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CLINICAL ARTICLE

Randomized controlled study of pre-conception thromboprophylaxis among patients with recurrent spontaneous abortion related to antiphospholipid syndrome

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ABSTRACT

Objectives: To investigate the effects of pre-conception thromboprophylaxis among patients with recurrent spontaneous abortion and antiphospholipid syndrome. *Methods:* A randomized placebo-controlled trial enrolled patients with a history of recurrent spontaneous abortions and antiphospholipid syndrome who attended an Egyptian center between January 2011 and June 2013. Using a computer-generated sequence, patients were randomly allocated to receive 41 mg enoxaparin subcutaneously plus 81 mg aspirin daily pre-conception, or to receive placebo pre-conception. All patients received enoxaparin and aspirin following identification of fetal heart pulsation. The primary outcomes were live-birth rate and clinical-pregnancy rate at 0–6 months, and at 6–12 months. Intention-to-treat analyses were performed. Clinicians, investigators, and data analysts were masked to the treatment assignments. *Results:* The study enrolled 180 patients(90 in each group). No significant difference was observed between the intervention and control groups in the live-birth rate (67[74%] vs 59[66%]; $P = 0.25$). At 0–6 months, the clinical-pregnancy rate was higher in the intervention group (50[56%]vs 30[33%], $P = 0.02$). No significant difference between the intervention and control groups was observed in the clinical-pregnancy rate at 6–12 months (32[36%] vs 35[39%], $P = 0.52$). *Conclusion:* Among patients with recurrent spontaneous abortion and antiphospholipid syndrome, pre-conception enoxaparin increased the clinical-pregnancy rate at 0–6 months, but did not affect the clinical-pregnancy rate at 6–12 months or the live-birth rate.

ClinicalTrials.gov: NCT01661439

1. Introduction

Recurrent spontaneous abortion is defined as the occurrence of three or more consecutive spontaneous abortions [1]. Among complications occurring during all pregnancies, the incidence of recurrent spontaneous abortion is approximately 1%–2% [2,3]. The causes of recurrent spontaneous abortion are multifactorial and include congenital anomalies of the uterus, disorders of the endocrine system, immunological disorders, infections, and chromosomal anomalies [4].

Antiphospholipid syndrome (APS) is the most commonly reported cause of recurrent spontaneous abortion. Adverse pregnancy outcomes in patients experiencing recurrent spontaneous abortion are associated with the circulation of the antiphospholipid antibodies, which include lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein-I antibodies [5,6]. Among patients experiencing recurrent spontaneous abortions, 15% exhibit antiphospholipid antibodies [7]. There are many mechanisms through which APS can cause complications and morbidity during pregnancy, one of which is the modulation of the expression and function of trophoblastic tissues [8,9]. Another mechanism through which APS exerts effects on pregnancy is the activation of the complement pathway at the maternal–fetal interface, leading to the initiation of inflammatory pathways and venous thromboembolism [10].

The American College of Obstetricians and Gynecologists (ACOG) has recommended that women with APS are given low-dose (81 mg) aspirin, as well as unfractionated heparin or low-molecular-weight heparin subcutaneously every day [11]. ACOG guidelines recommend starting this therapy once pregnancy has been diagnosed and continuing administration until delivery. The rationale for using low-dose aspirin and low-molecular-weight heparin, aside from their anticoagulant effects, is that they have anti-inflammatory and immune-modulatory actions that suppress the cytotoxicity of natural killer cells and inhibit

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the binding of interferon-γ to the cell surface [12,13]. Although this treatment can improve overall pregnancy outcomes, patients experiencing recurrent spontaneous abortion remain at high risk of preterm labor, premature rupture of membranes, fetal-growth restriction, pre-eclampsia, and placental abruption [14].

The success of anticoagulants in the treatment of APS has led to the investigation of empirical anticoagulation treatment in all women with recurrent spontaneous abortion with or without genetic thrombophilia [15,16]. To the best of our knowledge, no randomized controlled trial has evaluated the potential of administering anticoagulants during the pre-conception period with the aim of preventing early- and late-pregnancy spontaneous abortions. The aim of the present study was to assess the effect of pre-conception thromboprophylaxison conception and pregnancy outcomes in patients diagnosed with APS-associated recurrent spontaneous abortions.

2. Materials and methods

The present randomized placebo-controlled trial was conducted at the Women's Health Hospital, Assiut University, Egypt between January 1, 2011 and June 30, 2013. All patients attending the gynecology outpatient clinic who reported recurrent spontaneous abortion and had an established APS diagnosis were screened for study eligibility before being counseled regarding participation. Written informed consent for participation was obtained from all patients before enrollment. The protocol of the present study was approved by the Assiut Medical School Ethical Review Board.

Diagnosis of APS was made on the basis of two positive test results, at least 12 weeks apart, for the presence of either lupus anticoagulant or anticardiolipin antibodies (immunoglobulin G and/or immunoglobulin M antibodies present in a medium or high titer of over 40 mL/L, or above the 99th percentile). Testing for the presence of lupus anticoagulant was performed using the Kaolin cephalin clotting time, employing sensitive reagents or using the Dilute Russell's viper venom time combined with a platelet-neutralization procedure using frozen-thawed platelets (Siemens AG, Erlangen, Germany). Eligible patients had a history of three or more consecutive first-trimester (≤13 weeks) spontaneous abortions, or two or more second-trimester spontaneous abortions (13–24 weeks) with the same partner. All potential study participants were interviewed and evaluated, including taking a complete history, making a physical examination, evaluating patient body mass index and vital signs, performing paternal karyotyping, examination by hysterosalpingography or hysteroscopy to detect any uterine anomalies, evaluating mid-luteal progesterone, and measuring the serum prolactin and thyroid stimulating hormone levels. Potential participants also underwent screening to identify any patients that had concurrent genetic thrombophilia; this was identified through the presence of any of the following anomalies: prothrombin gene mutation, factor V Leiden mutation, protein C deficiency (<0.73 IU/mL), protein S deficiency (<0.57 IU/mL), and high factor VIII (≥1.5 IU/mL). Participants that had thrombophilia with any cause other than APS were excluded from the study.

Patients with a history of thromboembolic events, bleeding tendencies, hypersensitivity to aspirin or enoxaparin, congenital anomalies of the uterus, cervical insufficiency, uncontrolled diabetes mellitus, or chromosomal anomalies affecting either participants or their partners were excluded from the study. Patients who were pregnant at study enrollment following the use of assisted reproductive techniques were also excluded from the study.

Using a computer-generated sequence, participants were randomly allocated in a 1:1 ratio to receive enoxaparin plus aspirin or placebo. Patient allocations were noted and placed in sealed envelopes by an independent secretary. A minimization procedure employing a computer-based algorithm was applied to avoid chance imbalances in important stratification variables. To ensure allocation concealment, an independent secretary stored all the sealed envelopes containing each participant's group assignment; all envelopes were kept closed until data analysis was completed. Additionally, a central telephone system was used whereby an independent secretary spoke with patients to arrange all follow-up visits. If patients experienced any severe complications, their group allocation could be revealed. Study drugs and placebo were prepared by the pharmacy department of the study institution, with all placebo treatments manufactured to be identical to study medications. Study drugs and placebo were stored in identical ampoules and as tablets of identical size, shape, and color; study treatments were distributed to participants by study institution staff without informing them of their treatment assignment. Clinicians, investigators, and data analysts were masked to the group assignments.

Following documentation of ovulation using ultrasonographic criteria and/or luteinizing hormone kits, participants in the intervention group received 40 mg of enoxaparin as a subcutaneous injection (Clexan; Sanofi, Paris, France) plus 81 mg of aspirin; those in the control group received a subcutaneous placebo injection and a placebo tablet. All participants had been taught to self-inject.

The pregnancy rate was reported for both groups. Patients attended the study institution where serial blood tests were performed, beginning 14 days after documentation of ovulation, and the concentration of the beta subunit of human chorionic gonadotropin (β-hCG) was recorded. An increase in these measurements was used to define pregnancy; patients were re-tested 48 hours after a positive test result to confirm pregnancy. Biochemical pregnancy (not proceeding to clinical pregnancy) was defined as a decreasing β-hCG concentration across serial measurements, while clinical pregnancy was defined as the presence of the gestational sac, with a positive fetal heartbeat, detected using transvaginal ultrasonography, with a β-hCG concentration above 1500 IU/L occurring at any time during the study period.

After the documentation of fetal heart pulsations using ultrasonography, all patients received 40 mg of enoxaparin as a subcutaneous injection plus 81 mg of aspirin for the duration of the study. The fetal pole and cardiac pulsation were monitored and documented until 38 weeks of pregnancy, 24 hours before the induction of labor, or 12 hours before the administration of regional anesthesia for elective cesarean delivery. This method is in accordance with the American Society of Regional Anesthesia guidelines and ACOG guidelines [11].

If no pregnancy was observed, treatment (intervention or control) was continued until the first day of menstrual bleeding. Treatment was stopped during the follicular phase and recommenced during the next luteal phase. According to the study-hospital protocol, all patients received routine supplementary folic acid and calcium.

Patient follow-up was performed according to the standard protocol of supportive care at the study hospital. Briefly, at a patient's first clinic visit (occurring immediately following a positive serum pregnancy test result), an ultrasonography examination was performed to detect the fetal pole and fetal heart pulsations, if present. Patients were then scheduled to visit the study hospital every 2 weeks throughout the first trimester. In addition to the visits to the study hospital, patients were instructed to visit their own obstetrician at 8 weeks, 10 weeks, 14 weeks, 18 weeks, 24 weeks, 28 weeks, 32 weeks, and 36 weeks of pregnancy. Ultrasonography was performed at each visit. Patients were asked to record any adverse events or complications (e.g. vaginal bleeding) on a case report form. Additionally, a platelet count was performed at each follow-up visit. Participants in both groups restarted enoxaparin after delivery for 6 weeks.

The primary outcomes were the rate of livebirth after 24 weeks of pregnancy and the clinical-pregnancy rate at 0–6 months and at 6–12 months. The secondary outcomes were the rate of first- and second-trimester spontaneous abortion, vaginal bleeding during pregnancy, pre-eclampsia(diagnosed as blood pressure of 140/90 mmHg or higher with proteinuria exceeding 300 mg per 24 hours after 20 weeks of pregnancy),pregnancy-induced hypertension (blood pressure ≥ 140/90 mmHg without proteinuria after 20 weeks of pregnancy), abruptio placentae, preterm delivery (at 24–37 weeks of pregnancy), and

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