

Research Article

A1298C Polymorphism of Fetal Methylenetetrahydrofolate Reductase (MTHFR) Gene as a Risk Factor for Spontaneous Abortion

Polimorfisme A1298C Gen Metilentetrahidrofolat Reduktase (MTHFR) Fetus sebagai Faktor Risiko Aborsi Spontan

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Abstract

Objective: To investigate the role of A1298C polymorphism of fetal methylenetetrahydrofolate reductase (MTHFR) gene in spontaneous abortion.

Method: The case control study design recruited 96 subjects in Siti Fatimah and Pertiwi mother and child hospital, Dr. Wahidin Sudirohusodo, Pelamonia, Bhayangkara, Syekh Yusuf, Haji and Labuang Baji hospital from March to September 2014. All subjects fulfilling the inclusion criteria were taken tissue samples from mothers experiencing spontaneous abortion and blood samples from normally born baby. The data were analyzed using Pearson chi-square with significant rate of 5% ($p < 0.05$).

Result: There were 49 samples as case group consisting of 36 samples (62.1%) with mutant genotype of MTHFR gene (1298AC + 1298CC) paired with 22 samples (37.9%) for the control group and also 13 samples (34.2%) with normal genotype gene (1298AA) from case group paired with 25 samples (65.8%) from control group.

Conclusion: A1298C polymorphism of fetal MTHFR gene has correlation to the rate of spontaneous fetal abortion.

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Keywords: A1298C polymorphism, spontaneous fetal abortion

Abstrak

Tujuan: Untuk mengetahui peran kejadian polimorfisme A1298C dari gen metilentetrahidrofolat reduktase (MTHFR) fetus pada abortus spontan.

Metode: Penelitian dengan desain kasus kontrol dilakukan dengan mengambil 96 subjek di RSIA Siti Fatimah dan Pertiwi, RS Dr. Wahidin Sudirohusodo, RS Pelamonia, RS Bhayangkara, RSUD Syekh Yusuf, RSUD Haji, RSU Labuang Baji selama periode Maret hingga September 2014. Seluruh subjek yang memenuhi kriteria inklusi diambil sampel jaringan dari hasil aborsi spontan dan sampel darah dari bayi yang lahir normal. Analisis data menggunakan tes Pearson chi-square dengan angka kemaknaan 5% ($p < 0,05$).

Hasil: Dari hasil penelitian didapatkan 49 sampel untuk kelompok kasus dan 47 sampel untuk kelompok kontrol. Sebanyak 36 sampel (62,1%) dengan mutasi genotip gen MTHFR (1298AC+1298CC) dari kelompok kasus dan 22 sampel (37,9%) sebagai kelompok kontrol. Selain itu, 13 sampel (34,2%) dengan gen genotip normal (1298AA) dari kelompok kasus dan 25 sampel (65,8%) dari kelompok kontrol.

Kesimpulan: Polimorfisme A1298C dari gen MTHFR memiliki hubungan dan berpotensi untuk terjadinya abortus spontan.

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Kata kunci: abortus spontan, polimorfisme A1298C

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INTRODUCTION

Spontaneous abortion (miscarriage) is used to explain the spontaneous end of pregnancy during the first 20 weeks and considered as a common failure of pregnancy. Some studies stated that 10-25% of all pregnancies would be ended as spontaneous abortion, whereas 50-75% of those cases were caused by chromosomal abnormality at the level of embryo or fetus.¹⁻³

There are several predisposing factors of abortion, such as parity and maternal age. As a risk factor, the rate of abortion is increased after 40 years old compared to below 30 years old. Another factor

which also contributing is the heterogeneity between maternal and paternal chromosome. Genetical code analysis in spontaneous abortion cases showed a role of certain enzymes in metabolic crisis pathway, including methylenetetrahydrofolate reductase (MTHFR) fetal gene.^{4,5}

Recent studies in literature showed an involvement of gene mutation in MTHFR C677T and A1298C as a risk factor of fetal death in recurrent spontaneous abortion, particularly in MTHFR homozygote related to fetal viability. Moreover, Moeljono in his thesis stated that gene mutation of A1298C was a risk factor towards spontaneous abortion cases, and its impact as a risk factor had

been proven to be unrelated with parental genetic, as opposite within C677T gene mutation where spontaneous mutation occurred along with hereditary pattern of the parents.^{6,7}

Therefore, this study aims to analyze the role of A1298C polymorphism of fetal MTHFR gene in spontaneous abortion.

METHODS

The analytical study through case control approach analyzed the role of A1289C polymorphism of fetal MTHFR gene in spontaneous abortion. The samples were taken from several hospitals, such as Dr. Wahidin Sudirohusodo, Pelamonia, Labuang Baji, Bhayangkara, Haji and Syekh Yusuf hospital, St. Fatimah and Pertiwi mother and child hospital. The samples were collected to be further measured using PCR in NECHRI laboratory.

All spontaneous abortion were taken as the case and term babies as the control. The sample were conception tissues as the result of curettage procedure from women with spontaneous abortion and umbilical cord blood from normally born baby. Data analysis used SPSS program through Pearson chi-square test and odds ratio to determine the correlation between two characteristics of nominal and ordinal data. The significant rate was 5% ($p < 0.05$).

RESULTS

In case group, 14 of 49 samples of women were more than 30 years old; meanwhile in control group, 14 of 33 samples were more than 30 years old. About 25 samples in case group and 29 samples in control group were multigravida. In Shapiro Wilk analysis, the data between two groups were normally distributed ($p > 0.05$).

The distribution of natural homozygote genotype of 1298AA (couple allele A) among case group was 13 samples (26.5%) compared to 25 samples (53.2%) in control group; meanwhile homozygote

genotype of mutant 1298CC (couple allele C) among case group was 12 samples (44.9%) and 4 samples (8.5%) in control group. The rest was heterozygote genotype of 1298 AC.

Table 2. Correlation between A1298C Polymorphism of Fetal MTHFR Gene Towards Spontaneous Abortion

Variable	OR (Exp B)	95% CI	p value
Parity			
Multigravida	1.6	0.2-2.4	0.47
Primigravida	1		
Gestational age			
≤ 12 weeks	2.1	1.1-4.1	0.02
≥ 12 weeks	1		
Maternal age			
< 30 years	1.2	0.2-3.9	0.87
≥ 30 years	1		

DISCUSSION

In this study, there was not association between case and control group according to maternal age and parity. Theoretically, the increasing of women age is in accordance with the risk of genetical abnormality. The increasing of maternal age in 3rd or 4th decade goes along with oocyte aging. As a risk factor, the condition of primordial follicle in reserve oocyte is stated to be able to reproduce some egg cells with lower quality of follicles.

As opposite, the highest number of spontaneous abortion cases in this study was found in less than 30-years-old women both in case and control group, although the maternal age had not related to the rate of spontaneous abortion. Some studies showed a risk enhancement equal to maternal parity in spontaneous abortion. This phenomenon was caused by reproductive compensation (the failure of pregnancy could be related to some attempts of repetitive conception in multigravida) and short interval between each maternal pregnancy. Along with this study, there was no significant correlation found between maternal parity and spontaneous abortion.

Table 1. Comparison between Polymorphism Genotype of Mutant Fetal MTHFR Gene A1298C (1298AC + 1298CC) and Normal (1298AA) in Case and Control Group

Fetus MTHFR genotype 1298	Case Group (n=49) %	Control Group (n=47) %	p value*	OR (95% CI)
AC + CC	36 (62.1)	22 (37.9)	0.008	3.2 (1.3-7.4)
AA	13 (34.2)	25 (65.8)		

*Pearson Chi Square

The frequency of genotype A1298C polymorphism of fetal MTHFR gene was showed by couple alleles of A, C, and AC. The highest frequency of genotype among case group was in couple allele C, sequentially followed by mutant heterozygote and normal or couple allele A. According to statistical analysis, if genotype 1298AC and 1298CC were united as one and compared to genotype 1298AA, the result of this would be statistically significant with p value around 0.008 and OR 3.2. This basically showed that a role of A1298C polymorphism of fetal MTHFR gene was related to the rate of spontaneous abortion. Study by Kim Y revealed that A1298C polymorphism of fetal MTHFR gene was related to the risk enhancement of gene chromosomal abnormality in spontaneous abortion. According to some studies in MTHFR, the two homozygote mutations both MTHFR 1298CC and 677TT stated to be related to the reducing of DNA methylation level which could lead to hypomethylation in DNA.

Theoretically, domain 1298 of MTHFR gene works in genetical regulation centre. Chronologically, there are two mechanisms for the influence from enzyme mutation of MTHFR gene. The first mechanism occurs through MTHFR enzyme as a catalyst of homocystein to metionin (an important amino acid for body), where the defect of MTHFR gene can lead to hyperhomocysteinemi. The second mechanism happens in genetical regulation, namely abnormal MTHFR gene. The failure of DNA methylation can lead to further genetical change and bring more tendency to worsen the current condition and even end up as fetal death.

The role of A1298C polymorphism of fetal MTHFR gene in spontaneous abortion can be correlated with some theories. Generally, abortion is started by fetal death which can be caused by the abnormality of fetus, embryo, and zygote growth. Chromosomal abnormality, particularly trisomal abnormality becomes the cause of 50-75% from spontaneous abortion. Moreover, the death of conception which occurred in the first trimester of pregnancy happens to be greatly influenced by fetus genome as the main determinant.

Other factors influencing the risk of spontaneous abortion are folic metabolism, vein thrombosis, and hyperhomocysteinemi. Folic metabolism and vein thrombosis impact to process of embryo genesis. The abnormality of enzyme activity acts to control this folic metabolism; therefore it can lead to the abnormality or even the death of fetus.

The recent study done in Indonesia by Moeljono ER stated that A1298C polymorphism of fetal MTHFR gene had an important role in the rate of spontaneous abortion, yet there was a little difference in the type of mutant genotype which considered to have more impact. Therefore, further study should be conducted to know this issue particularly in Indonesia.

CONCLUSION

A1298C polymorphism of fetal MTHFR gene has a correlation with the rate of spontaneous abortion. Further studies to assess the A1298C polymorphism of fetal MTHFR gene in both parents and fetus should be conducted to enrich the information regarding this correlation.

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