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PROTEIN PUZZLE: A CASE SERIES ON RECURRENT PREGNANCY LOSS UNMASKING PROTEIN S DEFICIENCY

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Abstract

Aim

This case series investigates the correlation between unexplained recurrent pregnancy loss (RPL) and Protein S deficiency, emphasizing the importance of targeted thromboprophylaxis in affected patients.

Background

Recurrent fetal loss (RPL) is one of the most common causes of sterility.Pregnancy as such is a hypercoagulable state with differing levels of coagulatory proteins. Functionally, the enzymatic active form of protein Cregulates blood clot formation. Protein S serves as a cofactor for the anticoagulant effect of protein C[(1)].In 1999 Brenner et al (1999) identified thrombophilia as a principal cause in more than 40% of women affected by RPL[(2)]. Functional protein C or S levels do not change significantly during pregnancy. Only the free protein S levels tend to fall significantly during the first and second trimesters of pregnancy, but there is no further decrease during the third trimester. Protein S deficiency is more commonly identified than protein C deficiency. Protein S deficiency is a hereditary thrombophilia that can lead to a prothrombotic state, significantly increasing the risk of RPL and adverse pregnancy outcomes.Women with these deficiencies have a higher risk of developing thrombosis of the placental vessels, leading to placental insufficiency and pregnancy loss. This condition exacerbates the naturally occurring hypercoagulable state during pregnancy, raising the likelihood of complications such as placental thrombosis and venous thromboembolism. This case series aims at detecting protein S deficienciesin pregnancy and its effects and outcomes on both mother and baby.

Clinical Significance

This study highlights the critical role of identifying Protein S deficiency in patients experiencing RPL. By implementing targeted management strategies, healthcare providers can mitigate risks associated with this condition, ultimately enhancing pregnancy outcomes. Routine screening for Protein S deficiency should be considered in clinical practice for women with unexplained RPL to facilitate appropriate treatment and care.

Methods: Between December 2023 and May 2024, three antenatal women with a history of recurrent pregnancy losses were evaluated at our institution. Each patient underwent a comprehensive assessment that included detailed obstetric histories, laboratory investigations for thrombophilia (including Protein S activity levels), and imaging studies as needed. The management strategies implemented for each patient included low molecular weight heparin (LMWH) and aspirin therapy, tailored to their specific clinical scenarios. Outcomes were monitored through regular follow-ups, including ultrasound assessments for fetal growth and Doppler flow studies. This case series analyses various risk factors, obstetric histories, gestational ages at presentation, complications encountered, and treatment outcomes for each patient.

Conclusion

The findings from this case series underscore the necessity for routine screening and proactive intervention in high-risk pregnancies. Early diagnosis and management of Protein S deficiency can

lead to improved maternal and fetal outcomes, thereby reducing the distress associated with recurrent pregnancy loss.
Keywords: Protein S deficiency, recurrent pregnancy loss, thrombophilia, low molecular weight heparin, obstetric management, fetal outcomes, anticoagulant, pregnancy complications, antiphospholipid antibody syndrome.

INTRODUCTION

Protein S deficiency is a relatively uncommon inherited disorder associated with an increased risk of pregnancy loss. While the exact mechanism behind this condition is not fully understood, it is estimated to affect approximately 1 in 500 to 1 in 3,000 individuals. This deficiency is characterized by an impairment in the inactivation of clotting factors Va and VIIIa, resulting in a hypercoagulable state that can contribute to complications in pregnancy. During pregnancy, functional levels of Protein C and S generally remain stable; however, there is a notable decline in free Protein S levels during the first and second trimesters, with no significant changes in the third trimester. Protein S deficiency occurs more frequently than Protein C deficiency. The precise reasons for recurrent pregnancy loss (RPL) are complex and not entirely understood, but the hypercoagulable state induced by a deficiency of antithrombotic factors can lead to placental thrombosis, insufficient blood flow, and ultimately fetal demise. Additionally, some researchers propose that maternal-fetal immune system interactions may disrupt immune homeostasis, contributing to the risk of complications like miscarriage. Proper remodeling of maternal uterine spiral arteries is essential for normal fetal development, emphasizing the intricate interplay between coagulation factors and immune responses in influencing pregnancy outcomes. Since protein S deficiency can be found isolated as well as in combination with other inherited thrombophilia, screening can also become a part of routine APLA testing.

Objective

This case series aims to determine the correlation between unexplained recurrent pregnancy loss and Protein S deficiency, thereby assisting obstetricians in managing this challenging condition.

Case Description

Case 1: A 23-year-old woman, gravida 2, para 1, presented at 28 weeks of gestation. She had previously been diagnosed with Protein S deficiency during her first pregnancy, which was complicated by a cerebrovascular accident (CVA) at 12 weeks of gestation. Laboratory investigations revealed a protein S activity level of 29.4%, accompanied by a negative antiphospholipid antibody (APLA) profile. An MR angiogram indicated the presence of a chronic infarct with hemosiderin deposition. The patient was managed with low molecular weight heparin (LMWH) at a dosage of 40 mg daily, in conjunction with aspirin at 150 mg. Throughout her pregnancy, normal fetal growth was observed, and Doppler flow assessments conducted at 34 weeks demonstrated no abnormalities. She successfully delivered a healthy baby at term.

Case 2: A 31-year-old woman, gravida 5, para 3, with a history of recurrent third-trimester intrauterine demise attributed to uteroplacental insufficiency, presented at 36 weeks of gestation. Investigations revealed a protein S activity level of 35% and a negative APLA profile. The patient was initiated on LMWH therapy upon confirmation of pregnancy. At 37 weeks, she underwent an elective cesarean section and delivered a healthy-term infant without any complications.

Case 3: A 28-year-old woman, gravida 3, abortus 2, presented at 11 weeks of gestation with vaginal bleeding and a history of recurrent first-trimester abortions. Investigations indicated a protein S activity level of 40%, positive beta-2 glycoprotein (IgM), and negative for other APLA markers. Ultrasound examination confirmed a missed miscarriage; consequently, she underwent surgical termination via suction and evacuation. The patient was counseled regarding the use of prophylactic LMWH and aspirin for future pregnancies to mitigate the risk of recurrent pregnancy loss.

DISCUSSION

Protein S deficiency is notably distinct from deficiencies of other vitamin K-dependent plasma proteins as well as factor VIII deficiency. Most individuals with Protein S deficiency have either normal or only slightly reduced levels of protein S antigen in their plasma[3]. Pregnant women with this deficiency are often heterozygous. It is advisable that the partners of affected women undergo screening for potential neonatal homozygosity or combined defects, as prenatal diagnosis may be an option in such cases. Women who have genetic or acquired forms of thrombophilia face a significantly heightened risk of venous thromboembolism both during pregnancy and after delivery, and therefore should receive thromboprophylaxis throughout pregnancy and the postpartum period[4,5]. Protein S deficiency is an important hereditary thrombophilia that can lead to serious complications during pregnancy, especially recurrent pregnancy loss (RPL). The underlying mechanism of Protein S deficiency is linked

to the reduced inactivation of clotting factors Va and VIIIa, resulting in a state of increased clotting propensity. This heightened risk of thrombotic complications may present as issues such as placental insufficiency, fetal growth restriction, or repeated miscarriages.

A study conducted by Ruchi et al. analyzed a population of 578 women diagnosed with inherited thrombophilia, revealing 35 instances of Protein S deficiency associated with recurrent pregnancy loss (RPL). Among these cases, 20 women experienced early pregnancy loss, defined as miscarriages occurring prior to 20 weeks of gestation[6]. This finding is consistent with our own case series, in which all participating women reported recurrent miscarriages. Such results underscore the imperative for clinicians to be acutely aware of the potential implications of Protein S deficiency in early pregnancy complications. Additionally, a meta-analysis performed by Kovalevsky et al. established a robust association between RPL and carriers of Protein S deficiency, indicating that affected women possess a twofold increase in the risk of experiencing pregnancy loss compared to women without thrombophilia markers[7]. This highlights the critical need for comprehensive screening in patients presenting with recurrent pregnancy losses.

Preston and colleagues clarified that, although the risk of miscarriage does not significantly increase with deficiencies in Protein C or S alone, these conditions are associated with a moderate rise in the risk of stillbirth[8]. Furthermore, Rey and his team found that deficiencies in protein C and antithrombin were not linked to fetal loss, whereas protein S deficiency was associated with late-term fetal loss[9]. This distinction is essential for obstetric management, emphasizing the importance of monitoring both early pregnancy outcomes and potential complications in the later stages for affected individuals.

A study conducted in the United States indicated that women with Protein S deficiency who were treated with daily fondaparinux experienced successful live births without notable complications[10]. This finding implies that proactive management approaches can lead to positive outcomes even in high-risk pregnancies. In our case series, all three patients diagnosed with Protein S deficiency received treatment with low molecular weight heparin (LMWH) and aspirin, which is consistent with current guidelines that recommend prophylactic anticoagulation for this demographic. Additionally, another study revealed that the use of LMWH for prophylactic anticoagulation significantly increased live birth rates among these patients[11].

Furthermore, research conducted by Eva and colleagues has demonstrated that the combination of heparin—whether unfractionated or low molecular weight—alongside aspirin during pregnancy may enhance live birth rates compared to the use of aspirin alone[12]. Heparin is notable for its inability to cross the placenta; as a result, there is no associated risk of teratogenesis or fetal hemorrhage. Additionally, both heparin and warfarin can be administered safely to nursing mothers. This combination therapy appears to be particularly effective in patients with thrombophilia, thereby underscoring the importance of developing individualized treatment plans tailored to specific patient profiles. Despite the advancements achieved in the understanding and management of Protein S deficiency during pregnancy, significant gaps remain in clinical practices concerning screening protocols. While many practitioners routinely screen for antiphospholipid antibodies due to their established association with adverse pregnancy outcomes, our research emphasizes the necessity of assessing women for Protein S deficiency, particularly those with unexplained recurrent pregnancy loss and those who are antiphospholipid syndrome-positive and have a history of recurrent pregnancy loss, despite treatment. The identification of Protein S deficiency facilitates the implementation of targeted management strategies which can markedly improve pregnancy outcomes

CONCLUSION

Recurrent pregnancy loss is a profoundly distressing experience that imposes significant physical, emotional, and financial burdens on the family. Despite extensive investigations into the underlying causes, many instances of RPL remain unexplained, with Protein S deficiency emerging as a notable contributor. Given the substantial impact of Protein S deficiency on pregnancy outcomes, this condition must be thoroughly evaluated in high-risk cases. Early diagnosis and timely intervention are crucial in mitigating the risks associated with this thrombophilia, ultimately leading to improved maternal and fetal outcomes. As such, healthcare providers should consider routine screening for Protein S deficiency in patients with a history of recurrent pregnancy loss, thereby facilitating targeted management strategies that enhance the likelihood of successful pregnancies.

Clinical significance

This case series emphasizes the critical importance of identifying Protein S deficiency as a significant contributing factor to unexplained recurrent pregnancy loss (RPL). Early detection and targeted management of this hereditary thrombophilia are essential in mitigating substantial risks, including placental thrombosis and subsequent pregnancy loss. The findings advocate for the implementation of routine screening for Protein S deficiency in women with a history of unexplained RPL, which is crucial for guiding effective treatment strategies.Specifically, the use of anticoagulation therapies, such as low molecular weight heparin (LMWH) and aspirin, has shown promise in improving maternal and fetal outcomes. These interventions not only enhance the likelihood of

successful pregnancies but also significantly improve the overall quality of care for patients classified as high-risk. By reducing the emotional and physical burdens associated with recurrent pregnancy loss, this research underscores the necessity of a proactive and individualized approach to screening and management.Furthermore, the findings from this case series pave the way for better reproductive health outcomes by encouraging healthcare providers to consider Protein S deficiency in their diagnostic evaluations. This proactive stance can lead to more tailored treatment plans that address the specific needs of patients, ultimately fostering improved reproductive health and well-being.

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