

Folate supplementation in pregnancy

Dr. Yasser AL – Ankoodi *

*Department of laboratory medicine Nizwa Hospital Sultanate of Oman.

Abstract

Objectives: To determine the prevalence of low, normal and high folate levels in Omani population. Folate supplement given routinely during pregnancy. Folate added into multi-vitamins supplement as well as into food products. This leads to decrease the prevalence of low folate or increase prevalence of people with excess folate. Low and high folate level leads to adverse side effects.

Methods: 3706 folate samples analyzed in Cobas e 601 chemical analyzer. The results separated into three main groups (low, normal and high).

Results: Only 0.3% of the study sample shows low folate level. Five (0.2%) out of 2335 female samples show low folate level. Three (0.2%) out of 1371 male samples shows low folate level.

Conclusion: Routine folate intake during pregnancy, supplement to the general population for wellbeing and food fortification might lead to excess folate status. Folate testing before supplementation help in avoiding high folate adverse effects.

Key words: Folate; Pregnant women; Nizwa Hospital; Oman; low folate; high folate; un-metabolized folic acid.

Folate was isolated in 1941 and finally synthesized in 1946.^{1,2} The name folate is a generic term for all related compounds that show vitamin activity similar to folic acid. Folic acid consists of three parts; a pteridine ring, p-aminobenzoic acid and one molecule of L-glutamic acid.³ Normally, human health depends on exogenous sources of preformed folate that consists of dietary folate and folate synthesized by the normal microflora of the large intestine.³ Factors affecting folate absorption and bioavailability include: 1-nutrient status of the body, 2-food processing, 3-food matrix, 4-de-conjugation of polyglutamyl folates and 5-polymorphism (677C-T) in a key folate enzyme methylenetetrahydrofolate reductase.^{4,5}

Low serum folate:

Low serum folate implicated in causing birth defects (Table 1). The most common types of these defects are congenital heart defects (CHDs) and neural tube defects (NTDs). Some of these defects are serious. Like anencephaly is inconsistent with life and spina bifida may lead to extremely severe clinical consequences that seriously impair quality of life.⁶ Craniofacial malformations include cleft lip and cleft palate are other birth defects because of folate deficiency.⁶⁻⁸ Some evidence indicates that low serum folate can lead to 1-placenta abruption, 2-placenta infarction, 3-pre-eclampsia and 4-spontaneous abortion.⁹⁻¹¹

Excess serum folate:

The process of absorption and biotransformation of folic acid to its active form (5- methyltetrahydrofolate) is saturated at doses in region of 200 – 400 ug of folic acid.¹²⁻¹⁴ Because of low activity of dihydrofolate reductase (DHFR) , the liver and other tissues have limited ability to reduce folic acid.

The limitation of this metabolic process results in inability to metabolized high doses of folic acid. The low activity of DHFR leads to the appearance of un-metabolized folic acids (UFA) in the circulation.¹⁵

A study showed that UFA detected in most serum samples from USA children and adults post folic acid fortification of grains.¹⁶ Daily doses of 200ug of folic acid lead to increasing level of UFA in serum of healthy adult over one week.¹³

Consumption of folic acid has increased in many countries worldwide. Concerns have arisen regarding the potential adverse effects folic acid may have.¹⁷ According to the USA institute of Medicine and European food safety Authority suggest the tolerable upper limit of folic acid to be 1000 µg.

High folic acid intakes linked to increased cancer risk and progression within certain patient groups (Table 1). Also, to insulin resistance in children, interaction with epileptic medications, masking vitamin B12 deficiency and hepatotoxicity.¹⁸⁻²⁰ High folic acid during gestation were associated with insulin resistance and greater adiposity in children at 5 years of age.²¹⁻²⁴

Women with a homozygous deletion (DHFR19del) which slows conversion of UFA to intracellular folate and who took folic acid during pregnancy were significantly more likely to have retinoblastoma in their offspring.²⁵ On other study, these women might have offspring with lower cognitive scores.²⁵ High maternal levels of folic acid may increase the occurrence of epileptic seizures within their offspring.¹⁹ UFA folic acid increases the metabolism of anti-epileptic drugs and thus increasing the likelihood of seizures.²⁶ Folic acid interacts with anti-folate drugs (e.g. methotrexate) and decreases their efficacy.²⁷

This study done in Nizwa Hospital laboratory. Nizwa Hospital is a secondary referral hospital in a dakhlia governorate Sultanate of Oman. The hospital is 305 beds. The standard does for folate supplement in Oman is 0.5 mg per day for the pregnant women. Some institutes due to an availability of 0.5 mg, might prescribe 5mg per day as a standard supplement does during pregnancy.²⁸

Table 1: Side effects of low and high folate level.

Side effects	Low folate	High folate
1	Congenital heart defects	Increase cancer risk
2	Neural tube defects: Anencephaly. Spina bifida.	Cancer progression
3	Craniofacial: Cleft lip. Cleft palate.	Insulin resistance
4	Placenta abruption.	Interaction with: epileptic medications Increasing likelihood of seizure. Anti-folate drugs decreasing their efficacy.
5	Placenta infarction.	Masking B12 deficiency.
6	Pre-eclampsia.	Hepatotoxicity.
7	Spontaneous abortion.	Greater adiposity in children.
8		Retinoblastoma.
9		Offspring with low cognitive scores.

Aims of This Study:

- 1- To determine folate level in the study sample (Low, Normal and High).
- 2- To determine folate level in Omani women.
- 3- To determine folate level in Omani men.

Method:

The data in this study obtained from a shifa program. This program used in all ministry of health hospital in Sultanate of Oman. The platform used in this study is Cobas e 601 chemical analyzer. Competitive immunoassay principle used for folate testing. During four years period (1-1-2017/ 31-12-2020), three thousand seven hundred and six samples tested and statistically analyzed. Folate results separated into three different groups in relation to the reference range (Low < 4.5 nmol/L, Normal = 4.5 – 45 nmol/L and High > 45 nmol/L).

Results:

Table 2: Folate level in the study samples (Low, Normal and High).

Total Samples	Mean age Years	Female	Male	Percent Low	Percent Normal	Percent High
3706	48	2335 (62.9%)	1371 (37.1 %)	8 (0.3 %)	2971 (80 %)	727 (19.7%)

Table 3: Folate level in Omani women (Low, Normal and High).

Total Samples	Mean age years	Percent Low	Percent Normal	Percent High
2335	46	5 (0.2%)	1756 (75.2%)	574 (24.6%)

Table 4: Folate level in Omani men (Low, Normal and High).

Total Samples	Mean age Years	Percent Low	Percent Normal	Percent High
1371	51	3 (0.2%)	1215 (88.7%)	153 (11.1 %)

Discussion:

This study shows 0.3% having low folate (Table 2), 80% normal and 19.7 % high folate level. In women 0.3% having low folate (Table 3), 75.2% normal and 24.6% high folate level. In men 0.2% having low folate (Table 4), 88.7% normal and 11.1 having high folate level.

Conclusion:

Low folate level is affecting the health of general population including the mother and their fetus. On the other hand, with the growing scientific evidence, high folate levels have adverse side effects. This study shows less than 1% of the study samples have low folate. The majority having high folate level. The high folate level in women can be explained partially due to the folate supplement during pregnancy. Men included in this study the majority of them have high folate level. Testing for folate level before given the supplement will identify who needs supplement. It will minimized high folate adverse effects.

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Conflicts Of Interest:

No conflicts of interest.

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