

# Protein-C Deficiency and Bad Obstetric History: Rare Successful Outcome in Twin Pregnancy

Monika Anant<sup>1</sup>, Sonam Yadav<sup>2</sup>, Anita Paswan<sup>3</sup>, Mrinal Sharma<sup>4</sup>, Priyanka Raj<sup>5</sup>, Anuja Pritam<sup>6</sup>

## ABSTRACT

Inherited thrombophilias in pregnant females have increased risk of venous thromboembolism as well as adverse outcomes in pregnancy like miscarriage, fetal demise, fetal growth restriction, and abruptio placenta. Majority (50–60%) of cases of inherited thrombophilias are due to FVL (factor V Leiden) and prothrombin G20210A (also called the prothrombin gene mutation [PGM]) whereas deficiencies in protein S, protein C, and antithrombin account for the remaining cases. Pregnancy with thrombophilias requires adequate thromboprophylaxis during antenatal and postnatal periods depending upon the type and other factors, but the available evidence for their management is not sharply defined. This case reports a successful outcome in case of twin pregnancy with protein C deficiency with a personal history of venous thromboembolic (VTE) event and a bad obstetric history (BOH). She had multiple factors increasing her VTE risk: (1) previous thrombosis history; (2) inherited thrombophilia; (3) multiple pregnancy and hence was on continued anticoagulant therapy in antenatal and puerperal period. Although only a possible weak association with pregnancy losses has been suggested for protein C deficiency, this case emphasizes that thromboprophylaxis throughout antenatal course improves pregnancy outcome in those with recurrent pregnancy losses.

**Keywords:** Bad obstetrics history, Multiple pregnancy, Perinatal outcome, Protein C deficiency.

*Journal of South Asian Federation of Obstetrics and Gynaecology* (2021): 10.5005/jp-journals-10006-1955

## INTRODUCTION

Inherited thrombophilias increases the risk for venous thromboembolic (VTE) events, miscarriage, fetal demise, stillbirth, placental abruption, and hypertensive disorders of pregnancy.<sup>1</sup> Factor V Leiden mutation, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin deficiency are the inherited thrombophilias and their thrombogenic potential increased further by physiological hypercoagulability of pregnancy.

Activated protein C, a vitamin K-dependent anticoagulant synthesized in liver, inactivates the coagulation factors 5a and 8a, necessary for thrombin generation and factor 10 activation. Two to three per 1,000 individuals can have protein C deficiency, but many individuals do not have thrombosis as its phenotypic expression is highly variable.<sup>2</sup> Protein C activity has been known to increase modestly but significantly throughout the first half of pregnancy.

Fifty percent of the cases of VTE in pregnancy are associated with inherited thrombophilias, of which 10.3% are due to protein C deficiency.<sup>3</sup> Protein C deficiency can cause warfarin-induced skin necrosis, stroke, thrombosis in deep veins, embolism in mesenteric and pulmonary veins.<sup>4</sup> VTE in cerebral, portal and superficial veins are also reported due to Protein C deficiency.<sup>5</sup>

In a healthy pregnant women, the risk of VTE is 1:1,000 which increases two to eleven times in protein C deficiency.<sup>6</sup> Recurrent fetal losses attributed to thrombophilia is a treatable and preventable condition if adequate anticoagulation is maintained in the antenatal period.<sup>7,8</sup>

This case is being reported because of a rare successful outcome which occurred in a women of bad obstetric history having history of thrombosis treated throughout pregnancy with anticoagulation and the paucity of evidence for management of such pregnancies with thrombophilia having a prior VTE in protein c deficiency.

<sup>1–6</sup>Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Patna, Bihar, India

**Corresponding Author:** Monika Anant, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Patna, Bihar, India, e-mail: drmonika.anant@gmail.com

**How to cite this article:** Anant M, Yadav S, Paswan A, et al. Protein-C Deficiency and Bad Obstetric History: Rare Successful Outcome in Twin Pregnancy. *J South Asian Feder Obst Gynae* 2021;x(x):xx–xx.

**Source of support:** Nil

**Conflict of interest:** None

## CASE DETAILS

A 26-year third gravida with no living issues was registered with our obstetric unit at 8 weeks of gestation. She had two pregnancy losses of 6 and 7 months period of gestation, 4 and 5 year ago with nonanomalous babies. Current pregnancy was spontaneously conceived and diagnosed at 7 weeks by urine pregnancy test at home. She was a diagnosed case of protein C deficiency, detected on evaluation for bad obstetric history with gastro-intestinal symptoms and jaundice. She was on oral Coumarin anticoagulant (Nicoumalone 3/4 mg on alternate day) since 2 years after IVC angioplasty which was done for thrombotic hepatic vein outflow tract obstruction. There was no history of thrombophilia in family. She had history of gestational hypothyroidism and jaundice in second trimester in both earlier pregnancies. She was also a known case of beta thalassemia trait.

Dating scan revealed monochorionic diamniotic twin at 8 weeks gestation when unfractionated heparin (UFH) 5,000 units four times a day was started at 8 weeks (at INR 2.5). Gestational subclinical hypothyroidism was also diagnosed in first trimester. Other routine antenatal investigation and second trimester anomaly scan were

within normal on follow up. Regular antenatal visits, by two weekly ultrasounds to detect the complications of monochorionicity, were done, along with monitoring of any possible thrombotic events with continuation of anticoagulation with a target PT-INR between 2 and 3.

At 32 4/7 weeks of gestation, she presented to obstetrics emergency with watery leakage per vaginum for 3 days, fever, and decreased fetal movements for 2 days. On examination, premature preterm rupture of membranes was diagnosed not in labor, so antibiotic prophylaxis for chorioamnionitis prevention and antenatal corticosteroid therapy were started. All other investigations were within normal limits except a low PT INR—1.15.

Admission ultrasound showed first twin as breech (average gestational age 29 4/7 weeks day and estimated fetal weight of 1228 g), second twin—was oblique (AGA 30 1/7 weeks and EFW 1504 g) with single deep vertical liquor pocket—4 cm. Patient was monitored for signs of chorioamnionitis and well-being of fetuses but with constant leaking developed anhydramnios 3 days after admission.

Elective cesarean section was planned at 33 weeks in view of anhydramnios and fetuses in breech and oblique lie. UFH stopped 24 hours before cesarean section which was performed under neuraxial spinal anesthesia. A 1.5 kg female and 1.2 kg male baby were delivered. Neonatal intensive unit care was required for both premature babies, 1 week (female) and 16 days (male). Later, both babies were discharged in good health after establishment of breastfeeding.

The patient had uneventful intraoperative and postoperative course. UFH 5,000 units QID was re-started 12 hours after cesarean delivery. Overlapping was done with tablet nicoumalone 3/4 mg alternate day from postoperative day three (POD-3) till PT-INR rose to 2–3. UFH was stopped on POD-8 (INR-2.27) with continuation of oral anticoagulant.

During entire period of hospitalization (20 days), she was put on thigh length deep vein thrombosis compression stockings also. She was discharged at INR 2.5 on POD-16 on advice for regular INR monitoring and the babies in good condition.

Postpartum follow up at 4 weeks, mother, and both the babies were healthy with no complications or complaints.

## DISCUSSION

Morrison AE first reported VTE with pregnancy with protein C deficiency in 1988.<sup>9</sup> A fatal cerebral venous thrombosis (CVT) at 6 months pregnancy due to protein C deficiency was reported by Maeda et al. The same authors also reported a familial Protein C deficiency with CVT at 8 weeks pregnancy in a woman with protein C deficiency. These reports suggest a significantly increased risk of thrombosis in pregnancy with protein C deficiency.<sup>10</sup>

According to Vogel et al. VTE risk in pregnancy is 500–1000 times in protein C deficiency as compared to normal women.<sup>11</sup> While others estimated the relative risk of protein C deficiency related VTE during antepartum as 3–10% and during postpartum as 7–19%.<sup>12</sup>

A meta-analysis published in 2017 attributed high absolute risk of pregnancy-related VTE of 7.8% in protein C deficiency and concluded that antepartum or postpartum thromboprophylaxis or both should be given in women with Protein C deficiency.<sup>13</sup> Anticoagulation therapy for pregnancy is usually decided on the history of VTE other thrombophilias.

Anticoagulation in the first trimester for full antenatal period should be initiated, even in those with no history of VTE in Protein C deficiency pregnancies considering evidence of increased thrombotic events.

Protein C-deficient women on oral anticoagulation should be counselled regarding possible teratogenic effects of oral anticoagulation like warfarin in preconception counselling. As warfarin and other vitamin K antagonists, freely cross the placenta and are teratogenic or can cause fetal bleeding, their switch to LMWH or UFH from first trimester is warranted to avoid these complications. LMW heparins do not cross the placenta and do not cause fetal anticoagulation.

As postpartum risk of VTE is higher than antepartum risk, and thrombo-prophylaxis dosage should be aggressive post-delivery till 6–12 weeks. Vitamin K antagonists do not collect in breast milk and can be safely continued during breast feeding.

Because of the proven efficacy and safety for fetus, heparin remains the preferred anticoagulant for most pregnant women. Unfractionated heparin (UFH) is less expensive, safe even for end stage renal diseases. It is advantaged by rapid control and reversal of its anticoagulant effect as compared to Low Molecular Weight Heparin. In contrast to UFH, LMWHs have longer half-life, maintain a dose dependent plasma level, can be used at home with good predictability, even long-term use carries lesser risk of osteoporosis and heparin induced thrombocytopenia.<sup>14</sup>

Apart from a past VTE event, repeated second trimester nonanomalous fetal losses were also present in this case, with no other detectable cause except protein C deficiency. As reported by Folkeringa et al., there are high rates of fetal losses in women with hereditary deficiencies of antithrombin, protein C or protein S, which can be improved with anticoagulant treatment during pregnancy. They found an adjusted relative risk of fetal loss in women who received thromboprophylaxis as 0.07 (95% confidence interval 0.001–0.7;  $p = 0.02$ ) compared to those women who did not.<sup>7</sup> Considering this evidence, we continued the anticoagulation throughout pregnancy and postpartum for our patient.

American College of Obstetricians and Gynecologists (ACOG) and an American Society of Hematology (ASH) guideline from 2018 have recommended that subcutaneous LMW or UFH should be discontinued when spontaneous labor begins, or 12–24 hours before planned induction of labor or cesarean delivery.<sup>15</sup>

Postpartum heparin needs to be started 4–6 hours after a vaginal delivery or 6–12 hours after cesarean delivery in patients with normal postpartum bleeding. Warfarin therapy can begin immediately after delivery since it takes 3–4 days to achieve anticoagulation.<sup>16</sup> Oral warfarin and heparin are started simultaneously on the therapeutic dose of UFH or LMWH and till the INR is in therapeutic range for two consecutive days. This was done to avoid the paradoxical thrombosis and skin necrosis from early anti-protein C effect seen in warfarin.

Case-based anticoagulation prophylaxis needs to be incorporated in antenatal care of thrombophilia. Those with previous thromboembolic events, or having very low activity of protein C or having previous fetal losses likely due to thrombophilia are candidates for full thromboprophylaxis. This case highlights that full thromboprophylaxis throughout antenatal period in patient with protein C deficiency and having history of thrombo-embolic event with previous fetal losses can result in successful pregnancy outcome by preventing thrombosis in maternal as well as feto-placental vessels.

## ORCID

Monika Anant  <https://orcid.org/0000-0001-7957-379X>

## REFERENCES

- Greer IA. The challenge of thrombophilia in maternal-fetal medicine. *N Engl J Med* 2000;342(6):424–425. DOI: 10.1056/NEJM200002103420610.
- Anderson JAM, Weitz JI. Hypercoagulable states. *Crit Care Clin* 2011;27(4):933–952, vii. DOI: 10.1016/j.ccc.2011.09.007.
- Gerhardt A, Scharf RE, Beckmann MW, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. *N Engl J Med* 2000;342(6):374–380. DOI: 10.1056/NEJM200002103420602.
- Martinelli I, Mannucci PM, De Stefano V, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. *Blood* 1998;92(7):2353–2358. PMID: 9746774.
- Vaidyanathan A, Bhuvana S. Antepartum cortical vein thrombosis. *J South Asian Fed Obstet Gynaecol* 2017;9(2):200–202. DOI: 10.5005/jp-journals-10006-1494.
- Lussana F, Coppens M, Cattaneo M, et al. Pregnancy-related venous thromboembolism: risk and the effect of thromboprophylaxis. *Thromb Res* 2012;129(6):673–680. DOI: 10.1016/j.thromres.2012.01.017.
- Folkerling N, Brouwer JLP, Korteweg FJ, et al. Reduction of high fetal loss rate by anticoagulant treatment during pregnancy in antithrombin, protein C or protein S deficient women. *Br J Haematol* 2007;136(4):656–661. DOI: 10.1111/j.1365-2141.2006.06480.x.
- Singh N, Acharya N, Acharya S. Homocysteinemia: a rare cause of recurrent pregnancy loss coexisting with deep vein thrombosis. *J South Asian Fed Obstet Gynaecol* 2021;12(5):328–330. DOI: 10.5005/jp-journals-10006-1824.
- Morrison AE, Walker ID, Black WP. Protein C deficiency presenting as deep venous thrombosis in pregnancy. Case report. *Br J Obstet Gynaecol* 1988;95(10):1077–1080. DOI: 10.1111/j.1471-0528.1988.tb06518.x.
- Maeda Y, Satoh K, Haboshi T, et al. [A case report of congenital protein C deficiency with cerebral venous sinus thrombosis during early pregnancy period]. *No Shinkei Geka* 2017;45(10):913–918. DOI: 10.11477/mf.1436203617.
- Vogel JJ, de Moerloose PA, Bounameaux H. Protein C deficiency and pregnancy: a case report. *Obstet Gynecol* 1989;73(3 Pt 2):455–456. PMID: 2915872.
- Sugiura M. Pregnancy and delivery in protein C-deficiency. *Curr Drug Targets* 2005;6(5):577–583. DOI: 10.2174/1389450054545971.
- Croles FN, Nasserinejad K, Duvekot JJ, et al. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. *BMJ* 2017;359:j4452. DOI: 10.1136/bmj.j4452.
- Hao C, Sun M, Wang H, et al. Low molecular weight heparins and their clinical applications. *Prog Mol Biol Transl Sci* 2019;163:21–39. DOI: 10.1016/bs.pmbts.2019.02.003.
- Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv* 2018;2(22):3317–3359. DOI: 10.1182/bloodadvances.2018024802.
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 196: thromboembolism in pregnancy. *Obstet Gynecol* 2018;132(1):e1–e17. DOI: 10.1097/AOG.0000000000002706.