Original Article

Frequency of Thrombophilia in Patients with Adverse Pregnancy Outcome

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Abstract

Objective: To determine the association between adverse pregnancy outcomes and thrombophilia.

Methods: This is a descriptive study, incorporating retrospective analysis of patients with recurrent pregnancy losses, intrauterine deaths, abruptio placenta and early onset pre eclampsia. Patients with adverse pregnancy outcomes in whom co-morbid factors were excluded underwent screening for both acquired and inherited thrombophilia.

Results: A total of 40 patients were screened for acquired and inherited thrombophilia with adverse pregnancy outcomes. Anticardiolipin antibodies were found positive in 55% of patients and 45% of patients were found deficient for natural anticoagulants protein C and S. Two patients were found positive for both acquired and inherited thrombophilia.

Conclusion: Thrombophilia, both acquired and inherited are associated with adverse pregnancy outcomes. Patients in whom other co-morbid factors are excluded, should be offered screening for thrombophilia. Liaison between hematologist and obstetrician is the corner stone for success (JPMA 55:245;2005).

Introduction

Pregnancy is known as a hypercoaguable state with an increased thrombotic risk during the antenatal period, labour and in postnatal period. A successful outcome of pregnancy is dependant upon development of efficient uteroplacental circulation. The establishment of an effective foeto-maternal circulatory system may be compromised by disturbances of haemostasis leading to prothrmbotic state.

Thrombophilia refers to a group of disorders that is characterized by deficiency in the anticoagulant mechanism, leading to increased predisposition to thromboembolism.[1] They may be acquired or inherited. Inherited thrombophilias include activated protein C resistance (Factor V Leidin mutation), prothrombin gene mutation, hyperhomocysteinemia, and deficiencies of natural anticoagulants like protein C, S and antithrombin 111. Women harbouring these thrombophilia may present with clinical symptoms of vascular complications for the first time in pregnancy and in the post natal period. These vascular complications lead to defective utero-placental circulations, which in turn leads to early intrauterine growth restriction, still birth, abruptio placenta and intrauterine death.

Among the acquired thrombophilia, antiphospholipid syndrome is recognized by the presence of elevated titers of anticardiolipin antibodies and lupus anticoagulant. Diagnosis of antiphosphospholipid (APL) syndrome is made on raised titers of anticardiolipin antibodies on at least two occasions, six weeks apart. The risk of obstetric complications associated with APL syndrome and recurrent pregnancy loss is well established).[2] This study was carried out to see the association between adverse pregnancy outcome and thrombophilia.

Patients and Methods

This is a descriptive case series, incorporating a retrospective analysis of patients with recurrent pregnancy loss, intrauterine deaths, abruptio placenta, unexplained stillbirth and in patients with early onset pre eclampsia. Screening for thrombophilia was carried out in patients with above obstetric complications, in whom co-morbid factors had been excluded. A total of 40 patients were screened in the above series, from January 2002 to July 2004, over a period of 30 months.Thrombophilia screening was carried out from a single laboratory providing test facilities for both acquired and inherited thrombophilia.

In the majority of patients this screening was carried out six weeks after delivery. But in cases where it was done during pregnancy, the cutoff value was adjusted to take into account the anticoagulant effect of pregnancy. Recurrent pregnancy loss is defined as three consecutive first trimester pregnancy losses. Women having bad obstetric history viz three first trimester losses, or two fetal losses during second trimester or one fetal loss during third trimester were also included in the study.[3]

Intrauterine deaths, where the foetus dies in utero, not related to maternal or foetal causes were also included in the study. Abruptio placenta was diagnosed on the basis of clinical criteria, viz: uterine tenderness, concealed or revealed haemorrhage, foetal distress or demise associated with or without maternal coagulopathy.Intrauterine growth

restriction was defined by a birth weight below the fifth percentile for gestational age.[4]

Women with medical disorders or with congenitally malformed baby leading to IUGR were excluded.

Results

Results are summarized in Tables 1 and 2. Table 1 shows reasons for thrombophilia screening. Recurrent pregnancy losses and unexplained intrauterine deaths were the main reasons for carrying out the screening, followed by severe pre-eclampsia, abruptio placenta and history of venous thrombosis.

Table 1. Patients with adverse pregnancy outcome(n=40).

Recurrent pregnancy loss	14
Intra uterine death	13
Severe early pre eclampsia	9
Abruptio placenta	2
H/O deep venous thrombosis	2

Table 2 shows the results of screening. Beside anticardiolipin antibodies, natural anticoagulants protein C and S were found deficient in majority of patients (45%). Anticardiolipin antibodies were found positive in 55% of patients.

Table 2. Thrombophilia screen in patients with adverse pregnancy outcome (n=40).

Anticardiolipin antibodies	12
Protein C deficiency	9
Protein S deficiency	9

Two of the patients had combined defects for both acquired and inherited thrombophilia, where as, two patients had combined protein C and S deficiency. Out of 40 patients who were screened, 30 (75%) patients were found screen positive for thrombophilia.

Discussion

Pre-eclampsia is defined as a multi system syndrome, recognized by new onset hypertension and proteinuria in second half of pregnancy. Women with early pre eclampsia associated with foetal growth restriction, stillbirth or abruption may require screening for thrombophilia.[5]

This was a descriptive study, which was done to see the association between adverse pregnancy outcomes and acquired and inherited thrombophilia.

The mechanism, leading to adverse pregnancy outcomes involves impaired placental development and function. The association between recurrent pregnancy losses and anticardiolipin antibodies is well established. Out of 14 women with recurrent loss, 12 screened positive for anticardiolipin antibodies. Two of these patients had combined defects, both acquired and inherited thrombophilia. Anticardiolipin antibodies are associated with pregnancy loss at all gestational ages, intrauterine growth restriction and pre eclapmpsia. APL may or may not be associated with thrombocytopenia and SLE.[2]

Inherited thrombophilias are known to be associated with adverse pregnancy outcomes. They are also associated with recurrent pregnancy loss. In our series six patients with recurrent pregnancy losses (RPL), screened positive for protein C and S deficiency. The association between RPL and inherited thrombophilia is well documented.[6] Women deficient in natural anticoagulants like protein C and S and antithrombin 111, have been found more prone to uteroplacental microthrombosis, leading to RPL.[7] Recurrent losses have also been attributed to Factor V Leiden mutation.[8]

Thrombophilia is also associated with intra uterine growth restriction. It is necessary to exclude foetal causes, chromosomal disorders and maternal causes leading to chronic vascular disease, before taking thrombophilia as a causative factor. Verspyck et al, in a case control study, found combined thrombophilic defects as the cause of severe small for gestational age infants.[9] Previously deVries et al, found hyperhomocystenemia and Protein S deficiency specifically associated with early IUGR.[10] Similarly Kupferminc et al., detected thrombophilia to be associated with early severe pre-eclampsia, abruptio placenta. They recommended that those pregnancies which are complicated by severe pre eclampsia, abruption or unexplained foetal growth restriction, and in women whose pregnancies end up in unexplained still birth should be tested for genetic or acquired markers for thrombophilia.[11] These complications do recur in subsequent pregnancies and prophylaxis in the form of folic acid, aspirin and heparin is recommended for healthy outcome in subsequent pregnancies.

Abruptio placenta, occurs in 0.5% of gestations, but carries high maternal and foetal morbidity and mortality. In this series there were two patients with sudden and severe abruption, who tested positive for protein C and S deficiencies 6-8 weeks later.

Though the incidence of thrombophilia is low in general population, there is a strong association with adverse pregnancy outcomes. These complications do recur in subsequent pregnancies, hence there is advantage of

screening and offering prophylaxis in the subsequent pregnancy for healthy outcomes.

References

1. Higgins JR, Said J. The clinical implications of thrombophilia in pregnancy. In Bonnar J, Dunlop W. (eds). Recent advances in obstetrics and gynaecology 22. The Royal Society of Medicine Press Ltd., U.K., 2003, pp.13-25.
2. Gates S. Thromboembolic disease in pregnancy. Curr Opin Obstet Gynecol 2000;12:117-22.
3. Carp JA. Antiphospholipid syndrome in pregnancy. Curr Opin Obstet Gynecol 2004;16:129-35.
4. Kupferminc Michael J, Many A, Bar-Am A, Lessing JB, Landsberg J. Mid-trimester severe intrauterine growth restriction is associated with a high prevalence of thrombophilia.Br J Obstet Gynaecol 2002;109;1373-6.
5. Brenner B. Clinical management of thrombophilia-related placental vascular complications. Blood 2004;103:4003-9.
6. Brenner B, Hoffman R, Blumenfeld Z, Younis J. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxapirin.Thromb Haemost.2000;83:693-7.
7. Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus EC, HamulYak K, et al. Increased risk for fetal loss in carriers of the factor V Leiden mutation. Ann Intern Med1999;130:pp 736-9.
8. Verspyck E, Le CD, Goffinet F,Tron F, Marpeau L, Borg JY. Thrombophilia and immunological disorders in pregnancies as risk for small for gestational age infants. Br J Obstet Gynaecol 2002;109:28-33.
9. de Vries Jl, Dekker GA, Huijgens PC, Jacobs C, Bloomberg BA, van Geign HP. Hyperhomocysteinaemia and protein S deficiency in complicated pregnancies. Br J Obstet Gynaecol. 1997;104:1248-54.
10. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999;340:9-13.