



Influence of folic acid on pregnancy outcome: Review study

Lubna J. Abdulmalek

Department of family & community medicine, Faculty of medicine, University of Benghazi, Benghazi, Libya

E-mail address: Lubna.abdulmalek@uob.edu.ly

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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 unclear. 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 elevated 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.

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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 unplanned 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 unclear. 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 homocysteine "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; WLD 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 et al., 2004) reported an association between maternal folate level and congenital heart defects in infants. They showed a significant reduced risk of congenital heart defects among fetuses whose 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.

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