



Thrombophilia: Cause of Recurrent Pregnancy Loss

Authors

Dr Meenakshi Rana¹, Dr Ankita Jamwal^{2*}

¹Junior Resident Department of Obstetrics and Gynaecology, IGMC Shimla

²Junior Resident Department of, Obstetrics and Gynaecology IGMC Shimla

*Corresponding Author

Dr Ankita Jamwal

Junior Resident Department of Obstetrics and Gynaecology, IGMC Shimla, India

Introduction

The association between thrombophilia and recurrent pregnancy loss (RPL) has become an undisputed fact. Thrombophilia leads to a hypercoagulable state which in turn leads to arterial and/or venous thrombosis at the site of implantation of embryo or in the placental bed blood vessels. Anticoagulants are suggested to be an effective treatment against RPL in women with acquired thrombophilia due to antiphospholipid syndrome. However the use of anticoagulants in treatment of RPL in women with inherited thrombophilia (IT) are also satisfactory. Although the reported side-effects for anticoagulants are rare and usually reversible, the current recommendation is not to use anticoagulants in women with RPL and IT, or for those with unexplained losses. This review examines the strength of the association between thrombophilia and RPL.

Case Report

A 32 year old lady presented to antenatal opd for confirmation of pregnancy and initial antenatal check-up. Patient gave the history of positive

urine pregnancy done 3 days back at home. Along with routine investigations patient advised to get her initial ultrasound scan done in radiology department. Ultrasound showed a pregnancy of 7wk+2d with cardiac activity. In her obstetric history patient was G6P0+5. Patient had history of 5 previous abortions out of which initial three abortions were spontaneous pain abdomen followed by bleeding per vaginum followed by expulsion of product of conception. In her fourth pregnancy she was investigated for the bad outcome and patient was found to have protein c and protein s deficiency rest of the investigations were normal and after confirmation of pregnancy pt was put on low molecular weight heparin 40 mcg OD. But patient had missed abortion at 10wks+3d and medical termination of pregnancy done. Patient had her fifth pregnancy diagnosed at 6wk+6d and patient was again started low molecular weight heparin 40 mcg OD. And missed abortion occurred at 17wk +3D and medical termination of pregnancy was done. karyotyping of husband and wife was normal and microarray was normal. In her sixth pregnancy patient was reported to our hospital and after

confirmation of pregnancy patient was again investigated for bad outcome and found to have protein c and protein s deficiency with rest of the normal investigations and patient was admitted and started on low molecular weight heparin 60 mcg od .patient had no history of thrombophilia in family and no history and thrombotic event. Patient had her repeated ultrasound scan at 14 wk which found to have corresponding parameter with normal nuchal translucency and nasal bone was present and dual scan of the patient done which had low risk for trisomies and neural tube defect. Patient was continued with inj LMWH .ultrasound scan for congenital malformations scheduled at 18wk and ultrasound showed a fetus of 15wk with no cardiac activity with Spaulding sign. with this patient was scheduled for medical termination of pregnancy and placenta sent for histopathological examination. Counselling of patient done.

Discussion

Inherited thrombophilias are heterogenous group of genetic disorders that have been linked to adverse pregnancy outcome and increased risk of thromboembolism. Inherited thrombophilias have been divided into high risk and low risk based on risk of venous thrombo-embolism. Thrombophilia in general is a common cause of recurrent pregnancy loss and may seen in 40-50% cases .clinical studies suggest that hypercoagulation is main underlying pathophysiological mechanism which lead to uteroplacental insufficiency and subsequently pregnancy loss.

Antithrombin Deficiency may result from hundreds of different mutations that are almost always autosomal dominant. Type I deficiency is the result of reduced synthesis of biologically normal antithrombin, and type II deficiency is characterized by normal levels of antithrombin with reduced functional activity (Anderson, 2011). Homozygous antithrombin deficiency is lethal (Katz, 2002). Antithrombin deficiency is rare—it affects approximately 1 in 2000 to 5000 individuals, and it is the most thrombogenic of the

heritable coagulopathies. Sabadell and associates (2010) studied the outcomes of 18 pregnancies complicated by antithrombin deficiency. Twelve of these were treated with low-molecular-weight heparin, and six were not treated because antithrombin deficiency had not yet been diagnosed. Three of the untreated patients suffered a thromboembolic episode compared with none in the treated group. Untreated women also had a 50-percent risk of stillbirth and fetal-growth restriction. By comparison, none of the treated women had a stillbirth, and approximately a fourth developed fetal-growth restriction. Seguin and coworkers (1994) reviewed the outcomes of 23 newborns with antithrombin deficiency and described 11 cases of thrombosis and 10 deaths.

Protein C Deficiency: protein c activity is largely unchanged in pregnancy (Appendix, p. 1288). Based on their study of 440 healthy women, however, Said and associates (2010b) found that protein C activity increases modestly but significantly throughout the first half of pregnancy. These investigators speculated that this increase may play a role in maintaining early pregnancy through both anticoagulant and inflammatory regulatory pathways. The prevalence of protein C deficiency is 2 to 3 per 1000, but many of these individuals do not have a thrombosis history because the phenotypic expression is highly variable.

Protein S Deficiency: prevalence is approximately 2 per 1000 (Lockwood, 2012). Protein S deficiency may be measured by antigenically determined free, functional, and total S levels. All three decline substantively during normal gestation, thus the diagnosis in pregnant women—as well as in those taking certain oral contraceptives—is difficult (Archer, 1999). If screening during pregnancy is necessary, threshold values for free protein S antigen levels in the second and third trimesters have been identified at less than 30 percent and less than 24 percent, respectively. Among those with a positive family history, the venous thromboembolism risk

in pregnancy has been reported to be 6 to 7 percent (ACOG, 2013).

Factor V Leiden Mutation: The most prevalent, characterized by resistance of plasma to the anticoagulant effects of activated protein C. This missense mutation in the factor V gene results from a substitution of glutamine for arginine at position 506 in the factor V polypeptide, which gains resistance to degradation by activated protein C. The unimpeded abnormal factor V protein retains its procoagulant activity and predisposes to thrombosis

The association between thrombophilia and recurrent pregnancy has become an undisputed fact. thrombophilia creates a hypercoagulable state which lead to arterial and venous thrombosis at site of implantation or in the placental blood vessels. Anticoagulants are effective treatment against recurrent pregnancy loss in women with acquired thrombophilia but various studies have shown that use of anticoagulant in treating recurrent pregnancy loss in women with inherited thrombophilia is encouraging.

In this case there was deficiency of protein s and protein c and making the diagnosis of inherited thrombophilia. As the patient was asymptomatic (there was no episode of venous thromboembolism and there was no family history) treatment was given as prophylactic dose of low molecular weight heparin . Pregnancy continued for 18 weeks normally without any event when it was found to be intrauterine fetal demise at ultrasonography. A few studies reported the benefit of low molecular weight heparin in inherited thrombophilia while some say there is no proven benefit .in this case there was underlying thrombosis of placental vessel which has caused the fetal demise and this case reported as recurrent pregnancy loss in inherited thrombophilia inspite of prophylactic dose of low molecular weight heparin is one of a kind.

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