PROTEIN S DEFICIENCY IN PREGNANCY: TO TREAT OR NOT TO TREAT. A CASE SERIES.

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**ABSTRACT**

**Introduction:** Protein S deficiency is rare occurring in only about 3 out of 10,000 women. Thrombophilias, whether inherited or acquired, have been associated with adverse reproductive outcomes such as recurrent first trimester pregnancy losses, second and third trimester pregnancy losses, pre-eclampsia, fetal growth restriction, placental abruption and venous thrombo-embolism. Treatment of protein S deficiency with anticoagulation in pregnancy is usually individualized depending on patient prior history and presenting symptoms. We report of 2 cases of women with protein S deficiency in pregnancy who had varied management and conduct a literature review on the salient features of this condition in pregnancy.

**Cases:** Two women, who were sisters and had a prenatal diagnosis of protein S deficiency, were managed in their current pregnancies. One was on her fifth pregnancy having had adverse pregnancy outcomes and the other in her first pregnancy. One of the lady was on anti-thrombotic agents prior to the pregnancy which was continued during the pregnancy and the other was not started on anti-coagulation. They both had good pregnancy outcomes in the documented pregnancies.

**Conclusion:** Protein S deficiency in pregnancy is a rare medical condition which most clinicians may not come across in their practice. The patients outlined had a prenatal diagnosis and hence presented no diagnostic dilemma. However, thrombophilias should be suspected in women with recurrent adverse pregnancy outcomes that have not been explained with other causes. The management of these patients largely involve use of anti-thrombotic agents with multi-disciplinary care being of benefit in improving outcomes.

**Keywords:** Protein S deficiency; thrombophilia; Pregnancy; Anti-thrombotic agents

**INTRODUCTION**

Protein S deficiency is rare occurring in only about 3 out of 10,000 women (1). This prevalence is even lower in African countries either due to a ‘true’ lower prevalence or paucity of data on the condition (2). Despite being rare in occurrence, inherited thrombophilias are of clinical significance due to their impact on reproductive outcomes (2-4).

Thrombophilias, whether inherited or acquired, have been associated with adverse reproductive outcomes such as recurrent first trimester pregnancy losses, second and third trimester pregnancy losses, pre-eclampsia, fetal growth restriction, placental abruption and venous thrombo-embolism (VTE) (2,5).

More so, Proteins S deficiency in pregnancy has been strongly correlated with mainly second and third trimester loss and VTE and despite there being inconsistent evidence on its impact on the other adverse pregnancy outcomes, one cannot totally rule out its implication in pregnancy (2,6).

Treatment of protein S deficiency with anticoagulation in pregnancy is usually individualized depending on patient prior history and presenting symptoms (2,7). General consensus seems to suggest that women with prior history of recurrent first trimester miscarriages, second and third trimester miscarriages and previous VTE may benefit from anticoagulant therapy in pregnancy (2, 8, 9). The recommended anticoagulants are usually Aspirin...
and Heparin with guidelines stating that starting them before 12 weeks is best for optimal impact on reduction of adverse reproductive outcomes (8-10).

However, it is important to note that treatment in pregnancy is still an area of many unknowns and most of the evidence is derived from expert opinion as opposed to firm evidence (2).

Proteins S deficiency is rare and seems to be of significant clinical impact on reproductive outcomes, we therefore report of 2 cases of women who were sisters with protein S deficiency in pregnancy who had varied management and conduct a literature review on the salient features of this condition in pregnancy.

CASE PRESENTATION

Case 1

N.S. is a 39 year old lady whom we managed in her fifth pregnancy. She came for her initial antenatal visit at 8 weeks. She had no complaints at the point and had an uneventful pregnancy so far. She was a known patient with protein S deficiency diagnosed 2 years prior with a protein S activity level of 18% (Normal is 50-134) and was on warfarin 5 milligrams (mgs) once a day. Her antecedent pregnancies were as follow: the first was in 2004 and she had a term delivery via caesarean delivery due to fetal distress in labor. The second was in 2005 which ended in an intra-uterine fetal death at 24 weeks, it was complicated with high blood pressures and pre-eclampsia. Her third pregnancy was in 2007 which ended in a live birth through caesarean delivery due to placental abruption. Her last pregnancy ended in an intra-uterine fetal death at 24 weeks due to placental abruption. In her past medical history, she had been treated for a right ilio-femoral deep vein thrombosis and pulmonary embolism in 2011. She had two sisters who had also been diagnosed with protein S deficiency. The first had a protein S activity level of 12% (was off anticoagulation - heparin) and had two surgeries (myomectomy and incisional hernia repair) in the United States which were uneventful.

The second sister in the other case discussed in this series whom we managed in pregnancy. Her antenatal profile tests at the booking visit were all normal. She had a hemoglobin level of 12.2 grams/ deciliter (g/dl) and a platelet count of 162 cells per micro-liter. Her antenatal serology were all negative (Hepatitis B, syphilis and Human Immunodeficiency Virus (HIV)).

The initial plan was to stop her warfarin and we started her of on Enoxaparin (Clexane) injections at a dose of 40 international units (iu) subcutaneously per day. She was also started on oral junior aspirin (Ascard) at a dose of 75 milligrams a day.

Her follow up was as follows: she had an ultrasound scan at 13 weeks and a double test which showed a low risk for downs syndrome. She had a fetal anomaly scan at 21 weeks which revealed normal fetal anatomy, a placenta which wasn’t low lying and a normal cervical length of 4 centimeters (cm). At 27 weeks she had an episode of intense lower abdominal pains but no clinical or sonographic evidence of preterm labour or placental abruption. She was subsequently put on oral nifedipine at 10mgs four times a day and given betamethasone injections at 12mgs daily on consecutive days. At 32 weeks she complained of leg cramps which were worse on the right leg compared with the left leg. She had bilateral lower limb venous Doppler that revealed no evidence of deep vein thrombosis. She was treated conservatively with oral painkillers and calcium supplementation. She was delivered at 39 weeks via caesarean section with outcome being a live female infant with a weight of 2.9 kilograms (kgs). She had a concomitant bilateral tubal ligation. She developed high blood pressures post-delivery and was maintained on the nifedipine which seemed to control her blood pressures. She was converted back to warfarin at 3 weeks post-delivery. She had subsequent normal visits and was referred to a hemato-oncologist to continue her management of the protein S deficiency.

Case 2

L.S. a 29 year old primigravida whom we managed in her first pregnancy. She was the sister of the first case discussed and came in for her first antenatal visit at 5 weeks gestation. She had an antenatal profile tests which revealed a hemoglobin level of 10.2 g/dl, a negative serology (HIV, hepatitis B
and syphilis) and an antenatal scan which revealed a normal intra-uterine gestation with a left ovarian hemorrhagic cyst measuring 6.2 cms. She had a strong family history of Protein S deficiency with 2 sister having been diagnosed with it so we requested a protein S activity level at 18 weeks gestation which revealed a level of 24% (Normal 42-68). However, due to her low symptom level we decided not to put her on antenatal anti-coagulation.

Her follow up was as follows; she had subsequent ultrasounds which revealed that the cyst was becoming larger (7cms). She was scheduled for a laparoscopic left ovarian cystectomy at 10 weeks gestation which was uneventful. She had a normal 20 weeks fetal anomaly scan. She required antenatal iron supplementation due to borderline low hemoglobin levels (11.02 g/dl). She had a normal antenatal period with a normal growth scan at 34 weeks. She had an early induction of labour at term due to pre-labor rupture of membranes at 40 weeks. She had a normal vaginal delivery to a male infant weighing 3.9 kgs. Her puerperium was uneventful and had a copper coil inserted at 6 weeks postdelivery for contraception.

**DISCUSSION**

The cases outlined document 2 rare cases of protein S deficiency in pregnancy. Their varied management may point out important aspects in individualizing treatment in patients with this condition.

Protein S deficiency is rare in the general population and even rarer in women in the reproductive age (1,2). The documented cases represent the index patients with confirmed Protein S deficiency managed at our institution and this adds weight on the rarity of its occurrence. A few risk factors of Protein S deficiency have been identified. The main risk factor that has been identified in literature is family history of Protein S deficiency which seems to increase the risk of having the disorder by 10 fold (11). This was the case with the outlined cases because both of them had a first degree relative with Protein S deficiency. Japanese race seems to confer a higher risk of having Protein S deficiency with them having a 5 fold higher incidence of this condition compared to Caucasians (12). The incidence seems to be much lower in Asians and Africans. Both the patients discussed were African ladies and hence had a low risk of having Protein S deficiency. Age is another risk factor identified with most women having symptomatic Protein S deficiency being under 45 years and this is in keeping with the current series where both women were under 45 years in age(11).

Protein S deficiency and other thrombophilias have been associated with several adverse pregnancy outcomes (2). These include recurrent first trimester pregnancy losses, second and third trimester pregnancy losses, pre-eclampsia, fetal growth restriction, placental abruption and VTE (13,14). However, second and third trimester losses and VTE seem to have the strongest association with Protein S deficiency (2). In the current series none of the pregnancies were associated with these adverse outcomes, however the first patient discussed had antecedent pregnancies complicated with high blood pressure and placental abruption. She also had a VTE diagnosed prior to the discussed pregnancy and was already on anti-coagulation. Moreover, the first patient seemed to have further pregnancy issues with episodes of lower abdominal pain but no increased blood pressures or evidence of abruption.

The mainstay of treatment of Protein S deficiency in pregnancy involves use of anti-thrombotic agents (2). The role of these agents is to decrease the risk of second and third trimester losses and the development of VTE(8,9). Since there has been no strong correlation between protein S deficiency and recurrent miscarriages, there is no strong indications for starting anti-coagulation early (2). With regards to prevention of VTE, it seems reasonable for the patients to be on antithrombotic agents from diagnosis of pregnancy and throughout the pregnancy till puerperium (15). The agents of choice in anticoagulation include Coumarin derivatives (warfarin) after 12 weeks pregnancy, unfractionated heparin and low molecular weight heparin (LMWH) like enoxaparin (7). These agents seem to have minimal fetal effect since they don’t cross the placenta and also have a good side effect profile (7,16). Moreover, a combination of aspirin (dosage of 75-150mg daily) from 12 weeks onwards in pregnancy with these agents seems to improve pregnancy outcomes with reduction of
occurrence of hypertensive disorders and small for gestational age fetuses (17). However, it is important to note that the decision to start antithrombotic therapy is individualized to the patients and a good number may not even be on any therapy during pregnancy. In the current series, one patient was on anticoagulant therapy due to VTE prior to pregnancy and this was continued throughout the pregnancy while the other was not put on any anticoagulation which elicits the point of individualized management.

The outcomes of pregnancies in women with thrombophilia is generally good with multidisciplinary care and initiation of antithrombotic agents (2,6). This is especially so when women are on LMWH during the pregnancy (18). The current patients both had a good pregnancy outcome in their pregnancies. Although the second patient was not on any antithrombotic therapy, she still had a term live birth with no adverse pregnancy complications. This further outlines the importance of individualization of the need of anti-thrombotic therapy in these patients.

CONCLUSION

In conclusion, protein S deficiency in pregnancy is a rare medical condition which most clinicians may not come across in their practice. The patients outlined had a prenatal diagnosis and hence presented no diagnostic dilemma. However, thrombophilias should be suspected in women with recurrent adverse pregnancy outcomes that have not been explained by other causes. The management of these patients largely involves use of antithrombotic agents with multi-disciplinary care being of benefit in improving outcomes.

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