Journal of Taibah University Medical Sciences (2018) 13(1), 93–96

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com

Brief Communication

Maternal methyltetrahydrofolate reductase gene mutation in patients with missed abortions

Helmy A. Rady, MD

Obst. & Gyn. Department, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

Received 20 February 2017; revised 20 April 2017; accepted 24 April 2017; Available online 14 July 2017

Abstract

Background: Missed abortions are a common problem, often caused by thrombophilia in both recurring and non-recurring cases.

Aim: To determine whether the presence of a mutation in the methyltetrahydrofolate reductase (*Mthfr*) gene correlates with missed abortions.

Patients and methods: We selected two hundred patients for this study in two groups: the study group, which consisted of one hundred patients with a history of missed abortion; and the control group, which consisted of one hundred patients with no history of missed abortion.

Results: Of the 200 patients, mutations in *Mthfr* were only found in forty-four patients—thirty-four from the study group and ten from the control group.

Conclusions: *Mthfr* gene mutation is a common cause of both recurring and non-recurring missed abortions.

Keywords: Habitual abortion; Missed abortion; *Mthfr*; Recurrent miscarriage; Thrombophilia

Corresponding address: Elshatby Hospital, Alexandria, Egypt.
E-mail: helmyabdelsatar@gmail.com

Peer review under responsibility of Taibah University.

Production and hosting by Elsevier

Introduction

Missed miscarriage is a common multifactorial disease that may be recurrent; recurrent pregnancy loss refers to cases where the patient experiences two or more consecutive missed miscarriages. Missed miscarriages affect approximately 1% of fertile couples.[1]

The World Health Organization defines miscarriage as the loss of a foetus or embryo weighing less than 500 g, which corresponds to approximately 20–22 weeks of gestation.[2]

Recurrent missed abortions can often cause psychological and emotional distress for affected couples.[3,4]

Abortions for either clinically recognized or unrecognized pregnancies affect 10–12% of couples. The risk of recurrent missed abortions increases based on previous abortions: there is a 24% chance of recurrence in patients who have had one abortion, a 26% chance in patients who have had two abortions, and a 32% chance in patients who have had three abortions.[5]

Many factors are associated with recurrent miscarriages in terms of maternal, foetal, or paternal gene polymorphisms. Maternal polymorphisms may be caused by many factors, such as genetic causes, haematological causes, anatomy, and endocrine problems. Up to 50% of cases of recurrent missed abortions remain unexplained.[6]

Normal placental circulation and foetal vasculature are important for maintaining a normal healthy pregnancy; any abnormalities in placental circulation can lead to severe complications, including termination of the pregnancy.[7]

Thrombophilia may be an inherited or acquired condition that increases the risk of thromboembolisms. Inherited thrombophilia is a well-known cause of spontaneous pregnancy loss.[8]

Folate is important for normal RNA and DNA synthesis and is required for homocysteine metabolism. It is also important for normal foetal growth and development; during pregnancy, folate requirements are increased. The level of

1658-3612 http://dx.doi.org/10.1016/j.jtumed.2017.04.004

homocysteine in the body is mainly affected by dietary intake of folate and vitamin B12, as well as polymorphisms in genes that encode enzymes or transport proteins involved in folate- and vitamin B12-dependent homocysteine metabolism.[9]

Decreased folate intake will affect homocysteine metabolism and lead to an increase in homocysteine levels in the blood.[10]

Methylenetetrahydrofolate reductase (MTHFR) is an important regulatory enzyme in the metabolism of homocysteine, which catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Mutations in the *Mthfr* gene can cause decreased enzyme activity and hyperhomocysteinaemia, which induces platelet aggregation by enhancing endothelial oxidative damage. Many mutations within the *Mthfr* gene have been identified; the two most common and important mutations are C677T and A1298C. The former mutation has been shown to cause early pregnancy loss.[6]

Aim

The aim of this study is to determine whether mutations in the *Mthfr* gene are a cause of missed abortions.

Materials and Methods

Two hundred pregnant women were recruited for this study from the outpatient clinic of the El Shatby Maternity University Hospital. They were divided into two groups:

The first group included one hundred women with a history of one or more missed first trimester abortions, where the cause was unknown.

The second group included one hundred women with no history of abortion; all participants in this group were previously pregnant without complications, and have living children.

All women agreed to participate in this research and signed a written consent form.

All the women in this study were aged 20–30 years old.

Pregnancy was diagnosed by ultrasound, B-HCG, and physical examination. All diagnoses of missed abortions in the first trimester were made after excluding other possible causes of spontaneous pregnancy loss, such as anatomical or endocrine-related causes.

Blood serum was taken from the patients, and presence of the maternal *Mthfr* C667T mutation was determined by PCR.

Patients were categorised into groups based on the presence or absence of this mutation, as well as the number of abortions received.

Results were compared between different groups.

Statistical analysis

Data were collected and analysed bioinformatically. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 20.0) software.

The following statistical tests were performed:

The Chi square test (X^2) was used for categorised parameters. The arithmetic mean and standard deviation were also calculated. The Student's paired *t*-test was used for parametric data. A value of $P < 0.05$ was considered statistically significant.

Results

The mean age of patients was 25.6 years old in the first group and 24.9 years old in the second group (Table 1).

In the studied group, 31% of patients had two abortions, and 23% had five abortions (Table 2).

In the control group, all women delivered a living child at least once (Table 3).

Presence of the *Mthfr* gene mutation was significantly higher in patients with missed abortions than in the control group (Table 4).

Presence of the *Mthfr* gene mutation significantly differed depending on the number of abortions (Table 5 and Figure 1).

Discussion

Many factors may contribute to sporadic and recurrent missed abortions. The presence of *Mthfr* gene mutations was studied as a potential cause for this phenomenon.

In this study, the age of patients ranged from 20 to 30 years in both groups; the mean age was 25.6 years in the study group, and 24.9 years in the control group.

In a study performed by L. Zhu[11]; patients were aged between 22 and 44 years, with a mean age of 29.8 ± 4.3 years. Their control group consisted of 174 participants aged between 21 and 24 years, with a mean age of 28.5 ± 4.0 years. The age difference between the two groups was not statistically significant ($P > 0.05$).

In a study by Wendell Vilas Boas et al.,[12] the median age of the women in the study group was 29.4 ± 5.4 years, while the average age in the control group was 23 ± 5.5 years. The median abortion number in the study group was 3.2 ± 1.9, ranging from two to thirteen abortions in which forty-one (47%) women had two spontaneous abortions, twenty-five

Table 1: Comparison of ages of patients in the two studied groups.

	First group	Second group
Range	21–30	20–29
Mean ± S.D.	25.65 ± 2.65	24.92 ± 2.46
T	0.106	
P	0.69	

Table 2: Distribution of the number of abortions in the studied group.

No. of abortions	No.	%
1	7	7.0
2	31	31.0
3	17	17.0
4	19	19.0
5	23	23.0
6	1	1.0
7+	2	2.0

Table 3: Distribution of the number of deliveries and living children in the control group.

No. of deliveries and living children	No.	%
1	16	16.0
2	30	30.0
3	29	29.0
4+	25	25.0

Table 4: Presence of the methylenetetrahydrofolate reductase (*Mthfr*) gene mutation in all patients.

Gene mutation	First group		Second group	
	No.	%	No.	%
Positive	34	34.0	10	10.0
Negative	66	66.0	90	90.0
X^2	16.8			
P	0.0001*			

Table 5: Relationship between the number of abortions and presence of the methylenetetrahydrofolate reductase (*Mthfr*) gene mutation.

No. of abortions	Total number of patients	Positive		Negative	
		No.	%	No.	%
1	7	7	100.0	0	0.0
2	31	12	38.7	19	61.3
3	17	4	23.5	13	76.5
4	19	3	15.8	16	84.2
5	23	5	21.7	18	78.3
6	1	1	100.0	0	0.0
7+	2	2	100.0	0	0.0
P		0.001*			

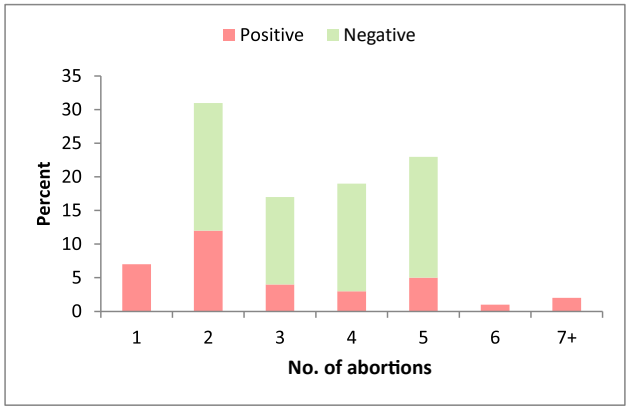

Figure 1: Relationship between the number of abortions and presence of the methylenetetrahydrofolate reductase (*Mthfr*) gene mutation.

(29%) women had three spontaneous abortions, and twenty-one (24%) women had more than three abortions. In our study, 31% of patients had two abortions, and 23% of patients had five abortions.

Our study showed a strong association between *Mthfr* gene mutation and missed abortions. This is in line with the results of previous studies such as Cao Y et al.,[13] Govindaiah V et al.,[14] Puri M et al.,[15] and Nair RR.[16]

However, some studies failed to find a correlation, such as Wendell Vilas Boas et al.,[12] Sinem Yalcintepe et al.,[17] and Puri M et al.[15]

Conclusions

Mutations in the *Mthfr* gene are a common cause of recurring or non-recurring missed miscarriages.

Conflicts of interest

The author has no conflict of interest to declare.

References

1. Hoff Man Schorge, Schaffer Halvorson, Bradshaw Cunningham. First-trimester abortion. In: *Williams gynecology*. 2nd ed. McGraw-Hill Medical; 2012. pp. 170–179.
2. Mangalgiri Ashutosh S, Pathak SA. Cytogenetics in recurrent abortions. **People's J Sci Res 2008**; 1: 5–8.
3. Van den Akker Olga BA. The psychological and social consequencies of miscarriage. **Expert Rev Obstet Gynecol 2011**; 6(3): 295–304.
4. Nakano Yumi, Akechi Tatsuo, Sugiura Ogasawara Mayumi. Cognitive behavior therapy for psychological distress in patients with recurrent miscarriage. **Psychol Res Behav Manag 2013**; 6: 37–43.
5. Simpson J, Carson S. **Glob Libr Women's Med 2013**. http://dx.doi.org/10.3843/GLOWM.10319.
6. Chaithra PT, Malini Suttur S, Sharath Kumar C. An overview of genetic and molecular factors responsible for recurrent pregnancy loss. **Int J Hum Genet 2011**; 11(4): 217–225.
7. Khankin EV, Royle C, Karumanchi SA. Placental vasculature in health and disease. **Semin Thromb Hemost 2010**; 36: 309–320.
8. Rabinovich A, Cohen JM, Prandoni P, et al. Association between thrombophilia and the post-thrombotic syndrome: a systematic review and meta-analysis. **J Thromb Haemost 2014**; 12: 14–23.
9. Cao Y, Xu J, Zhang Z, Huang X, Zhang A, Wang J, et al. Association study between methylenetetrahydrofolate reductase polymorphisms and unexplained recurrent pregnancy loss: a meta-analysis. **Gene 2013**; 514(2): 105–111.
10. Creus M, Deulofeu R, Peñarrubia J, Carmona F, Balasch J. Plasma homocysteine and vitamin B12 serum levels, red blood cell folate concentrations, C677T methylenetetrahydrofolate reductase gene mutation and risk of recurrent miscarriage: a case-control study in Spain. **Clin Chem Lab Med 2013**; 51(3): 693–699.
11. Zhu L. Polymorphisms in the methylene tetrahydrofolate reductase and methionine synthase reductase genes and their correlation with unexplained recurrent spontaneous abortion susceptibility. **Genet Mol Res 2015**; 14(3): 8500–8508.
12. Vilas Boas Wendell, Gonçalves Rozana Oliveira, Costa Olívia Lúcia Nunes, Goncalves Marilda Souza. Metabolism and gene polymorphisms of the folate pathway in Brazilian women with history of recurrent abortion. **Ginecol Obstet Feb. 2015**; 37(2). Rio de Janeiro.

13. Cao Y, Xu J, Zhang Z, et al. Association study between methylenetetrahydrofolate reductase polymorphisms and unexplained recurrent pregnancy loss: a meta-analysis. **Gene 2013**; 514: 105–111.
14. Govindaiah V, Naushad SM, Prabhakara K, et al. Association of parental hyperhomocysteinemia and C677T Methylene tetrahydrofolate reductase (MTHFR) polymorphism with recurrent pregnancy loss. **Clin Biochem 2009**; 42: 380–386.
15. Puri M, Kaur L, Walia GK, Mukhopadhhyay R, Sachdeva MP, Trivedi SS, et al. MTHFR C677T polymorphism, folate, vitamin B12 and homocysteine in recurrent pregnancy losses: a case control study among North Indian women. **J Perinat Med 2013**; 41(5): 549–554.
16. Nair RR, Khanna A, Singh R, Singh K. Association of maternal and fetal MTHFRA1298C polymorphism with the risk of pregnancy loss: a study of an Indian population and a meta-analysis. **Fertil Steril 2013**; 99(5). 1311.e4–1318.e4.
17. Yalcintepe Sinem, Ozdemir Ozturk, Hacivelioglu Servet Ozden, Akurut Cisem, Koc Evrim, Uludag Ahmet, Cosar Emine, Silan Fatma. Multiple inherited thrombophilic gene polymorphisms in spontaneous abortions in Turkish population. **IJMCM Spring 2015**; 4(2). Original Article.

How to cite this article: Rady HA. Maternal methyltetrahydrofolate reductase gene mutation in patients with missed abortions. J Taibah Univ Med Sc 2018;13(1):93–96.