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ORIGINAL ARTICLE

Enoxaparin and aspirin therapy for recurrent pregnancy loss due to anti-phospholipid syndrome (APS)

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KEYWORDS

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Antiphospholipid syndrome;
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Abstract *Background:* Recurrent miscarriage affects 1–2% of women. Thrombophilia included antiphospholipid syndrome has been identified in about 50% of women with recurrent miscarriage. Aspirin and heparin therapy is frequently prescribed for APS, yet there is no robust evidence for the most efficacious regime.

Objective: To determine maternal and foetal outcomes in women with APS managed with aspirin or enoxaparin plus aspirin during pregnancy.

Design: Prospective non randomized study.

Setting: High-risk pregnancy unit-Benha University Hospital.

Methods: Seventy selected patients during pregnancy with clinical and/or serological findings of antiphospholipid syndrome were divided into two Groups: Group A ($n = 47$) had received aspirin (81 mg once daily orally) plus LMWH enoxaparin (40 mg subcutaneously/day) while Group B ($n = 23$) had received low-dose aspirin (81 mg day orally).

Main outcome measures: Maternal outcomes included thromboembolic, haemorrhagic complications and pregnancy-induced hypertension. Prematurity, intrauterine growth restriction and neonatal death were considered as foetal complications.

Results: There were significant differences between Groups A and B in the rate of miscarriages (4 in Group A (9%) versus 8 in Group B (35%); $p = 0.02$), number of live births (43/47(91%) versus 15/23(65%); $p = 0.02$), mean gestational age (37.86 ± 1.8 versus 36.13 ± 2.39 weeks; $p = 0.005$), neonatal birth weight (3252 ± 459 versus 2907 ± 618 g; $p = 0.03$) and rate of pre-eclampsia (3/43 (7%) versus 6/15 (40%); $p = 0.009$). Although not statistically significant, women in Group

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A tended to have lower rates of preterm births (6/43 (14%) versus 3/15 (20%); $p = 0.89$) and IUGR (5/43 (12%) versus 5/15 (33%); $p = 0.13$) than in Group B.

Conclusions: Use of low dose aspirin and enoxaparin 40 mg subcutaneously daily in patients with RPL due to antiphospholipid syndrome resulted in higher live birth rates compared to low dose aspirin alone. Solid conclusions from this study are limited due to the small number of patients, non-randomization of groups and discrepancy in number between groups because the choice of the interventional drug was left to patient's preference after counselling. A larger RCT is needed.

1. Introduction

Nowadays, APS is recognized as the most significant cause of RPL (recurrent pregnancy loss). In women with RPL the incidence of APS is between 20% and 40%. Some authorities claim that the unifying feature of these processes is abnormal placental function due to necrosis, infarction and thrombosis. Some others associate abnormalities in the decidual spiral arteries with foetal loss in APS especially thickening, atherosis and fibrinoid necrosis. These conditions may result from thrombosis during the development of the normal maternoplacental circulation. However, there is a wide variety of related clinical manifestations, and obstetric morbidity is one of the major manifestations of APS. There are three primary classes of antibodies associated with the antiphospholipid syndrome: (1) anticardiolipin antibodies (aCL), (2) the lupus anticoagulant (LA) and (3) antibodies directed against specific molecules including a molecule known as beta-2-glycoprotein 1 (anti-b2GPI). Lupus antibody is the most powerful predictor of thrombosis and recurrent miscarriages. Anti-b2-glycoprotein-1 antibodies are not associated with recurrent miscarriage in isolation; however, in combination with positive results for lupus anticoagulant (LA) and aCL, there is a high risk of obstetric complications (1).

Antiphospholipid antibodies can be detected in 1–5% of healthy women. The prevalence of positive antiphospholipid antibodies increases to 15% in women with recurrent first trimester pregnancy losses and up to 20% in women suffering a stroke at or before the age of 50 years. Around 40% of women with lupus have antiphospholipid antibodies; it is estimated that less than 40% of them will eventually develop thrombotic events. The prevalence of APS is unknown, but it has been estimated to be 0.5% in the general population (2).

Antiphospholipid antibodies bind to negatively charged phospholipids, protein-binding phospholipids, or both, triggering the activation of endothelial cells, monocytes and platelets. In addition, antiphospholipid antibody complexes, mainly formed by b2 glycoprotein I and anti-b2 glycoprotein I, activate the classical and alternative complement pathways. Therefore, complement deficiency or inhibition of complement activation proved to have a protective effect against pregnancy loss and thrombosis in a murine model. This fact could explain the benefits of low dose heparin, owing to its capacity of complement inactivation rather than by its antithrombotic effects (3).

Our understanding of the aetiology and pathogenesis of the antiphospholipid syndrome is limited, but it has generally been considered a thrombophilic disease and hence treatment has focused on anticoagulation. Agents such as aspirin and heparin administered alone or in combination have been used in the management of obstetric patients with APS. Recent findings from research in animal models of APS challenge the dogma that this syndrome is a non-inflammatory, thrombotic disease and provide evidence that activation of complement is crucial for development of complications in pregnancy (4).

A sporadic spontaneous abortion occurs in up to 15% of all recognized pregnancies, and recurrent miscarriage occurs in about 1% of women at reproductive age. They can be caused by chromosomal, anatomic, hormonal (progesterone, oestrogens, diabetes or thyroid disease), coagulation or platelet abnormalities. Taking into account all possible causes, APS could be responsible for 10–15% of recurrent miscarriages, whereas antiphospholipid antibodies could be identified in 5–20% of these women (3).

Early onset, severe preeclampsia, complicated with HELLP syndrome (haemolysis, liver enzyme elevation and thrombocytopenia), is a frequent association probably due to shared pathogenic mechanisms. In the general obstetric population, the incidence of HELLP is between 0.01% and 0.2% while in pregnancies complicated by preeclampsia/eclampsia, an incidence of 10–12% has been reported. About one-third of untreated women with APS may develop pre-eclampsia during pregnancy, and more than 10% of these women will deliver small for gestational age infants (1).

Several mechanisms have been proposed to explain the role of presence of antiphospholipid antibodies in the pathogenesis of hypercoagulable state of APS. Firstly these antibodies have been shown to cause endothelial cell and monocyte activation, leading to a prothrombotic phenotype, which is characterized by the expression of adhesion molecules and tissue factors. In order to activate these effector cells and cause thrombosis antiphospholipid antibody b2GPI complexes interact with cell surface receptors, such as annexin II receptors which induces a signalling cascade (5). Secondly, platelets also become prone to aggregate after exposure to antiphospholipid antibodies as β_2GP_1 dimers bound to antiphospholipid antibodies on platelets interact with the apolipoprotein E_2 receptor to trigger the activation and release of thromboxane, which facilitates platelet aggregation (6); not only this, thrombosis in the placenta and other vascular beds is induced by antiphospholipid antibody mediated interference with the annexin A5 anticoagulant shield on phospholipid surfaces of trophoblasts and impairment of both intrinsic and extrinsic fibrinolysis (7).

Furthermore, antiphospholipid antibodies have been shown to alter the maturation and invasiveness of trophoblast cells *in vitro*. This suggests that the antibodies cause defective