Enoxaparin versus unfractionated heparin in the management of recurrent abortion secondary to antiphospholipid syndrome

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ABSTRACT

Objective: To determine whether low molecular weight heparin (LMWH) plus low-dose aspirin (LDA) is comparable in efficacy and safety to unfractionated heparin (UFH) plus LDA in the management of pregnant women with a history of recurrent spontaneous abortion secondary to antiphospholipid syndrome (APS).

Methods: In a randomized prospective study, 60 women with a history of 3 or more consecutive spontaneous abortions and positive antiphospholipid antibodies were assigned in equal numbers to receive either UFH (5000 units, twice daily) plus LDA, or LMWH (enoxaparin 40 mg, once daily) plus LDA as soon as pregnancy was diagnosed.

Results: Twenty-four women in the LMWH group (80%) and 20 women in the UFH group (66.67%) delivered a viable infant (P=0.243). There were no significant differences in pregnancy complications or neonatal morbidity between the 2 groups. There were no incidences of excessive bleeding, thrombocytopenia, or osteoporotic fractures in either group.

Conclusion: LMWH plus LDA was successfully used as an alternative to UFH plus LDA in the management of recurrent abortion secondary to APS. The results highlight the need for a larger randomized controlled trial to determine whether LMWH plus LDA should be the treatment of choice for recurrent abortion secondary to APS.

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1. Introduction

Women with antiphospholipid syndrome (APS) have a spontaneous abortion rate as high as 90% for pregnancies without pharmacologic treatment [1]. APS is strongly correlated with recurrent abortion and pregnancy complications such as intrauterine growth restriction (IUGR), preterm labor, preeclampsia, and intrauterine fetal death (IUFD). The adverse effects of antiphospholipid antibodies on trophoblast differentiation and invasion, placental infarctions, and thrombosis are thought to be responsible for recurrent abortion and pregnancy complications associated with APS [2,3].

During the past 27 years, several treatments such as unfractionated heparin (UFH), low molecular weight heparin (LMWH), plasmapheresis, moderate-to-high dose prednisone, intravenous immunoglobulin, and low-dose aspirin (LDA) have been used in the management of pregnant women with history of recurrent pregnancy loss secondary to APS [2]. A meta-analysis of 13 randomized or quasi-randomized controlled trials of various management options for pregnant women with a history of recurrent abortion secondary to APS found that combined UFH and LDA was the best management option, reducing pregnancy loss by 54% [3].

In the past decade, LMWHs have been widely used in the prophylaxis and treatment of patients with venous and arterial thrombosis, with an efficacy and safety superior or at least equivalent to those of UFH [4]. Although recent studies have found that LMWHs are effective in the management of pregnant women with a history of recurrent pregnancy loss secondary to APS [5,6], it is not clear whether the efficacy and safety of LMWHs are equivalent to those of UFH [7,8]. Furthermore, no randomized controlled trial has compared the efficacy and safety of LMWH plus LDA with those of UFH plus LDA.

The aim of the present randomized controlled trial was to determine the impact of LMWH (enoxaparin) plus LDA treatment on the pregnancy outcome of women with recurrent abortion secondary to APS and to determine whether LMWH plus LDA is comparable in efficacy and safety to UFH plus LDA.

2. Materials and methods

The present study was a 2-arm, prospective, open-labeled, multicenter randomized controlled trial of 60 women with a history...
of 3 or more consecutive pregnancy losses before 10 weeks of gestation and positive antiphospholipid antibodies on 2 or more occasions at least 12 weeks apart [9]. The study was conducted between June 28, 2006, and November 24, 2008, at Cairo University Hospital, Cairo, Egypt, and between June 28, 2006, and December 14, 2009, at Ahmed Elgazzar Hospital, Cairo, Egypt. The study protocol was approved by the Ethics Committee of each hospital. The women were counseled about the benefits and risks of heparin and aspirin therapy, and informed consent was obtained from all participants.

We evaluated data from 242 women who were referred to the study institutions for recurrent abortion to identify those who could be included in the study. The inclusion criteria were: a history of 3 or more consecutive spontaneous abortions before 10 weeks of gestation, and positive lupus anticoagulant (LAC) and/or anticardiolipin antibodies (IgG and IgM) on 2 or more occasions at least 12 weeks apart; age between 18 and 37 years; and body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) between 19 and 29. The exclusion criteria were: paternal chromosomal abnormalities; uterine malformation detected by hysterosalpingography or office hysteroscopy; cervical incompetence; luteal-phase defect; abnormal thyroid function tests; hyperprolactinemia; polycystic ovary syndrome; hereditary thrombophilia; systemic lupus erythematosus; previous venous or arterial thrombotic episodes; diabetes mellitus; kidney or liver disease; gastric ulcer; and sensitivity to aspirin, UFH, or enoxaparin.

Serum IgG and IgM anticardiolipin antibodies were assayed by using a commercially available standardized enzyme linked immunosorbent assay (Varelisa; Pharmacia Diagnostics, Freiburg, Germany). Positive IgG and IgM values were defined as more than 40 GPL units and more than 40 MPL units, respectively. An activated partial thromboplastin time test and a dilute Russell viper venom test were performed to screen for LAC. If either of these tests was prolonged, the presence of LAC was documented by mixing and confirmatory tests. All LAC tests were measured on an STA compact CT coagulation analyzer (Diagnostica Stago, Asnières, France). All of the women with positive LAC and/or anticardiolipin antibodies were tested for all included women with hereditary thrombophilia.

The 60 women who fulfilled the inclusion criteria and enrolled in the study were randomly allocated to 1 of 2 groups via a computer-generated randomization list and sequentially numbered, opaque sealed envelopes, each containing the allocation information written on a card. The computer-generated randomization list and the sealed envelopes were prepared by a statistician not involved in the study. The envelopes were opened sequentially by a staff nurse to assign the women to receive either UFH plus LDA (n = 30) or LMWH plus LDA (n = 30). Neither the women nor the doctors were blind to the treatment assigned.

All of the women became pregnant after randomization. Administration of prenatal vitamins and combined oral calcium and vitamin D3 (600 mg and 400 IU, respectively, twice daily [Maxical; Grand Pharma, 10th Ramadan City, Egypt]) was started before conception and continued throughout pregnancy. Administration of LDA (75 mg, once daily [Aspicod Paediatric; Chemical Industries Development, Giza, Egypt]) was started before conception and continued through pregnancy until 36 weeks of gestation. Anticoagulation treatment was started as soon as the serum pregnancy test became positive. The women in the UFH group received heparin calcium (5000 U subcutaneously, twice daily [Cal-Heparine; Amoun Pharmaceutical, Cairo, Egypt]), and the women in the LMWH group received enoxaparin (40 mg subcutaneously, once daily [Lexane; Sanofi-Aventis, Paris, France]).

Fetal viability was confirmed by transvaginal ultrasound at 6 weeks of gestation. Prenatal check-ups were carried out every 2 weeks from enrollment to 32 weeks of gestation, then weekly until delivery. Serial ultrasound examinations at 2-week intervals were started at 24 weeks of gestation to monitor fetal growth. To detect the development of thrombocytopenia, the platelet count was measured before therapy was started, then every 2 weeks for the first 2 months, followed by every 4 weeks. Heparin therapy was discontinued if the platelet count was less than 100000/mL or if there was a 50% drop in the baseline platelet count.

Two days before the planned induction of labor or elective cesarean delivery, enoxaparin was stopped and twice-daily UFH was started. The evening UFH dose was cancelled before the planned induction of labor or elective cesarean. UFH and enoxaparin were discontinued at the start of spontaneous labor pains. Starting 1 day after delivery, enoxaparin (40 mg subcutaneously, once daily) was administered for 6 weeks to decrease the risk of thromboembolism.

The primary endpoint was the live-birth rate, and the secondary endpoints were excessive hemorrhage (defined by a 10% decline in the hematocrit value or the requirement of a blood transfusion), thrombocytopenia (platelet count < 100000/mL), IUGR (birth weight lower than the tenth percentile for gestational age), pre-eclampsia (blood pressure ≥ 140/90 mm Hg and proteinuria ≥ 300 mg/day), IUFD, and spontaneous osteoporotic fractures. For the infants, the secondary endpoints were preterm labor (birth of infant at < 37 weeks of gestation), neonatal bleeding, and congenital anomalies.

The sample size was calculated on the basis of the most recent study at the time of study design. In a pilot study with 25 patients in each arm, Noble et al. [7] compared UFH plus LDA with LMWH (enoxaparin 40 mg, once daily) plus LDA in the management of women with 3 or more consecutive abortions and positive antiphospholipid antibodies. In the LMWH plus LDA group, 84% of women delivered a viable infant, compared with 80% of women in the UFH plus LDA group. To detect this small difference between the 2 groups, a sample size of 1447 women would have to be recruited to achieve a study power of 80% at a significance level of 0.05 (2-tailed). The recruitment of such a large number of participants was not possible in the present study, which was planned for completion within 2 years. We chose on an arbitrary basis to perform the analysis when 30 women were recruited to each arm of the trial.

Statistical analysis was performed via t, Mann–Whitney U, and χ2 tests, as appropriate. A Yates correction equation was used when the expected frequency was less than 5. P < 0.05 was considered to be statistically significant. All statistical calculations were performed using Excel version 7 (Microsoft, New York, NY, USA) and SPSS (SPSS, Chicago, IL, USA).

3. Results

In the present study, 60 women were recruited, with 30 women randomized to each group. Table 1 shows the demographic characteristics of the participants and the laboratory criteria used for diagnosis of APS. The flow of participants through the study is shown in Fig. 1.

In the LMWH plus LDA group, 80% of women delivered a viable infant, compared with 66.67% of women in the UFH plus LDA group (P = 0.243). Spontaneous abortion occurred during the first trimester in 6 women in the LMWH plus LDA group. Among the women receiving UFH plus LDA, spontaneous abortion occurred in the first trimester in 9 women and in the second trimester in 1 woman. Two participants in the UFH plus LDA group and 1 in the LMWH plus LDA group delivered infants weighing less than the tenth percentile (IUGR). Mild pre-eclampsia developed in 2 women in the LMWH plus LDA group, and severe pre-eclampsia (blood pressure, 170/100 mm Hg; proteinuria, 4+) developed in 1 woman in the UFH plus LDA group. In the UFH plus LDA group, 3 women delivered by elective cesarean (indications for cesarean delivery were poor obstetric history, IUFD, and pre-eclampsia) and 1 woman delivered by emergency cesarean (owing to failure of progress in labor). In the LMWH plus LDA group, 4 women delivered by
elective cesarean (indications for cesarean delivery were previous upper segment cesarean, IUGR, preeclampsia, and breech presentation) and 2 women delivered by emergency cesarean (indications for cesarean delivery were failure of progression in labor and fetal distress).

There were no significant differences between the LMWH plus LDA group and the UFH plus LDA group with respect to the gestational age at delivery (38.54±1.41 versus 38.15±1.84 weeks; P=0.313) or birth weight (3183±382 versus 3087±563 g; P=0.757). In the LMWH plus LDA group, the gestational age at delivery ranged from 35 weeks to 41 weeks and the birth weight ranged from 1900 g to 3700 g. In the UFH plus LDA group, the gestational age at delivery ranged from 33 weeks to 41 weeks, and the birth weight ranged from 1950 g to 3800 g.

All of the infants were examined by a pediatrician shortly after delivery. No congenital anomalies or neonatal bleeding were observed. In each group, 2 infants were admitted to a neonatal intensive care unit because of prematurity. Ventilatory support was not required for any of these infants (Table 2).

The LDA, LMWH, and UFH were well tolerated by the women, and there were no symptomatic complaints apart from subcutaneous bruises, which occurred in 3 participants in each group, and a local allergic skin reaction, which occurred in 1 participant in the UFH plus LDA group. No spontaneous osteoporotic fractures, excessive hemorrhaging, venous or arterial thrombotic episodes, or heparin-induced thrombocytopenia occurred in either of the treatment groups (Table 2).

4. Discussion

In the present study, LMWH plus LDA treatment resulted in a high live-birth rate in women with recurrent spontaneous abortion secondary to APS. Several studies have revealed that LMWHs are effective in the treatment of pregnant women with thrombophilic disorders or APS. For example, Brenner et al. [10] prospectively evaluated the efficacy of LMWH (enoxaparin) plus LDA during 166 pregnancies in 166 thrombophilic women with recurrent pregnancy loss, including 9 women with APS. The dose of enoxaparin was 40 mg for
women with a solitary thrombophilic defect and 80 mg for women with combined thrombophilic defects. The enoxaparin dose of 40 mg/day resulted in live birth in 68% of gestations, compared with 83% of gestations for women treated with enoxaparin at 80 mg/day.

In addition, a randomized controlled trial comparing LMWH plus LDA with intravenous immunoglobulin in the treatment of women with recurrent pregnancy loss associated with APS revealed that LMWH plus LDA resulted in a highly significant higher live-birth rate (72.5% versus 39.5%) [6].

A prospective pilot study also compared LMWH (enoxaparin 40 mg, once daily) plus LDA with UFH (5000 U, twice daily) plus LDA in the management of pregnant women with recurrent abortion secondary to APS. LMWH plus LDA resulted in live birth in 84% of gestations, compared with 80% of gestations for women treated with UFH plus LDA (P = 1.00) [7]. A randomized controlled trial comparing LMWH (dalteparin) with UFH in the management of women with recurrent abortion secondary to APS found that LMWH (dalteparin) resulted in a higher live-birth rate than did UFH (69% versus 31%), but this difference failed to reach statistical significance because of the small sample size of both groups (14 patients in each group) [8].

Despite the high cost of LMWHs, they have several advantages over UFH. In contrast to UFH, LMWHs have lower anti-IIa activity than anti-Xa activity, resulting in a lower risk of bleeding at similar levels of anticoagulation. LMWHs also have a longer half-life, and more stable and predictable pharmacokinetics, and therefore can be administered once daily without the need for monitoring [11,12]. There is evidence that, compared with UFH, LMWHs are associated with a lower risk of excessive bleeding, heparin-induced osteoporosis, and thrombocytopenia [13]. Furthermore, in contrast to warfarin, no teratogenic effects or neonatal bleeding episodes have been reported because LMWHs do not cross the placental barrier [14]. These advantages make LMWHs the anticoagulant of choice during pregnancy [13].

A systematic review of 64 studies reporting the use of LMWHs for prophylaxis or treatment of venous thromboembolism in 2777 pregnant women found that 0.04% of women had osteoporotic spontaneous fractures and 0% of women had heparin-induced thrombocytopenia [15]. On the other hand, Carlin et al. [16] reported that bone loss associated with the long-term use of prophylactic doses of LMWH was not significantly different from physiologic losses during pregnancy. On the other hand, Dahlam et al. [17] reported that prolonged use of UFH in pregnant women was associated with a 2.2% incidence of osteoporotic fractures. In a randomized controlled trial comparing LMWHs with UFH in the prophylaxis of postoperative venous thromboembolism, heparin-induced thrombocytopenia occurred in 2.7% of women who received UFH, compared with 0% of women who received LMWHs [18].

Although there has not been a systematic meta-analysis comparing the risk of major bleeding in pregnant women treated with UFH or LMWHs [13], 2 systematic meta-analyses comparing LMWHs with UFH in the prophylaxis or treatment of venous thromboembolism in non-pregnant women found that the risk of major bleeding was higher with UFH [19,20]. Therefore, it is reasonable to assume that LMWHs are associated with a lower risk of major bleeding in pregnant women compared with UFH [13].

In the present study, the live-birth rate was 80% in the LMWH plus LDA group and 66.7% in the UFH plus LDA group. This difference was not significant because of the small sample size of both groups. To detect a significant difference in favor of LMWH plus LDA, a sample size of 410 women would have had to be recruited to achieve a study power of 80% at a significance level of 0.05 (2-tailed). The main limitation of the present study was the small sample size. The aim of the present study was to compare the efficacy and safety of LMWH plus LDA with those of UFH plus LDA, and the results of the study could be used in future meta-analyses comparing both management options. A further limitation was that the trial was not blind because it was considered unethical to give women in the LMWH group a once-daily placebo injection until the end of pregnancy.

In conclusion, the results of the present study indicate that the efficacy and safety of LMWH plus LDA in the management of women with recurrent spontaneous abortion secondary to APS were superior or at least equivalent to those of UFH plus LDA. The results highlight the need for a larger randomized controlled trial to determine whether LMWH plus LDA should be the treatment of choice for women with recurrent abortion secondary to APS.

Conflict of interest

The authors have no conflicts of interest.

References