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Influence of folic acid on pregnancy outcome: Review study

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ABSTRACT

Adequate folic acid intake is essential throughout gestation to ensure normal fetal growth and development. Although the causal relationship between the deficiency of folic acid (Plasma total homocysteine"tHcy" level is elevated) and risk of neural tube defects are well proved, the relation between folic acid deficiency and other pregnancy complications is still un clear. The present study aims to review the data published about the relationship between serum folate and pregnancy complications.

By reviewing 57 studies, this study concludes that folic acid deficiency leads to elevate plasma homocysteine, which increased risk of serious complications of pregnancy and delivery. So, it is recommended for women to take 400 microgram of folic acid supplements daily, before pregnancy to prevent those complications.

1. Introduction

Folic acid (vitamin B9) plays a major coenzymatic role in one-carbon metabolism and is a key participant in the biosynthesis of DNA, RNA and certain amino acids (Cunningham et al., 1993). There are many physiologic changes taking place during pregnancy that maintain the mother's health but still allow for the development of the fetus, these changes affect the mother's nutritional status by increasing her energy and nutrient needs (Sauberlich et al., 1987). Foods that have the most folate include:

- green leafy vegetables such as broccoli, spinach, and green salad.
- chickpeas, dried beans and nuts.
- orange juice and some fruits.

There are many types of bread, breakfast cereals and other packaged foods contain added folate. These are called folate-fortified foods (Cunningham et al., 1993; Sauberlich et al., 1987). In the early 1990s, supplementation with folic acid in the first week of pregnancy was proved to reduce the incidence of neural tube defects (NTD), Wagner, (1995). To protect women with un planned pregnancies, the U.S. public Health services has recommended that all women of childbearing age consume 400 µg/d of folate to reduce the risk of NTD and for normal fetal growth and development (Scott et al., 1995). Although the causal relationship between the deficiency of folic acid (Plasma total homocysteine"tHcy" level is elevated) and risk of neural tube defects are well proved, the relation between folic acid deficiency and other pregnancy complications is still un clear. The present study aims to review the data published about the relationship between serum folate and pregnancy complications.

2. The objectives

1- To review the evidence about the relationship between folic acid and pregnancy complications.
2- To review the evidence about the relationship between folic acid and fetal growth & development.

3. Subjects and methods

(i) Study period: from 1-6-2015 to 1-11-2015

(ii) Study design: review article of selected epidemiological studies on folic acid and their impact on pregnancy outcome.

*(iii) Selection criteria***:** the present review focuses on the relation between pregnancy outcome and folate nutrition and metabolism, homocysteine metabolism. so conducted literature search for the terms "folate, folic acid, pregnancy, and fetus growth and development." limiting the search to English language articles and studies conducted in humans, full text , abstracts are excluded, the study must be published in a scientific journal .

(iv) Number of the studies reviewed:
57 epidemiological studies on folic acid and its relation to pregnancy outcome were reviewed.

4. Results and discussion

(I) Pregnancy complications:

Placental abruption:

Is defined as premature separation of a normally inserted placenta from the endometrium. Six studies indicated an association of elevated Plasma total homo-cysteine"tHcy" level (as a result of folic acid deficiency) with an increased incidence for placental abruption (Hibbard & Hibbard 1963; Hibbard 1964; Menon et al.,1964; Henry 1968; Steriff & Little 1967; Hibbard et al., 1969) only two studies Hall (1972) and Pritchard et al., (1991) found no association. Therefore, the association is still uncertain and needs further studies.

Preeclampsia: pregnancy-induced hypertension.

Although many studies reported that preeclampsia might be due to elevated Plasma total homocysteine"tHcy" level that affect the vascular endothelial cells. 12 studies were reviewed (Whalley et al., 1970; Molina et al., 1974; Rajkovic et al., 1997; Powers et al., 1998; Laivuori et al., 1999; Hogg et al., 2000; Wang et al., 2000; van der Molen et al., 2000; Hietala et al., 2001; Cotter et al., 2001; Sanchez et al., 2001; Murakami et al., 2001). Most of them

showed that there is no association between folic acid deficiency and incidence of preeclampsia.

Spontaneous abortion:

Five studies (Nelen et al. 2000; Weerd 2003; Ronnenberg et al., 2002; George 2002; WLDM 2000) indicated that pregnant women with folic acid deficiency had a higher risk for abortion than did those with higher plasma folate**.** These studies reported that hyperhomocystinemia might be the underlying cause of spontaneous abortion**.**

Stillbirth:

Three studies (Giles 1966; Ainley 1966; Vollset et al., 2000) showed that the stillbirth rate was associated with folic acid deficiency and hyperhomocystinemia whereas another study (Varadi, 1966) found no such association.

(II) Fetal growth & development and Folic acid:

Folic acid and birth weight:

Birth weight is an important nutritional and health indicator. Seven studies (Wilcox 2001; Whiteside et al., 1968; Baker 1977; Tamura 1992; Frelut 1995; Rondo & Tomkins 2000; Shaw 1977) indicated that prenatal folic acid supplementation increased birth weight. While other Five studies (Mitchell et al., 2004; Burke et al., 1992; Murphy et al., 2004; Ronnenberg et al., 2002; Infante-Rivard et al., 2003) showed that there was no association between folic acid level among the pregnant women and their babies birth weight. The discrepancy between the studies might be due to different demographic, socioeconomic and nutritional factors. There was a recent report from California indicated that fetal growth is promoted by folic acid supplementation (Shaw et al., 2004).

Folic acid and preterm delivery:

Five studies (Varadi 1966; Wilcox 2001; Shaw et al., 2004; Kramer et al., 2001; Valdez et al., 2004) showed that folic acid deficiency might lead to preterm delivery (which is defined as a delivery before 37 wk of pregnancy) because of the hyperhomocystinemia and its effect on the endometrial vessels. However, such result may be affected by other confounding factors and need further studies to evaluate it.

(III) Fetal development and folic acid

Child neurodevelopment and maternal folic acid:

A study (Rosenblatt & Fenton 2001) showed that mental retardation might be due to inborn errors of folate metabolism. Two other studies (Gross et al., 1974; Tamura et al., 2005) reported an association between maternal level of folic acid and fetal neurodevelopment.

Down syndrome and folic acid:

Three studies (Chadefaux et al., 1985; Chadefaux et al., 1988; James et al., 1999) reported no relation between maternal level of folic acid and the development of autosomal trisomy (Down syndrome) among the fetus.

(IV) FETAL MALFORMATIONS and folic acid

Because the association between folic acid deficiency and neural tube defects were well proved, so this study reviews the possible relation with other fetal malformations.

Orofacial clefts (OFCs):

Giving high folic acid supplementation (10 mg/d), prenatally to a pregnant women who delivered before a child with OFCs will prevent its recurrence, this was reported in 2 studies (Tolarova et al., 1982; Czeizel et al., 1999). In contrast two studies (Hayes et al., 1996; Shaw et al., 1996) showed no such protective effect. So further studies must be done to clarify the relation between folic acid and OFCs.

Congenital heart defects:

Several Studies (Shaw et al., 1995; Czeizel 1996; McBride e al., 2004) reported an association between matenal folate level and congenital heart defects in infants. They showed a significant reduced risk of congenital heart defects among fetuses whose their mother receive folic acid supplementations. But these studies used small sample size that may affect the statistical power of their results. So further studies with a large sample size are needed to prove such association.

5. Conclusions

Folic acid deficiency leads to elevate plasma homocysteine, which increases risk of serious complications of pregnancy and delivery like spontaneous abortion and preterm delivery. However, evidence is not clear to conclude there is a causal relationship between folic acid deficiency and the following pathologies (preeclampsia, oro –facial clefts (OFCs) and Down syndrome).

6. Recommendations

1. Pregnant women are advised to consume fresh green leafy vegetables and fruits (folic acid rich foods) in addition to folic acid–fortified foods.
2. It is recommended for women to take 400 microgram of folic acid supplements before pregnancy (planned pregnancy) or at least once discovered she is pregnant (in the first trimester) to decrease the folate deficiency effects on pregnancy outcome.
3. Horizontal and longitudinal studies are recommended to evaluate the effects and safety of folic acid.

References

Ainley, N.J. (1961) Megaloblastic anaemia of pregnancy and the puerperium. J Obstet Gynaecol Br Comm; 16: pp. 9–21.

Baker, H., Thind, I.S., Frank, O., DeAngelis, B., Caterini, H., Louria, D.B. (1977) Vitamin levels in low-birth-weight newborn infants and their mothers. Am J Obstet Gynecol; 129: pp. 521–524.

Burke, G., Robinson, K., Refsum, H., Stuart, B., Drumm, J., Graham, I. (1992) Intrauterine growth retardation, perinatal death, and maternal homocysteine levels. N Engl J Med; 326: pp. 69–70.

Chadefaux, B., Rethore, M.O., Raoul, O. et al., (1985) Cystathionine beta synthase: gene dosage effect in trisomy 21. Biochem Biophys Res Comm; 128: pp. 40–44.

Chadefaux, B., Ceballos, I., Hamet, M., et al., (1988). Is absence of atheroma in Down syndrome due to decreased homocysteine levels? Lancet; 2:741

Cotter, A.M., Molloy, A.M., Scott, J.M., Daly, S.F. (2001) Elevated plasma homocysteine in early pregnancy: a risk factor for the development of severe preeclampsia. Am J Obstet Gynecol; 185: pp. 781–785.

Cunningham, F.G., MacDonald, P.C., Gant, N.F., Leveno, K.J. & Gilstrap L.C., eds. (1993) Physiology in pregnancy. In: Williams Obstetrics, pp. 209–247. Appleton & Lange, Norwalk, CT.

Czeizel, A.E. (1996) Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. Am J Med Genet; 62: pp. 179–83

Czeizel, A.E., Tímár, L., Sárközi (1999) A. Dose-dependent effect of folic acid on the prevention of orofacial clefts. Pediatrics [serial online]; 104:e66

Frelut, M.L., de Courcy, G.P., Christidès J-P, Blot. P., Navarro, J. (1995) Relationship between maternal folate status and foetal hypotrophy in a population with a good socio-economical level. Int J Vitam Nutr Res; 65: pp. 267–271

George, L., Mills, J.L., Johansson, ALV. et al. (2002) Plasma folate levels and risk of spontaneous abortion. JAMA; 288: pp. 1867–1873.

Giles, C. (1966) An account of 335 cases of megaloblastic anaemia of pregnancy and the puerperium. J Clin Pathol; 19:pp. 1–11.

Gross, R.L., Newberne, P.M., Reid, JVO. (1974) Adverse effects on infant development associated with maternal folic acid deficiency. Nutr Rep Int; 10: pp. 241–248.

Hall, M.H. (1972) Folic acid deficiency and abruptio placentae. J Obstet Gynaecol Br Commonw; 79:pp. 222–225.

Hayes, C., Werler, M.M., Willett, W.C., Mitchell, A.A. (1996). Case-control study of periconceptional folic acid supplementation and oral clefts. Am J Epidemiol; 143:pp. 1229–1234

Henry, G.R. (1968) The aetiology of abruptio placentae with special reference to folate metabolism. Irish J Med Sci; 7: pp. 509–515.

Hibbard, B.M, Hibbard E.D. (1963) Aetiological factors in abruptio placentae. Br Med J; 2: pp. 1430–1436.

Hibbard, B.M. (1964) The role of folic acid in pregnancy with particular reference to anaemia, abruption and abortion. J Obstet Gynaecol Br Comm; 71: pp. 529–42.

Hibbard, B.M., Hibbard, E.D., Hwa, T.S., Tan, P. (1969) Abruptio placentae and defective folate metabolism in Singapore women. J Obstet Gynaecol Br Commonw; 76: pp. 1003–1007.

Hietala, R., Turpeinen, U., Laatikainen, T. (2001) Serum homocysteine at 16 weeks and subsequent preeclampsia. Obstet Gynecol ; 97: pp. 527–728.

Hogg, B.B., Tamura, T., Johnston, K.E., DuBard, M.B., Goldenberg, R.L. (2000) Second-trimester plasma homocysteine levels and pregnancy-induced hypertension, preeclampsia and intrauterine growth restriction. Am J Obstet Gynecol; 183: pp. 805–809.

Infante-Rivard, C., Rivard, G.E., Gauthier, R., Théorêt, Y. (2003) Unexpected relationship between plasma homocysteine and intrauterine growth restriction. Clin Chem; 49: pp. 1476–1482.

James, S.J., Pogribna, M., Pogribny, I.P. et al., (1999) Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. Am J Clin Nutr; 70: pp. 495–501.

Kramer, M.S., Goulet, L., Lydon, J., et al. (2001) Socio-economic disparities in preterm birth: causal pathways and mechanisms. Paediatr Perinat Epidemiol; 15(suppl): pp. 104–23.

Laivuori, H., Kaaja, R., Turpeinen, U., Viinikka, L., Ylikorkala, O. (1999) Plasma homocysteine levels elevated and inversely related to insulin sensitivity in preeclampsia. Obstet Gynecol; 93: pp. 489–493.

McBride, K.L., Fernbach, S., Menesses, A. et al., (2004) A family-based association study of congenital left-sided heart malformations and 5, 10 methylenetetrahydrofolate reductase. Birth Defects Res A Clin Mol Teratol; 70: pp. 825–830.

Menon, M.K., Sengupta, M., Ramaswamy N. (1966) Accidental haemorrhage and folic acid deficiency. J Obstet Gynaecol Br Comm; 73: pp. 49–52.

Mitchell, E.A., Robinson, E., Clark, P.M. et al., (2004) Maternal nutritional risk factors for small for gestational age babies in a developed country: a case-control study. Arch Dis Child Fetal Neonat; 89: pp. F431–435.

Molina, R.A., Diez-Ewald, M., Fernández, G., Velázquez, N. (1974) Nutritional anaemia during pregnancy. A comparative study of two socio-economic classes. J Obstet Gynaecol Br Comm; 81: pp. 454–458.

Murakami, S., Matsubara, N., Saitoh, M., Miyakawa, S., Shoji, M., Kubo, T. (2001) The relation between plasma homocysteine concentration and methylenetetrahydrofolate reductase gene polymorphism in pregnant women. J Obstet Gynaecol Res; 27: pp. 349–352.

Murphy, M.M., Scott, J.M., Arija, V., Molloy, A.M., Fernandez-Ballart, J.D. (2004) Maternal homocysteine before conception and throughout pregnancy predicts fetal homocysteine and birth weight. Clin Chem; 50: pp. 1406–1412

Nelen, WLDM, Blom, H.J., Steegers, EAP, den Heijer, M., Thomas, CMG, Eskes, TKAB. (2000) Homocysteine and folate levels as risk factors for recurrent early pregnancy loss. Obstet Gynecol; 95: pp. 519–524.

Powers, R.W., Evans, R.W., Majors, A.K. et al. (1998) Plasma homocysteine concentration is increased in preeclampsia and is associated with evidence of endothelial activation. Am J Obstet Gynecol; 179: pp. 1605–1611.

Pritchard, J.A., Cunningham, F,G,, Pritchard, S.A., Mason, R.A. (1991) On reducing the frequency of severe abruptio placentae. Am J Obstet Gynecol; 165: pp. 1345–51.

Rajkovic, A., Catalano, P.M., Malinow, M.R. (1997) Elevated homocysteine levels with preeclampsia. Obstet Gynecol; 90: pp. 168–171.

Ray, J.G. (2004) Folic acid food fortification in Canada. Nutr Rev; 62: pp. S35–39.

Rondo, PHC., Tomkins, A.M. (2000) Folate and intrauterine growth retardation. Ann Trop Paediatr; 20: pp. 253–258.

Ronnenberg, A.G., Goldman, M.B., Chen, D., et al., (2002) Preconception homocysteine and B vitamin status and birth outcomes in Chinese women. Am J Clin Nutr; 76: pp. 1385–1391.

Ronnenberg, A.G., Goldman, M.B., Chen, D., et al. (2002) Preconception folate and vitamin B_6 status and clinical spontaneous abortion in Chinese women. Obstet Gynecol; 100: pp. 107–113.

Rosenblatt, D.S., Fenton, W.A. (2001) Inherited disorders of folate and cobalamin transport and metabolism. In: Scriver CR, Beaud et al., Valle D, et al., eds. The Metabolic and Molecular Basis of Inherited Disease. 8th ed. New York, NY: McGraw-Hill: pp. 3897–3933.

Sanchez, S.E., Zhang, C., Malinow, M.R., Ware-Juaregui, S., Larrabure, G., Williams, M.A. (2001) Plasma folate, vitamin B_{12}, and homocysteine concentrations in preeclamptic and normotensive Peruvian women. Am J Epidemiol; 153: pp. 474–80.

Sauberlich, H. E., Kretsch, M. J., Skala, J. H., Johnson, H. L. & Taylor, P. C. (1987) Folate requirement and metabolism in nonpregnant women. Am. J. Clin. Nutr. 46: pp. 1016-1028.

Scott, J. M., Wier, D. G. & Kirke, P. N. (1995) Folate and neural tube defects. In: Folate in Health and Disease (Bailey, L. B., ed.), pp. 329–360. Marcel Dekker, Inc., New York, NY.

Shaw, G.M., Carmichael, S.L., Nelson, V., Selvin, S., Schaffer, D.M. (2004) Occurrence of low birthweight and preterm delivery among California infants before and after compulsory food fortification with folic acid. Public Health Rep; 119: pp. 170–173.

Shaw, G.M., Liberman, R.F., Todoroff, K., Wasserman, C.R. (1977) Low birth weight, preterm delivery, and periconceptional vitamin use. J Pediatr; 130: pp. 1013–4.

Shaw, G.M., O'Malley, C.D., Wasserman, C.R., Tolarova, M.M., Lammer, E.J. (1995) Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. Am J Med Genet; 59:pp. 536–545.

Steriff, R.R., Little, A.B. (1967) Folic acid deficiency in pregnancy. N Engl J Med; 276: pp. 776–779.

Tamura, T., Goldenberg, R.L., Chapman VR, Johnston KE, Ramey SL, Nelson, K.G. (2005) Folate status of mothers during pregnancy and mental and psychomotor development of their children at five years of age. Pediatrics; 116: pp. 703–708

Tamura, T., Goldenberg, R.L., Freeberg, L.E., Cliver, S.P., Cutter, G.R., Hoffman, H.J. (1992) Maternal serum folate and zinc concentrations and their relationships to pregnancy outcome. Am J Clin Nutr; 56: pp. 365–370.

Tolarova, M., (1982) Periconceptional supplementation with vitamins and folic acid to prevent recurrence of cleft lip. Lancet: 217.

Valdez, L.L., Quintero, A., Garcia, E. et al., (2004) Thrombophilic polymorphisms in preterm delivery. Blood Cells Mol Dis; 33: pp. 51–56.

Van der Molen, E.F., Arends G.E., Nelen, WLDM, et al. (2000) A common mutation in the 5,10-methylenetetrahydrofolate reductase gene as a new risk factor for placental vasculopathy. Am J Obstet Gynecol; 182: pp. 1258–1263.

Varadi, S., Abbott, D., Elwis, A. (1966) Correlation of peripheral white cell and bone marrow changes with folate levels in pregnancy and their clinical significance. J Clin Pathol; 19: pp. 33–36.

Vollset SE, Refsum H, Irgens LM, et al. (2000) Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine Study. Am J Clin Nutr; 71: pp. 962–968

Wagner, C. (1995) Biochemical role of folate in cellular metabolism. Bailey, L.B. eds. Folate in Health and Disease: 23-42 Marcel Dekker New York, NY.

Wang, J., Trudinger, B.J., Duarte, N., Wilcken, D.E., Wang, X.L. (2000) Elevated circulating homocyst(e)ine levels in placental vascular disease and associated pre-eclampsia. Br J Obstet Gynaecol; 107: pp. 935–938.

Weerd, S., Steegers-Theunissen, RPM, de Boo TM, Thomas, CMG, Steegers, EAP. (2003) Maternal periconceptional biochemical and hematological parameters, vitamin profiles and pregnancy outcome. Eur J Clin Nutr; 57:pp. 1128–1134.

Whalley, P.J., Scott, D.E., Pritchard, J.A.(1970) Maternal folate deficiency and pregnancy wastage. III. Pregnancy-induced hypertension. Obstet Gynecol; 36: pp. 29–31.

Whiteside, M.G., Ungar, B., Cowling, D.C. (1968) Iron, folic acid and vitamin B_{12} levels in normal pregnancy, and their influence on birth-weight and the duration of pregnancy. Med J Aust; 2: pp. 338–342.

Wilcox, A.J. (2001) On the importance—and the unimportance—of birthweight. Int J Epidemiol; 30: pp. 1233–1241.

WLDM, Blom HJ, Steegers EAP, den Heijer M, Eskes, TKAB. (2000) Hyperhomocysteinemia and recurrent early pregnancy loss: a meta-analysis. Fertil Steril; 74: pp. 1196–1199