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CASE REPORT

# Pregnancy and Its Outcome in a Rare Case of Combined Protein C and Protein S Deficiency with Severe Adenomyosis

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## Introduction

Pregnancy itself is a hypercoagulable state due to alteration in the level of coagulation proteins. Thrombophilia in pregnancy further complicates it by leading to arterial and/or venous thrombosis resulting in increased feto-maternal risk. Thrombosis in maternal veins may lead to deep venous thromboembolism (DVT) and in placental circulation may lead to recurrent pregnancy loss (RPL), pre-eclampsia, abruption placentae, fetal growth restriction (FGR), intrauterine fetal death (IUFD), still birth. Protein C (PC) and protein S (PS) deficiencies are included under low-risk inherited thrombophilias. Both PC and PS deficiencies are associated with a variably increased risk of thrombosis. Combined deficiency of protein C and protein S is rare, and only few confirmed cases have been reported.

Adenomyosis manifests as an enlarged, globular uterus that can result in heavy menstrual bleeding and dysmenorrhea but is often asymptomatic. There is an association between adenomyosis and adverse pregnancy outcomes, including fetal loss, preterm delivery and preterm premature rupture of membranes (PPROM), IUGR [1].

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## Case Report

A 29-year-old female, married for 3 years, presented with complaints of 3 recurrent first trimester pregnancy losses. On detailed history, it was revealed that all 3 conceptions were spontaneous, and miscarriages (spontaneous) were between 6 and 8 weeks which were medically managed. She was thoroughly evaluated for her bad obstetric history. She had no history of any thromboembolic event. In her thrombophilia screen, she was diagnosed with Protein C (PC) and Protein S (PS) deficiency, both functional and immunogenic [Protein C (functional): 57% (70–130%), ELISA: 40% (80–140%); Protein S (functional): 50% (73–104%); ELISA: 30% (80–140%); LA (by dRVVT): 27 s (36–50), SLE ruled out]. She was referred to a hematologist for consultation in view of PC and PS deficiency Tablet aspirin 75 mg OD was started thereafter.

USG plate of adenomyotic uterus.

On per abdominal examination, her uterus was found to be grossly enlarged, approximately up to 20 weeks size. On ultrasonography (USG) severely adenomyotic uterus was diagnosed

with uterus size measuring 14.4 × 9.4 cm with thickened echogenic walls. MRI revealed uterus size of 17 × 15 × 13 cm, with multiple small variable areas of heterogeneous echotexture seen scattered in myometrium (adenomyotic). Her menstrual cycles were regular with no menstrual abnormality. Decision for in vitro fertilization (IVF) was taken in view of grossly enlarged adenomyotic uterus which required medical treatment to reduce the size of uterus, after counseling the patient and her family. Her oocyte retrieval was done using antagonist protocol, and embryos were cryopreserved after fertilization. Before doing the embryo transfer, her grossly enlarged sized uterus size was required to be reduced, in order to retain pregnancy. So, for this purpose total 4 doses of gonadotropin-releasing hormone (GnRH) analogue, triptorelin 3.75 mg were given intramuscularly, with 4-week interval between subsequent doses. After that, USG was repeated which showed significant reduction in the size of uterus, measuring 9.7 × 9.1 × 6.6 cm. Thereafter 3 embryos were transferred after thawing. Patient was diagnosed with twin pregnancy. Injection low molecular weight heparin (LMWH), i.e., enoxaparin 40 mg subcutaneously OD, was started. Routine antenatal care was provided.

At 8 weeks of gestational age, she had bleeding per vaginum for which she was admitted in the hospital and was managed conservatively for threatened abortion. Tablet aspirin was stopped, and LMWH was continued along with progesterone support. Her B.P. was within normal range throughout pregnancy, although hypertension is often noticed in such cases of thrombophilia. Decision for Elective LSCS at 37 weeks was taken in view of transverse lie of one of the twin fetus. LMWH was stopped a day before LSCS. And 2 units of PCV were cross-matched. A healthy male baby (vertex) weighing 3100 g and a healthy female baby (transverse) weighing 2090 g were born, both alive and well now. Uterus was found to be severely adenomyotic and enlarged. Intra-operatively, patient landed up in post-partum hemorrhage and mild DIC. Uterotonics like Inj. Oxytocin 20 units in 500 ml Ringer lactate was given intravenously, Inj. Methergine 0.2 mg was given intravenously, and in addition 800 µg of Tab. misoprostol was kept per rectally. 3 units packed cell volume (PCV) was given, and patient was shifted to ICU. Post-operatively 3 more units of PCV and 4 units of fresh frozen plasma (FFP) were required to be given. Thromboembolic deterrent (TED) stockings were advised. Patient was shifted to ward on post-op day 3, and LMWH was restarted and was advised to continue for 6 weeks post-partum. Patient was discharged on post-op day 6.

## Discussion

Inherited deficiencies of the natural coagulants are uncommon. Protein C deficiency occurs in approximately 1 of every 200–500 people, whereas protein S deficiency can be expected in approximately 1 of every 500 individuals [2]. Only a few cases of combined PS and PC deficiency have been reported in literature, so its prevalence rate is still not established. It is a unique case of pregnancy and related complications in a patient with combined PS and PC deficiency with adenomyosis, as no similar case is yet reported in scientific papers. The deficiency of clotting inhibitors, like PS, PC and/or antithrombin, has been clearly associated to RPL in many past studies. The association between thrombophilia and recurrent pregnancy loss (RPL) has become an undisputed fact [3]. PC and PS deficiency tests should be done in pre-pregnancy state, as results are less reliable in pregnant state because during pregnancy resistance to the anticoagulant protein C is increased, and the protein S level, a cofactor to protein C, decreases. To manage these patients, the antithrombotic therapy plays a vital role. Patients who have no personal history of VTE, as was our patient, are advised prophylactic dose of LMWH with or without aspirin, whereas the patients with history of VTE should be advised intermediate or therapeutic dose of LMWH. These patients should be closely monitored for other risks associated with thrombophilia throughout pregnancy. Mostly patients with thrombophilia may never develop VTE, but there is always certain risk of developing VTE in pregnant patients having thrombophilia. Chaudhari et al. [4] also reported such a case of combined PS and PC deficiency who had 4 RPL and developed superior sagittal sinus thrombosis post-operatively.

Adenomyosis interferes with natural conception and normal implantation. GnRH analogues are used for medical management and exert a direct antiproliferative action on myometrium. GnRH agonists can markedly reduce the inflammatory reaction and angiogenesis; it also induces apoptosis in adenomyotic tissues. It overall results in shrinking enlarged adenomyotic uterus [5]. In 2017, a metaanalysis suggested that adenomyosis reduces the chance for pregnancy and increases the risk for miscarriage, and GnRH may be beneficial in such cases [6]. The progesterone receptors present on endometrial tissue and the elevated progesterone levels in pregnancy result in stromal decidualization of adenomyosis foci. This heavily decidualized adenomyosis can then lead to uterine wall weakness, further resulting in uterine rupture or uncontrolled bleeding during pregnancy. In a case reported by Tatsis V, et al., at the time of LSCS, extensive transmural adenomyosis with decidualization was noted, ultimately requiring a Cesarean hysterectomy due to intra-operative hemorrhage. Similarly our patient had intra-operative hemorrhage but fortunately could be managed conservatively. Thus, it is important to counsel patients regarding the potential implications of suspected adenomyosis where clinically relevant and to consider maternal–fetal outcomes.

## Conclusion

Thrombophilia screening is justified in women with recurrent pregnancy loss, and treatment with low molecular weight heparin should be considered for those with pregnancy loss and thrombophilia. 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 to mortality. As we know adenomyosis has impaired pregnancy outcome and it is very difficult for a grossly enlarged adenomyotic uterus to retain even singleton pregnancy and to continue till term. But with proper scientific management, we can also allow twin pregnancy to reach term. Also, in case adenomyosis is suspected prior to or during pregnancy, clinicians should contemplate for bleeding complications secondary to potential decidualization of that tissue and should take necessary measures beforehand.

### Compliance with Ethical Standards

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

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## About the Author

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