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Effectiveness of long-term folic acid supplementation for the prevention of preeclampsia in pregnant women with and without folate cycle disorders

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Abstract

Introduction. Preeclampsia remains one of the leading causes of maternal and perinatal morbidity worldwide. Accumulated evidence indicates that disturbances in folate metabolism and elevated homocysteine levels may contribute to the development of hypertensive disorders of pregnancy. This study evaluated the effectiveness of long-term folic acid supplementation for the prevention of preeclampsia in pregnant women with and without polymorphisms in folate cycle genes.

Methods. A single-center randomized controlled study included 320 women in the control group (folic acid intake until 12 weeks of gestation) and 894 women in the main group (folic acid intake throughout pregnancy). The main group was stratified by dosage: 400 μg, 800 μg, and 1200 μg. Clinical, biochemical, and genetic assessments were performed, including measurement of homocysteine levels and

genotyping of MTHFR, MTR, and MTRR polymorphisms. Pregnancy outcomes and the incidence of hypertensive complications were compared between groups.

Results. Long-term folic acid supplementation was associated with a lower overall incidence of hypertensive disorders of pregnancy compared with the control group (RR 1.43; p = 0.038). The incidence of preeclampsia was 1.67 times lower in the main group, indicating a favorable trend. No significant differences in blood pressure dynamics or perinatal outcomes were found among groups receiving different folic acid doses. Homocysteine levels were significantly higher in all women who subsequently developed preeclampsia, regardless of folic acid dosage. Genotype distribution demonstrated population-specific frequencies of MTHFR and MTR polymorphisms; however, no clear dose–response relationship was observed.

Conclusion. Long-term folic acid supplementation reduces the risk of hypertensive disorders of pregnancy, including a tendency toward a decreased incidence of preeclampsia, and is safe at all studied doses. The potential benefit is particularly relevant for populations with a high prevalence of genetic variants affecting folate metabolism. Further multicenter randomized studies are required to determine the optimal dosage and duration of supplementation.

Keywords: preeclampsia, folate cycle, folic acid.

1. Introduction

Preeclampsia is one of the serious and potentially life-threatening pregnancy-related conditions that lead to numerous maternal and fetal complications [1], and its prevalence is increasing in developed countries [2]. The global trend toward delayed childbearing in high-income countries contributes to the rise in risk factors associated with preeclampsia, such as advanced maternal age, obesity, insulin resistance, and the accumulation of comorbid somatic conditions [2]. Inadequate or absent prenatal care partly explains the high prevalence of preeclampsia in developing countries [1–3].

Despite significant progress in understanding the preeclampsia pathogenesis, effective methods of primary prevention remain limited. The exact etiological factors of preeclampsia are still unclear. However, it is believed that two critical mechanisms play a major role in the pathogenesis of preeclampsia: abnormal placentation, followed by the development of a maternal-placental syndrome associated with an excess of anti-angiogenic factors [1,2,4,5,6]. These well-established hypotheses conceptualizing preeclampsia as a placental disorder contribute to understanding and appropriate management of the complications associated with the condition.

Recent research continues to identify factors that may reduce the risk of developing preeclampsia [6]. Numerous studies have been conducted to explore possible approaches to prevent and manage preeclampsia [1,3,7–9]. Growing evidence indicates that disturbances in folic acid metabolism and elevated homocysteine levels may contribute to the development of hypertensive disorders during pregnancy, including preeclampsia [8–10]. One such potential protective factor is folic acid supplementation, traditionally prescribed during preconception and the first trimester for the prevention of neural tube defects [9]. In recent years, researchers have increasingly focused on the possible role of long-term folic acid supplementation in reducing the likelihood of hypertensive pregnancy complications, including preeclampsia. Potential mechanisms linking folate deficiency and hyperhomocysteinemia with preeclampsia include endothelial dysfunction, oxidative

stress, and impaired DNA methylation, all of which may lead to vascular dysregulation and placental perfusion abnormalities [9,10]. Many studies confirm that folic acid supplementation can help reduce elevated levels of homocysteine in the blood [8,12–18]. However, the relationship between folic acid intake and reduced risk of preeclampsia has produced conflicting findings, and the recommended doses vary widely [7,8,19–24]. Whether folic acid supplementation during pregnancy can reduce the risk of preeclampsia remains unclear [7].

The mechanisms underlying the proposed protective effect of folic acid are not fully understood; its involvement in the regulation of endothelial function, homocysteine metabolism, and antioxidant protection has been suggested. Given the clinical importance of the problem and accessibility of the intervention, investigating the role of folic acid in preeclampsia prevention presents significant scientific and practical interest.

The present study aims to evaluate the effectiveness of long-term folic acid supplementation in reducing the risk of preeclampsia among pregnant women with and without folate-metabolism impairments.

Hypothesis: Long-term folic acid supplementation lowers the risk of developing preeclampsia in pregnant women with and without folate-metabolism disorders.

2. Materials and research methods

Design: a single-center, randomized controlled trial.

Study Material: the study included 320 pregnant women in the control group, who received folic acid from the moment pregnancy was confirmed until 12 weeks of gestation for the prevention of congenital fetal malformations, and 894 pregnant women in the study group, who received folic acid throughout the entire duration of pregnancy. The study group was stratified according to folic-acid dosage: 400 mcg (n = 332), 800 mcg (n = 257), and 1200 mcg (n = 305).

The sample size for the randomized controlled trial was calculated according to the standard formula [20]. The sample size for the nested cohort was determined using the Epi Info statistical software (CDC, USA), based on previously published data on the frequency of polymorphisms in the MTHFR (C677T, A1298C), MTRR (G66A), and MTR (G2756A) genes among pregnant women in the Kazakh population [21]. The calculation was based on the lowest frequency polymorphism among those under study, specifically MTR (rs1805087), with a prevalence of 17.9%, and considering the prevalence of preeclampsia (PE) of 5.5% in the population of 18,000 pregnant women in Aktobe. Allowing for a 30% attrition rate, the required sample size was determined to be 536 pregnant women.

Participant selection and randomization method: a stratified sampling method was applied to form the study groups, based on the presence or absence of established risk factors for PE, in accordance with recommendations from previous research [22].

Inclusion Criteria: Kazakh ethnicity; age ≥18 years; ultrasound-confirmed singleton intrauterine pregnancy; gestational age up to 14 weeks at enrollment; written informed consent; and adherence to the study protocol.

The clinical component of the study was conducted in city polyclinics, at the Regional Perinatal Center of Aktobe, and at Kargalinsk City Hospital.

The laboratory component was conducted at the Scientific and Practical Center of West Kazakhstan Marat Ospanov Medical University and at INVITRO-Kazakhstan.

A complete blood count with platelet count was performed using the MEK-7300K automated hematology analyzer (Nihon Kohden Corporation, Japan, series 2845). Biochemical measurements, including bilirubin levels and cytolytic enzyme activity (ALT and AST), were performed using the Respons-910 biochemical analyzer (Germany).

Proteinuria was assessed using either a single urine sample and/or a 24-hour urine collection, analyzed

on the Uriscan Optima analyzer (YD Diagnostics, South Korea).

Homocysteine levels were measured using an immunochemiluminescent assay (ICLA) on the automated IMMULITE® 2000 XPi analyzer (Siemens, Germany) with Immulite® 2000 Homocysteine reagents (Siemens, Germany). The determination of homocysteine concentration (Hcy) in serum or EDTA-stabilized plasma was performed according to the immunochemiluminescent method using the IMMULITE® 2000 XPi analyzer (Siemens Healthcare Diagnostics, Germany).

The analytical method is based on competitive binding between endogenous homocysteine in the patient's sample and an enzyme-labeled methylated derivative of homocysteine for a limited number of specific antibodies immobilized on a solid phase. After binding and washing of unbound components, a substrate for alkaline phosphatase is added, which produces a chemiluminescent signal detected by the analyzer's photometer. The intensity of the emitted signal is inversely proportional to the concentration of homocysteine in the sample.

Samples were processed in EDTA-stabilized plasma or in serum obtained after centrifugation at 3000 rpm for 10 minutes. Storage conditions were as follows: at +2°C to +8°C for no more than 48 hours; at −20°C for up to 3 months. Frozen samples were thawed at room temperature and mixed before analysis. Repeated freeze-thaw cycles were not permitted. The analysis utilized the Siemens IMMULITE® 2000 Homocysteine Assay Kit, which includes a solid phase with immobilized anti-Hcy antibodies, an enzyme conjugate (alkaline phosphatase–homocysteine), calibrators (2–50 μmol/L), control materials (low and high levels), and the chemiluminescent substrate. Prepared samples, calibrators, and controls were loaded into the designated positions of the IMMULITE® 2000 XPi analyzer, which automatically performed sample pipetting, incubation, washing, substrate addition, and chemiluminescent signal measurement.

Genotyping of Folate Metabolism Gene Polymorphisms: venous blood (2.0 ml) was collected by venipuncture into K2-EDTA tubes (EcoPharm International, Kazakhstan). DNA extraction was performed using the PROBA-RS-GENETIKA reagent kit (DNA-Technology, Russia). DNA concentration was measured using the NanoDrop Lite spectrophotometer (USA), where a minimum DNA concentration of at least 1.0 ng/ml per PCR tube was required, corresponding to Ct ≤ 32.0 on the VK detection channel (Sy5). Molecular genetic analysis was performed using real-time polymerase chain reaction (Real-Time PCR) on the DTprime 4 instrument (DNA-Technology, Russia), with determination of genotypes for the polymorphisms under study: MTHFR (C677T, A1298C), MTRR (G66A), and MTR (G2756A). Ready-to-use primers were used: MTHFR 677 C>T (Ala222Val), MTHFR 1298 A>C (Glu429Ala), MTR 2756 A>G (Asp919Gly), and MTRR 66 A>G (IIe22Met) (DNA-Technology, Russia).

Blood Collection and Genomic DNA Isolation: For the analysis, after overnight fasting, 5.0 milliliters of peripheral blood samples were obtained from each of the study subjects in EDTA-containing tubes. Genomic DNA was extracted from the cell pellet in whole blood using the Promega Wizard® Genomic DNA Purification Kit following a standard method according to the producer's instructions. The real-time polymerase chain reaction (RT-PCR) using CFX-96 Real-Time System (Singapore) and Vector Best (Russia) reagents with specific primers for PCR were used to perform the analysis for detection of the MTR A2756G, MTRR A66G, and MTHFR C677T genotypes. The following RT-PCR cycle parameters were followed: 94 ◦C for 2 min, then 35 cycles of amplification (94 ◦C 30 s, 60 ◦C 30 s, and 72◦ 30 s). The final elongation step of 10 min, 72 ◦C, and 5 mL of the reaction product were analyzed in a 1.5% agarose gel. The normal, heterozygous, and homozygous mutant genotype profiles of each of the genes were identified.

Statistical analysis. Statistical analysis and data visualization were performed using the R statistical computing environment, version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics were presented as absolute and relative frequencies for categorical variables, and as medians with interquartile ranges (1st–3rd quartiles) for continuous variables with asymmetric distributions. Assessment of normality for continuous variables was

conducted using the Shapiro–Wilk test, evaluation of the skewness coefficient (where an absolute value >1.96 was considered indicative of significant deviation from normality), and visual inspection of histograms and quantile–quantile (Q–Q) plots.

Compliance of observed genotype frequencies with theoretical Hardy–Weinberg equilibrium was assessed using Pearson's χ^2 test and the inbreeding coefficient (f).

Comparisons between two groups for quantitative variables were performed using the Mann–Whitney U test, whereas comparisons among three or more groups were conducted using the Kruskal–Wallis test, with post-hoc pairwise analyses performed using Dunn's test. Group comparisons for categorical variables were conducted using Pearson's χ^2 test and Fisher's exact test when the minimum expected frequency in contingency table cells was <5. The Holm correction was applied to adjust for multiple pairwise comparisons. Relative risk (RR) with corresponding 95% confidence intervals (95% CI) was used to assess the strength of association between binary outcomes and potential predictors. For the analysis of changes in quantitative and binary outcomes across repeated measurements, generalized estimating equations (GEE) were employed, including models with interaction terms between gestational-age indicators and group assignment.

Stepwise predictor selection for inclusion in the prognostic model was performed using the Akaike Information Criterion (AIC). Selected predictors were incorporated into a multivariable logistic regression model without interaction terms. Model performance was evaluated using Nagelkerke's pseudo-R^2, Somers' Dxy coefficient, and the concordance index (C-index, AUC). Additionally, metrics corrected for potential overfitting were obtained using non-parametric bootstrapping (B = 1000). The optimal threshold probability for classification was determined using Youden's J-statistic, followed by calculation of predictive accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), all with corresponding 95% CI.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. Written informed consent was obtained from all participants prior to sample collection. Ethical approval was granted by the Local Bioethics Committee of the West-Kazakhstan Medical University (Minutes No. 7, dated 03 March 2025). Throughout the study, the investigators adhered to established principles of biomedical research ethics and scientific integrity. No personally identifiable information was accessible to the research team at any stage of the study.

3. Results

The mean age of pregnant women in the main and control groups was 30.2 ± 5.7 and 29.4 ± 4.9 years, respectively, with no statistically significant differences identified between them ($p < 0.001$; see Table 1 in the appendix). There were no statistically significant differences between the groups with respect to body weight ($p = 0.83$); the mean body weight of all examined participants was 58.7 ± 8.9 kg and 58.8 ± 8.7 kg, respectively. The average body mass index (BMI) was 22.5 ± 3.2 and 22.6 ± 3.1 kg/m², indicating the absence of such risk factors for preeclampsia as obesity or excessive body weight. No significant intergroup differences were detected in social status ($p = 0.994$), family history, or personal medical history, including arterial hypertension, diabetes mellitus, cholecystitis, or prior surgical interventions, which might influence the development of preeclampsia. A positive family history of malignant neoplasms of various localizations was observed only among participants receiving the 800-mcg folic acid dose ($p = 0.01$).

Comparative analysis of gynecological and obstetric histories revealed that women in the main study group exhibited a tendency toward a higher age at sexual debut ($p = 0.059$). The prevalence of cervical erosion was significantly higher among participants in the control group ($p < 0.001$), whereas uterine fibroids were observed only among participants in the main group ($p = 0.076$) (see table in the appendix). Therefore, no statistically

significant differences were identified between the main and control groups regarding major demographic or medical history characteristics that could influence the outcomes of the study. Comparative analysis of systolic blood pressure (SBP) dynamics throughout pregnancy demonstrated no statistically significant differences between the groups (p = 0.522) (Table 1).

Table 1 - Dynamics of systolic blood pressure in the study groups

Gestational age	Control group	Study group			p[1]
		400 mcg	800 mcg	1200 mcg	
10-14 weeks	103,7 (±7,8) 100 (100; 110)	103,2 (±7,9) 100 (100; 110)	104,5 (±7,5) 110 (100; 110)	103,6 (±7,7) 100 (100; 110)	0,216
14-20 weeks	104,5 (±8,3) 110 (100; 110)	103,8 (±8,3) 100 (100; 110)	105,2 (±8,4) 110 (100; 110)	104,6 (±8,6) 110 (100; 110)	0,251
20-24 weeks	105 (±8,6) 105 (100; 110)	104,1 (±8,9) 100 (100; 110)	105,3 (±9) 105 (100; 110)	105,2 (±8,8) 105 (100; 110)	0,289
24-30 weeks	105,6 (±8,7) 110 (100; 110)	104,2 (±9,1) 100 (100; 110)	106,4 (±8,6) 110 (100; 110)	105,1 (±9) 110 (100; 110)	**0,031**
30-34 weeks	107,8 (±11,3) 110 (100; 110)	106,8 (±9,8) 110 (100; 110)	107,8 (±10,2) 110 (100; 110)	106,1 (±9,5) 110 (100; 110)	0,112
34-38 weeks	111,6 (±13,4) 110 (100; 120)	110,8 (±13,6) 110 (100; 120)	110,9 (±12,2) 110 (100; 120)	109,4 (±11,4) 110 (100; 115)	0,183
40-42 weeks	113,8 (±11,6) 110 (110; 120)	114 (±10,8) 110 (110; 120)	114 (±10,9) 110 (110; 120)	113,7 (±10,4) 110 (110; 120)	0,989
p[2]	**<0,001**	**<0,001**	**<0,001**	**<0,001**	–

Note: p[1] - ; p[2] -

In all groups, a statistically significant increase in SBP was observed as the pregnancy period increased, especially in the later stages (Table 2).

Table 2 - Results of comparative analysis of the dynamics of SBP in the study groups

Group	Comparison	14-20 weeks	20-24 weeks	24-30 weeks	30-34 weeks	34-38 weeks	40-42 weeks
Control group	vs. baseline period	0,359	0,066	0,003	<0,001	<0,001	<0,001
	vs. preceding period	0,422	0,870	0,668	0,001	<0,001	0,072
400 mcg	vs. baseline period	0,53	0,231	0,212	<0,001	<0,001	<0,001
	vs. preceding period	0,617	0,978	>0,999	<0,001	<0,001	0,001
800 mcg	vs. baseline period	0,460	0,473	0,004	<0,001	<0,001	<0,001
	vs. preceding period	0,539	>0,999	0,161	0,081	<0,001	0,003
1200 mcg	vs. baseline period	0,105	0,006	0,013	<0,001	<0,001	<0,001
	vs. preceding period	0,119	0,672	>0,999	0,234	<0,001	<0,001

At 24-30 weeks, the group of patients taking 400 mcg of folic acid showed a statistically significantly lower SBP level compared to the group of patients taking 800 mcg of folic acid (p=0.023) (Table 4).

Pairwise comparisons of the other groups revealed no statistically significant differences.

A comparative analysis of diastolic blood pressure between the study groups revealed no statistically significant differences between the groups in pregnancy dynamics (p=0.383) (see table in the appendix).

All study groups showed a statistically significant increase in DBP with increasing gestational age (p<0.001), most pronounced in the second half of the gestational period (Table 3).

Table 3 - Results of comparative analysis of the dynamics of DBP in the study groups

Group	Comparison	14-20 weeks	20-24 weeks	24-30 weeks	30-34 weeks	34-38 weeks	40-42 weeks
Control group	vs. baseline period	0,568	0,01	<0,001	<0,001	<0,001	<0,001
	vs. preceding period	–	0,184	0,65	0,059	<0,001	0,014
400 mcg	vs. baseline period	0,841	0,460	0,003	0,001	<0,001	<0,001
	vs. preceding period	–	0,958	0,103	0,968	<0,001	<0,001
800 mcg	vs. baseline period	0,101	0,355	0,001	<0,001	<0,001	<0,001
	vs. preceding period	–	>0,999	0,149	0,37	<0,001	<0,001
1200 mcg	vs. baseline period	0,988	0,209	0,021	0,016	<0,001	<0,001
	vs. preceding period	–	0,024	0,811	>0,999	<0,001	<0,001

No statistically significant differences were found between the groups in terms of proteinuria dynamics during pregnancy (p=0.285). However, a statistically significant increase in the frequency of proteinuria was noted in the control group and in the group of participants taking folic acid in doses of 400 mcg and 1200 mcg (p<0.001 and p<0.028).

Table 4 - Dynamics of proteinuria frequency in the study groups

Gestational age	Control group	Study group			p^1
		400 mcg	800 mcg	1200 mcg	
10-14 weeks	0/306 (0%)	0/331 (0%)	0/255 (0%)	0/304 (0%)	–
14-20 weeks	0/306 (0%)	0/331 (0%)	0/255 (0%)	0/304 (0%)	–
20-24 weeks	0/306 (0%)	0/331 (0%)	0/255 (0%)	0/304 (0%)	–
24-30 weeks	0/305 (0%)	0/330 (0%)	0/253 (0%)	0/304 (0%)	–
30-34 weeks	2/306 (0,7%)	0/330 (0%)	1/254 (0,4%)	0/304 (0%)	0,389
34-38 weeks	7/306 (2,3%)	10/330 (3%)	4/254 (1,6%)	2/304 (0,7%)	0,083
40-42 weeks	6/295 (2%)	9/323 (2,8%)	4/252 (1,6%)	5/299 (1,7%)	0,754
p^2	0,133	<0,001	0,218	0,028	–

Note: p^1 - differences between the control and main groups; p^2 - differences in the same group between the previous and subsequent indicator.

The incidence of general (non-hypertensive) pregnancy complications (such as anemia and threatened miscarriage) was 18.1% in the control group and 19.2% in the study group, which did not have a statistically significant difference (P=0.82). The highest incidence of general pregnancy complications in both groups occurred in the second trimester due to an increase in anemia.

A comparative analysis of all pregnancy complications, including hypertensive conditions, revealed a trend toward a higher incidence of pregnancy complications among patients in the control group (RR=1.07 [95% CI: 0.99; 1.15], p=0.076). The incidence of hypertensive conditions (arterial hypertension without proteinuria, proteinuria without hypertension, preeclampsia, arterial hypertension with proteinuria) in the study group was 9.6%, and did not differ significantly from the control group (P=0.038). The incidence of preeclampsia was 1.67 [95% CI: 0.94; 3.28] times significantly lower in the study group compared to the control group (p=0.077).

The overall incidence of hypertensive conditions during pregnancy among patients in the study group was statistically significantly 1.43 [95% CI: 1.02; 2.53] times lower (p=0.038) than in the control group.

Table 5 - Features of the course of pregnancy in the study groups

Variables	**Control group n=306**	**Study group n=894**	**p**
Pregnancy complications	160(52,2%)	388 (43,4%)	0,076
I trimester	14 (4,4%)	39 (4,4%)	0,876
II trimester	24 (7,5%)	76 (8,5%)	0,719
III trimester	20 (6,25%)	56 (6,3%)	0,866
Pregnancy-induced hypertension	12 (3,75%)	24 (2,7%)	0,274
Preeclampsia	15 (4,68%)	25 (2,8%)	0,077
Pregnancy-induced proteinuria	17 (5,3%)	37 (4,1%)	0,302
Total hypertensive disorders	44 (13,75%)	86(9,6%)	0,038

The results of the comparative analysis of the study groups in terms of the characteristics of the pregnancy course (Table 6) showed that general pregnancy complications were slightly more common among the participants taking 1200 mcg folate compared to the control group (OR=1.13 [95% CI: 1.01; 1.27], p=0.028, Figure 7); other pairwise intergroup comparisons revealed no statistically significant differences in the incidence of pregnancy complications. No statistically significant differences were found between the groups in terms of the incidence of arterial hypertension and preeclampsia (p=0.565 and 0.237, respectively); however, a trend towards a higher incidence of proteinuria was found among the control group participants who did not take folic acid (p=0.06).

Table 6 - Complications during pregnancy depending on the dose of folic acid taken

Variables	Control group (n=306)	Study group (n=894)			p
		400 mcg (n=332)	**800 mcg** (n=257)	**1200 mcg** (n=305)	
Pregnancy complications	160(52,2%)	97(29,2%)	83(32,2%)	77 (25,2%)	**0,025**
I trimester	14 (4,6%)	14 (4,2%)	10 (3,9%)	15 (4,9%)	0,94
II trimester	24 (7,8%)	30 (9%)	23 (8,9%)	23 (7,5%)	0,876
III trimester	20 (6,5%)	14 (4,2%)	23 (8,9%)	19 (6,2%)	0,139
Pregnancy-induced hypertension	12 (3,9%)	8 (2,4%)	9 (3,5%)	7 (2,3%)	0,565
Preeclampsia	15 (4,9%)	10 (3%)	9 (3,5%)	6 (2,0%)	0,237
Pregnancy-induced proteinuria	17 (5,6%)	21 (6,3%)	9 (3,5%)	7 (2,3%)	**0,06**

There were no statistically significant differences in platelet levels (p=0.363) between the control group and the groups of patients taking folic acid at doses of 400, 800, and 1200 mcg (see table in the appendix).

There were no statistically significant differences between the groups of patients taking folic acid in terms of AST (p=0.841) and ALT (p=0.931) levels.

The concentration of serum homocysteine levels in the first trimester of pregnancy in the control group was statistically comparable with pregnant women with further folic acid intake at dosages of 400, 800, and 1200 mcg in both pregnant women with further development of preeclampsia and non-preeclampsia cases Table 7. However, we found that in all cases of further development of preeclampsia, serum homocysteine concentrations in all groups were significantly higher in comparison with pregnant women without developing preeclampsia during pregnancy Table 7.

Thus, at the start of the folic acid supplementation study, pregnant women had no differences in serum homocysteine concentrations.

Table 7 - Serum homocysteine concentrations in the first trimester of pregnancy depends on the development of preeclampsia

		Control group n=306	Folic acid supplementation groups			p-value
			FA 400 n=334	**FA 800 n=259**	**FA 1200 n=305**	
HCY concentrations, umol/L, Me (25-75IQR)	PE	13.1 (9.1-15.6)	14.7 (12.2-20.2)	15.5 (14.6-18.8)	16.9 (11.5-23.8)	0.704[1]
	non-PE	5,9 (5.4-6.7)	6.0 (4.9-7.5)	5.8 (4.9-7.4)	6.0 (4.9-7.3)	0.05[1]
p-value		< 0.0001[2]	< 0.0001[2]	< 0.0001[2]	< 0.0001[2]	

[1] - Kruskal-Wallis ANOVA test; [2] - Mann-Whitney U Test

HCY – homocysteine; PE - preeclampsia

Analysis of the condition of the fetus in the study groups (Table 8) did not show statistically significant differences between the groups with respect to the anthropometric characteristics of newborns and assessment according to the Apgar scale at the 1st (p=0.675) and 5th (p=0.695) minutes.

Table 8 - Fetal condition in the study groups

Variables	Control group	Study group			p
		400 mcg	800 mcg	1200 mcg	
Body weight (g)	3450 (3120; 3750)	3440 (3100; 3720)	3470 (3100; 3704)	3400 (3094; 3720)	0,506
Body length (cm)	54 (52; 56)	53 (52; 55)	54 (52; 56)	53 (51; 55)	0,313
Apgar score					
at 1 minute	9 (8; 9)	9 (8; 9)	9 (8; 9)	9 (9; 9)	0,675
2 points	1/306 (0,3%)	0/331 (0%)	2/254 (0,8%)	2/303 (0,7%)	
3 points	–	–	–	–	
4 points	–	–	–	–	
5 points	2/306 (0,7%)	1/331 (0,3%)	0/254 (0%)	0/303 (0%)	
6 points	10/306 (3,3%)	9/331 (2,7%)	6/254 (2,4%)	6/303 (2%)	
7 points	23/306 (7,5%)	21/331 (6,3%)	17/254 (6,7%)	22/303 (7,3%)	
8 points	47/306 (15,4%)	59/331 (17,8%)	45/254 (17,7%)	41/303 (13,5%)	
9 points	223/306 (72,9%)	241/331 (72,8%)	184/254 (72,4%)	232/303 (76,6%)	
at 5 minutes	10 (9; 10)	10 (9; 10)	10 (9; 10)	10 (10; 10)	0,695
6 points	2/306 (0,7%)	0/331 (0%)	2/254 (0,8%)	2/303 (0,7%)	
7 points	7/306 (2,3%)	8/331 (2,4%)	6/254 (2,4%)	5/303 (1,7%)	
8 points	23/306 (7,5%)	21/331 (6,3%)	14/254 (5,5%)	21/303 (6,9%)	
9 points	51/306 (16,7%)	61/331 (18,4%)	48/254 (18,9%)	43/303 (14,2%)	
10 points	223/306 (72,9%)	241/331 (72,8%)	184/254 (72,4%)	232/303 (76,6%)	
Congenital malformation	5/306 (1,6%)	4/331 (1,2%)	2/255 (0,8%)	1/304 (0,3%)	0,408
Transfer to the acute renal failure/intensive care unit	19/306 (6,2%)	19/331 (5,7%)	10/255 (3,9%)	15/304 (4,9%)	0,64

Table 9 and Figures 1, 2, 3 present the results of genotyping of patients in the main group in relation to polymorphic loci of the MTR, MTRR, and MTHFR genes. The analysis of the correspondence between the observed genotype frequency at the studied loci and the theoretical one determined by the Hardy-Weinberg equilibrium in relation to the polymorphic loci rs1801394 of the MTRR gene (f= -0.008, χ^2=0.013, p=0.909) and rs1801131 of the

MTHFR gene (f=0.078, χ^2=3.08, p=0.079) did not reveal any significant deviation of the observed frequencies from the theoretical ones; the distribution of genotypes at the polymorphic loci rs1805087 of the MTR gene (f=0.19, χ^2=17.74, p<0.001) and rs1801133 of the MTHFR gene (f=0.161, χ^2=13.603, p<0.001) was statistically significant deviated from the theoretical distribution (Figure 1).

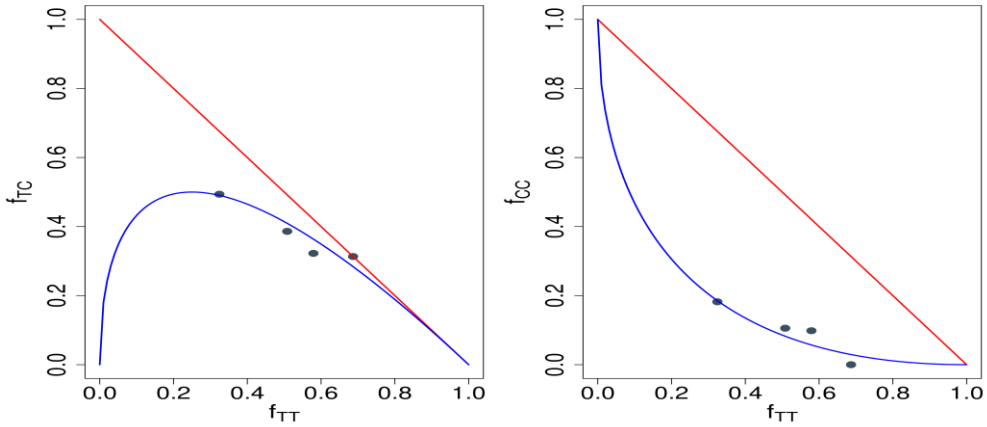


Figure 1 - Correspondence between the observed genotype frequency at the studied loci and the theoretical frequency determined by the Hardy-Weinberg equilibrium (B is the minor allele)

A comparative analysis revealed a lower proportion of CC homozygotes in the group of patients receiving 1200 mcg folate compared to those receiving 400 (p=0.005) or 800 mcg (p=0.144). Table 8 presents a multivariate model developed using stepwise selection of predictors with exclusion based on the Akaike information criterion (AIC) to predict the likelihood of developing obstetric complications among patients receiving folate.

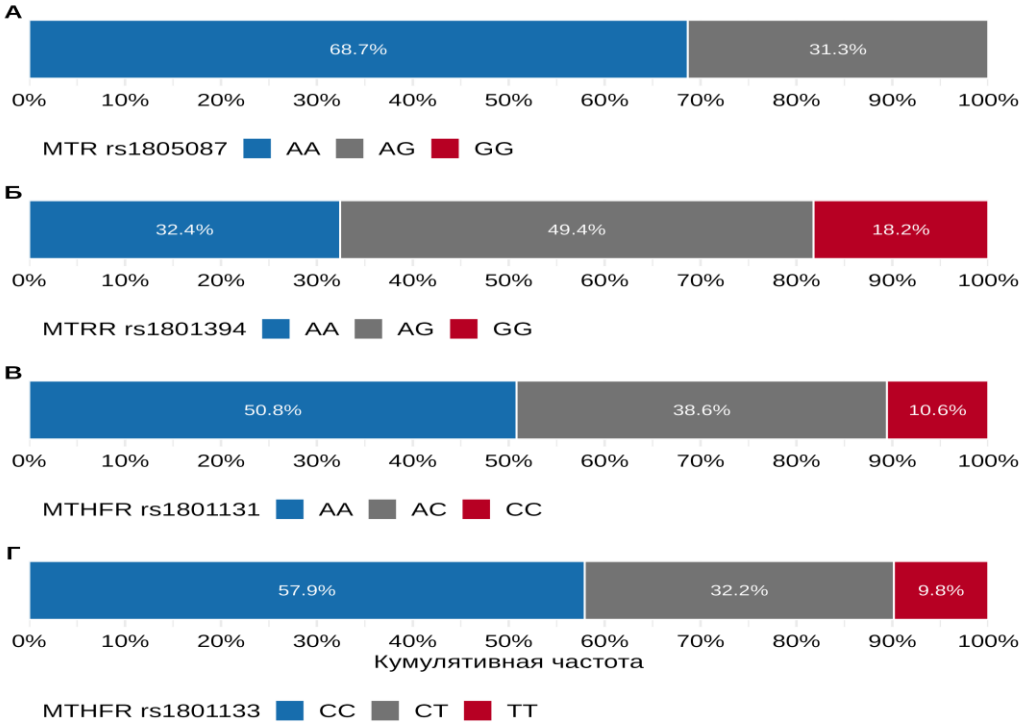
The resulting model was characterized by a Nigelkerke pseudo-R^2 value of 0.03, Sommers' D_{XY} coefficient of 0.14 (adjusted value - 0.1), and AUC of 0.58 [95% CI: 0.53; 0.63] (adjusted value - 0.55) (Figures 2 and 3). Based on the model coefficients, a prognostic nomogram was developed to assess the likelihood of developing obstetric complications among patients taking folates (Figure 4).

Table 9 - Genotyping results

Locus	All patients (n=549)	400 mcg (n=199)	800 mcg (n=162)	1200 mcg (n=188)	p
MTR rs1805087					0,671
AA	377 (68,7%)	140 (70,4%)	107 (66%)	130 (69,1%)	
AG	172 (31,3%)	59 (29,6%)	55 (34%)	58 (30,9%)	
MTRR rs1801394					0,12
AA	178 (32,4%)	62 (31,2%)	44 (27,2%)	72 (38,3%)	
AG	271 (49,4%)	105 (52,8%)	81 (50%)	85 (45,2%)	
GG	100 (18,2%)	32 (16,1%)	37 (22,8%)	31 (16,5%)	
-/G	371 (67,6%)	137 (68,8%)	118 (72,8%)	116 (61,7%)	0,076
MTHFR rs1801131					0,499

AA	279 (50,8%)	106 (53,3%)	86 (53,1%)	87 (46,3%)	
AC	212 (38,6%)	73 (36,7%)	57 (35,2%)	82 (43,6%)	
CC	58 (10,6%)	20 (10,1%)	19 (11,7%)	19 (10,1%)	
-/C	270 (49,2%)	93 (46,7%)	76 (46,9%)	101 (53,7%)	0,307
MTHFR rs1801133					0,01
CC	318 (57,9%)	125 (62,8%)	96 (59,3%)	97 (51,6%)	
CT	177 (32,2%)	50 (25,1%)	49 (30,2%)	78 (41,5%)	
TT	54 (9,8%)	24 (12,1%)	17 (10,5%)	13 (6,9%)	
-/T	231 (42,1%)	74 (37,2%)	66 (40,7%)	91 (48,4%)	0,076

Figure 2 - Results of genotyping of polymorphic loci rs1805087 of the MTR gene (A), rs1801394 of the MTRR gene (B), rs1801131 (C) and rs1801133 (D) of the MTHFR gene



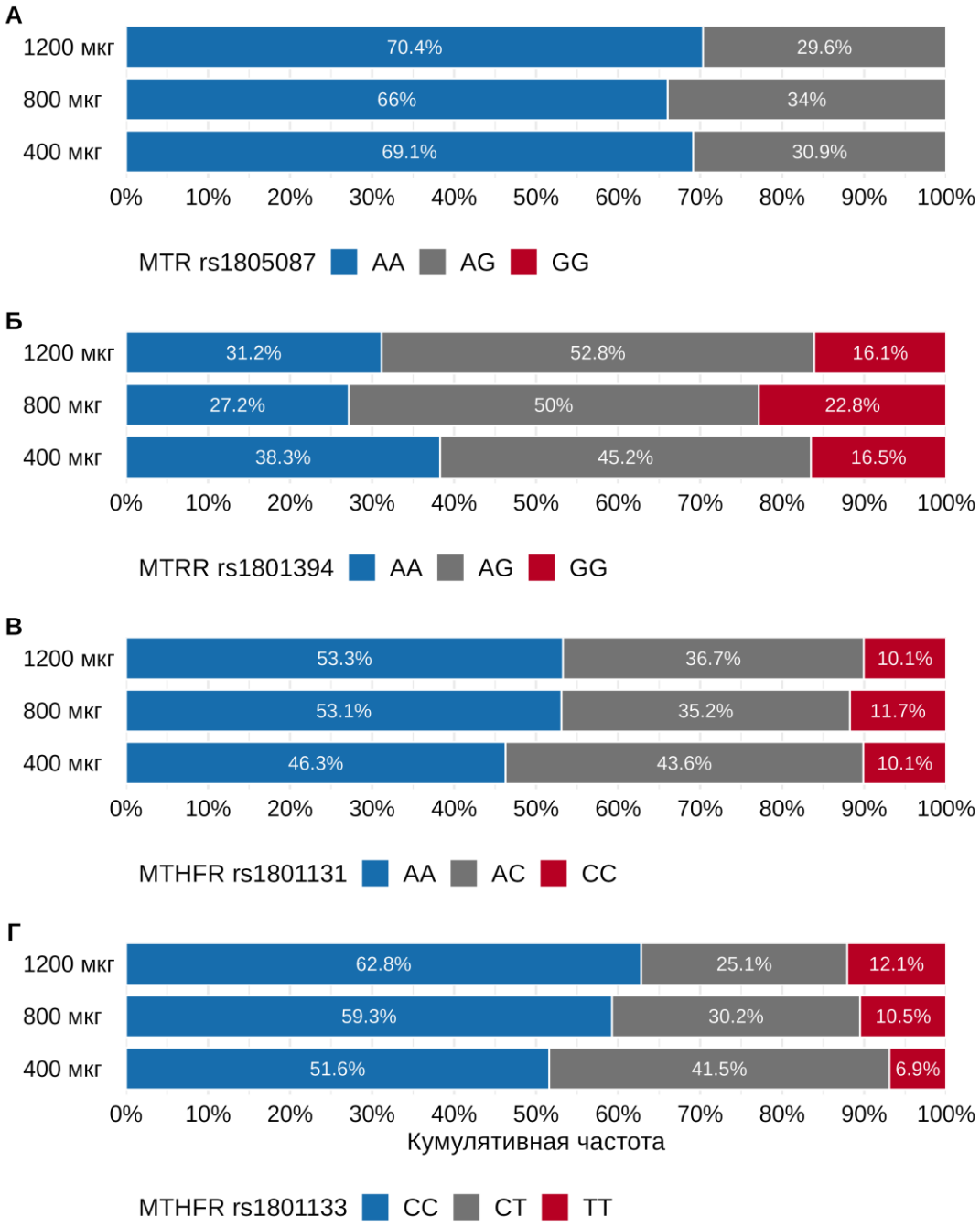


Figure 3 - Results of genotyping of polymorphic loci rs1805087 of the MTR gene (A), rs1801394 of the MTRR gene (B), rs1801131 (C) and rs1801133 (D) of the MTHFR gene in the study groups

Using a 25% cutoff for the predicted probability of developing obstetric complications among folate-supplemented patients, the resulting model had 49.2% [95% CI: 44.9; 53.4] predictive accuracy, 75.9% [95% CI: 68.5; 82.4] sensitivity, and 38.4% [95% CI: 33.5; 43.4] specificity. The positive predictive value was 33.2% [95% CI: 28.4; 38.4], and the negative predictive value was 79.8% [95% CI: 73.3; 85.3] (Table 9).

Table 10 - Coefficients in the resulting model for predicting the likelihood of developing complications during childbirth among patients taking folates

Predictor	β SE)	OR	95% CI	p	VIF
Intercept	-1,53 (0,25)	–	–	–	–
Genotype at MTHFR rs1801133					
CC	0	1	–	–	–
CT	0,49 (0,21)	1,64	1,07; 2,50	0,022	1,17
TT	0,3 (0,36)	1,34	0,65; 2,69	0,412	1,27
Carrier of C allele at MTHFR rs1801131	0,33 (0,21)	1,39	0,92; 2,12	0,115	1,23
Carrier of G allele at MTRR rs1801394	0,38 (0,21)	1,46	0,97; 2,22	0,072	1,01

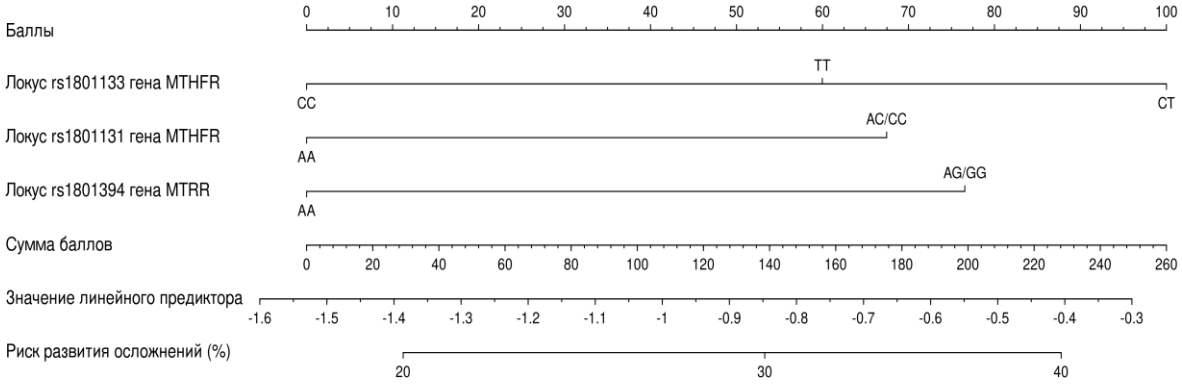


Figure 4 - Nomogram for predicting the likelihood of developing obstetric complications among patients taking folate. To estimate the likelihood of developing obstetric complications, it is necessary to determine the score corresponding to the predictor value by lowering the normal to the appropriate scale. Then, it is necessary to find the sum of the scores and, by lowering the normal to the appropriate scale, find the estimate of the linear predictor value (the logarithm of the odds of the event) and the likelihood of developing obstetric complications

4. Discussion of Study Results

This study evaluated the effectiveness of long-term folic acid supplementation at different doses (400, 800, and 1200 mcg) for the prevention of preeclampsia in pregnant women and examined its relationship with folate metabolism markers and pregnancy outcomes. The study results show a trend toward reduced preeclampsia incidence in the group taking folic acid overall, with no statistically significant differences in the primary outcomes between the dosage groups. Some differences were noted in the frequency of overall complications and homocysteine levels. These observations partially align with and partially differ from previously published.

Results from the large international randomized FACT trial demonstrated that high doses of folic acid (4 mg/day) after the first trimester do not prevent the development of preeclampsia in high-risk women [1]. This is consistent with our data, where significant

preeclampsia prevention from high (compared to low) doses was not observed.

Some meta-analyses and reviews have shown conflicting results: some studies reported a positive effect of folic acid or folate-containing multivitamins in reducing the risk of hypertensive disorders of pregnancy, whereas other reviews and meta-analyses did not support a significant impact of folate therapy on preeclampsia risk. Our findings—absence of a pronounced clinical effect when comparing doses—align with recent systematic reviews highlighting the ambiguity of existing data and the need for further high-quality research [27-33].

Several recent studies have noted associations between polymorphisms in folate metabolism genes (specifically MTHFR C677T and A1298C) and increased risk of preeclampsia, as well as imbalances in angiogenic markers. Our study considered the frequency of these polymorphisms in the local Kazakh population, which is important for interpreting responses to folate therapy since genetic background can modify both folate metabolism and clinical response. These observations are consistent with studies in other populations, including a Tunisian cohort and broader analyses of variant population frequencies [27].

Possible Reasons for Discrepancies and Agreements

1. Dose and timing of therapy: differences in study design (folic acid doses, timing of initiation, and duration) complicate direct comparison. FACT used a dose of 4 mg in late pregnancy, whereas our study examined lower therapeutic doses throughout pregnancy, including the periconceptional period, which may explain partial differences in results.

2. Population structure and genetic background: population differences in the frequency of folate metabolism gene polymorphisms (e.g., MTHFR) and baseline prevalence of folate deficiency/hyperhomocysteinemia may influence the observed effect size of supplementation. Our data from the Kazakh population emphasize the importance of accounting for genetic and epidemiological characteristics.

3. Methodological differences and study power: our results should be interpreted in the context of a randomized design with an adequate sample size for primary comparisons; however, the potential influence of confounders and effect sizes approaching statistical significance for some outcomes (e.g., reduced preeclampsia incidence in the main group, $p \approx 0.077$) warrant cautious interpretation and confirmation in future studies.

Clinical Significance and Recommendations for Future Research

Our data confirm that routine high-dose folic acid supplementation solely for preeclampsia prevention lacks strong evidence, although periconceptional folate intake remains standard for neural tube defect prevention. Further studies are needed to:

- Stratify risks considering genetic profiles (polymorphisms of MTHFR, MTRR, etc.);
- Compare the effect of folate monotherapy versus complex multivitamin regimens;
- Investigate potential biomarkers (homocysteine levels, sFlt-1/PlGF) as predictors of therapy response.

The results demonstrate consistency with large randomized studies and partial alignment with some meta-analyses: folic acid remains an important nutrient during pregnancy, but its role in primary preeclampsia prevention is uncertain and likely depends on dose, timing, and population genetics.

In this study, we analyzed the effectiveness of long-term folic acid supplementation in preventing preeclampsia among pregnant women with and without folate cycle disorders. The results showed a trend toward reduced hypertensive disorders and preeclampsia among participants taking folic acid throughout pregnancy compared to the control group. Although some differences did not reach statistical significance, the overall risk of pregnancy complications was lower in women receiving folic acid.

Dose comparisons indicated that 800 mcg was associated with a relatively low incidence of hypertensive complications, while 1200 mcg showed no significant advantage over lower doses. This aligns with previous studies highlighting the effectiveness of moderate folic

acid doses without additional benefits from higher doses. Proteinuria analysis also showed a trend toward reduced frequency in groups with long-term folic acid intake, particularly in late pregnancy. However, these differences were mostly not statistically significant, likely due to sample size and population heterogeneity. Importantly, long-term folate supplementation did not negatively affect laboratory parameters (platelet count, ALT, AST), confirming the safety of this intervention. Observed differences in homocysteine levels support the role of folate metabolism in hypertensive pregnancy complications.

Comparison with the literature shows consistency with systematic reviews and meta-analyses emphasizing folic acid's role in reducing the risk of gestational hypertension and preeclampsia, especially in women with folate metabolism gene polymorphisms (MTHFR, MTRR, MTR). However, variability in results depending on dose and duration of supplementation persists, similar to our findings. Practical significance long-term folic acid supplementation may be considered an accessible, safe, and relatively inexpensive strategy for preeclampsia prevention in clinical practice. This is especially relevant in regions with high prevalence of folate cycle gene polymorphisms and limited access to specialized prevention. Thus, these results can inform clinical guidelines for managing pregnant women, including those at high risk for hypertensive complications, indicating the level of evidence.

The findings demonstrate reduced risk of hypertensive complications and preeclampsia among women taking long-term folic acid, consistent with systematic reviews and meta-analyses. Literature indicates that folic acid improves endothelial function, lowers homocysteine levels, and may reduce the likelihood of gestational hypertension. However, as in our study, many studies show conflicting results regarding doses and duration, underscoring the need for further clinical trials.

Given conflicting data and limited statistical significance of some results, additional multicenter randomized studies are needed to clarify optimal folate doses and duration in pregnant women.

Practical Implications

Long-term folate supplementation is an accessible, safe, and cost-effective method for preventing pregnancy complications. Implementing this strategy is particularly important in populations with high prevalence of folate metabolism gene polymorphisms. Routine long-term folic acid use may reduce preeclampsia incidence and thereby improve perinatal outcomes.

Study Limitations

The study has several limitations. First, not all differences reached statistical significance, possibly due to limited sample size and population heterogeneity. Second, additional factors such as diet, physical activity, or comorbidities cannot be excluded. Third, the study was conducted in a single region, limiting generalizability. These factors should be considered when interpreting results and planning future research. Inclusion of only one population (Central Asian) may limit generalizability. There may also be limitations regarding follow-up duration and monitoring of concomitant nutrient status (particularly vitamins B12 and B6).

5. Conclusion

Long-term folic acid supplementation may be considered a promising method for preeclampsia prevention, particularly in women with folate metabolism disorders. Multicenter randomized trials are needed to determine optimal doses and duration of therapy.

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Author Contributions.

Conceptualization: Tusupkaliev A.B.; Methodology: Gaiday A.N.; Data curation: Urazova U.M.; Formal analysis: Dinets A.V.; Resources: Ayazbaeva L.K.; Writing – original draft: *Kaldygulova L.K.;* Writing – review & editing: A.A., Gaiday A.N.; Project administration: Tusupkaliev A.B..

All authors have read and approved the final version of the manuscript.

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Appendix

Demographic and anamnestic characteristics of the study and control groups

Characteristic	**Control group (n=320)**	**Main group (n=894)**	**p**
Age (years)	29,4 (±4,9) 29 (26; 31)	30,2 (±5,7) 30 (26; 34)	<0,067
Height	161,4 (±5,7) 161 (158; 165)	161,6 (±5,4) 161,5 (158; 165)	0,732
Weight (kg)	58,8 (±8,7) 58 (52; 64)	58,7 (±8,9) 58 (52; 64)	0,83
BMI (kg/m²)	22,6 (±3,1) 22,2 (20,4; 24,1)	22,5 (±3,2) 22 (20,2; 24,2)	0,529
Social status			0,994
Employed	150 (49%)	438 (49%)	
Unemployed	156 (51%)	456 (51%)	
Family history	20 (6,5%)	66 (7,4%)	0,62
Hypertension	12 (3,9%)	34 (3,8%)	0,926
Diabetes mellitus	8 (2,6%)	29 (3,2%)	0,582
Thyroid disease	0 (0%)	3 (0,3%)	0,575
Past medical history			
Appendicitis	44 (14,4%)	97 (10,9%)	0,098
Hepatitis A	12 (3,9%)	22 (2,5%)	0,184
Chickenpox	9 (2,9%)	24 (2,7%)	0,813
Urinary tract infections	2 (0,7%)	2 (0,2%)	0,27
Calculous cholecystitis	1 (0,3%)	1 (0,1%)	0,445
Surgical interventions in history	61 (19,9%)	146 (16,3%)	0,15
Chronic gynecological diseases	23 (7,5%)	57 (6,4%)	0,49

Features of the gynecological and obstetric history of the study participants

Characteristic	Control group	Main group	p
Age at menarche (years)	13 (13; 14)	13 (13; 14)	0,813
Age at onset of sexual activity (years)	21,2 (±2,6) 21 (20; 22)	21,6 (±2,9) 21 (20; 22)	0,059
Irregular menstruation	9 (2,9%)	28 (3,1%)	0,868
Gynecological diseases	69 (22,5%)	159 (17,8%)	0,067
Cervical erosion	64 (20,9%)	99 (11,1%)	<0,001
Ovarian cyst	1 (0,3%)	12 (1,3%)	0,203
Endometrial polyp	1 (0,3%)	11 (1,2%)	0,315
PCOS (Polycystic Ovary Syndrome)	1 (0,3%)	10 (1,1%)	0,307
Uterine fibroids	0 (0%)	11 (1,2%)	0,076
STIs (Sexually Transmitted Infections)	0 (0%)	5 (0,6%)	0,337
History of pregnancies	209 (68,3%)	601 (67,2%)	0,729
History of deliveries	196 (64,1%)	564 (63,1%)	0,762
History of abortions	62 (20,3%)	148 (16,6%)	0,141
History of miscarriages/stillbirth	44 (14,4%)	147 (16,4%)	0,394
Gestational age (weeks)	12 (11; 12)	12 (11; 13)	0,409

Dynamics of diastolic blood pressure in the study groups

Gestational age	Control group	Main group			p¹
		400 mcg	800 mcg	1200 mcg	
10-14 weeks	65,5 (±6,6) 60 (60; 70)	65,6 (±7,3) 70 (60; 70)	66,2 (±5,8) 70 (60; 70)	66,1 (±7,2) 70 (60; 70)	0,48
14-20 weeks	66,1 (±6,5) 70 (60; 70)	66 (±6,8) 65 (60; 70)	67,1 (±6,7) 70 (60; 70)	65,9 (±6,3) 70 (60; 70)	0,131
20-24 weeks	66,9 (±6,6) 70 (60; 70)	66,3 (±6,7) 70 (60; 70)	67 (±7) 70 (60; 70)	67 (±6,9) 70 (60; 70)	0,484
24-30 weeks	67,5 (±6,5) 70 (60; 70)	67,3 (±6,5) 70 (60; 70)	68 (±6,7) 70 (60; 70)	67,5 (±6,7) 70 (60; 70)	0,584
30-34 weeks	68,7 (±8,4) 70 (60; 70)	67,5 (±7,6) 70 (60; 70)	68,8 (±7,6) 70 (60; 70)	67,6 (±6,5) 70 (60; 70)	0,059
34-38 weeks	71,8 (±9,3) 70 (65; 80)	71,3 (±9,2) 70 (60; 80)	71,6 (±8,1) 70 (70; 80)	70,3 (±8,4) 70 (60; 80)	0,157
40-42 weeks	73,8 (±8,4) 70 (70; 80)	74,5 (±8,4) 70 (70; 80)	74,7 (±8,8) 70 (70; 80)	73,9 (±7) 70 (70; 80)	0,624
p²	**<0,001**	**<0,001**	**<0,001**	**<0,001**	–

Note: p¹ - ; p² -

Results of the study of individual laboratory blood parameters in pregnant women of the study groups

Parameters	Control group	Main group			p
		400 mcg	800 mcg	1200 mcg	
Platelets (×10⁹/L)	227,5 (200; 264)	230 (208; 272)	230 (202; 263)	230 (203; 269)	0,363
ALT (U/L)	–	12 (12; 18)	12 (8; 18)	13 (8,6; 18)	0,841
AST (U/L)	–	23 (20; 29)	23 (20; 29,1)	24 (19; 29,1)	0,931
Homocysteine (μmol/L)	5,7 (4,6; 7)	6 (5; 7,6)	5,9 (5; 7,6)	6 (5; 7,3)	**0,02**

Фолий циклінің бұзылуы бар және онсыз жүкті әйелдерде преэклампсияның алдын алу үшін ұзақ мерзімді фолий қышқылын енгізудің тиімділігі

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Түйіндеме

Кіріспе. Преэклампсия бүкіл әлемде ана мен ұрық аурушаңдығының жетекші себептерінің бірі болып қала береді. Жинақталған деректер фолат алмасуының бұзылыстары мен гомоцистеин деңгейінің жоғарылауы жүктілік кезіндегі гипертензиялық асқынулардың дамуына ықпал етуі мүмкін екенін көрсетеді. Бұл зерттеуде фолаттық цикл гендерінің полиморфизмдері бар және жоқ жүкті әйелдерде преэклампсияның алдын алу үшін фолий қышқылын ұзақ уақыт қолданудың тиімділігі бағаланды.

Әдістері. Бір орталықты рандомизацияланған бақыланатын зерттеуге бақылау тобына 320 әйел (фолий қышқылын жүктіліктің 12 аптасына дейін қабылдаған) және негізгі топқа 894 әйел (фолий қышқылын жүктілік бойы қабылдаған) енгізілді. Негізгі топ дозалар бойынша стратификацияланды: 400 мкг, 800 мкг және 1200 мкг. Клиникалық, биохимиялық және генетикалық зерттеулер жүргізілді, оның ішінде гомоцистеин деңгейін анықтау және MTHFR, MTR және MTRR полиморфизмдерінің генотиптелуі қамтылды. Жүктілік нәтижелері мен гипертензиялық асқынулардың жиілігі топтар арасында салыстырылды.

Нәтижелері. Фолий қышқылын ұзақ уақыт қабылдау бақылау тобымен салыстырғанда жүктілік кезіндегі гипертензиялық бұзылыстардың жалпы жиілігінің төмендеуімен байланысты болды (RR 1,43; p=0,038).

Негізгі топта преэклампсияның жиілігі 1,67 есе төмен болды, бұл қолайлы үрдісті көрсетеді. Фолий қышқылының әртүрлі дозаларын қабылдаған топтар арасында артериялық қысым динамикасы мен перинаталдық нәтижелер бойынша айтарлықтай айырмашылықтар анықталған жоқ. Кейін преэклампсия дамыған барлық әйелдерде гомоцистеин деңгейі фолий қышқылының дозасына тәуелсіз түрде айтарлықтай жоғары болды. Генотиптердің таралуы MTHFR және MTR полиморфизмдерінің популяцияға тән жиіліктерін көрсетті, алайда «доза–әсер» айқын байланысы анықталмады.

Қорытынды. Фолий қышқылын ұзақ уақыт қолдану жүктілік кезіндегі гипертензиялық асқынулардың, соның ішінде преэклампсия жиілігінің төмендеу үрдісін қоса алғанда, даму қаупін азайтады және барлық зерттелген дозаларда қауіпсіз болып табылады. Оның әлеуетті пайдасы фолат алмасуына жауапты генетикалық варианттардың таралуы жоғары популяциялар үшін ерекше маңызды. Оңтайлы доза мен қабылдау ұзақтығын анықтау үшін көп орталықты рандомизацияланған зерттеулер қажет.

Түйін сөздер: преэклампсия, фолий циклі, фолий қышқылы.

Эффективность длительного приема фолиевой кислоты для профилактики преэклампсии у беременных с и без нарушения фолатного цикла

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Резюме

Введение. Преэклампсия остаётся одной из ведущих причин материнской и перинатальной заболеваемости во всём мире. Накопленные данные свидетельствуют о том, что нарушения фолатного обмена и повышенный уровень гомоцистеина могут способствовать развитию гипертензивных осложнений беременности. В данном исследовании оценивалась эффективность длительного приёма фолиевой кислоты для профилактики преэклампсии у беременных женщин с наличием и отсутствием полиморфизмов генов фолатного цикла.

Методы. В одноцентровое рандомизированное контролируемое исследование были включены 320 женщин в контрольной группе (приём фолиевой кислоты до 12 недель беременности) и 894 женщины в основной группе (приём фолиевой кислоты на протяжении всей беременности). Основная группа была стратифицирована по дозам: 400 мкг, 800 мкг и 1200 мкг. Проводились клинические, биохимические и генетические исследования, включая определение уровня гомоцистеина и генотипирование полиморфизмов

MTHFR, MTR и MTRR. Показатели исходов беременности и частота гипертензивных осложнений сравнивались между группами.

Результаты. Длительный приём фолиевой кислоты ассоциировался с более низкой общей частотой гипертензивных осложнений беременности по сравнению с контрольной группой (RR 1,43; p=0,038). Частота преэклампсии была в 1,67 раза ниже в основной группе, что отражает благоприятную тенденцию. Значимых различий в динамике артериального давления и перинатальных исходах между группами с различными дозами фолиевой кислоты выявлено не было. Уровень гомоцистеина был достоверно выше у всех женщин, у которых в дальнейшем развилась преэклампсия, независимо от дозы фолиевой кислоты. Распределение генотипов продемонстрировало популяционно-специфические частоты полиморфизмов MTHFR и MTR, однако чёткой зависимости «доза–эффект» выявлено не было.

Заключение. Длительный приём фолиевой кислоты снижает риск развития гипертензивных осложнений беременности, включая тенденцию к снижению частоты преэклампсии, и является безопасным во всех изученных дозах. Потенциальная польза особенно значима для популяций с высокой распространённостью генетических вариантов фолатного обмена. Для определения оптимальной дозы и продолжительности приёма необходимы дальнейшие многоцентровые рандомизированные исследования.

Ключевые слова: преэклампсия, фолатный цикл, фолиевая кислота.