VIA MEDICA

RECOMMENDATIONS

Ginekologia Polska
2017, vol. 88, no. 11, 633–636

ISSN 0017–0011

DOI: 10.5603/GP.a2017.0113

# Folate supplementation during the preconception period, pregnancy and puerperium

## Polish Society of Gynecologists and Obstetricians Guidelines

**Dorota Bomba-Opoń[1], Lidia Hirnle[2], Jarosław Kalinka[3], Agnieszka Seremak-Mrozikiewicz[4]**

*[1] 1st Chair and Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland*
*[2] 1st Chair and Department of Gynecology and Obstetrics, Medical University of Wroclaw, Poland*
*[3] Department of Perinatology, 1st Chair of Obstetrics and Gynecology, Medical University of Lodz, Poland*
*[4] Division of Perinatology and Women's Diseases, Poznan University of Medical Sciences, Poznan, Poland*

The proper supply of folate during the preconception period, pregnancy and lactation largely determines the proper development and growth of the fetus and newborn infant. Foliates is among the most essential elements of fast-dividing cells as it plays an important role in DNA synthesis. An increased demand for folate, which is not synthesized in the human body, during pregnancy can be met only partially by the supply of foods rich in folate — about 150–250 µg [1]. Folate deficiency is associated with a higher risk of neural tube defects in the fetus, as well as cleft lip and palate and Down syndrome [2]. Disorders of folate metabolism can lead to hyperhomocysteinaemia and more frequent complications of pregnancy, such as recurrent miscarriage, intrauterine growth restriction (IUGR) and preeclampsia [3, 4].

## FOLATE SUPPLEMENTATION

Randomized and cohort studies conducted in the 1980s and 1990s show that folic acid supplementation significantly reduces the risk of neural tube defects [5–12]. The follow-up observations also indicate that folate supplementation reduces the occurrence of heart defects, urinary tract defects, limb defects, cleft lip and palate and preeclampsia [3, 4, 13–15].

Recent studies have shown that 12-week supplementation is necessary in the preconception period to achieve adequate red blood cell folate concentration [16, 17].

Folic acid consumed in the form of vitamin supplements must undergo a number of biochemical reactions to reach its active form — 5-methyltetrahydrofolate. Vitamin B12 is one of the important cofactors of these changes. Vitamin B12 deficiency is particularly unfavourable with high folate concentrations [18]. The resulting disorders in the conversion of homocysteine to methionine lead to hyperhomocysteinemia, which increases the risk of pregnancy complications. Unmetabolized folic acid in the blood can have a negative effect on the human body, as it may affect the activity of natural killer cells and the immune system [19]. Accumulation of unmetabolized folic acid can be avoided by supplementation with appropriate doses and active folate forms. High doses of folic acid may increase the risk of fetal damage in early pregnancy, as well as obesity, insulin resistance and type 2 diabetes in the later life of the offspring [20]. The supplementation dose should be determined based on factors that increase the risk of folate deficiency and fetal defects. The preparations used should also contain vitamin B12.

### Recommendations

- All women of childbearing age should include in their diet foods rich in folate (lettuce, spinach, cabbage, broccoli, whole grains, liver, eggs, nuts and cheeses) and fortified foods. (Level B)
- When planning a pregnancy, women of childbearing age should additionally use folate supplementation for at least 12 weeks before conception. (Level B)
- Women should continue to use folate supplementation throughout their pregnancy, puerperium and lactation period. They should use preparations with documented composition and action. (Level D)

**Corresponding author:**
Dorota Bomba-Opoń
1st Chair and Department of Obstetrics and Gynecology
Medical University of Warsaw
Starynkiewicza Sq. 1/3, 02–015 Warsaw, Poland

## RECOMMENDED DOSES OF FOLATE SUPPLEMENTATION DURING THE PRECONCEPTION PERIOD, PREGNANCY AND LACTATION (TABLE 1)

### A group at low risk of fetal defects and pregnancy complications

Randomized, cohort and observational studies have shown a reduction in the risk of neural tube defects in women taking a daily supplement containing 0.4 to 0.8 mg of folic acid. According to the principle of using the lowest effective dose, women who are not at risk of folate metabolism disorders are recommended to take 0.4 mg of folic acid during the preconception period, pregnancy and lactation.

**Recommendation**

Women in the low-risk group are recommended to take supplements containing 0.4 mg of folate per day. (Level B)

### A group at increased risk of fetal defects and pregnancy complications

The occurrence of fetal defects, IUGR and preeclampsia in the previous pregnancy, may indicate an increased risk of folate deficiency or folate metabolism disorders. This group of women is recommended to take a double dose of folic acid including active forms of folate.

Frequent occurrence of defects in the nervous system has also been observed in fetuses of women with type 1 and type 2 diabetes [21]. It seems that both hyperglycemia and insulin resistance may interfere with folate metabolism. Cohort analysis has indicated a lower percentage of neural tube defects in women with pre-gestational diabetes mellitus taking supplements containing more than 0.4 mg of folic acid [21]. Special attention should be paid to women with polycystic ovary syndrome using metformin. It has been reported that deficiency of folate and vitamin B12 during metformin therapy results in elevated homocysteine levels [22].

Folate deficiency and an increased risk of neural tube defects may be associated with chronic gastrointestinal diseases (colitis ulcerosa, coeliac disease, Crohn's disease) that interfere with absorption. Vitamin deficiencies, including folate deficiency, also occur in women after bariatric surgery [23].

Spina bifida also occurs more frequently in obese women. Studies on folic acid supplementation in this group of

**Table 1.** Recommended doses in individual groups at risk of fetal defects

| Low-risk group | Increased-risk group | High-risk group |
|---|---|---|
| 0.4 mg/day<br>within 12 weeks before planned pregnancy, during pregnancy and lactation | 0.8 mg/day<br>including active folate and vitamin B12<br>within 12 weeks before planned pregnancy, during pregnancy and lactation | 5 mg/day<br>including active folate and vitamin B12<br>within 12 weeks before planned pregnancy and in the first trimester of pregnancy<br>0.8 mg/day<br>in the second and third trimesters and during lactation |
| Healthy women without their own and family history of fetal defects | Fetal defects in the patient's or the closest family history | Neural tube defects in the mother, father or their offspring |
| | IUGR or/and preeclampsia in the history | |
| | Pre-gestational diabetes type 1 or 2 | |
| | Digestive diseases:<br>Colitis ulcerosa<br>Crohn's disease<br>Coeliac disease | |
| | Hepatic failure | |
| | Renal failure — dialysis | |
| | Condition after bariatric surgery | |
| | Obesity | |
| | Drugs:<br>Anti-epileptics<br>Metformin<br>Methotrexate<br>Cholestyramine<br>Sulfasalazine | |
| | Stimulants:<br>Smoking<br>Alcoholism | |
| | Decreased MTHFR activity | |

women show lower efficacy of routine supplementation in a group with BMI greater than 24 and a significantly lower risk of spina bifida in children of obese women with high levels of red cell folate [24, 25].

Antiepileptic drug therapy is a risk factor for reduced serum levels of folate in women and supplementation with folic acid during the preconception period may have a beneficial effect on reducing the risk of deficiency. However, the use of high doses, especially above 5 mg, is unreasonable and may lead to a reduction in seizure threshold [26].

Impaired folic acid metabolism and impaired remethylation of homocysteine to methionine, resulting in increased homocysteine levels and decreased plasma folate levels, may be due to reduced methylthetrahydrofolate reductase (MTHFR) activity [27]. There are over 40 types of MTHFR polymorphisms, the most common of which are C677T, A1298C and G1793A. MTHFR 677 C > T is the most common and the best described of them; its frequency varies according to population: in Asian population, the frequency of homozygous dominant individuals ranges from 10% to 15% and heterozygous dominant individuals is up to 50%; in Europe, the frequency of homozygous dominant individuals ranges from 8% to 18% , and in Poland, it is from 5% to 11% [27]. This results in a protein with reduced enzymatic activity — about 70% for homozygous genotypes TT and about 40% for heterozygous genotypes CT. The results of studies conducted in non-pregnant female carriers of different MTHFR genotypes have shown that active forms of folate have increased plasma folate concentrations significantly more than folic acid [28]. Increased supply of folate in pregnancy can mask vitamin B12 deficiency and at the same time increase metabolic disorders leading to hyperhomocysteinaemia [18]. Therefore, it is recommended that supplementation wi`th particularly higher folate doses be supplemented with vitamin B12.

**Recommendation**

Women in the increased-risk group are recommended to take supplements containing 0.4 mg of folate per day and an additional 0.4 mg, preferably of active folate, per day. Supplements additionally enriched with vitamin B12 are recommended. (Level C)

### A group at high risk of fetal defects and pregnancy complications

Neural tube defects may be related to genetic disorders of folate metabolism and chromosomal abnormalities. Research results confirm that the use of folic acid supplementation before pregnancy reduces the risk of reoccurrence by up to 85% [29]. Unfortunately, only 35% of women in whose offspring a neural tube defect reoccurred took preparations containing folate [30]. Currently there are no studies confirming that empirically recommended high doses of folate are effective. However, due to the high risk of defects, most panel experts recommend doses of 4 to 5 mg during the preconception period and the first trimester of pregnancy. Considering the possibility of negative effects of high doses of folate on the fetus in the next trimesters of pregnancy, the dose should be reduced to 0.8 mg after the first trimester of pregnancy and continued until the end of lactation.

**Recommendation**

Women in the high-risk group are recommended to take 5 mg of folate per day including active forms of folate and vitamin B12 during the preconception period and the first trimester of pregnancy. The dose of folate should be reduced to 0.8 mg per day during the next trimesters of pregnancy and lactation. (Level D)

**Table 2.** Recommendations of the Polish Society of Gynaecologists and Obstetricians (PTGP): Folate supplementation during the preconception period, pregnancy and puerperium

| |
|---|
| 1. All women of childbearing age should include in their diet foods rich in folate (lettuce, spinach, cabbage, broccoli, whole grains, liver, eggs, nuts and cheeses) and fortified foods. (Level B) |
| 2. When planning a pregnancy, women of childbearing age should additionally use folate supplementation for at least 12 weeks before conception. (Level B) |
| 3. Women should continue to use folate supplementation throughout their pregnancy, puerperium and lactation period. They should use preparations with documented composition and action. (Level D) |
| 4. Women in the low-risk group are recommended to take supplements containing 0.4 mg of folate per day (Level B). |
| 5. Women in the increased-risk group are recommended to take supplements containing 0.4 mg of folate per day and an additional 0.4 mg, preferably of active folate, per day. Supplements additionally enriched with vitamin B12 are recommended (Level C). |
| 6. Women in the high-risk group are recommended to take 5 mg of folate per day including active forms of folate and vitamin B12 during the preconception period and the first trimester of pregnancy. The dose of folate should be reduced to 0.8 mg per day during the next trimesters of pregnancy and lactation (Level D). |

**Table 3.** Strength of recommendations

| |
|---|
| **Level A** — recommendations are based on evidence obtained from randomized, controlled trials |
| **Level B** — recommendations are based on evidence obtained from controlled trials without randomization |
| **Level C** — recommendations are based on evidence obtained from cohort or case–control analytic studies and from multiple time series with or without the intervention |
| **Level D** — recommendations are based on expert committee reports or opinions or clinical experience of respected authorities |

## REFERENCES


1. Institute of Medicine Food and Nutrition Board.Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. National Academies Press, Washington, DC.: : 1998.
2. Bean LJH, Allen EG, Tinker SW, et al. Lack of maternal folic acid supplementation is associated with heart defects in Down syndrome: a report from the National Down Syndrome Project. Birth Defects Res A Clin Mol Teratol. 2011; 91(10): 885–893, doi: 10.1002/bdra.22848, indexed in Pubmed: 21987466.
3. Li Z, Ye R, Zhang Le, et al. Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. Hypertension. 2013; 61(4): 873–879, doi: 10.1161/HYPERTENSIONAHA.111.00230, indexed in Pubmed: 23399716.
4. Wen SWu, Guo Y, Rodger M, et al. Folic Acid Supplementation in Pregnancy and the Risk of Pre-Eclampsia-A Cohort Study. PLoS One. 2016; 11(2): e0149818, doi: 10.1371/journal.pone.0149818, indexed in Pubmed: 26901463.
5. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992; 327(26): 1832–1835, doi: 10.1056/NEJM199212243272602, indexed in Pubmed: 1307234.
6. Mulinare J, Cordero JF, Erickson JD, et al. Periconceptional use of multivitamins and the occurrence of neural tube defects. JAMA. 1988; 260(21): 3141–3145, doi: 10.1001/jama.1988.03410210053035, indexed in Pubmed: 3184392.
7. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA. 1989; 262(20): 2847–2852, doi: 10.1001/jama.1989.03430200091032, indexed in Pubmed: 2478730.
8. Centers for Disease Control (CDC). Use of folic acid for prevention of spina bifida and other neural tube defects — 1983–1991. MMWR Morb Mortal Wkly Rep. 1991; 40(30): 513–516, indexed in Pubmed: 2072886.
9. Bower C, Stanley FJ. Dietary folate as a risk factor for neural-tube defects: evidence from a case-control study in Western Australia. Med J Aust. 1989; 150(11): 613–619, indexed in Pubmed: 2725375.
10. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet. 1991; 338(8760): 131–137, doi: 10.1016/0140-6736(91)90133-a, indexed in Pubmed: 1677062.
11. Atta CAM, Fiest KM, Frolkis AD, et al. Global Birth Prevalence of Spina Bifida by Folic Acid Fortification Status: A Systematic Review and Meta-Analysis. Am J Public Health. 2016; 106(1): e24–e34, doi: 10.2105/AJPH.2015.302902, indexed in Pubmed: 26562127.
12. Boulet SL, Yang Q, Mai C, et al. National Birth Defects Prevention Network. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Res A Clin Mol Teratol. 2008; 82(7): 527–532, doi: 10.1002/bdra.20468, indexed in Pubmed: 18481813.
13. Shaw GM, O'Malley CD, Wasserman CR, et al. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. Am J Med Genet. 1995; 59(4): 536–545, doi: 10.1002/ajmg.1320590428, indexed in Pubmed: 8585581.
14. Czeizel AE, Dobó M, Vargha P, et al. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. Am J Med Genet. 1996; 62(2): 179–183, doi: 10.1002/(SICI)1096-8628(19960315)62:2<179::AID-AJMG12>3.0.CO;2-L, indexed in Pubmed: 8882400.
15. Yazdy MM, Honein MA, Xing J. Reduction in orofacial clefts following folic acid fortification of the U.S. grain supply. Birth Defects Res A Clin Mol Teratol. 2007; 79(1): 16–23, doi: 10.1002/bdra.20319, indexed in Pubmed: 17177274.
16. Norsworthy B, Skeaff CM, Adank C, et al. Effects of once-a-week or daily folic acid supplementation on red blood cell folate concentrations in women. Eur J Clin Nutr. 2004; 58(3): 548–54.
17. Hursthouse NA, Gray AR, Miller JC, et al. Folate status of reproductive age women and neural tube defect risk: the effect of long-term folic acid supplementation at doses of 140 µg and 400 µg per day. Nutrients. 2011; 3(1): 49–62, doi: 10.3390/nu3010049, indexed in Pubmed: 22254076.
18. Paul L, Selhub J. Interaction between excess folate and low vitamin B12 status. Mol Aspects Med. 2017; 53: 43–47, doi: 10.1016/j.mam.2016.11.004, indexed in Pubmed: 27876554.
19. Selhub J, Rosenberg IH. Excessive folic acid intake and relation to adverse health outcome. Biochimie. 2016; 126: 71–78, doi: 10.1016/j.biochi.2016.04.010, indexed in Pubmed: 27131640.
20. Yajnik CS, Deshpande SS, Jackson AA, et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia. 2008; 51(1): 29–38, doi: 10.1007/s00125-007-0793-y, indexed in Pubmed: 17851649.
21. Parker SE, Yazdy MM, Tinker SC, et al. The impact of folic acid intake on the association among diabetes mellitus, obesity, and spina bifida. Am J Obstet Gynecol. 2013; 209(3): 239.e1–239.e8, doi: 10.1016/j.ajog.2013.05.047, indexed in Pubmed: 23711668.
22. Zhang Q, Li S, Li L, et al. Metformin Treatment and Homocysteine: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2016; 8(12), doi: 10.3390/nu8120798, indexed in Pubmed: 27941660.
23. Shankar P, Boylan M, Sriram K. Micronutrient deficiencies after bariatric surgery. Nutrition. 2010; 26(11-12): 1031–1037, doi: 10.1016/j.nut.2009.12.003, indexed in Pubmed: 20363593.
24. Wang M, Wang ZP, Gao LJ, et al. Maternal body mass index and the association between folic acid supplements and neural tube defects. Acta Paediatr. 2013; 102(9): 908–913, doi: 10.1111/apa.12313, indexed in Pubmed: 23750819.
25. McMahon DM, Liu J, Zhang H, et al. Maternal obesity, folate intake, and neural tube defects in offspring. Birth Defects Res A Clin Mol Teratol. 2013; 97(2): 115–122, doi: 10.1002/bdra.23113, indexed in Pubmed: 23404872.
26. Jędrzejczak J, Bomba-Opoń D, Jakiel G, et al. Managing epilepsy in women of childbearing age — Polish Society of Epileptology and Polish Gynecological Society Guidelines. Ginekol Pol. 2017; 88(5): 278–284, doi: 10.5603/GP.a2017.0053, indexed in Pubmed: 28580576.
27. Tsang BL, Devine OJ, Cordero AM, et al. Assessing the association between the methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism and blood folate concentrations: a systematic review and meta-analysis of trials and observational studies. Am J Clin Nutr. 2015; 101(6): 1286–1294, doi: 10.3945/ajcn.114.099994, indexed in Pubmed: 25788000.
28. Prinz-Langenohl R, Brämswig S, Tobolski O, et al. [6S]-5-methyltetrahydrofolate increases plasma folate more effectively than folic acid in women with the homozygous or wild-type 677C-->T polymorphism of methylenetetrahydrofolate reductase. Br J Pharmacol. 2009; 158(8): 2014–2021, doi: 10.1111/j.1476-5381.2009.00492.x, indexed in Pubmed: 19917061.
29. Grosse SD, Collins JS. Folic acid supplementation and neural tube defect recurrence prevention. Birth Defects Res A Clin Mol Teratol. 2007; 79(11): 737–742, doi: 10.1002/bdra.20394, indexed in Pubmed: 17990333.
30. Arth A, Tinker S, Moore C, et al. Centers for Disease Control and Prevention. Supplement use and other characteristics among pregnant women with a previous pregnancy affected by a neural tube defect — United States, 1997-2009. MMWR Morb Mortal Wkly Rep. 2015; 64(1): 6–9, indexed in Pubmed: 25590679.