vitamin B12 or deficiency of vitamin B12 reported increased concentrations of homocysteine and methylmalonate[23]. Saturated Dihydrofolate and unmetabolize plasma FA is also the effect of low vitamin B12 [24]. Therefore, the study by Prathibha et al, 2013 showed the proportional relationship between low vitamin B12 and increased FA (unbalanced ratio of vitamin B12 and Folic acid) with SGA infants in the population.

A study conducted by Muthayya et al, 2006 in 478 urban south Indian women to assess the dietary micronutrients status in healthy pregnant women and to evaluate the outcome of low vitamin B12 status in pregnant women. The follow-up study showed that the women with low serum vitamin B12 had a higher significance of

intrauterine growth retardation (IUGR) risk in all the three trimesters of pregnancy stating that, low levels of vitamin B12 is associated with IUGR and early detection of vitamin B12 is important to reduce the risk of IUGR. The two essential micronutrients folate and vitamin B12 are very important for normal brain development. Many studies have being take up to understand the relationship of vitamin B12 and folate during pregnancy and their effects on cognitive functions of offspring. As there is a hypothesis made that, low folate and vitamin B12 with increased homocysteine during pregnancy is associated with poor neurodevelopment. Veena Sargoor etal, 2010 conducted a study on 536 children of 9 to 10 years of age at Holdsworth memorial hospital, Mysore. In this cohort study they measured cognitive function and other additional tests to measure learning, long-term storage/ retrieval, concentration and attention, visuo-spatial and verbal abilities. In addition to this, they also measured maternal folate, vitamin B12 and homocysteine levels in pregnant women at 30 ± 2 gestational age. This study concluded that, there is no association of maternal vitamin B12 and homocysteine levels with cognitive performance in childhood. This study showed the positive effect of folate i.e. high maternal folate levels during pregnancy led to better cognitive abilities in children, irrespective of vitamin B12 levels. This stated the importance of folate both in the prevention of neural tube defects and for proper brain development, better cognitive functions too. The study assumed that only when maternal vitamin B12 levels are extremely low poor cognitive function is seen or may be the adaptation of this population for low levels of maternal vitamin B12 had not shown its association with poor cognitive abilities.

However, there are many studies conducted to understand the effects of altered ratio of vitamin B12 and FA and to learn the association of vitamin B12 and FA in developing fetuses showed contradicting results. A study in humans stated that, mothers with low folate levels with maternal megaloblastic anemia are associated with abnormal fetal development and poor mental development [25]. Some case reports revealed that, low vitamin B12 during pregnancy causes delayed neurodevelopment in infants seen in patients with pernicious anemia or in strict vegetarians [26,27,28]. A similar study but in elderly had also shown impaired cognitive function and anemia in subjects with high folate and low or deficient vitamin B12 deficiency [29]. Yet another study conducted in Pune, India noticed that children born to mothers with low vitamin B12 levels <77pmol/L poor performance for the tests like sustained attention and short- term memory when compared with children born to mothers with high vitamin B12 levels (>224pmol/L).

The effect of vitamin B12 and folic acid on thyroid hormones

The first study conducted by [30] in animals (adolescent rats) to learn the prolonged effects of folate supplementation in adolescence. They learnt that, high folate levels effect thyroid function and thyroid hormone-mediated signaling in the hippocampus, stating that increased folate supplementation had a suppressive effect on thyroid hormones (T3 and T4), that had possibly led to motivational deficits and memory impairments in adolescent rats. It had not showed any effect on TSH levels. The exact mechanism of folate leading to suppression of thyroid hormone is unclear. They assumed that this effect was seen because it occurred during the developmentally important adolescent period, few studies in this regards stated, low freeT4 and also subclinical hypothyroidism has been associated with depressive symptoms, behavioral problems and attention deficit behavior in human at adolescence. [31] But, this animal study had confirmed that the animals were functionally hypothyroid during the administration of folate. If the same effect implies in humans with increased folate supplementation during pregnancy i.e. high folate intake may lead to suppression of maternal plasma thyroid hormonal levels, would have alarming implication for the health of the fetus. However, the association of endocrine changes and behavioral phenotypes has yet to be studied. The overall conclusion of the study by is increased folate supplementation of had led to decrease in peripheral thyroid hormone levels and the hippocampal changes of thyroid receptor (TR) levels further causing both motivational changes and memory impairment suggesting, the increased levels of folate supplementation alone may be harmful not only during fetal development and on growing infant but also in the adolescent period. Other adverse effects of high folate include the stimulation of Gs gamma proteins in membranes of brain with its greatest effect in the hippocampus and cerebellum.There are evidences that increased folate promote or stimulate cancer [32]. The detrimental effect of high folate on endocrine and behavioral parameters is of high concern and suggests that, “anything in excess is bad or less is more”.

CONCLUSION

The current review provides detailed account of association of folic acid and vitamin B12 in pregnancy and the effect of vitamin B12 and folic acid on thyroid hormones. Understanding these associations will help to plan effective therapies for the benefit of pregnant women in general.

REFERENCES

1. Abalovich M, Amino N, Barbour LA, cobin RH, Degroot LJ, Glinoer D, Mandel SJ, Stagnaro-Green A. Management of thyroid dysfunction during pregnancy and post partum: an Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology and Metabolism.2007; 92(8 suppl): S1-47. DNA Methylation Patterns inWistar Rats. PLoS ONE 6(3): e17706.

2. Krassas GE, Popper K, Glinoer D. Thyroid function and human reproductive health. Endocrine Reviews.2010; 31(5): 702-755.

3. Blencowe, H., Cousens, S., Modell, B. & Lawn, J.Folic acid to reduce neonatal mortality from neural tube disorders. IntJ Epidemiol. 2010;**39**(Suppl. 1), i110–i121.

4. Zhuo, J.M. & Pratico, D. Acceleration of brain amyloidosis in an Alzheimer's disease mouse model by a folate, vitamin B6 and B12-deficient diet. Exp Gerontol.2010; 45, 195–201.

5. Beydoun MA, Fanelli Kuczmarski MT, Beydoun HA, Shroff MR, Mason MA, Evans MK, Zonderman AB.The sex-specific role of plasma folate in mediating the association of dietary quality with depressive symptoms.J Nutr.2010; 140(2):338-47.

6. Allan WC, Hadow JE, palomaki GE, Williams JR, Mitchell ML, hermos RJ, Faix JD, Klein RZ . Maternal thyroid deficiency and pregnancy complications: implications for population screening. Journal of medical screening.2000;7(3):127-130.

7. Hadow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, O'Heir CE, Mitchell ML,

   Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child.New England Journal of Medicine.1999; 341(8):549-555.

8. Yi Y., Lindemann M., Colligs A., Snowball C. Economic burden of neural tube defects and impact of prevention with folic acid: A literature review. Eur. J. Pediatr.2011; 170:1391–1400.

9. Frey L., Hauser W.A. Epidemiology of neural tube defects. Epilepsia.2003; 44:4–13.

10. Steen M.T., Boddie A.M., Fisher A.J., Macmahon W., Saxe D., Sullivan K.M., Dembure P.P., Elsas L.J. Neural-tube defects are associated with low concentrations of cobalamin (vitamin B12) in amniotic fluid. Prenat.Diagn.1998;18:545–555.

11. Dunlevy, L.P.; Burren, K.A.; Mills, K.; Chitty, L.S.; Copp, A.J.; Greene, N.D. Integrity of the methylation cycle is essential for mammalian neural tube closure. Birth Defects Res.2006;76, 544–552.

12. Shoob, H.D.; Sargent, R.G.; Thompson, S.J.; Best, R.G.; Drane, J .W.; Tocharoen, A . Dietary methionine is involved in the etiology of neural tube defect -affected pregnancies in humans. J. Nutr.2001;131, 2653–2658. (167-169).

13. Graham, A.; Brender, J.D.; Sharkey, J.R.; Zhu, L.; Felkner, M.; Suarez, L.; Canfield, M.A.Dietary methionine intake and neural tube defects in Mexican-American women. Birth Defects Res.2010; 88, 451–457.

14. Chang, H.; Zhang, T.; Zhang, Z.; Bao, R.; Fu, C.; Wang, Z.; Bao, Y.; Li, Y.; Wu, L.; Zheng, X.; et al. Tissue-specific distribution of aberrant DNA methylation associated with maternal low-folate status in human neural tube defects. J. Nutr. Biochem.2011; 22, 1172–1177.

15. Greene, N.D.; Stanier, P.; Moore, G.E.The emerging role of epigenetic mechanisms in the etiology of neural tube defects. Epigenetics.2011; 6, 875–883.

16. Furness DLF, Yasin N, Dekker GA, Thompson SD, Roberts CT . Maternal red blood cell folate concentration at 10-12 weeks gestation and pregnancy outcome. J Matern Fetal Neonatal Med.2012; 25:1423–7.

17. Refsum H, Yajnik CS, Gadkari M, Schneede J, Vollset SE, O¨ rning L, Guttormsen AB, Joglekar A, Sayyad MG, Ulvik A, et al . Hyperhomocysteinemia and elevated methylmalonic acid indicate a high prevalence of cobalamin deficiency in Asian Indians. Am J Clin Nutr.2001; 74:233–41.

18. Kirke PN, Molloy AM, Daly LE, Burke H, Weir DG, Scott JM . Maternal plasma folate and vitamin B12 are independent risk factors for neural tube defects. Q J Med.1993;86:703–8.

19. Muthayya S, Kurpad AV, Duggan C, Bosch RJ, Dwarkanath P, Mhaskar A, Mhaskar R, Thomas A, Vaz M, Bhat S, et al . Low maternal vitamin B12 status is associated with intrauterine growth retardation in urban South Indians. Eur J Clin Nutr.2006; 60:791–801

20. Antony AC. Vegetarianism and vitamin B-12 (cobalamin) deficiency.Am J Clin Nutr.2003;78:3–6(13).

21. Selhub J, Paul L. Folic acid fortification: why not vitamin B12 also? Biofactors.2011;37:269–71.

22. Pratibha Dwarkanath, Julie R Barzilay, Tinku Thomas, Annamma Thomas, Swarnarekha Bhat, and Anura V Kurpad. High folate and low vitamin B-12 intakes during pregnancy are associated with small-for-gestational age infants in South Indian women: a prospective observational cohort study Am J Clin Nutr.2013;10.3945/ajcn.112.056382. 1-9.

23. Selhub J, Jacques PF. In vitamin B12 deficiency, higher serum folate is associated with increased total homocyateine and methylamalonic acid concentrations. Proc natl Acad Sci USA.2007; 104:19995-20000.

24. Kelly P, McPartlin J, Goggins M, Weir DG, Scott JM . Unmetabolized folic acid in serum: acute studies in subjects consuming fortified food and supplements. Am J Clin Nutr. 1997;65:1790-5.

25. Del Rio Garcia C, Torres-Sanchez L, Chen J, Schnaas L, Hernandez C, Osorio E, Portillo MG, Lopez-Carrillo L. Maternal MTHFR 677C>T genotype and dietary intake of folate and vitamin B12: their impact on child neurodevelopment. Nutr Neurosci.2009; 12:13-20.

26. Ramakrishna T . Vitamins and brain development. Physiol Res.1999; 48:175-87).

27. Black MM. Micronutrient deficiencies and cognitive functioning.J Nutr.2003; 133 (11 Suppl 2): S3927-31).

28. Black MM . Effects of vitamin B12 and folate deficiency on brain development in children.Food Nutr Bull.2008; 29:S126-86).

29. Selhub J, Morris MS, Jacques PF, Rosenberg IH . Folate –vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. Am J Clin Nutr.2009; 89:S702-6.

30. Sittig, L.J., Herzing, L.B., Shukla, P.K. & Redei, E.E. Parent-of-origin allelic contributions to deiodinase-3 expression elicit localized hyperthyroid milieu in the hippocampus. Mol Psychiatry.2011; 16, 786–787.

31. Haviland, M.G., Sonne, J.L., Anderson, D.L., Nelson, J.C., Sheridan-Matney, C., Nichols, J.G., Carlton, E.I. & Murdoch, W.G. Thyroid hormone levels and psychological symptoms in sexually abused adolescent girls. Child Abuse Negl .2006;30, 589–598.

32. Collin, S.M., Metcalfe, C., Refsum, H. ***et al.*** Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: a case-control study, systematic review, and meta-analysis.Cancer Epidemiol Biomarkers Prev.2010; 19, 1632–1642