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Case Report

Management and therapeutic implications of combined protein C and S deficiency in pregnancy: a case report

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ABSTRACT

The pregnancy is an immunocompromised state. Thus, autoimmune diseases may affect pregnancy and get worsen during pregnancy. Here authors discuss a rare autoimmune thrombophilia disorder, protein C and S deficiency which may cause recurrent pregnancy losses by affecting haemostatic mechanisms in the body. This patient with recurrent pregnancy loss when evaluated extensively was found to have combined inherited protein C and S deficiency. It was successfully managed with thromboprophylaxis therapy, which resulted in the delivery of healthy baby. Long term anticoagulant prophylaxis should be considered weighing the risk of bleeding to thrombotic recurrence in such cases. In conclusion, combined protein C and S deficiency and that too presenting as recurrent pregnancy loss is very rare. Thrombophilia screening should be considered in cases of recurrent pregnancy losses. Adequate and appropriate thromboprophylaxis is an important part of the management of pregnant women with inherited thrombophilia.

Keywords: Case report, Thrombophilia, Protein C, Protein S, Recurrent pregnancy loss

INTRODUCTION

Pregnancy loss is one of the scariest realities for couples trying for conception. This event commonly occurs in 15%-25% of all the pregnancies and increases with maternal age.¹

'Thrombophilias' which includes both hereditary or acquired hypercoagulation disorders, promotes thrombosis and forms the molecular basis, otherwise unexplained fetal loss in many cases.² In thrombophilia the microvascular thrombosis in placental vessels presents with recurrent miscarriages, intrauterine growth restriction, preeclampsia, abruption placentae, and stillbirth.³

Protein C and protein S deficiencies are amongst inherited thrombophilias.⁴ There are very few reported cases of combined deficiency of protein C and protein S. Authors report here a case of combined protein C and

protein S deficiency with a successful maternal and fetal outcome.

CASE REPORT

A 29-year-old P0120 presented to outpatient department in August 2018 preconceptionally for counselling with 3 previous pregnancy losses. Her first conception had resulted in a spontaneous abortion at 6 weeks in May 2015. She conceived spontaneously for the second time towards the end of the same year, but unfortunately had an early fetal demise at 11 weeks of gestation for which a medical termination was performed. In this conception fetal cardiac activity was documented at 6 weeks by a transvaginal scan. After 2 years, her third pregnancy once again ended as preterm vaginal delivery at 22 weeks POG the baby of 700 gms who was not able to survive the past first neonatal day.

The investigations carried out as part of work-up revealed deficit protein C and protein S levels in patient serum at

53% and 64.5% respectively against reference values of 70-130% and 72-128%. The screen for acquired thrombophilia was reported negative for beta 2 glycoprotein IgM and IgG, anti-cardiolipin antibodies, lupus anticoagulant and mutation testing for factor V Leiden. Patient had normal blood sugar profile and thyroid function tests.

The autosomal dominant nature of protein S and C deficiency was explained to the couple and was started on Aspirin 150 mg once a day and folic acid preconceptionally. Patient conceived naturally for the 4th time in December 2018. Low molecular weight heparin (enoxaparin 40 mg) once a day subcutaneously was started after documentation of fetal cardiac activity. Empirically patient was also started with vaginal progesterone support. Aspirin was stopped at 20 weeks after a history of epistaxis while enoxaparin was continued till 34 weeks. She was given dexamethasone course at 27 weeks for lung maturity in anticipation of her history of preterm delivery. She was diagnosed to have associated gestational diabetes mellitus at 24+1 weeks, which was controlled on medical nutrition therapy. The patient developed generalized itching all over the body more on palms and soles at 26 weeks. A bile acid level of 90 units and 157/225 I/U level of SGOT/PT following exclusion of other possible causes prompted the diagnosis of intrahepatic cholestasis of pregnancy (IHCP) for which patient received 900 mg of ursodecholic acid per day in 3 divided doses.

Ultrasound at 32 weeks showed good interval growth. She had biweekly non stress test, weekly bile acids and an ultrasound every 15 days from 32 weeks onward for antepartum fetal surveillance.

In consideration of worsening serum bile acid levels despite treatment, decision of termination of pregnancy was taken over through informed consent at 36+4 weeks of gestation. During her intrapartum period, she developed abruption for which expedited ventouse assisted delivery was accomplished. She delivered a female child of 2780 gms with Apgar 8 and 9 at 1 and 5 min respectively in August 2019. The neonate was evaluated by the pediatrician and thrombotic profile of the baby was advised.

Her postnatal period was uneventful. She was followed for 6 weeks postpartum and both mother and baby were fine.

DISCUSSION

Protein C and protein S deficiency is a rare, independently inherited autosomal dominant thrombophilia's.¹ Incidence of symptomatic protein S deficiency is 1:20 000 and that of symptomatic protein C deficiency lies between 1:16,000 to 1:32,000 persons.⁵ Combined protein C and protein S deficiencies are still rare, and few cases have been reported in the literature.

Protein S molecule weighs 69,000 MW and is a vitamin-K-dependent natural anticoagulant protein. It is synthesized in hepatocytes and endothelial cells.¹ It is a cofactor to activated protein C which facilitates its function on factors Va and VIIIa and thus assists in the downregulation of thrombin formation.^{3,4} Protein S deficiency can be classified as type I (decreased levels of both total and free protein S antigen), type II (decreased activated protein C-cofactor activity but, total and free protein S antigen levels within their normal ranges), and type III (decreased levels of free protein S antigen levels only).⁶ The women with protein S deficiency are usually heterozygous. The protein S gene is located on chromosome 3.⁴ And over 200 different mutations of the protein S gene has been documented, most of them are non-sense and mis sense.^{7,8} Gross deletions and insertions of PROS1 are present in approximately 30% of the point mutation-negative families.^{9,10}

The gene of protein C lies on chromosome 2.³ Deletion or mutation of this gene is recognized in over 160 different variations.

Pregnant women with known thrombophilia are at very high risk of antenatal and postpartum venous thromboembolism and are advised thromboprophylaxis during pregnancy and puerperium. Heparin is the anticoagulant of choice as it does not cross the placenta, causing no risk of teratogenicity or fetal haemorrhage. LMWH has a lesser side-effect (reduced risk of osteopenia and thrombocytopenia), safe for mother and fetus, and easier compliance thus it is the drug of choice. Warfarin being teratogenic is best avoided in pregnancy. Heparin and warfarin can be safely administered to nursing mothers. In conclusion, thrombophilia screening might be justified in setting of recurrent pregnancy losses.⁵ and adequate and appropriate thromboprophylaxis is an important part of the management of pregnant women with inherited thrombophilia.

Hence, thrombophilia screening might be justified in women with pregnancy loss, and treatment with low molecular weight heparin might be considered for those with pregnancy loss and thrombophilia.¹⁰ Women with thrombophilia are also more prone to venous thromboembolism in pregnancy and puerperium. Special care and precautions should be taken in post-partum/post-operative period to prevent the catastrophic event of venous thromboembolism, which could lead not only to major morbidity but also mortality.

CONCLUSION

Patients with either protein C or S deficiency may remain asymptomatic or present with thromboembolic incidents, whereas with combined deficiency of protein C and S the risk of thrombosis is higher and occurs early in life. Long term anticoagulant prophylaxis should be considered weighing the risk of bleeding to thrombotic recurrence.

Learning points

- Combined protein C and S deficiency is a rare thrombophilia which may lead to recurrent pregnancy loss.
- The patient of recurrent pregnancy loss on pre-conceptual workup was found to have protein C and S deficiency and after management had good fetal and maternal outcome.
- Thrombophilia Screening should be considered in cases of recurrent pregnancy losses.
- When managed with adequate and appropriate thromboprophylaxis of pregnant women with inherited thrombophilia gives good maternal and fetal outcome.

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