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Prevalence of MTHFR C677T Polymorphism in Preeclampsia in North-West Rajasthan

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Abstract
Background: *Preeclampsia, a pregnancy related complication is a very common occurrence affecting 4.6% of pregnancies worldwide and 1.8-16.7% of pregnancies in developing countries. There are several risk factors for it's development including MTHFR C677T polymorphism. Hence, we planned to study the prevalence of MTHFR C677T polymorphism in preeclampsia.*
Methods: *A total of 156 pregnant women diagnosed with Pre-eclampsia were selected based upon Inclusion and exclusion criteria. After getting proper informed written consent from the participants a simple questionnaire asked for socio-demographic characteristics and 2ml of venous blood sample was collected and genotype was identified with PCR-RFLP.*
Result*: In the Preeclamptic women, the wild-type CC genotype was detected in 120 (76.92%) patients, while the heterozygous CT and homozygous TT genotypes were observed in 26 (16.67%) and 10 (6.41%) women, respectively. This provides the prevalence of the T allele (CT and TT genotypes) in the Pre-eclampsia in comparison to the baseline data and strongly suggests a potential genetic predisposition in women with preeclampsia.*
Conclusion*: In our study we found that MTHFR C677T gene polymorphism is quite prevalent in Preeclamptic women in north-west part of Rajasthan. However, further studies are required with large sample sizes to generalize the findings on population.*
Keywords: *pre-eclampsia, MTHFRC677T, PCR-RFLP, mutation, homozygous*

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I. Introduction

Pre-eclampsia is a multi-systemic disorder of pregnancy which is defined as new-onset hypertension, often after 20 weeks' gestation and frequently near term along with new-onset proteinuria. Pre-eclampsia is a common complication that occurs during pregnancy affecting 4.6% of pregnancies worldwide and 1.8-16.7% of pregnancies in developing countries (11% prevalence rate in India as reported in an Indian study). Pre-eclampsia is the primary cause of maternal complications such as abruption of placenta, disseminated intravascular coagulation, pulmonary oedema , acute renal failure , heart rhythm disturbances, and effects on other organs like liver, brain and lungs as well as perinatal complications (like foetal growth retardation, preterm deliveries, and fetal deaths). There are several maternal risk factors associated with the development of pre-eclampsia, including MTHFR C677T polymorphism, Which involves a cytosine (C) to a thymine (T) substitution at position 677, thus changing an alanine to a valine in the enzyme. This substitution increases thermo-lability of MTHFR enzyme and causes impaired folate binding and reduced activity of the same. This change in the enzyme activity is responsible for decreased homocysteine metabolism and hyperhomocysteinemia, which causes vascular and endothelial dysfunction, explaining the pathophysiology of Pre-eclampsia. As there is no baseline data available for this gene mutation in north-west Rajasthan, hence, we planned to study the prevalence of MTHFR C677T gene polymorphism in our region.

II. Methods

The study was conducted at PBM Hospital, a tertiary care facility in Bikaner, Rajasthan. This hospital serves as a primary center for obstetric and gynaecological care in the region and caters to a diverse population, making it an ideal location for the research. 156 pregnant women were selected diagnosed with Pre-eclampsia based on inclusion and exclusion criteria, which are as follows:-

Inclusion Criteria
- Age: Women aged ≥18 years.
- Pregnancy Gestational Age: Women with a gestational age of >20 weeks.
- Preeclampsia Diagnosis: Women with a confirmed diagnosis of preeclampsia in the case group or normal pregnancies in the control group. S
- Consent: Women who were willing to provide informed written consent to participate in the study.

Exclusion Criteria
- Women refusing to provide informed consent.
- Women with infectious diseases, such as HIV, Hepatitis B or C, etc.
- Women who engage in substance abuse, smoking, or alcohol consumption during pregnancy.
- Women with pre-existing medical conditions like chronic hypertension, diabetes, or coagulopathies.
- Women with multifetal pregnancies.

After confirming eligibility, women were provided with detailed information about the study's purpose, procedure, and potential risks. Informed consent was obtained from all participants before enrollment. Venous blood sample was collected in EDTA vials for DNA extraction. The DNA was isolated using a commercially available QIAGEN DNA isolation kit. DNA concentration and purity was checked using a spectrophotometer. The quality of the extracted DNA was assessed by running an agarose gel electrophoresis and amplified in conventional PCR using the following primers: **Forward Primer**: 5' - TGAAGGAGAAGGTGTCTGCGGGA - 3' and **Reverse Primer**: 5' - AGGACGGTGCGGTGAGAGTGAGG - 3'. After amplification, the PCR products were analyzed for their quality and size using agarose gel electrophoresis. To detect the MTHFR C677T mutation, the PCR products were subjected to HinfI restriction enzyme digestion.

Figure no. 1: Conventional PCR

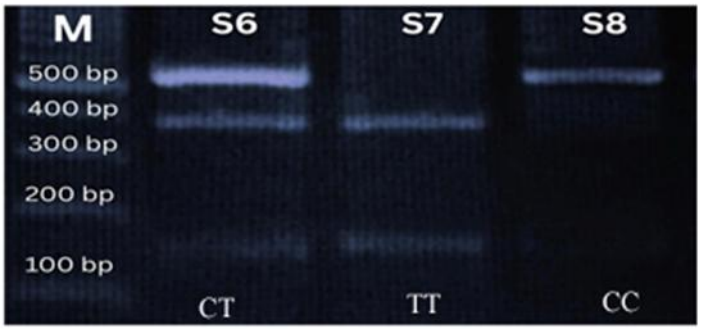

Figure no. 2 Gel Electrophoresis of MTHFR C677T Gene and it's Variants.

III. Results

The socio-economic characteristics of women included in the study are mentioned in table no. 1. The mean age 25.67 ± 4.22 years and the mean BMI was 27.62 ± 3.88 kg/m². In our study the mean systolic blood pressure was 168.17 ± 19.95 mmHg and a mean diastolic blood pressure was 105.87 ± 14.65 mmHg. Table no. 2 shows the distribution and frequency of genotype variants in Preeclamptic women . Among preeclamptic women,

the frequency of the wild-type CC genotype was 120 (76.92%), while the heterozygous CT and homozygous TT genotypes were observed in 26 (16.67%) and 10 (6.41%) women, respectively. The increased prevalence of the T allele (CT and TT genotypes) in the Pre-eclampsia as compared to the baseline data strongly suggests a potential genetic predisposition in women with preeclampsia. The MTHFR C677T mutation is known to reduce the activity of the methylenetetrahydrofolate reductase enzyme, leading to elevated plasma homocysteine levels, which in turn may cause endothelial damage, oxidative stress, and vascular inflammation.

Table 1: Demographic and Clinical Features of Study Group

Characteristic	Category	Study Group (n=156)
Age (years)	Mean age	25.67
Residence Type	Rural (R)	76 (48.72%)
	Urban (U)	80 (51.28%)
Education Level	Uneducated	66 (42.31%)
	Primary	55 (35.26%)
	Secondary	22 (14.10%)
	Senior Secondary	9 (5.77%)
	Graduate	4 (2.56%)
Socioeconomic Status	Upper Class (1)	1 (0.64%)
	Upper Middle Class (2)	10 (6.41%)
	Lower Middle Class (3)	76 (48.72%)
	Upper Lower Class (4)	51 (32.69%)
	Lower Class (5)	18 (11.54%)
Body Mass Index (kg/m²)	Mean BMI	27.62 ± 3.88
Blood Pressure (mmHg)	Mean BP	168.17 ± 19.95 /105.87 ± 14.65

Table no. 2 : Distribution of MTHFR C677T Genotype in Study Group

Genotype	Number (n = 156)	Frequency (%) (n = 156)
Wild Type (CC)	120	76.92%
Heterozygous (CT)	26	16.67%
Homozygous Mutant (TT)	10	6.41%

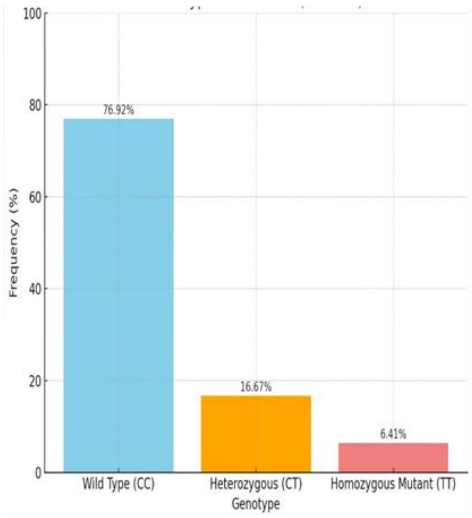

Figure no. 3 Genotype Distribution in the Study Group

IV. Discussion

Our study demonstrated that preeclamptic women had a higher prevalence of the CT (16.67%) and TT (6.41%) genotypes as compared to baseline data available. This is consistent with Frosst et al.[3] who first identified the C677T mutation, explaining its role in impaired folate metabolism and increased homocysteine levels, both of which contribute to endothelial dysfunction and vascular complications, central to the development of preeclampsia. Yadav et al.[6] Studied for the Prevalence of MTHFR C677T globally in healthy population and the prevalence proportion with 95 % CI was used to determine global prevalence of T allele and TT genotype. Meta-analysis was performed by Open meta-analyst. In 1000 blood samples analyzed, the frequency of T allele and TT genotype was 11 and 1 % respectively. Results of the meta-analysis showed that the global prevalence of T allele and TT genotype were 24.0 % (95 % CI 21.7-26.5) and 7.7 % (95 % CI 6.5-8.9) respectively. In sub-group meta-analysis, the lowest frequency of T allele was found in Africans (10.3 %; 95 % CI 3.8-16.8), and highest in Europeans (34.1 %; 95 % CI 31.9-36.3). The frequency of T allele in the North India is 11 %. The results of the meta-analysis showed that the frequency of the T allele and the TT genotype of C677T is highest in the Caucasian population. Moreover, studies like Veerabathiran et al.[1] found a significant association between the TT genotype and increased preeclampsia risk. Similarly, the present study reinforces this by showing higher frequencies of the TT genotype in preeclamptic women, suggesting that genetic mutations in MTHFR may play a crucial role in preeclampsia development. Furthermore, studies like Ahmed et al.[5] found that the *MTHFR C677T* variation was significantly more frequent in women with preeclampsia (16.2%) than in healthy pregnant women (1.8%) (OR = 10.1, 95% CI = 3.0-34.2, $P < 0.001$) and they concluded that a higher prevalence of *MTHFR C677T* polymorphism is seen in women with preeclampsia compared with healthy pregnant women suggesting involvement of this variation in preeclampsia in Sudan. Salimi et al.[2] pointed out that early-onset preeclampsia (EOPE) was particularly associated with MTHFR mutations, which is in line with our findings that the TT genotype was more common in preeclamptic women, indicating potential early-onset disease. Additionally, elevated homocysteine levels associated with MTHFR mutations contribute to oxidative stress, a key factor in preeclampsia. This is supported by Zhang et al.[4] who found that women with higher homocysteine levels and the TT genotype were more likely to experience adverse pregnancy outcomes, further corroborating the role of MTHFR C677T polymorphism in preeclampsia. While some studies, like Salimi et al.[2] , did not find a strong association between MTHFR polymorphisms and preeclampsia, the overall evidence strongly supports the idea that MTHFR C677T mutations increase preeclampsia risk, particularly in women with the CT and TT genotypes. These findings suggest that genetic screening for MTHFR polymorphisms could help identify women at higher risk for preeclampsia, enabling better management of high-risk pregnancies.

V. Conclusion

From this study we concluded that the mutant variants of MTHFR C677T polymorphism are highly prevalent in Preeclamptic women. The study group exhibited a higher prevalence of the mutant genotype CT (16.67%) and TT (6.41%) as compared to the baseline data. This suggests that women with these genetic mutations may be more susceptible to preeclampsia, as MTHFR mutations are known to impair folate metabolism, increase homocysteine levels, and contribute to endothelial dysfunction, a key factor in the development of preeclampsia. Although, further studies with larger sample size are required to confirm the association and it's impact on feto-maternal outcome.

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