International Journal of Medicine and Medical Research

ISSN 2413-6077, e-ISSN 2414-9985
Journal homepage: https://ijmr.com.ua/
Volume 11, No. 2. 2025

UDC 577.21:577.218
DOI: 10.63341/ijmmr/2.2025.74

Article's History:
Received: 19.08.2025; Revised: 27.11.2025;
Accepted: 30.12.2025; Published: 06.01.2026

MTHFR and *MTRR* polymorphisms associations with unexplained female infertility

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Abstract. Polymorphic alleles in genes of folate metabolism are associated with such failures of female infertility like impaired ovulation or fertilisation; however, the data about the single gene polymorphisms in genes which code the enzymes of folate metabolism are controversial. This study aimed to analyse the correlation of polymorphic variants C677T (Ala222Val), A1298C (Glu429Ala) of *MTHFR* gene and A66G (Ile22Met) of *MTRR* gene with the oocytes' maturation and early embryo development in women with unexplained infertility. DNA extraction was performed with extraction kits, real-time polymerase chain reaction was applied for single nucleotide polymorphisms determinations, gonadotropin-releasing hormone antagonists were used for controlled ovarian stimulation, obtained oocytes were fertilised by the method of intracytoplasmic sperm injection, early embryo development *in vitro* was analysed according to the Istanbul

Suggest Citation:
Feskov O, Zhylkova Ye, Feskova A, Yehunkova O, Blazhko O. *MTHFR* and *MTRR* polymorphisms associations with unexplained female infertility. Int J Med Med Res. 2025;11(2):74–80 . DOI: 10.63341/ijmmr/2.2025.74

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Consensus, statistical hypotheses were tested at significance levels of 0.05 and 0.01. The part of good-quality cleavage stage embryos was statistically lower for infertile patients-carriers with mutant allele A1298C of *MTHFR* gene in genotype ($\chi 2_{crit.}$ = 18.0361, P = 0.000022). A presence of mutant allele A66G of *MTRR* gene led to decrease in the number of mature MII oocytes in women with unexplained infertility ($\chi 2_{crit.}$ = 11.1469, P = 0.000842). No correlations of studied polymorphisms of *MTHFR* and *MTRR* genes with total number of received oocytes, fertilisation rate and blastocysts formation rate were found out in studied group. Examination of polymorphic variants in genes of folate metabolism C677T (Ala222Val), A1298C (Glu429Ala) of *MTHFR* gene and A66G (Ile22Met) of *MTRR* gene could be included to the tests necessary for women with unexplained infertility

Keywords: single nucleotide polymorphism; folate cycle; oocytes; embryo development; *in vitro* fertilisation

Introduction

According to recent studies, female factors are the cause of infertility in approximately 35% of women who have difficulty conceiving, with the most common etiological factors being ovulation disorders, which usually manifest as irregular or absent menstruation [1]. At the same time, in 10-20% of cases, the cause of infertility cannot be determined, which indicates the presence of unexplored mechanisms of reproductive disorders. In this regard, it is particularly important to study the underlying molecular causes of disorders in the development and maturation of oocytes, as well as to investigate the decisive role of maternal effects and genetic determinants associated with unexplained female infertility.

The enzymes of the folate cycle may have a significant impact on the processes of oogenesis, embryogenesis and endometrium implantation. However, the presented in the literature data about the correlation of polymorphic alleles of genes *MTHFR* (methylenetetrahydrofolate reductase) and *MTRR* (methionine synthase reductase) with the outcome of *in vitro* fertilisation (IVF) cycles are ambiguous. For example, H. Ishitani *et al.* [2] showed that *MTHFR* polymorphisms reduced the blastocyst rate but did not correlate with other stages of embryo development. Nevertheless, the possibility that folate cycle is of major importance during the period before the 8- to 16-cell stage for embryo quality that is not assessed by developmental failure was not excluded in mentioned study. In turn Y.R. Ko *et al.* [3] proved that good-quality embryo rate was higher for *MTHFR* 677CT than those for 677CC and 677TT (40.0% vs 29.4%, p = 0.001 and 40.0% vs 33.3%, p = 0.025, respectively). Besides that, the authors demonstrated that the oocyte maturation rate was significantly lower in 677TT than in 677CC 1298AA/677CC 1298AC and 677CC 1298CC/677CT 1298AA/677CT 1298AC (71.4% vs 76.7%, p = 0.012 and 71.4% vs 75.7%, p = 0.029, respectively). However, no differences were observed in the transplantable embryo rate between *MTHFR* genotypes. H. Zeng *et al.* [4] demonstrated the association of *MTHFR* 677TT with decreased number of good-quality embryos and decreased cumulative live birth rate. But the correlation of *MTHFR* C677T genotypes (677CC, 677CT, 677TT) with the clinical pregnancy rate, miscarriage rate and live birth rate at the first embryo transfer cycle was not proved in this work. The literature provided data on the impact of polymorphic variants of genes which code folate cycle enzyme on female reproductive function and pregnancy outcome. According to the results mentioned in literature, heterozygous polymorphism for the C/T allele of the *MTHFR* 677 gene and an increased frequency of the A/C allele of the *MTHFR* 1298 gene are associated with early pregnancy loss. O.V. Trokhymovych *et al.* [5] in their work mentioned that in women with early pregnancy loss and adenomyosis, a significant increase in the frequency (50%) of the heterozygous polymorphism for the C/T allele of the *MTHFR* 677 gene and a decrease in the frequency of detection of neutral A/A allele and increased frequency (80%) of *MTHFR* 1298 gene allele polymorphism (A/C and C/C) were observed. From the other hand S. Jose [6] summarised the results of different researches and demonstrated that data about the relationship between the *MTHFR A*298C polymorphism and recurrent pregnancy loss risk are still debatable and unclear. In turn Y. Zhang *et al.* [7] demonstrated that the combination of genotypes 677TT and 1298CC of the *MTHFR* gene and 66GG of the *MTRR* gene significantly increase the risk of recurrent pregnancy loss (RPL). In mentioned investigation it was found out that the *MTHFR* c.677C > T heterozygote was associated with lower RPL risk, while the *MTHFR* c.1298A > C variant and *MTRR* c.66A > G heterozygote were correlated with higher RPL risk. In addition, T.L. Arkhypkina *et al.* [8] considered the role of polymorphic variants of folate cycle genes as candidate genes for the development of polycystic ovary syndrome in women of reproductive age. The number of studies demonstrated that the presence of the *MTHFR* A1298C mutation directly correlates with an increase in homocysteine concentration and the risk of polycystic ovary syndrome.

However, the question of the association of single nucleotide polymorphisms of the *MTHFR* and *MTRR* genes both with early embryo development and quality of female gametes requires detailed study. The aim of the present study was to analyse the relationship of polymorphic variants in genes of folate metabolism – C677T (Ala222Val), A1298C (Glu429Ala) of *MTHFR* gene and A66G (Ile22Met) of *MTRR* gene with quality of oocyte and embryo development in IVF cycles in women with unexplained infertility (UI).

Materials and Methods

Between January 2023 and December 2024, 26 couples with the UI underwent infertility treatment using the assisted reproduction techniques in the Reproduction Centre

"Clinic of Professor O.M. Feskov" (Kharkiv, Ukraine). Only couples with normal male karyotype 46,XY and normal female karyotype 46,XX were included to the Experimental Group. Couples with the female-partner aged more than 40 y.o. excluded from the study. Data collection, laboratory examinations and cycles of *in vitro* fertilisation were carried out at the Clinic of Professor O.M. Feskov (Centre of Human Reproduction, Sana-Med Ltd.). All participants gave their informed consent to participate in the study on condition that the data would remain anonymous, which was done. Design of the study was approved by the Institutional Review Board, protocol No. 3 dated 2022 December 20. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Declaration of Helsinki [9].

In mentioned group with UI the age of female partners was 31.8 ± 3.3 years old, the pattern age was 35.6 ± 3.8 years old. All the men had normal spermogram indices according to the World Health Organization [10]. The correlation between polymorphic variants in genes of folate metabolism C677T (Ala222Val), A1298C (Glu429Ala) of *MTHFR* gene and A66G (Ile22Met) of *MTRR* gene in female partners and the oocytes maturation, fertilisation rate, the part of good-quality cleavage stage embryos and blastocysts formation rate in IVF cycles for the group with UI was analysed. The Control Group was formed by 25 egg donors with the middle age 28.1 ± 5.2 y.o. Donors' eggs were fertilised by donor sperm. The age of the sperm donors was 33.7 ± 5.2 y.o The frequency of alleles and genotypes of studied polymorphisms for *MTHFR* and *MTRR* genes were calculated both for infertile women and for egg donors. DNA extraction was performed with standard kits (Macherey- Nagel, NucleoSpin® Blood, Germany) [11]. Single nucleotide polymorphysms (SNPs) were determined by the technique of real-time polymerase chain reaction (PCR) with the ABI PRISM 7500 real-time PCR system (USA) and Applied BioSystem kits (USA). Primers with the following nucleotide sequence were used: gene *MTHFR*, C677T (rs1801133): GAAAAGCTGCGTGATGATGAAATCG[G/A] CTCCCGCAGACACCTTCTCCTTCAA; gene *MTHFR*, A1298C (rs1801131): AAGAACGAAGACTTCAAAGACACTT[G/T]CTTCACTGGTCAGCTCCTCCCCCCA; gene *MTRR* (rs1801394): AGGCAAAGGCCATCGCAGAAGAAAT[A/G]TGTGAGCAAGC TGTGGTACATGGAT.

Controlled ovulation stimulation (COS) of patients in couples and egg donors was performed using the protocol with gonadotropin-releasing hormone antagonists (ant-GnRH). Fertilisation of the obtained oocytes was done by intracytoplasmic sperm injection (ICSI) technique. Embryo culture beginning from the stage of zygote and to the blastocyst stage was performed in GAIN medium Single-step (Austria) at a temperature of 36.9-37.1°C and a CO2 content of 5.5-5.8% [12]. Cleavage stage embryos and embryos that reached the blastocyst stage were evaluated by morphological characteristics according to D.K. Gardner criteria, mentioned to the Istanbul Consensus [13]. A difference was considered statistically significant if $P<0.05$. To test the associations between genotypes and qualitative variables, the chi-squared test was used [14]. The Apache Open Office 4.0.0 software package (Sana-Light Ltd., Sana-Med Ltd.) was used for calculation.

Thus, this study was designed as a controlled comparative analysis involving couples with unexplained infertility and a control group of egg donors, with clearly defined inclusion and exclusion criteria. A comprehensive methodological approach combined clinical IVF outcomes with molecular genetic analysis of key polymorphic variants in folate metabolism genes in female participants. This design enabled evaluation of the relationship between maternal genetic background and oocyte maturation, fertilisation efficiency, and embryo developmental potential under standardised assisted reproduction techniques conditions.

Results and Discussion

The frequency of alleles and genotypes of studied polymorphisms for *MTHFR* and *MTRR* genes were calculated for women in group with UI and for egg donors in Control Group. For studied SNP C677T of *MTHFR* gene the frequencies of alleles among egg donors were $P_C = 0.71$; $Q_T = 0.29$. In women with UI there were the next the frequencies of alleles for SNP C677T of *MTHFR* gene was $P_C = 0.77$; $Q_T = 0.23$. There were the next frequencies of alleles of polymorphic variant of *MTHFR* gene A1298C were $P_A = 0.62$ and $Q_C = 0.38$ for the patients in UI-group; for Control Group – $P_A = 0.72$ and $Q_C = 0.28$, respectively. As for studied SNP A66G for *MTRR* gene the allele frequencies were $P_A = 0.35$ $Q_G = 0.65$ for UI-Group, $P_A = 0.42$ and $Q_G = 0.58$ in the Control Group respectively. It should be noted that in subpopulations from different regions of Ukraine, genotypes with low-functional alleles prevail. The most studied is the population frequency of polymorphic variants of the *MTHFR* gene C677T. The average frequency of its genotypes C/C, C/T and T/T among practically healthy individuals in Ukrainian population is 46.0, 48.4 and 5.6%, respectively [15]. A.O. Fesai *et al.* [16] showed that the frequency of at least one low-functional allele of the *MTHFR*, *MTRR*, and *MTR* genes in women with repeated miscarriages was 83%. That is, it can be assumed that in every second Ukrainian woman of reproductive age, folates are not converted into an active form and are not absorbed by the body to a sufficient extent.

As a result of COS, totally 306 oocytes were obtained from patients in group with UI. There were 208 oocytes at the MII maturity stage in mentioned experimental group (68.0% of received oocytes). The fertilisation rate in this group, when using the ICSI method, was 83.2% (173 normal zygotes with two pronuclei). In UI-Group the part of good-quality cleavage stage embryos was 60.1% (104 cleavage stage embryos); blastocyst formation rate (BFR) reached 35.8% (62 blastocyst obtained from 173 normal zygotes with two pronuclei). As for the Control Group, there were 455 oocytes in total, and 387 oocytes at the MII

maturity stage (85.1% of obtained oocytes). The fertilisation rate of donor eggs was 81.9% (317 normal zygotes). In Control Group the part of good-quality cleavage stage embryos was 73.8% (234 cleavage stage embryos); BFR reached 55.8% (177 blastocyst obtained from 317 normal zygotes with two pronuclei).

The part of oocytes at the MII maturity stage was statistically lower in women with UI comparing with this one in egg donors (68.0% vs 85.1%, $\chi2_{crit.} = 30.305$, $P < 0.00001$). The part of good-quality cleavage stage embryos was statistically higher in the Control Group than in Experimental Group (73.8% vs 60.1%, $\chi2_{crit.} = 9.1892$, $P = 0.002434$). Good-quality cleavage stage embryo is presented on Figure 1. Oocyte maturation arrest could be a hidden cause of unexplained infertility. Abnormalities of the oocytes' maturation have not been studied enough in reproductive medicine yet. In most cases, oocyte-specific factors underlying infertility remain undetected until the assessment of oocytes retrieved during *in vitro* fertilisation cycles. The obtained results assumed that the process of the oocytes' maturation in patients with unexplained infertility could play a key role in a proper embryo development.

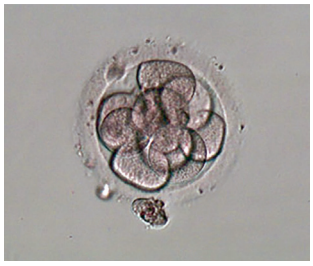

Figure 1. Good-quality cleavage stage embryo according to the Istanbul Consensus *in vitro*
Note: Magnification: x250
Source: compiled by the authors

There was no statistically significant difference in fertilisation rate and blastocyst formation rate between the group of patients with UI and the Control Group. A photo of human blastocyst is shown in Figure 2. The IVF indices like a part of MII mature oocytes and part of good-quality embryos depends on the process of oocytes maturation and oocytes quality. The obtained results demonstrated that donors' oocytes are more competent comparing with the eggs obtained in women with UI.

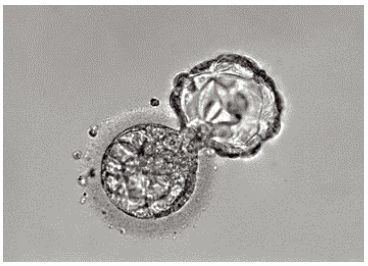

Figure 2. Blastocyst 5AA according to the D.K. Gardner classification *in vitro*
Note: Magnification: x250
Source: compiled by the authors

Based on the SNP C677T of *MTHFR* gene evaluation, there were 16 normal homozygote women with UI and 10 patients were classified as mutant homozygote or heterozygote. As for the laboratory variables, comparing the normal group with the mutant group, no differences were found regarding the total number of oocytes and MII-oocytes retrieved, normal fertilisation rate, good-quality cleavage stage embryos and blastocyst formation rate. Regarding the *MTHFR* polymorphism A1298C, 12 patients presented normal alleles and 14 patients presented mutated alleles. There was no difference in the number of total and mature MII-oocytes, fertilisation rates and BFR between normal genotype-women and the carriers of mutant allele. The part of good-quality cleavage stage embryos was statistically lower in patients with mutant allele in genotype ($\chi2_{crit.} = 18.0361$, $P = 0.000022$). As for studied SNP A66G for *MTRR* gene, there was no any difference in embryo development for normal genotype patients with UI and carriers of mutant allele. From the other hand a presence of mutant allele in mentioned genotype led to decrease in the number of mature MII oocytes in experimental group ($\chi2_{crit.} = 11.1469$, $P = 0.000842$). Obtained results were mentioned in Table 1.

Table 1. Laboratory variables according to presence of single nucleotide polymorphisms in folate-cycle genes

Variable	*MTHFR*, C677T		*MTHFR*, A1298C		*MTRR*, A66G	
	Normal, n = 16	Mutant, n = 10	Normal, n = 12	Mutant, n = 14	Normal, n = 6	Mutant, n = 20
Received oocytes, n	10.7 ± 2.8	11.7 ± 2.7	12.4 ± 3.2	11.2 ± 3.7	10.2 ± 1.7	11.3 ± 2.5
Mature MII oocytes, %	63.9	73.1	66.4	69.4	84.7**	62.8**
Normal fertilisation, %	83.6	82.6	78.8	87.2	83.6	82.9
Good-quality embryos, %	58.7	61.2	78.2*	45,2*	62.7	59.0
Blastocyst formation rate, %	33.7	38.3	41.0	31.6	35.2	36.1
Statistics	*df = 1, $\chi2_{crit.} = 18.0361$, $P = 0.000022$ **df = 1, $\chi2_{crit.} = 11.1469$, $P = 0.000842$					

Note: n – the number of the patients; * – significant; ** – significant; χ2 – Chi-Square test; P – significance level
Source: compiled by the authors

In this study the correlation between oocyte maturation and single nucleotide polymorphisms of *MTHFR* gene C677T and A1298C was not proved. But regarding the *MTHFR* polymorphism A1298C, the part of good-quality cleavage stage embryos was statistically lower in patients with mutant allele in genotype. Nevertheless, Y. Ko *et al.* [3] demonstrated earlier that the oocyte maturation rate was significantly lower in 677TT than in 677CC 1298AA/677CC 1298AC and 677CC 1298CC/677CT 1298AA/677CT 1298AC (71.4% vs 76.7%, p = 0.012 and 71.4% vs 75.7%, p = 0.029, respectively). Besides that, the mentioned authors found out that good-quality embryo rate was higher for *MTHFR* 677CT than those for 677CC and 677TT (40.0% vs 29.4%, p = 0.001). But there was no correlation between genotypes A/A, A/C and C/C for polymorphic variants of the *MTHFR* gene A1298C and good-quality embryo rate in that previous study.

The *MTHFR* gene encodes the 5-methylenetetrahydrofolate reductase enzyme, and thus it relates to folate metabolism. It was not defined the level of homocysteine in this study. But it could be assumed that polymorphisms in *MTHFR* could affect the content of folate and homocysteine. In turn folate deficiency and high concentration of homocysteine (hyperhomocysteinaemia) are considered as factors that increase the risk of infertility [17]. The current study demonstrated the association of *MTHFR* A1298C polymorphism with the decrease of the part of good-quality cleavage stage embryos. Folate deficiency and hyperhomocysteinaemia can affect the development of oocytes. Recent evidence suggests that human embryonic transcription is activated at the one-cell stage. M. Asami *et al.* [18] assumed that the oocyte provides the essential maternal proteins and transcripts needed to initiate embryonic genome activation (also called zygotic genome activation), a process where the embryo switches from maternal control to its own gene expression. The oocyte plays a crucial role in embryo development by storing maternal factors, completing meiosis, and reprogramming the sperm's genetic material. D.F. Albertini [19] demonstrated that oocyte provides the initial cellular machinery and essential components like proteins, mRNAs, and mitochondria needed for early embryogenesis until the embryo's own genome becomes active. Association of *MTHFR* A1298C polymorphism with decrease of good-quality cleavage stage embryos could be explained by the fact that hyperhomocysteinaemia affect the genome of oocytes.

In this investigation, a statistically significant decrease in oocyte maturity was observed in case of the *MTRR* polymorphism A66G. But earlier A.R. Palomares *et al.* [20] assumed that *MTRR* gene seems to have no direct impact on pregnancy consecution after IVF. Besides that, J. Zhou *et al.* [21] suggested that the *MTRR* c.66A > G variant was not significantly associated with the risk of pregnancy loss. From the other hand Y. Zhang *et al.* [7] demonstrated that *MTRR* c.66A > G heterozygote was correlated with higher recurrent pregnancy loss risk (*MTRR* c.66A > G, OR = 1.62, 95% CI = 1.20-2.19, p = 0.002). The *MTRR* gene provides instructions for the methionine synthase reductase enzyme, which affects negatively the folate and methionine cycle by reactivating the methionine synthase enzyme (*MTR*). A common variation in the *MTRR* gene c.66 A > G leads to an aminoacid substitution that marginally reduces the enzyme's biological activity. This change can affect folate metabolism and has been linked to increased homocysteine concentrations [22]. As folate and methionine metabolism is required for transmitting methyl groups for DNA methylation, the association of *MTRR* polymorphism A66G with decrease of part of MII mature oocytes could demonstrate affecting of mentioned polymorphism the process of oocyte maturation.

As literature data about the effect of polymorphic variants in genes of folate metabolism are controversial, the obtained results should be interpreted within the context of heterogeneous clinical and genetic backgrounds of infertile patients. The present findings indicated that polymorphisms of folate-cycle genes may exert a selective influence on oocyte competence and early embryo quality rather than uniformly affecting all stages of assisted reproduction. Such variability in reported associations may reflect differences in the relative contribution of oocyte-dependent mechanisms and metabolic conditions to reproductive outcomes in women with unexplained infertility.

Conclusions

The negative effect of polymorphic variants in genes of folate metabolism C677T, A1298C of *MTHFR* gene and A66G of *MTRR* gene on such IVF parameters as the rate of oocytes maturation and good-quality cleavage stage embryos in IVF cycles in women with unexplained infertility was demonstrated. It was shown that the part of good-quality cleavage stage embryos was statistically lower in patients-carriers with mutant allele A1298C of *MTHFR* gene in genotype (P = 0.000022). It was also observed that the presence of *MTRR* polymorphism A66G in genotype leads to decrease of part of MII mature oocytes in infertile patients (P = 0.000842). Comparative analysis demonstrated that oocyte developmental competence was higher in healthy women than in patients with UI, as reflected by a significantly lower proportion of MII oocytes in the UI group compared with egg donors (P < 0.00001) and a lower proportion of good-quality cleavage stage embryos (P = 0.002434). Association of *MTHFR* A1298C polymorphism with affected oocytes' genome was assumed. The association of polymorphic variants in genes of folate metabolism with the process of blastocyst formation was not proved. The study of the function of *MTHFR* and *MTRR* genes in oogenesis and early embryo development is perspective. Further investigations involving larger and more clinically homogeneous patient cohorts are needed to clarify the contribution of *MTHFR* and *MTRR* polymorphisms to IVF outcomes and early reproductive failures. A comprehensive approach that combines genetic profiling with detailed assessment of oocyte quality and embryo development may

contribute to a deeper understanding of infertility mechanisms affecting different stages of conception.

Acknowledgements
None.

Funding
None.

Conflict of Interest
None.

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Асоціація поліморфізмів генів *MTHFR* і *MTRR* з жіночим безпліддям невідомого походження

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Анотація. Поліморфні алелі генів фолатного циклу асоціюються з такими причинами жіночого безпліддя, як порушення овуляції або процесу запліднення. Проте дані про поліморфізми окремих генів, що кодують ферменти метаболізму фолатів, є суперечливими. Метою цього дослідження був аналіз кореляції поліморфних варіантів C677T (Ala222Val), A1298C (Glu429Ala) гена *MTHFR* та A66G (Ile22Met) гена *MTRR* з дозріванням ооцитів та раннім розвитком ембріонів у жінок з безпліддям невідомого походження. ДНК виділено за допомогою наборів для екстракції, визначення однонуклеотидних поліморфізмів виконано методом полімеразної ланцюгової реакції у реальному часі, для контрольованої стимуляції яєчників використовували антагоністи гонадотропін-рилізинг-гормону, отримані ооцити запліднювали методом інтрацитоплазматичної ін'єкції сперматозоїдів, особливості раннього розвитку ембріонів *in vitro* проаналізовано відповідно до Стамбульського консенсусу, статистичні гіпотези перевірено на рівнях значущості 0,05 та 0,01. Частка ембріонів морфологічно високої якості на стадії дроблення була статистично нижча для безплідних пацієнток-носіїв поліморфного алеля A1298C гена *MTHFR* у генотипі ($\chi 2_{крит.}$ = 18,0361, P = 0,000022). Наявність мутантного алеля A66G гена *MTRR* призводила до зменшення кількості зрілих ооцитів MII у жінок з безпліддям невідомого походження ($\chi 2_{крит.}$ = 11,1469, P = 0,000842). Не виявлено кореляції досліджуваних поліморфізмів генів *MTHFR* та *MTRR* із загальною кількістю отриманих ооцитів, частотою запліднення та частотою формування бластоцист у досліджуваній групі. Дослідження поліморфних варіантів генів метаболізму фолатів *MTHFR* C677T (Ala222Val), A1298C (Glu429Ala) та *MTRR* A66G (Ile22Met) може бути включено до тестів, необхідних для жінок з безпліддям невідомого походження

Ключові слова: однонуклеотидний поліморфізм; фолатний цикл; ооцити; розвиток ембріонів; запліднення *in vitro*