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Leading article

Recurrent miscarriage and blood disorders: Integrating haematology into reproductive care

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Abstract

Antiphospholipid syndrome (APS) and inherited thrombophilia are well-recognized haematological causes of recurrent miscarriages. APS is an acquired autoimmune disorder linked to both early and late pregnancy losses. A meta-analysis of 120 studies reported that antiphospholipid antibodies are present in about 6% of women with pregnancy complications. Diagnosis of APS requires at least one clinical criterion plus one or more laboratory criteria. Clinical criteria include venous, arterial or microvascular thrombosis or pregnancy morbidity while laboratory criteria include positive lupus anticoagulant (LAC), or moderate-to-strong positivity for anti-cardiolipin IgM/IgG or anti-β2 glycoprotein I IgM/ IgG antibodies. Women with obstetric or thrombotic APS should be managed jointly in haematology-obstetric clinics. Treatment with low-dose aspirin and heparin is the standard therapeutic approach. This combination improves live birth rates by preventing clot formation, enhancing placental function and reducing risks such as pre-eclampsia and fetal growth restriction. Inherited thrombophilias such as factor V Leiden, prothrombin gene mutation, protein S deficiency and antithrombin deficiency have been found to be associated with recurrent miscarriages.

Introduction

Miscarriage is defined as the spontaneous loss of a pregnancy before the fetus reaches viability, typically before 24 weeks of gestation[1]. Miscarriages can be either sporadic or recurrent. Sporadic miscarriage, which most commonly occurs in the first trimester, is often due to random fetal chromosomal abnormalities. Its incidence increases with maternal age and may affect between 10% and 50% of women aged 20 to 45 years, respectively[2]. Approximately 1% of miscarriages occur in the second trimester, where the rate of chromosomal anomalies is significantly lower.

Recurrent miscarriage is traditionally defined as three or more consecutive pregnancy losses[3], although some guidelines define it as two or more losses[4]. It has a variety of causes, including anatomical, genetic, endocrine, immunological and haematological factors. Among haematological causes, thrombophilia including antiphospholipid syndrome (APS) are important and potentially treatable contributors to recurrent miscarriage[1].

Haematological causes for recurrent miscarriage

1. Antiphospholipid Syndrome (APS)

This is an acquired autoimmune disorder associated with recurrent miscarriages including early and late pregnancy losses. In an analysis which included 120 studies, the frequency of anti-phospholipid antibodies was 6% among women with pregnancy complications[5]. Recurrent miscarriage is one clinical criterion for APS and both clinical and laboratory criteria should be fulfilled to confirm APS.

Lupus anticoagulant (LAC) is the strongest association with recurrent miscarriage[5]. Anti cardiolipin antibodies IgG and IgM are found to have the second strongest association with recurrent miscarriage and anti-beta 2 glycoprotein 1 antibodies have a positive association but are not statistically significant[5].

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2. Inherited Thrombophilia

Inherited thrombophilias mentioned below are known to be associated with second trimester miscarriages and late pregnancy complications[3].

a) Factor V Leiden mutation
b) Prothrombin gene mutation (G20210A)
c) Protein S deficiency
d) Antithrombin deficiency

But testing is not recommended except in research context or for a woman with additional risk factors for thrombophilia[4].

Non haematological causes for recurrent miscarriages

a) Uterine anomalies (inclusive of common acquired anomalies (e.g. fibroids) and more uncommon anatomical defects (e.g. uterine septae)
b) Endocrine disorders (e.g. thyroid disease)
c) Genetic causes
d) Chronic endometritis, infectious diseases, luteal phase deficiency, high sperm DNA fragmentation levels, polycystic ovary syndrome and high or very low body mass index (BMI), have been proposed but not confirmed[2,4]
e) High alcohol consumption[4]
f) Male factors (advanced paternal age, smoking, alcohol consumption, reduce exercise pattern, and extreme body weight)

Antiphospholipid syndrome

One clinical criterion with one or more laboratory criteria (positive LAC, moderate to strong positivity of anti-cardiolipin IgM or IgG antibodies or anti beta 2 glycoprotein 1 IgM or IgG) should be fulfilled to confirm APS. Clinical criteria include venous, arterial or microvascular thrombosis or pregnancy morbidity described below.

Obstetric criteria to diagnose APS

One or more obstetric criteria should be present in APS.

1. Three consecutive spontaneous miscarriages at <10 weeks gestation with alternative maternal/ paternal factors excluded (anatomical, hormonal, chromosomal)[5,6]
2. One unexplained death of a morphologically normal fetus at 10 or more weeks of gestation.
3. One birth of a morphologically normal neonate at <34 weeks' gestation due to:
   (i) Eclampsia or severe pre-eclampsia OR
   (ii) Placental insufficiency[5]

Laboratory criteria to diagnose APS

1. Lupus anticoagulant
2. Anticardiolipin antibodies IgG and IgM (i.e. more than 40 GPL or MPL, or more than 99th percentile).
3. Anti-β2 glycoprotein 1 IgG and IgM antibodies in high titre (i.e. more than 99th percentile)[5]

Laboratory tests for lupus anticoagulant (LAC) include clot-based APTT assays, lupus sensitive APTT, dilute Russell's viper venom time (DRVVT) and kaolin clotting time (KCT). APTT based assay results may be shortened following an acute event or during pregnancy as FVIII levels are increased which can give rise to false negative results. APTT may prolong with increased levels of C-reactive protein (CRP) in the acute phase and can give false positive results. Therefore, testing for LAC is not recommended in the acute phase[6].

Positive test for LAC, anti cardiolipin antibodies or anti-β2 glycoprotein 1 should be confirmed on repeat testing at least 12 weeks apart within 3 years of acute event to confirm APS.

Double or triple positivity of above tests in a higher strength is associated with adverse pregnancy outcome.

It is not recommended to use other antiphospholipids such as phosphatidic acid, phosphatidyl inositol, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidyl serine and testing may lead to confusion as well as over diagnosis of APS[5].

The pathophysiology of the obstetric manifestations of APS

Pathophysiology of APS is complex and different according to the stage of gestation. Inflammation, complement activation and placental thrombosis play main roles in obstetric APS[7].

A systematic review on placental histopathology in women with APS revealed placental infarction, decidual inflammation, impaired spiral artery remodelling, increase in syncytial knots and decrease in vasculosyncytial membranes[7].

Additionally, other evidence suggest there is a thrombo-inflammatory process leading to complement and neutrophil activation, tissue factor expression and formation of Neutrophil Extracellular Traps (NETs) in the intervillous spaces, reduced annexin-V on placental villi surfaces leading to phosphatidylserine exposure[8] leading to pregnancy complications.

Recurrent early miscarriage could be due to a strong local inflammatory response to anti-beta 2 glycoprotein 1 antibodies interfering with implantation and inhibition of trophoblast proliferation. Complement activation also plays a key role in early miscarriages. Late pregnancy losses due to APS could be due to antibody mediated complement activation and inhibition of trophoblast proliferation and differentiation. In addition, abnormal spiral artery development, placental fibrin deposition and placental infarctions leads to placental dysfunction[9].

Haematological management

1. Antiphospholipid syndrome (APLS)

I. Low-dose aspirin

Aspirin 75 mg daily is started preconception or as soon as pregnancy is confirmed. The dose of aspirin can be increased to 150 mg daily from 12 weeks of gestation.

II. Low-molecular-weight heparin (LMWH)

Prophylactic dose of LMWH is started after confirming pregnancy and continued throughout pregnancy and for 6 weeks postpartum[5].

Dose of LMWH depends on the body weight of the patient and the strength of positivity of antibodies. Unfractionated heparin (UFH) can be used, but using LMWH is more convenient[3].

Heparin and aspirin improve live birth rates in women with APS and recurrent miscarriage by reducing clot formation and improving placental function and reduce the risk of pre-eclampsia and fetal growth restriction[5].

Women with obstetric or thrombotic APS should be managed in a joint haematology obstetric clinic with expertise in these areas. These patients with APS need to be closely followed up throughout pregnancy. Uterine artery Doppler scan at 20-24 weeks of gestation and with serial growth scans thereafter are recommended[5].

All women with obstetric or thrombotic APS should have a clearly documented anticoagulation plan during pregnancy, during interventions, delivery and for post-partum period.

Women with thrombotic APS who are anticoagulated with warfarin need to be changed to therapeutic dose of LMWH on confirmation of a positive pregnancy test. This can be converted to warfarin post-partum. Warfarin or LMWH can be used during breast feeding[5].

Prednisolone, intravenous immunoglobulin (IVIG) and hydroxychloroquine treatment in women with APS and obstetric complications despite being on treatment with aspirin and LMWH, are considered only on a case-by-case basis[5].

Long term low dose aspirin postpartum needs to be considered in women with obstetric APS without a history of thrombosis considering individual risks and benefits.

Multidisciplinary care with close collaboration between haematology, obstetrics and feto-maternal medicine teams is especially important.

2. Inherited thrombophilia

Routine anticoagulation is not recommended for all inherited thrombophilia with recurrent miscarriage, particularly in the absence of a personal or strong family history of venous thromboembolism. LMWH is used in a woman with inherited thrombophilia if there is thrombotic history or following assessment of thrombotic risk and may improve the live birth rate of women with second trimester miscarriage[3].

3. Empirical treatment for unexplained recurrent miscarriage (controversial and individualized)

In women with unexplained recurrent miscarriage, the use of low dose aspirin or low dose aspirin with LMWH is not recommended, but may be considered on individual basis, particularly in those with a history of late pregnancy loss or in patients who are carriers of thrombophilia.

Further advise for the prevention of recurrent miscarriages

It is advised to maintain a BMI between 19 and 25 kg/m^2, stop smoking and alcohol consumption and limit caffeine to less than 200 mg per day for better pregnancy outcome[4].

Haematological approach to recurrent miscarriages; The CSHW model

Women with recurrent miscarriages referred to the haematology clinic at Castle Street Hospital for Women (CSHW) for evaluation to exclude APS are registered for APS screening.

DRVVT (LA1 and LA2), APTT and lupus sensitive APTT are performed to exclude lupus anticoagulant.

Six hundred and twenty-five DRVVT and lupus sensitive APTT tests were performed from February 2017 to December 2024 (excluding Covid period) and 38 patients (6.08%) were positive for DRVVT with repeat testing 12 weeks apart. This result is similar to international figures[5]. Out of them, twenty-five women were weakly positive, 11 women were moderately positive, and 6 women were strongly positive for LAC. (LA1/LA2 ratio of 1.2-1.5 indicates a weakly positive LAC, 1.5-2 indicates a moderately positive and a ratio greater than 2 indicates a strongly positive LAC[10]).

Out of 6 patients with strongly positive LAC, one patient was diagnosed as systemic lupus erythematosus (SLE). One woman with four first trimester (T1) miscarriages had an LA1/LA2 ratio of 2.47, while another woman with a history of intrauterine growth restriction (IUGR), pregnancy-induced hypertension (PIH) and one T1 miscarriage had a LA1/LA2 ratio of 3.0. One woman with eight T1 miscarriages had an LA1/LA2 ratio of 2.7, while another woman with three T1 miscarriages had a ratio of 2.21. One woman, with a history of two second trimester miscarriages, had a ratio of 3.1. Another patient with five T1 miscarriages had a ratio of 1.2. There was no relationship between number of miscarriages and the strength of positivity in DRVVT test.

One patient with a weak positive LAC (LA1/LA2 ratio of 1.2) had a history of deep vein thrombosis (DVT), and another patient with a moderately positive LAC (LA1/LA2 ratio of 1.4) had a history of left axillary venous thrombosis. A patient with two second trimester intrauterine deaths and a history of pulmonary embolism had a moderately positive LAC (LA1/ LA2 ratio of 1.6).

Anticardiolipin IgM and IgG testing was performed at the Medical Research Institute (MRI) for 135 women with recurrent miscarriages between 2022 and 2024, during the period when test facility was available. Five women (3.7%) were positive for anticardiolipin antibodies and met the criteria for diagnosis of antiphospholipid syndrome (APS). Twenty women (14.8%) tested positive for anticardiolipin antibodies, but the levels were not high enough to confirm diagnosis of APS. Three women (2.2%) had strongly positive anticardiolipin IgG levels with values greater than 100 GPL.

Haematological management of women with APS at CSHW

Treatment of all pregnant women with a history of recurrent miscarriages with LMWH is not justifiable

as only 6.08% patients were positive for LAC and 3.7% were positive for anticardiolipin antibodies to confirm as APS.

Testing to exclude APS is essential in patients with recurrent miscarriage before initiating treatment, as LMWH is an expensive drug, costing more than Rs. 600,000 for the treatment of single pregnancy. LMWH also carries risk of bleeding, particularly in cases of trauma or in women with hypertension.

Patients diagnosed with APS are treated with low-dose aspirin, which is started pre-pregnancy. LMWH, such as enoxaparin, is initiated after confirmation of pregnancy, with the dose determined on the patient's body weight. LMWH is continued throughout pregnancy and for six weeks postpartum, provided there is no increased risk of bleeding. Full blood count (FBC) and blood pressure are regularly monitored and medications with increased bleeding risk such as non-steroidal anti-inflammatory drugs (NSAID) are avoided. Prednisolone, hydroxychloroquine (HCQ), or IVIG) are not used for the obstetric management of APS, except in patients with SLE.

Fatal growth is monitored with serial ultrasound scanning by the obstetric team and the family is reassured with close follow up. They can contact the haematology team if there are any issues while taking LMWH.

Thrombotic events were not encountered while on LMWH but many women experienced mild bruising over the injection site. Few patients had few episodes of mild per vaginal bleeding. LMWH was temporary discontinued for few days and restarted with a lower dose and closely followed up during the pregnancy. None of the babies had any bleeding or thrombotic event during pregnancy or post-partum.

Summary

Thrombophilia's including APS and inherited thrombophilia are significant and potentially manageable haematological causes for recurrent pregnancy loss. APS is associated with early and late pregnancy losses while inherited thrombophilia are more commonly associated with late miscarriages. Establishing the diagnosis of APS in patients with recurrent miscarriages is essential to ensure judicious use of LMWH, while patient education and reassurance is necessary to reduce anticoagulation related complications and maternal anxiety.

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