Case Report

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Protein S Deficiency with Favourable Foetomaternal Outcome: A Case Report

Obstetrics and Gynaecology Section

SWATI SUGANDHA[1], SHIVANSHI SHARMA[2], MONIKA JINDAL[3], SANTOSH MINHAS[4]

ABSTRACT

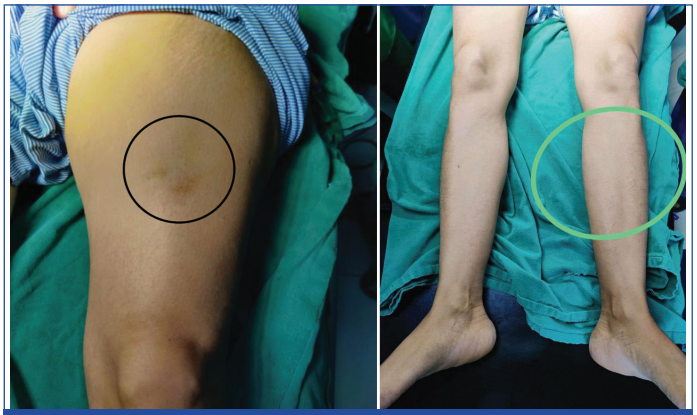
Protein S is a multifunctional plasma protein, whose deficiency, results in a rare congenital thrombophilia, inherited in an autosomal dominant pattern. It can aggravate the hypercoagulable state of pregnancy, when it presents in parallel with the condition, leading to adverse maternal outcomes and foetal loss. A 35-year-old female third gravida having previous 2 deliveries by Lower Segment Caesarean Section (LSCS) presented to emergency at 10 weeks pregnancy with chief complaints of pain and swelling in left thigh since 4-5 days. After thorough investigations and work-up, the patient was diagnosed with Protein S deficiency. She was managed conservatively and was delivered by elective LSCS with bilateral tubal ligation at 38 weeks of gestation with good foetal and maternal outcomes.The rarity of Protein S deficiency along with the successful outcome of the pregnancy makes this a unique case.

Keywords: Pregnancy, Plasmaprotein, Thrombophilia

CASE REPORT

A 35-year-old G3P2L2 lady visited the Outpatient Department (OPD) with a chief complaint of pain and swelling in the left leg at 10 weeks of gestation. She was non diabetic, normotensive and had a history of two Lower Segment Caesarean Sections (LSCS). The pain gradually increased over three to four days and was excruciating, not associated with any aggravating or relieving factor. Her menstrual cycles were regular without any menorrhagia. The first LSCS was done in an emergency at 38 weeks for non progress of labour and the second was an elective LSCS done at 38 weeks one day period of gestation. After the second delivery, she had a history of leg pain in the postpartum period within one week, but she did not report to any hospital.

During her present pregnancy, the patient was hemodynamically stable and moderately built. On examination, the abdomen was soft and had a well-healed suprapubic scar with no tenderness. On local examination, a bruise of size 3×2 inches was seen on the anterior aspect of the left thigh and swelling of the left leg [Table/Fig-1]. Left lower limb was enlarged by 2-4 cm as compared to right lower limb and calf tenderness and Homan sign was positive in left lower limb [Table/Fig-2]. She was admitted and managed medically. The consultation was sought from medicine; the haematology Department and the patient was advised Injection Low Molecular Weight Heparin (LMWH) 0.6 mg twice daily. The patient was also advised to test for Protein S levels at a later stage, once she was off anticoagulants.



[Table/Fig-1]: A bruise of size 3*2 inches on the anterior aspect of the left thigh.
[Table/Fig-2]: Swelling in left limb as shown in the circle as compared to right limb. (Images from left to right)

Her routine antenatal investigations were within normal limits and specific investigations related to coagulopathy [Table/Fig-3]. All the investigations mentioned in [Table/Fig-3] were done at admission before delivery and were found to be deranged except BT, CT, ACLA, APLA, LA. USG done at admission showed a single live intrauterine pregnancy at 10 weeks 2 days showing cardiac activity and Venous Colour Doppler showed Deep venous thrombosis involving left distal short saphenous vein, popliteal, tibio-peroneal trunk, saphenous-popliteal junction, peroneal vein, and proximal posterior tibial vein which shows an evidence of echogenic thrombus causing distention of lumen. No color flow was noted.

Investigations	Results
Bleeding time (BT)	1.15 (1-6 mins)
Clotting time (CT)	5.20 (5-11 mins)
D-dimer	2940 (< or=500 ng/mL FEU)
Antinuclear Ab (ANA)	0.564 negative (<0.8-negative)
Antiphospholipid Ab (APLA)	IgG-1.97 U/uL negative (<12-negative) IgM-2.62 U/uL negative (<20-negative)
Lupus Anticoagulant (LA)	0.88 normal (<1.3-normal)
Protein C	154%↑(non pregnant-70-130%;1st/2nd/3rd Trimester-upto (121%/133%/135%)
Protein S	Below 8% ↓ (non pregnant- 55-123%) (1st/2nd/3rd Trimester- up to 95%/68%/42%)
Anticardiolipin Ab (ACLA)	IgG-0.6 negative (<12- negative) IgM-0.9 negative (<20- negative)
Beta glycoprotein	IgG-2.96 AU/mL (<12- negative) IgM-2.60 AU/mL (<20- negative)

[Table/Fig-3]: Investigations of patient.

The patient was discharged at 12 weeks 3 days of gestation with improvement of pain and swelling of left lower limb. All the peripheral pulses were palpable post treatment and limb measurements were equal (28-36 cm) in both the limbs.

The patient continued injections of low molecular weight heparin throughout her pregnancy. She made follow-up visits at 18, 24,

and 28 weeks, during which she had her antenatal surveillance and interim lab work-up, which were all normal. She also had COVID-19 infection during the second trimester for which she was admitted to a tertiary care center. Her SpO_2 was 96%, respiratory rate 18 breaths/min. She received oxygen support and continued her anticoagulant therapy. She recovered and continued her antenatal surveillance.

At 36 weeks of gestation, she was admitted for safe confinement. She had a venous doppler for DVT which reported chronic deep venous thrombosis with partial recanalisation. Injection LMWH was stopped 12 hours prior to planned surgery and she underwent an elective LSCS in view of the previous 2 LSCS at 37 weeks 1 day period of gestation. Intraoperatively, the liquor was thin meconium stained and a healthy female child weighing 2.9 kg was delivered. The baby had cried immediately at birth and had a Apgar score of 7/9. The postoperative period was uneventful. The coagulation profile of the newborn was normal and was advised further testing of newborn and mother for protein C&S, ACLA, APLA, LA and D-dimer.

DISCUSSION

Protein S deficiency is a rare congenital thrombophilia with an autosomal dominant pattern, characterised by decreased activity of protein S, a plasma serine protease with crucial roles in coagulation, inflammation, and programmed cell death [1]. In general population, it is found in approximately 1 in 500 to 1 in 3,000 people [2]. In pregnancy, although rare, congenital Protein S deficiency increases the risk of Deep Vein Thrombosis (DVT) which may lead to maternal morbidity and loss. It is often associated with foetal losses in pregnancy. Lalan DM et al., reported a catastrophic and fatal thrombotic complication termed Purpura Fulminans (PF) in neonates with homozygous Protein S deficiency. In a patient with bad obstetric history [2]. The hypercoagulable state is a normal condition in pregnancy, but if it happened side by side with other conditions such as thrombophilia, it will be aggravated and lead to pregnancy complications [3]. Although inherited, it can be acquired due to deficiency of Vitamin K, antenatal period, anticoagulation therapy, sex hormone therapy, and chronic infections like HIV [2]. Individuals with a heterozygous deficiency of protein S can present with a risk for Venous Thromboembolism (VTE), whereas the homozygous entity can have fatal neonatal consequences [4].

Pregnancy is associated with profound alteration in the coagulation, the fibrinolytic system, along with increasing plasma volume leading to a dilutional effect to minimise postpartum blood loss. This may lead to low observed plasma protein S activity. These physiological falls in protein S and protein C activities during pregnancy make it difficult to diagnose protein S and C deficiency [5]. Hence, women with a thromboembolic event appearing for the first time during pregnancy should have investigations for protein S deficiency till the postpartum period, to evade misdiagnosis and late treatment [6]. Most obstetricians prefer the use of LMWH from early pregnancy till puerperium, and so was the scenario with the present case, due to better side-effect profile and good safety record of mother and fetus. LMWH is preferred over UFH (unfractionated heparin) and warfarin as it has a clear-cut advantage over HIT (Heparin induced thrombocytopenia) and osteopenia. However, LMWH, UFH, and warfarin are safe for breastfeeding mothers [7]. Similarly, a pilot study done in Taiwan on the East Asian population showed the benefit of anticoagulation therapy in women having recurrent pregnancy losses due to documented protein S deficiency [8]. Although LMWH is considered safe for the mother and foetus during pregnancy, but it poses higher chances of haemorrhage in postpartum.

CONCLUSION(S)

Through this case, the importance of early diagnosis and management of this rare entity is highlighted, which ensures a good outcome for the mother as well as the baby. Anticoagulant therapy is of paramount importance.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Obstetrics and Gynaecology, Maharishi Markandeshwar Medical College and Hospital, Solan, Kumarhatti, Himachal Pradesh, India.
2. Postgraduate Resident, Department of Obstetrics and Gynaecology, Maharishi Markandeshwar Medical College and Hospital, Solan, Kumarhatti, Himachal Pradesh, India.
3. Professor, Department of Obstetrics and Gynaecology, Maharishi Markandeshwar Medical College and Hospital, Solan, Kumarhatti, Himachal Pradesh, India.
4. Professor, Department of Obstetrics and Gynaecology, Maharishi Markandeshwar Medical College and Hospital, Solan, Kumarhatti, Himachal Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Swati Sugandha,
House No. B-503, MMMCH Campus, Kumarhatti, Solan, Himachal Pradesh, India.
E-mail: swati.sugandha90@gmail.com

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