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Maternal tetrahydrofolate reductase gene mutation in patients with missed abortion

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Abstract
Background: missed abortion is a common problem, thrombophilia is a common cause of missed abortion either recurrent or not
Aim of the work: to correlate presence of MTHFR gene mutation in patients with missed abortion
Patients and methods: the study included 200 patients divided into 2 groups; study group included 100 patients with history of missed abortion, and control group included 100 case with no history of missed abortion.
Results: of 200 patients only 44 was having MTHFR gene mutation, 34 of them was present in case group while 10 only in control group.
Conclusions: MTHFR gene mutation is acommon cause of missed abortion either recurrent or not

Keywords: missed abortion, recurrent miscarriage, habitual abortion, MTHFR, thrombophilia

1. Introduction

Missed miscarriage is a common multifactorial disease, it may be recurrent and if it is recurrent for two or more consecutive times we call it recurrent pregnancy loss, and it may affect about one percent of fertile couples [1].

World Health Organization defined miscarriage as loss of the fetus or embryo weighing less than 500g, which would normally be at 20-22 complete weeks of gestation [2].

Recurrent missed abortion usually causes psychological and emotional mental distress to the affected couples [3, 4].

Abortion in couples either clinically recognized or unrecognized pregnancies affectes about 10-12% of couples [5].

The risk of recurrence of missed abortion is affected by number of abortions; 24% recurrence in patients with one abortion, 26% with two abortions and 32% chance of recurrence in case of three abortion [6].

Many factors are associated with recurrent miscarriage in terms of maternal or fetal or paternal gene polymorphisms. maternal polymorphism are caused by many factors like: genetic causes, hematological causes, anatomical factors and endocrine problems [7]. 50% of cases with recurrent pregnancy remain unexplained [8].

Normal placental circulation and fetal vasculature are important to maintain normal healthy pregnancy, any abnoramlities in placental circulation may lead to many complication including pregnancy loss [9].

Thrombophilias may be inherited or acquired conditions both may predispose to thromboembolism (10). Inherited thrombophilia is well known cause of spontaneous pregnancy loss [11, 12],

Folate is important for normal RNA and DNA synthesis and it is required for homocysteine metabolism. It is also important for normal fetal growth and development, in certain situations like pregnancy folate requirements are increased [13]

homocysteine level in the body is affected mainly by folate and vitamin B12 intake in diet, and polymorphism in genes which encode enzymes or transport proteins involved in the folate- and vitamin B12-dependent homocysteine metabolism [14, 15].

Decreased folate intake will affect homocysteine metabolism and will lead to an increase in homocysteine level in circulation [16].

MTHFR is important regulatory enzymes in the metabolism of homocysteine that catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate [17].

Mutations in the MTHFR gene cause decreased activity of enzyme and subsequently hyperhomocysteinemia, which induces platelet aggregation through enhancement of endothelial oxidative damage [18].

Many mutations within the MTHFR gene were described, C677T and A1298C mutations are the two most common and important mutations [19]. MTHFR C677T gene polymorphism causes early pregnancy loss [20].

The MTHFR gene polymorphisms are frequently associated with increased homocystein level in circulation [21, 2]

hyperhomocysteinemia causes many complications during pregnancy like recurrent pregnancy loss, neural tube defects and pre-eclampsia [23]

Aim of the study

Is to study the MTHFR gene mutation as a cause of missed abortion

Patients and methods

The study included two hundred pregnant women recruited from outpatient clinic in El Shatby maternity university hospital, divided in to two groups:

First group included one hundred women with history of

one or more missed abortion
While the second group included one hundred women with no history of abortions, all of them have normal previous pregnancy and have living children.
All women accepting to participate in this research and sign a written consent Selected age for all women was ranging from 20 to 30 years.
Diagnosis of pregnancy was make using ultrasound, B HCG and physical examination, all of them diagnosed as missed abortion in the first trimester. after exclusion of other causes of spontaneous pregnancy loss like anatomical causes and endocrinal causes of abortion Serum blood was taken and sent for maternal tertrahydrofolate reductase gene mutation study by PCR technique (C677T polymorphisms of the methylenetetrahydrofalate reductase gene (MTHFR))
Patients were catogrized into groups regarding presence or absence of this gene mutation. Also categorization was done regarding number of abortions. Comparision among different groups was done

Statistical analysis
The Data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software.

The statistical test used as follow
Arthematic mean, standard deviation, for categorized parameters Chai square test was used. While for two groups t-test was used for parametric data. The level of significant was 0.05.

Results
The mean age for patient in the 1 st group was 25.6 years while in 2nd group is 24.9 years which is statistically insignificant. Table (1)

Table 1: Comparison between the two studied groups regarding the age of patients

	1 st group	2 nd group
Range	21-30	20-29
Mean±S.D.	25.65±2.65	24.92±2.46
T	0.106	
P	0.69	

Regarding number of abortions 31 % of patients in studied group aborted twice and 23% of them aborted 5 times. Table(2)

Table 2: Distribution studied group regarding number of abortions.

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

In control group all women delivered one time or more. Table (3)

Table 3: Distribution the second group regarding number of deliveries and living children

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

Presence of MTHFR gene mutation is significantly high in patients with missed abortion than control group. table (4)

Table 4: Presence of gene mutation in all groups

Gene mutation	1 st group		2nd group	
	No.	%	No.	%
Positive	34	34.0	10	10.0
Negative	66	66.0	90	90.0
X^2	16.8			
P	0.0001*			

Presence of MTHFR gene mutation is significantly differ regarding number of abortion.table (5)& figure (1)

Table 5: Relation between number of abortions and presence of 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*			

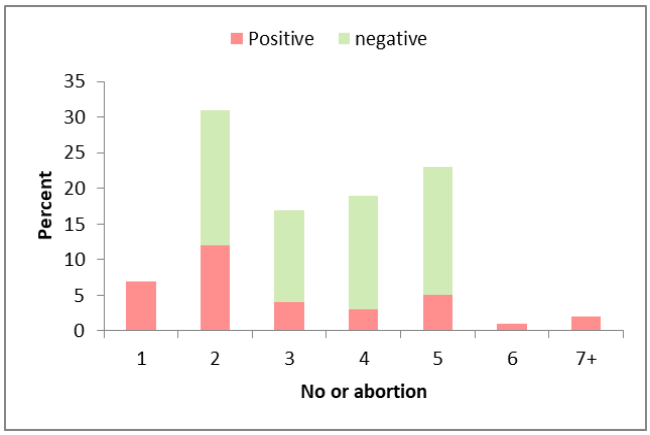

Fig 1: Relation between number of abortions and presence of MTHFR gene mutation

Discussion
Many factors may lead to sporadic and recurrent missed abortion, Presence of MTHFR gene mutation is studied as a cause of this problem In our study age group was ranging between 20 and 30 years in both groups,while the mean was 25.6 years in study group and 24.9 years in control group In a study performed by L. Zhu [24]; the patients were aged between 22 and 44 years, with a mean age of 29.8 ± 4.3 years. The control group consisted of 174 members, 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).

While in a study performed by Wendell Vilas Boas *et al* [25]; The median age of the 89 women in the study group was 29.4 (±5.4) years of age, ranging from 17 to 40 years old, and the control group aged 23 (±5.5) years old. The median abortion number in the study group was 3.2 (±1.9), ranging from 2 to 13 abortions, in which 41 (47%) women had two spontaneous abortions; 25 (29%) of them had three spontaneous abortions, and 21 (24%) of them had more than three abortions. But in our study 31% of patients aborted twice and 23% of them aborted 5 times.

In our study and many other studies; the association between MTHFR gene mutation and missed abortion is established for example: Cao Y *et al.* [26] Govindaiah V *et al.* [27], Puri M *et al*. [28] Kim NK *et al.* [29] and Nair RR [30]

While other studies showed that there is no association for example: - Vilas Boas *et al* [25] Sinem Yalcintepe *et al*. [31] Wendell and Puri M *et al*. [32]

Conclusions

MTHFR gene mutation is a common cause of missed miscarriage either recurrent or not.

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