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CASE REPORT

# A Case of Recurrent First Trimester Miscarriages Due to Inherited Multifactorial Thrombophilia in an Otherwise Asymptomatic Patient: A Clinical Dilemma

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## Introduction

Thrombophilias are haemostatic disorders and can be acquired, inherited or a combination of both. Inherited disorders include anti-thrombin III deficiency, protein S deficiency, protein C deficiency, factor V Leiden mutation, prothrombin gene G20210A mutation and methylenetetrahydrofolate reductase (MTHFR) mutation [1]. Protein S deficiency is a rare form of inherited thrombophilia, and its prevalence is only 0.2–0.3% in general population [1]. Its deficiency creates a hypercoagulable state and such condition predisposes a pregnant patient for risk of venous thromboembolism (VTE). The frequency of homozygous MTHFR mutation in the Asian women is 3.8% [2]. This mutation may also lead to a hypercoagulable state by increasing homocysteine levels in the blood. In the past, it was hypothesized that such inherited thrombophilias may lead to pregnancy loss by placental microthrombi and thrombosis. Due to lack of prospective data in untreated group, current guidelines do not recommend screening of patients with early pregnancy loss for inherited thrombophilias until they have any thrombotic complication in self or any family member in past or in present. Moreover, till date no studies have confirmed association of protein S deficiency with early pregnancy loss. Furthermore, there are only few case reports of multifactorial thrombophilia with recurrent first trimester miscarriages without any thrombotic complication in the patient or in any family member. We present such a rare case of concomitant

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protein S deficiency and MTHFR mutation, as a probable cause of recurrent first trimester pregnancy loss, without having any systemic thrombotic complication herself or in any family member, causing management dilemma.

## Case Report

A 33-year-old woman presented to our outpatient department with a history of recurrent pregnancy loss, five times consecutively between 6–10 weeks of gestation in the last 3 years. No specific treatment was administered during those pregnancies. She did not take any folic acid supplements at that time. She had regular menstrual cycles. The history was not suggestive of thyroid disorders, autoimmune disorders, any congenital syndrome in siblings/first-degree relatives, any thrombotic episode in self or any family member and any trauma preceding the previous pregnancy losses.

On examination, the patient had good built with stable vitals. Systemic examination was unremarkable. Per-speculum and per vaginum examination did not reveal any abnormality. She was screened for uterine malformations, chromosomal abnormalities, hormonal imbalance, infections, thyroid disorders and autoimmune diseases. Her full blood counts, thyroid function tests, Venereal Disease Research Laboratory test and karyotype of both the partners were found to be normal. In order to rule out antiphospholipid antibodies, testing for lupus anticoagulant, anticardiolipin antibody and anti-beta-2-glycoprotein 1 was advised, which was found negative. Her pelvic ultrasound showed a 5 × 4 cm intramural fibroid. Hysteroscopy was subsequently done which could not reveal any submucous component of the fibroid. After the above confirmation that fibroid was not the cause of pregnancy losses, as a next step, she was advised thrombophilia screening for inherited thrombophilias.

On screening for inherited thrombophilias, protein C activity was 96% (normal: 70–140%) and anti-thrombin III value was 97.5% (normal: 75–125%). No mutation was found in prothrombin gene G20210A. Protein S activity was found to be 17% (normal: 50–140%). Homozygous mutation was found in MTHFR C677T gene by polymerase chain reaction. The level of vitamin B12 was 305 pg/ml (normal: 211–911 pg/ml), serum folic acid was 5.0 ng/ml (normal: >5.38 ng/ml) and homocysteine level was 15.10 μmol/L (normal: 4.44–13.56 μmol/L). Patient was advised to report back when she misses her period and was prescribed periconceptional folic acid tablets 5 mg daily. When patient again conceived (spontaneously), she was admitted and started on subcutaneous injection of low molecular weight heparin (LMWH) 40 mg daily and tablet acetylsalicylic acid 75 mg daily, since 5 weeks of gestation after confirming viability, and were continued throughout the pregnancy. First trimester aneuploidy screening with maternal serum markers and nuchal translucency was negative. All routine antenatal investigations were normal including fasting blood glucose level. Detailed anomaly scan was done in second trimester and did not reveal any anomaly. Patient was diagnosed with gestational diabetes mellitus at 28 weeks of gestation. Subsequently, she was started on medical nutrition therapy (MNT) and weekly venous blood sugar profile was done. Patient's blood sugar was well controlled on MNT. Monitoring of her platelet counts was also done weekly to look for thrombocytopenia. Intensive foetal monitoring was done with daily foetal movement count (by patient) and biweekly biophysical profile since 32 weeks of gestation. Color Doppler done at 32 weeks of gestation showed normal Doppler flows. Elective caesarean section was planned at 39 weeks in view of her previous history. Patient underwent a lower segment caesarean section at 39 weeks delivering a healthy male baby with birth weight of 3.2 kg. The placenta weighed 620 g, and foetal–placental weight ratio was 5.16. Placental histopathological examination was found to be normal. After 12 h of caesarean section, injection LMWH was again started along with tablet warfarin 1 mg once a day. Dose of warfarin was stepped-up up to 5 mg once a day till INR value was between 2 and 3, and then LMWH was stopped. The tablet warfarin was continued till 6 weeks postpartum. Both mother and baby were discharged on postoperative day 11 in good health. The mother was advised for follow-up at 6 weeks and thereafter at 3 months especially to look for any sign or symptom of thrombosis and to check glucose tolerance.

## Discussion

Normal pregnancy is a prothrombotic state and has an increased risk of venous thromboembolism (1 in 1000 pregnancies). Inherited thrombophilias may adversely affect pregnancy outcomes in the prothrombotic state of pregnancy. Protein S is a vitamin K-dependent glycoprotein having either an activated protein C (APC)-dependent activity (as its non-enzymatic cofactor) or APC-independent activity, by causing direct inhibition of prothrombinase complex and thrombin-activatable fibrinolysis inhibitor (TAFI). Protein S deficiency has an autosomal dominant inheritance. MTHFR enzyme is required for the conversion of homocysteine to methionine and its mutation may lead to hyperhomocysteinemia. This mutation is caused by substitution of cytosine by thymine at position 677 of MTHFR gene making it a thermo-labile gene and reducing its activity up to 50%. High plasma level of homocysteine has been associated with an increased risk for both venous and arterial thrombosis.

With this case report, we want to put light on certain aspects of screening and management dilemma in such patients. Firstly, when a patient presents with recurrent first trimester miscarriages (otherwise asymptomatic) with all the routine investigations as normal, should we advise screening for inherited thrombophilias as next step? The causal relationship between heritable thrombophilia and pregnancy failure is still controversial [2]. Moreover, it has been observed that most of the women with inherited thrombophilias, even when not screened/treated, have normal pregnancy outcome. Screening of patients who do not have any systemic thrombotic complication will be equivalent to screening general population because such patients are less likely to be at risk of pregnancy complications and will not be cost-effective. This is probably the reason that current guidelines do not recommend screening of patients with recurrent first trimester miscarriage (in otherwise asymptomatic patients) for inherited thrombophilias. Women with any history of thromboembolic event should undergo such screening because they need further thromboprophylaxis, and moreover, they are also at high risk of pregnancy complications. However, our case was unique as screening for these disorders and subsequent treatment with anticoagulants resulted in successful pregnancy outcome after five consecutive pregnancy failures. Furthermore, we could not find any study in literature which can establish association of protein S deficiency and early pregnancy loss, though there are reports linking this disorder with late pregnancy loss. Moreover, it is still a debatable issue whether hyperhomocysteinemia due to MTHFR mutation leads to pregnancy loss or not [1].

Secondly, if a woman with recurrent early miscarriages is found positive for inherited thrombophilia, should she be treated with anticoagulants? Again guidelines based on latest evidences recommend against the treatment of such patients [1]. In a recent meta-analysis done by Skeith et al. [3] recommendation is not to use LMWH in patients with inherited thrombophilia and recurrent early pregnancy loss. However, in our case, such treatment resulted in a successful pregnancy after five consecutive failures. Similar to our approach, a patient of protein S deficiency was reported to be treated with LMWH and low dose acetylsalicylic acid leading to a successful outcome [4]. Till date due to lack of prospective randomised controlled trial for such patients, there is no consensus over the management options. Though effectiveness of anticoagulants for such patients is still a debatable issue, still we decided to start the patient on anticoagulants considering it as precious pregnancy, leading to successful outcome.

There have been only few case reports in literature till date of protein S deficiency (along with other defect, e.g. MTHFR mutation) with recurrent early pregnancy loss in otherwise asymptomatic patients. Screening for inherited thrombophilia is advisable for such patients in an era of easily available diagnostic/screening modalities, though we agree that management of single patient does not suffice evidence to make an opinion. Furthermore, possibility of placebo effect cannot be ruled out. Therefore, there is need for prospective studies regarding screening for inherited thrombophilias and the further management of diagnosed cases. This case report will help the obstetrics and gynaecology fraternity to consider inherited thrombophilia screening when in clinical dilemma regarding further management of otherwise asymptomatic patients with recurrent first trimester miscarriages.

**Compliance with Ethical Standards**

**Conflicts of interest** The authors declare that they have no conflict of interest.

**Human and Animals Rights** The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

## References

1. Davenport WB, Kutteh WH. Inherited thrombophilias and adverse pregnancy outcomes: a review of screening patterns and recommendations. Obstet Gynecol Clin North Am. 2014;41:133–44.
2. McNamee K, Dawood F, Farquharson R. Recurrent miscarriage and thrombophilia: an update. Curr Opin Obstet Gynecol. 2012;24:229–34.
3. Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood. 2016;31(127):1650–5.
4. Lalan DM, Jassawala MJ, Bhalerao SA. Succesful pregnancy outcome in a case of protein S deficiency. J Obstet Gynaecol India. 2012;62:21–2.