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CORRELATION BETWEEN MATERNAL METHYL TETRA HYDRO FOLATE REDUCTASE GENE POLYMORPHISM WITH RECURRENT MISCARRIAGE

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ABSTRACT

Background: Recurrent miscarriages are pregnancy losses before the 24th week of gestation, affecting 2% of all pregnancies. Caused by issues in the mother, father, fetus, or placenta, they can be linked to increased homocysteine levels in the blood, a genetic, environmental, and methylenetetrahydrofolate reductase gene polymorphism. **Aim of the study**: To know the prevalence and compare the C677T & A1298C gene polymorphism of methylenetetrahydrofolate reductase among cases of recurrent miscarriage. **Patients and Methods**: A prospective case control study involving 100 women from Al-Khansaa and Duhok teaching hospitals and private clinics. The case group included 50 women with three or more miscarriages without a history of pregnancy proceeded beyond 24+6 weeks?, while the control group included 50 women with at least one live child without a previous miscarriage. A blood sample was collected and examined for the presence of gene polymorphism of C677T and A1298C. Results were analyzed statistically. **Results:** The study found significant differences in the age of women at marriage and first conception for recurrent miscarriage compared to the control group. The C677T gene was detected in 18.0% of cases and 4.0% of controls, while the A1298C gene was detected in 8% of cases. All positive gene mutations in recurrent miscarriage cases had irregular menstrual cycles. **Conclusion:** Correlation between gene polymorphism and recurrent miscarriage risk can be found in methylenetetrahydrofolate reductase C677T but not in A1298C. The test for C677T is of certain significance for investigating idiopathic recurrent miscarriage.

KEYWORDS: A1298C, C677T, gene mutation, Methyl Tetra Hydrofolate Reductase (MTHFR), Recurrent Miscarriage.

INTRODUCTION

The recurrent miscarriage (RM) is a challenging clinical scenario with associated psychological trauma, which is defined as the loss of three or more consecutive pregnancies. It can be frustrating for both patients and obstetricians. Miscarriages occur in more than 15% to 25% of all pregnancies, and only approximately 2% of them experience repeated miscarriages.[1] Pregnancy is a stage in which there is a proper fusion of the sperm with the oocyte, a good embryonic development, and the achievement of the implantation of the blastocyst in the uterus. In addition, it is also the time when fetal development begins. The nutritional status of the mother is of great importance because the deficiency of nutrients such as vitamin B, folates, and vitamin B12 has been linked to adverse pregnancy outcomes, among which are low birth weight, prematurity, malformations, and others. The causes of RM in 50% of cases are still unknown.[2] RM is commonly accepted as a "multi-factorial" result (genetic disorders, uterine pathologies, endocrine dysfunctions, autoimmune diseases, acquired and inherited thrombophilia, as well as environmental factors).[1]

The methylenetetrahydrofolate reductase (MTHFR) gene is the major genetic modifier that affects the folate cycle and the homocysteine metabolism.[3] Folate is important for normal RNA and DNA synthesis and is required for

homocysteine metabolism. It is also important for normal fetal growth and development. During pregnancy, folate requirements are increased. Decreased folate intake will affect homocysteine metabolism and lead to an increase in homocysteine levels in the blood.[4] MTHFR polymorphisms are not an inherited thrombophilia; therefore, they should not be included as part of a thrombophilia workup or in any thrombophilia laboratory test panels. Furthermore, patients who carry these polymorphisms should be reassured that this common finding does not place them at increased thrombotic risk and they do not in fact carry a thrombophilia.[5]

Two common genetic polymorphisms in the MTHFR gene have been recognized: C677T and A1298C single-nucleotide polymorphisms. In C677T single nucleotide polymorphism, the cytidine residue at position 677 in the gene is substituted by thymidine, causing an alanine-to-valine conversion in the protein. The resultant variant is thermolabile, so the enzyme activity is reduced by 35% in carrier's genotype C/T, in comparison to normal genotype C/C, while it's reduced by 70% in homozygous genotype T/T.[6] On the other hand, (A1298C) polymorphism is a result of a missense mutation in exon-7 due to a transversion, which leads to a substitution of glutamate with alanine, without overtly affecting enzyme activity.[7]

It is known that heterozygous or homozygous C677T or A1298C variants of the MTHFR gene lead to decreased enzyme activity and hence could cause mild to moderate hyperhomocysteinemia, especially in folate or vitamin B12 deficiency.[3] However, unlike the 677T mutation, the 1298C mutation, heterozygous (1298AC) and homozygous (1298CC) mutations did not increase the homocysteine content.[6, 7] Also, the MTHFR C677T and A1298C mutant genotypes may be present in healthy women, and not all carriers experienced RM, indicating that the synergistic effect of multiple hereditary and nonhereditary thrombotic disorders maximizes the risk in women.[8] Furthermore, the estimated risk for RM in patients carrying the compound heterozygous (C677T/A1298C) genotype increased 4.86-fold compared with individuals with the wild-type (C677C/A1298A) genotype.[9] And the risk of RM increased as the number of mutations rose of MTHFR C677T and A1298C.[10] Besides that, the prevalence of the MTHFR C677T differs depending on location and ethnic background.[6-8]

The current study was aimed at knowing the prevalence of the C677T & A1298C gene polymorphism of MTHFR among cases of RM and comparing it with the control group.

MATERIALS AND METHODS

Study Design, Setting, and Data Collection Time

This is a prospective observational case-control study that includes 100 women who visited the obstetrical and gynecological departments at Al-Khansaa and Duhok teaching hospitals and private clinics in Iraq from 1st February to 31st October 2023. The data was collected from the answers of the women to the checklist questionnaire during direct interviews with the women and the review of their information by the researcher.

The present study involved 100 women aged between 20 and 34 years old with normal body mass index (BMI) and Rhesus positive. Fifty women constituted the case group (primary and clinical RM), and 50 others were the control group.

Case Definition: Any married women aged between 20 and 34 years having a history of three or more consecutive recurrent miscarriages during the 1st 23 weeks + 6 days of gestation without a history of any pregnancy ending after completing 24 weeks.

Control Definition: Any married women aged between 20 and 34 years with a history of previous successful pregnancy outcomes after completing 24 weeks of gestation and with no history of any pregnancy loss before 23 weeks + 6 days.

Exclusion Criteria: Any women who had one or more of the following were excluded from the present study for both the case and control study.

1. Age <18 & >35 years with BMI <18 & >25 kg/m², and Rh-negative groups.
2. History of hydatidiform mole or ectopic pregnancy or history of the following gynecological problems (uterine fibroid, polycystic ovarian syndrome, congenital uterine anomaly, and cervical weakness), or history of medical problems (diabetes mellitus, thyroid disease, systemic lupus erythematosus, chronic inflammatory disease, and thrombophilia (acquired & inherited)), or history of aspirin, low molecular weight heparin (LMWH), or methotrexate use.
3. Any women refuse to participate in the study.

Every woman asked about socio-demographic data, obstetrical data, data involving menstrual history, and past medical and surgical history. Family, social, and drug history were also evaluated. Moreover, each woman asked about previous investigations in detail.

Blood samples were collected in appropriate sterile EDTA tubes of about 5 cc and sent for specialized laboratory for DNA extraction and genotype analysis using real time polymerase gene reaction (RT-PCR) according to the kit leaflet to evaluate the association between MTHFR C677T, A1298C, and the risk of RM in these women. The result were obtained and analyzed statistically with data.

Statistical Analysis

Data coding and organization was performed via Microsoft Excel 2010. Descriptive and analytic statistics were performed using the Minitab version 20 software statistical program. The descriptive statistics include mean ± Standard Deviation (SD) for measurable variables and frequencies and percentages for categorical variables. A chi-square test was performed for comparison between categorical variables. An independent t-test of the two means was used for comparison between quantitative parameters. P-values < 0.05 were considered statistically significant.

RESULTS

In this study, there are 100 women chosen, 50 women as the case group and 50 women as the control group, and blood samples evaluated for MTHFR gene polymorphism (C677T, A1298C). No significant statistical differences were found concerning the age, weight, BMI, and residence. In addition, a higher number of primary school women is seen among control groups in comparison to case groups (88.0% versus 34.0%). While regarding university and higher education, the case group was higher than the control groups (24.0% versus 0.0%), respectively, and showed a statistically significant difference (p=0.001). According to occupation, the housewives showed a higher number in the control group in relation to the case group (100.0% versus 92.0%), respectively, while employees showed a higher number in the case groups in comparison with the control groups (8.0% versus 0.0%), respectively, and showed a significant statistical difference (p=0.041). Finally, regarding consanguinity, a higher number of consanguineous marriages among case groups in comparison to control groups (74.0% versus 26.0%) respectively and showed a significant statistical difference (p=0.001), as shown in table 1.

Table 1: Socio-Demographic Characteristics of the Study Sampled Women.

Characteristics		Cases [n = 50]	Control [n = 50]	P-value*
Mean maternal age, years		28.3 ± 3.91	28.0 ± 3.39	0.744
Mean weight (kg)		64.2 ± 3.42	65.5 ± 3.22	0.064
Mean BMI (kg/m²)		23.4 ± 0.98	23.7 ± 0.78	0.068
	No. (%)		**No. (%)**	
Residence	**Urban**	34 (68.0)	25 (50.0)	0.067
	Rural	16 (32.0)	25 (50.0)	
Education	**Illiterate**	18 (36.0)	4 (8.0)	**0.001**
	Primary	17 (34.0)	44 (88.0)	
	Secondary	3 (6.0)	2 (4.0)	
	University	12 (24.0)	0 (0.0)	
Occupation	**Housewives**	46 (92.0)	50 (100.0)	**0.041**
	Employees	4 (8.0)	0 (0.0)	
Consanguinity	**Yes**	37 (74.0)	13 (26.0)	**0.001**
	No	13 (26.0)	37 (74.0)	

* Independent T-test of two means was used for quantitative variables and a chi-square test for categorical variables.

Table 2: Comparison of Marriage's Information and Obstetrical History Between the Two Groups.

Items		Cases [n = 50] Mean ± SD	Control [n = 50] Mean ± SD	P-value*
Marriage's information:				
Obstetric history:		**No. (%)**	**No. (%)**	
Parity	**0**	50 (100.0)	0 (0.0)	---
	1	0 (0.0)	17 (34.0)	
	2 +	0 (0.0)	33 (66.0)	

***** Independent T-test of two means was used for quantitative variables and a chi-square test for categorical variables.

Regarding the relationship between the presence of MTHFR gene polymorphism (C677T & A1298C) and recurrent miscarriage in this study, sampled groups are shown in table (2). The percentage of the C677T gene detected in case groups was higher than in control groups (18.0% versus 4.0%), respectively, and showed high significant risk factors for RM (p=0.025, odd ratio=5.27). While the percentage of A1298C gene detected in case groups was 8.0%, no case was detected in the control group. in the control group, despite the high odd ratio (9.77), it still had no significant risk factors for RM, as seen by p=0.117. The relationship between the number and gestational age of miscarriage and gene mutation in RM cases was demonstrated in table (3); it elicited that the number of miscarriages (3 or ≥4) and gestational age (<13 wks or ≥13 ≥13wks) among the cases group in relation to gene mutation versus no gene mutations showed no significant statistical

difference (OR=1.29; p=0.725 versus OR=1.50; p=0.738), although the percentage of RM women who had 3 miscarriages without gene mutation is higher than those with gene mutation (69.2% vs. 63.6%), respectively. And the percentage of GA of RM women who were <13 weeks with gene mutation is higher than those with no gene mutation (90.9% vs. 87.2%), respectively, but the result was statistically no significant difference, as mentioned above.

Table 2: The Relationship Between Presence of MTHFR Gene Polymorphism (C677T & A1298C) and Recurrent Miscarriage in the Study Sampled Groups.

MTHFR gene polymorphism	Cases Recurrent Miscarriage		Control No recurrent miscarriage		Odd ratio	95% C.I.	P-value
	No.	%	No.	%			
C677T gene							
Detected **	9	18.0	2	4.0	5.27	1.08; 25.78	**0.025***
Not detected	41	82.0	48	96.0			
A1298C							
Detected **	4	8.0	0	0.0	9.77	0.51; 45.41	0.117
Not detected	46	92.0	50	100.0			
Total	50	100.0	50	100.0	---	---	---

*Seven cases of homozygous and two cases of heterozygous C677T gene mutation. Two cases of homozygous and two of heterozygous A1298C were detected, and it is impossible to calculate an odd ratio for each subtype independently because of the small sample size; *Chi-square test was used, d.f = 1; ** include homo or heterozygous.

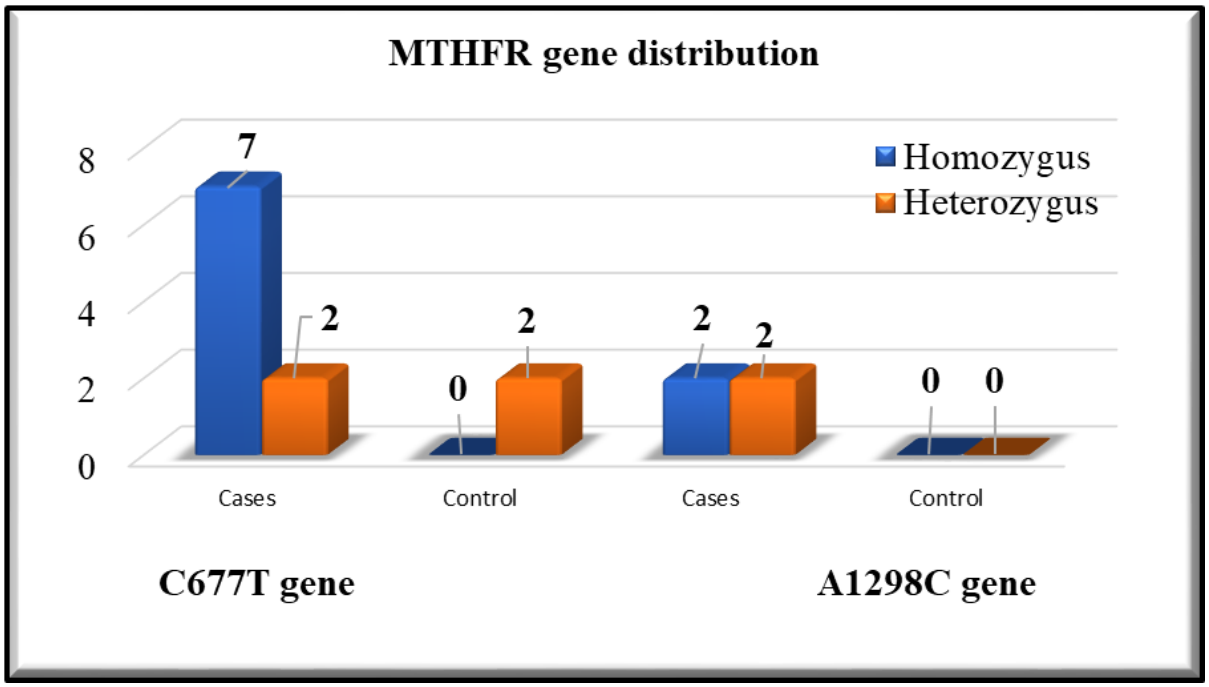

Figure (1): Distribution of MTHFR gene polymorphism among the study sampled population. (7 cases of homozygous C677T and 2 cases of homozygous A1298T; the other 2 patients from those who had the mutation had heterozygous genes of both C677T and A1298C (compound gene).

Table (3): The Relationship Between the No. and GA of Miscarriage and Gene Mutation in Recurrent Miscarriage Cases.

Miscarriage characteristics	Cases "Recurrent Miscarriage"				Odd ratio	95% C.I.	P-value *
	Gene mutation [n = 11]		No gene mutation [n = 39]				
	No.	%	No.	%			
No. of RM							
≥ 4	4	36.4	12	30.8	1.29	0.32; 5.24	0.725
3	7	63.6	27	69.2			
GA of RM							

< 13 weeks	10	90.9	34	87.2	1.50	0.15; 14.09	0.738
≥ 13 weeks	1	9.1	5	12.8			
*The chi-square test was used, d.f. = 1.							

The relationship between different obstetrical parameters and gene mutation in RM cases was demonstrated in table (4). According to the obstetrical parameters and gene mutation in RM cases, women's age at marriage was (30+) years, and those with gene mutation showed a higher percentage of RM in comparison with those whose ages were between 20 and 29 years (72.7% versus 27.3%), respectively. While in comparison between those that had no gene mutation and their ages between 20 and 29 years had a higher percentage of RM than those their ages were 30+ years (87.2% versus 12.8%), respectively, and showed a significant statistical difference (odd ratio=18.13, 95% CI=3.57; 92.12, P-value=0.001).

Women aged at first conception (≥30 years) and who had a gene mutation had a higher percentage of RM in comparison with those whose ages were <30 years (81.8% versus 18.2%), respectively. While in comparison between those that had no gene mutation and their ages < 30 years had higher percentages than those their ages ≥ 30 years (84.6% versus 15.4%), respectively. And showed a significant statistical difference (odd ratio=24.75, 95% CI=4.25; 101.13, P value=0.001).

About women with RM and who had a gene mutation with positive consanguinity showed a higher percentage than those without consanguinity (90.9% versus 9.9%), and those that had no gene mutation and positive consanguinity showed a higher percentage than those with negative consanguinity (69.2% versus 30.8%) and showed no significant statistical difference (odd ratio=26.73, 95% CI 0.51-38.74, P value=0.148).

Finally, regarding women with RM who had a gene mutation with an irregular menstrual cycle, they had a higher percentage than those with a regular menstrual cycle (100.0% versus 0.0%), respectively. While those with no gene mutation demonstrate a higher percentage of regular menstruation than those with irregular menstruation (53.9% versus 46.1%), respectively, and show significant statistical analysis (OR=26.73, 95% CI 2.54; 65.23, P- value=0.002).

Table (4): The Relationship Between Different Obstetric Parameters and Gene Mutation in Recurrent Miscarriage Cases.

Miscarriage characteristics	**Cases "Recurrent miscarriages"**				**Odd ratio**	**95% C.I.**	**P-value***
	Gene mutation [n = 11]		**No gene mutation [n = 39]**				
	No.	**%**	**No.**	**%**			
Women's age at marriage, years							
30 +	8	72.7	5	12.8	18.13	3.57; 92.12	**0.001**
20 – 29	3	27.3	34	87.2			
Women age at 1st conception, years							
≥ 30	9	81.8	6	15.4	24.75	4.25; 101.13	**0.001**
< 30	2	18.2	33	84.6			
Consanguinity							
Yes	10	90.9	27	69.2	4.44	0.51; 38.74	0.148
No	1	9.9	12	30.8			
Regularity of the cycle							
Irregular	11	100.0	18	46.1	26.73	2.54; 65.23	**0.002**
Regular	0	0.0	21	53.9			

***Chi-square test was used, d.f. = 1.**

Regarding women with RM who had gene mutation and whose blood groups were A+ and O+, a higher percentage of miscarriages was shown in comparison with those with no gene mutation (63.6% versus 36.4%), respectively, and there was no significant statistical difference (P-value = 0.260). as demonstrated in table (5).

Table (5): The Relationship Between Blood Groups and Gene Mutation in Recurrent Miscarriage Cases.

Blood groups	Cases "Recurrent miscarriage"				Total No. (%)	P-value*
	Gene mutation [n = 11]		No gene mutation [n = 39]			
	No.	%	No.	%		
A+	7	63.6	17	43.6	24 (48.0)	0.260
***AB*+**	*0*	*0.0*	*5*	*12.8*	*5 (10.0)*	
B+	0	0.0	6	15.4	6 (12.0)	
O+	4	36.4	11	28.2	15 (30.0)	

*Chi-square test was used, d.f. = 3.

DISCUSSION

The relationship between MTHFR polymorphisms and adverse obstetrical outcomes, including recurrent miscarriage, has been a topic of interest for years. Despite numerous studies, the results remain controversial, prompting this study.

In the current study, maternal age was matched between both groups to avoid its effect on RM and showed that the age of the RM patients did not significantly differ from that of the controls. In the same line, the case-control study conducted by Turgal *et al.*[10] matched ages in between the studied groups and reported no significant difference in mean age between the Syrian cases and control. While Hwang *et al.*[11] study reported that the age of the patients was lower than that of the controls, and the difference was statistically significant ($p < 0.001$). In the same line as maternal age, maternal BMI was also matched between both groups to avoid its effect on RM since there was an established link between risk of RM and maternal weight and obese state. Similarly, another study conducted by Matjila *et al.*[12] demonstrated a statistically significant association between raised BMI and risk of RM. On the other hand, Metwally *et al.*[13] study reported that the risk of further miscarriage within the RM population was significantly higher in underweight women. Most of the patients in the current study lived in urban areas, but no statistically significant difference was found in relation to controls. In the same line as the Ghana Maternal Health Survey[14], the miscarriages were found to be higher among urban residents but statistically insignificant. In rural areas, miscarriages have been reported by some studies, and a major contributory factor has been identified as poor sanitation conditions in rural settings.[15] The association of educational level with RM was a statistically significant difference, and it was more frequent among the primary school level (34%). In contrast, Tavoli *et al.'s*[15] study reported that the majority of women with RM had higher education (53.3%) but with insignificant statistical difference. Furthermore, Ali *et al.*[16] study found no difference between the cases and control groups in relation to education.

Among the present study groups, housewives were the most frequently found with a statistically significant difference (92%). Tavoli *et al.*[15] study showed that 72.4% of women with RM were housewives and 27.6% were employed; the difference was not statistically significant.

In the current study regarding the consanguinity, a statistically significant difference was found between the cases and control groups. Similar to that result was the results of the Warsy *et al.*[17] study, which showed that the frequency of consanguinity is significantly higher in women with RM.

Large studies worldwide consistently report a significant increased risk for RM in women age ≥35 years. A systematic review and meta-analysis showed that the maternal age of >35 years was associated with a 65% increased risk of an RM[18]; for that reason, the selection of the study was from age (20-34) years old. Previous studies demonstrate that women's age at conception is reported to serve as an independent risk factor for miscarriage.[19] According to the current study design, all the women with RM were nullipara while most of the control women was multipara. Moreover, irregular menstrual cycle was reported in 58% of women with RM meanwhile the result obtained from a case-control study conducted among the Iranian women by Hajipour *et al.*,[4] was 46.6% of the cases with RM had reported irregular cycle.

Rh negative was found to be a risk factor for RM in the case population. In the present study, blood group A+ was found in about half of cases, followed by blood group O+, with statistically no significant differences in comparison to controls. Similar to it was the AL-Hadrawi *et al.*[20] study, which showed that most women who suffer from recurrent miscarriage are of blood type (O and A). In a large case-control study conducted by Dentali *et al.*[21] *it was* revealed that women with non-O blood type—the most commonly inherited prothrombotic factor 10—carry a higher risk of developing early unexplained RM vs. women with O blood type. In Abd Allah *et al.'s*[22] study, group O shows the most frequency among RM women, followed by group A. The results of the present study indicate that there was no statistically significant difference between the A, B, AB, and O blood groups and thrombosis risk factors in women with RM. Consanguineous marriages are common in Arab populations, as reported by the Gazali *et al.*[8] study. There is controversy as to whether there is any correlation between RM and consanguinity. On the

other hand, Saad and Jauniaux[23] reported no association between consanguinity and RM in Qatar and concluded that this finding could be because autosomal recessive alleles are uncommon in Qatari populations.

Regarding the statistical risk association of the women with RM among the current study in comparison to that of controls in relation to the detectable C677T polymorphism, it was found that the association was 5.27 times. Similar to the result reported in China by Xu *et al.*[7], *a* study showed that those with RM were more likely to have the C677T. The C677T mutation causing reduced enzymatic activity is a known influencing factor of HHcy. However, the MTHFR C677T allele was not found to be associated with RMs in the Dell'Edera *et al.*[6] study. The significance of the MTHFR C677T polymorphism has been suggested in a meta-analysis by Chen *et al.*[9], wherein polymorphism at this particular locus was found to be associated with RM risk. An association of MTHFR C677T and RM has been reported by researchers. Previous results in which a case-control study conducted in Japanese women by Kobashi *et al.*[5] showed no association of the *MTHFR* C677T polymorphism with RM. Although the current study showed that the presence of A1298C was risky for the occurrence of RM, the statistical association was not significant. Another article[23] demonstrated the association between MTHFR A1298C and RM. The presence of two gene mutations in heterozygous form was reported in two patients with RM and unable to be analyzed statistically because of small sample size. Xu *et al.'s* study[7] found that the frequency of MTHFR C677T/A1298C compound genotypes in the RM group was higher compared with the control group. Moreover, Callejon *et al.'s* study[3] found an increased risk of RM as the number of mutations rose of MTHFR C677T and A1298C, although many studies have reported on the relationship between MTHFR A1298C and C677T polymorphisms and RM, the results have been inconsistent.[9] The inconsistency of results may be due to differences in genetics, race, regional eating habits, as well as the fact that the sample size is too small to objectively reflect the relevance. The current study showed no statistical significant difference regarding the no. of miscarriage in relation to gene mutation. The study of Huang *et al.*[11] reported that there was no difference in genotype distribution and the number of miscarriages. While the study of Rady[2] showed a strong association between MTHFR gene mutation and the number of miscarriages. Congenital abnormality was associated with RM in the first trimester. In the current study, 10 women out of the 11 cases with gene mutations had miscarriage in less than 13 weeks, with only one case having it above the 13 weeks. After reviewing the detailed history of that woman, it was found that she took the methylfolate in an interrupted way, which was not sufficient to prevent RM.

CONCLUSIONS

Correlation between gene polymorphism and recurrent miscarriage risk can be found in methylenetetrahydrofolate reductase C677T but not in A1298C. Also C677T is of certain guiding significance for investigating idiopathic recurrent miscarriage.

Declaration

This thesis is submitted in partial fulfillment of the requirements for the Iraqi Board for Medical Specializations in Obstetrics and Gynecology.

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