HEALTH PROMOTION

# Maternal methylenetetrahydrofolate reductase (MTHFR) A1298C polymorphism: implications in preventing recurrent pregnancy loss

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Keywords

Early pregnancy loss • MTHFR • Gene mutation • Adverse pregnancy outcomes • Methylenetetrahydrofolate reductase A1298C • Polymorphism • Case study

Dear Editor,

Adverse pregnancy outcomes, such as preeclampsia, gestational hypertension, preterm birth, recurrent pregnancy loss, and ectopic pregnancy, are typically caused by multiple factors and can endanger both maternal and neonatal health. An intricate interplay of factors, including maternal nutrition, age, lifestyle, socioeconomic status, and genetic predisposition from both parents, collectively influences the progression and outcome of a pregnancy [1, 2].

The MTHFR (Methylenetetrahydrofolate Reductase) enzyme plays a pivotal role in maintaining intracellular folate balance, a critical component for various cellular processes. This enzyme facilitates the conversion of 5, 10-methylenetetrahydrofolate into 5, 5-methyltetrahydrofolate, a critical methyl donor essential for methylation reactions. These reactions, in turn, influence DNA synthesis, repair, stability, purine, and pyrimidine nucleoside synthesis, and the generation of S-adenosyl methionine (SAM), another key methyl donor involved in biological processes like protein and nucleic acid methylation [3, 4].

The polymorphism MTHFR A1298C mimics a folate deficit by reducing enzymatic activity. The relationship between the MTHFR A1298C polymorphism and RPL risk has been the subject of several researches to far, however the findings are still debatable and unclear. MTHFR gene polymorphisms are relatively common, with estimated frequencies ranging from 5 to 14 percent in different populations [5].

Folate, a vital nutrient, plays a crucial role in the growth and development of both the placenta and fetus. Insufficient folate intake can lead to hyperhomocysteinemia, which damages the vascular endothelium and contributes to endothelial dysfunction and placental vasculopathy [5, 6]. These obstetric complications and thrombotic events primarily stem from hyperhomocysteinemia and disturbances in the homocysteine-related metabolic pathways [7, 8]. Proper homocysteine metabolism is vital, as elevated homocysteine levels can damage various cellular structures within the placenta, leading to inflammation and impaired fetal perfusion [5, 9, 10].

In this case report, we present the case of a pregnant woman with a history of recurrent early pregnancy loss and ectopic pregnancy. Early detection and management of her condition were critical in ensuring a healthy pregnancy outcome.

A 28-year-old woman from a low socioeconomic status background, presented with a history of four first-trimester miscarriages and a ruptured ectopic pregnancy. She had received genetic testing, which identified the MTHFR A1298C polymorphism. She was provided with genetic counseling and initiated on Planned Parenthood and folic acid supplementation during the preconception period. Her initial laboratory results indicated anemia and thrombocytopenia, categorizing her as a high-risk pregnancy. Subsequently, she was referred to a tertiary medical facility for further evaluation and management.

Given her history of recurrent pregnancy loss, prophylactic anticoagulation with low molecular weight heparin and low-dose aspirin were prescribed in the second trimester. Routine monitoring of her pregnancy, including biophysical profile studies and fetal movement tracking, was initiated to ensure the well-being of the fetus. At 38 full weeks of pregnancy, she gave birth to a healthy daughter who weighed 3.3 kg. The baby was active and crying right away, indicating a good neonatal outcome, and the labor and postpartum time went well.

## Discussion

DNA methylation is a crucial aspect of epigenetics that plays a vital role in cellular growth, differentiation, and the development of various human disorders. The MTHFR A1298C gene variation involves a change at position 1298 of the MTFHR gene, where the expected DNA base “A” is replaced by “C.” It’s worth noting that this specific MTHR A1298C variation does not significantly hinder enzymatic activity but resembles a deficiency in folate [11]. The link between the MTHFR A1298C polymorphism and the risk of recurrent miscarriage has been the subject of numerous studies, although the results

remain contentious and unclear [10, 12]. In contrast to Rai's findings in a meta-analysis that suggested no association between the A1298C polymorphism and recurrent pregnancy loss, Yang et al. reported that both maternal and paternal MTHFR gene C677T and A1298C polymorphisms are associated with recurrent adverse obstetrical outcomes [13, 14]. To reconcile these contradictory results, further research with larger, well-designed studies, addressing potential sources of heterogeneity, and considering gene-environment interactions, would be necessary. It's also important for the scientific community to engage in ongoing dialogue and conduct additional systematic reviews and meta-analyses to refine our understanding of the relationship between MTHFR gene polymorphisms and recurrent pregnancy loss.

It is well-established that MTHFR polymorphism leads to elevated levels of total homocysteine. Lowering total homocysteine levels is associated with engaging in regular physical activity and ensuring sufficient intake of folate and vitamin B-12. Consequently, individuals with MTHFR 1298 CC and 1298 AC genotypes can benefit from maintaining a balanced diet rich in folic acid and vitamin B-12, complemented by appropriate physical exercise [15, 16].

Research has indicated that the incidence of unexplained pregnancy losses can be reduced when hyperhomocysteinemia levels in the blood are lowered through oral folate supplementation [17]. However, there is no universally accepted recommendation regarding folic acid supplementation for populations with varying MTHFR genotypes. Therefore, further investigation is needed in this area.

At the primary healthcare level, identifying and registering pregnancies early, along with investigating adverse pregnancy outcomes, can help prevent recurrent pregnancy loss associated with MTFHR gene mutations. In the case presented here, early registration of the pregnancy and prompt reporting and investigation of repeated abortions could have potentially mitigated the unfavorable outcomes. Both the mother and the fetus could have benefited from appropriate treatments, including preconception folic acid supplements and nutritional guidance. It is imperative that healthcare workers in the community recognize the importance of early registration and reporting adverse pregnancy outcomes. Responsible authorities should conduct thorough investigations in the aftermath of such negative events, followed by swift implementation of effective measures, especially in resource-constrained settings.

This case underscores the importance of early detection of the MTHFR A1298C polymorphism in pregnant women with a history of recurrent pregnancy loss. Implementing proper folic acid supplementation and genetic counseling can significantly improve pregnancy outcomes. Healthcare providers at the community level must emphasize early registration of pregnancies and prompt investigation of adverse outcomes to provide timely interventions, particularly in resource-limited settings.

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## Conflict of interest statement

None.

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