Combined Therapy of Low Dose-Aspirin Plus Low Molecular Weight Heparin in Women with Recurrent Unexplained Miscarriage: A Randomized Controlled Study

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Abstract

Background: Both Heparin and aspirin are used in management of recurrent unexplained miscarriage with the aim to improve the live birth rate and reduce the pregnancy complication.

Methods: This is a controlled randomized study enrolling 100 patients with history of recurrent unexplained miscarriage. They were classified into two groups: Group A took low-dose of aspirin plus low molecular weight heparin and group B with no treatment.

Results: The live birth rate did not differ significantly between the two groups. The live birth rate was 74% in group A and 62% in group B. The rate of miscarriage was 26.7% versus 33.3% in group B. The preterm delivery was 10.5% in group A versus 29% in group B. The incidence of IUFD was 5.3% in group A versus 12.9% in group B. As regard IUGR the incidence was 5.3% in group A versus 19.4% in group B.

Conclusion: The use of aspirin plus heparin did not significantly increase the live birth rate in women with recurrent unexplained miscarriage.

Key Words: APS – ASA – IUGR – IUFD – PTL.

Introduction

RECURRENT pregnancy loss is defined as three or more consecutive losses, its incidence is approximately 1%, among those, 40% to 50% have no identifiable cause [1].

Phospholipids antibodies, lupus anticoagulant, and anticardiolipin are associated with recurrent miscarriage, thrombosis and thrombocytopenia, 15% of women with a history of recurrent miscarriage have persistently positive results for phospholipids antibodies [2]. These women have a rate of fetal loss of 90% when no specific treatment is given during pregnancy [3,4]. Miscarriage has been attributed to thrombosis of uteroplacental vasculature and placental infarction [5,6]. It has been suggested that in women with recurrent miscarriage with a diagnosis of antiphospholipid syndrome, treatment with aspirin and heparin may improve pregnancy outcome [7-9].

We investigated whether aspirin combined with low molecular weight heparin would improve the live birth rate among women with unexplained recurrent miscarriage. Treatment options for women with unexplained recurrent miscarriage are limited. There are two reported therapeutic clinical trials investigating this selected subgroup [10,11] evidence from these trials that these cases should be treated with thromboprophylaxis alone or combination treatment of prednisone, aspirin progesterone and folic acid during pregnancy. However, there is no inclusion of a placebo arm in any of such trials. Treatment of patients with unexplained recurrent miscarriage with a single dose aspirin per day seem to be safe, low cost, and easy administration [12].

It has been suggested that aspirin, because of its antiplatelet effect and its promoting action on the balance between prostacyclin and thromboxane may have therapeutic role in unexplained recurrent miscarriage [13].

Recently, thromboprophylaxis was associated with good pregnancy outcome among women with unexplained recurrent miscarriage in an uncontrolled trial [10]. The rational for using enoxaparin was based on the fact that there may be as yet unknown hypercoagulability state that presently is not diagnosed.
In addition to its anticoagulant effect, enoxaparin also has anti inflammatory effect, which may counteract the pro-inflammatory mechanism and cytokines responsible for pregnancy loss [14,15].

**Subjects and Methods**

Between September 2009 to September 2010 (100) pregnant women were sequentially included in this open-label randomized controlled trial. Recruited women were among those attending the antenatal clinics of Beni Suef and El Kasr El Aini Hospitals in their early stage of pregnancy seeking help because of their past history of unexplained recurrent early miscarriage (defined as 3 or more successive spontaneous pregnancy losses before completed 20 weeks calculated from the first day of last menstrual period). Miscarriage was only defined after clear documentation of pregnancy either by positive pregnancy test, ultrasonographic documentation or clear clinical manifestations of abortion (vaginal bleeding, abdominal pains and/or expulsion of a conceptus).

All included women should be 18 to 42 years of age, within the first 6 weeks of gestation (confirmed by sure dating of the first day of the last menstrual period and early done transvaginal sonography) and had done all available investigations (fasting and postprandial blood glucose, renal and liver function tests, thyroid function tests, homocysteine level, investigations for chronic infections, coagulation profile, family pedigree and karyotyping) to prove unexplained miscarriage or antiphospholipid syndrome (APS). APS was defined when at least one of the following tests was positive at 2 occasions 8 weeks apart; anticardiopilin IgG >15 GPL units, anticardiolipin IgM >25 MPL units, and a positive lupus anticoagulant test. Women with defined general disease (specially DM, thromboembolism, autoimmune, endocrinal or peptic ulcer) or uterine disorders (in ultrasonographic scan); on anticoagulant, steroids or chronic acetyl salicylic acid (ASA) therapy; hypersensitivity to acetyl salicylic acid, induced abortions, non documented previous pregnancies, loss of preclinical (biochemical) pregnancy and women refused to participate were excluded from the study. Consent was taken from every patient.

**Sample size calculation:**

Based on previous literature (16), the rate of live birth in women with untreated unexplained recurrent miscarriage was 30%. We considered that achievement of 60% live birth rate is the least clinically important difference. Using chi square test and adjusting the power to 80% with a-error at 0.05 yielded a sample size of 90 women. Taking into consideration that drop out rate will be about 10%, we decided to include 100 women. Since the reported prevalence of APS among recurrent aborters was between 5% to 15% [2], study population was divided into 10 cases with APS and 90 cases with unexplained recurrent miscarriage.

**Randomization:**

Participants were stratified into 2 strata; women with antiphospholipid syndrome (10 women) and those with no antiphospholipid syndrome (90 women). Two sets of identical opaque sealed envelopes were prepared for each stratum and each set was equally divided into 2 groups. Group A for women who will be treated with ASA plus enoxapine (5 and 45 respectively) and group B for those who will be treated with follow-up (5 and 45 respectively). After eligibility, every woman was allowed to chose one envelop once to determine to which group she will be assigned.

**Treatment protocol:**

Once randomized, women in group A (50 women) were treated with daily oral tablets containing 75mg ASA (CID Co.-Egypt) and when positive fetal heart activity was ultrasonographically established, daily enoxparine (clexane®, Aventis Pharma, Egypt) 20mg SC was added. Women in group B (50 women) were not given any medications. ASA and enoxparine treatment was continued till the woman reaches completed 36 gestational weeks, but was stopped if miscarriage or preterm labour occurs. All women were followed-up according to the routine protocol for high risk pregnancy till delivery (Routine antenatal visit every two weeks for the first and second trimester and every week in the third trimester ultrasound was done, measuring the blood pressure and weight of every patient) where the final outcome was recorded. Treatment with enoxparine was followed-up by INR weekly for the 1st treatment month then monthly. Four cases were dropped out in the ASA-enoxparine group and 3 cases in follow-up group (none in the APS cases). Intention to treat analysis was applied to treat drop out cases.

**Outcome measures:**

The primary outcome of the study is achievement of term pregnancy with a living fetus (pregnancies completed 37 weeks calculated from the first day of the last at menstrual cycle). Occurrence of miscarriage, intrauterine fetal death (pregnancy termination after completed 20 weeks), preterm delivery (delivery before completed 37 gestational weeks), intrauterine growth restriction (fetal weight below the 10th percentile for gestational age and sex), occurrence of preeclampsia, specially GIT...
and bleeding manifestations were considered secondary outcomes.

**Statistical analysis:**

Data were statistically described in terms of mean ± standard deviation (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Student's *t*-test for independent samples. For comparing categorical data, Chi square ($\chi^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (*p*-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

**Results**

Table (1): Baseline characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>ASA ± enoxparine (n = 50)</th>
<th>Follow-up</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization (years)</td>
<td>29.16±3.8</td>
<td>29.87±3.7</td>
<td>0.346</td>
</tr>
<tr>
<td>Gravidity</td>
<td>6.37±2.3</td>
<td>5.94±2.4</td>
<td>0.363</td>
</tr>
<tr>
<td>Parity</td>
<td>2.63±1.2</td>
<td>2.49±1.8</td>
<td>0.648</td>
</tr>
<tr>
<td>No. of previous miscarriage</td>
<td>3.97±2.6</td>
<td>4.10±2.4</td>
<td>0.796</td>
</tr>
<tr>
<td>GA at randomization (weeks)</td>
<td>4.73±0.94</td>
<td>4.57±0.83</td>
<td>0.369</td>
</tr>
</tbody>
</table>

Data described in mean ± SD.
ASA: Acetyl salicylic acid.
GA: Gestational age.

Table (2): Outcome of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>ASA ± enoxparine</th>
<th>Follow-up</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13/50 (26.0)</td>
<td>19/50 (38.0)</td>
<td>0.198</td>
</tr>
<tr>
<td>Among unexplained recurrent miscarriage</td>
<td>12/45 (26.7)</td>
<td>15/45 (33.3)</td>
<td>0.490</td>
</tr>
<tr>
<td>Among APS cases</td>
<td>1/5 (20.0)</td>
<td>4/5 (80.0)</td>
<td>0.206</td>
</tr>
<tr>
<td>Total birth rate</td>
<td>37/50 (74.0)</td>
<td>31/50 (62.0)</td>
<td>0.198</td>
</tr>
<tr>
<td>Live term birth rate</td>
<td>31/38 (81.6)</td>
<td>18/31 (58.1)</td>
<td>0.037</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>4/38 (10.5)</td>
<td>9/31 (29.0)</td>
<td>0.111</td>
</tr>
<tr>
<td>IUFD</td>
<td>2/38 (5.3)</td>
<td>4/31 (12.9)</td>
<td>0.490</td>
</tr>
<tr>
<td>IUGR</td>
<td>2/38 (5.3)</td>
<td>6/31 (19.4)</td>
<td>0.129</td>
</tr>
<tr>
<td>PE</td>
<td>3/38 (7.9)</td>
<td>7/31 (22.6)</td>
<td>0.142</td>
</tr>
<tr>
<td>Obstetric hemorrhage</td>
<td>2/38 (5.3)</td>
<td>1/31 (3.2)</td>
<td>0.821</td>
</tr>
</tbody>
</table>

Data described in no. of cases (%).
ASA: Acetyl salicylic acid.
IUFD: Intrauterine fetal death.
IUGR: Intrauterine growth restriction.
PE: Pre-eclampsia.

* Statistically significant difference.

Fig. (1-A,B): Outcome of the study groups.

**Discussion**

Recurrent pregnancy loss, defined as three or more spontaneous consecutive miscarriage, is very frustrating problem for both patients and physicians because many patients repeats miscarriage despite of various kinds of treatment. Undoubtedly, the use of empirical therapy in women with unexplained recurrent miscarriage is unnecessary in view of the fact that supportive care alone offers a chance of up to 75% for a successful pregnancy [17].

However, there is another group of patients needs more than reassurance. The hypothesis that women with unexplained miscarriage might benefit from aspirin or heparin or both was based on a presumption that this condition might be caused by thrombosis in decidual vessels [18,19].
This is randomized clinical trial in which we evaluated the efficacy of low molecular weight heparin (Enoxparine) plus low dose aspirin in management of patients with unexplained recurrent miscarriage. In this study participants were stratified into two strata, women with APLS (10 cases) and those with no apparent cause (90 cases). Women in each stratum were subsequently divided into two groups: Group A (women who took enoxparine + low dose aspirin) and group B (with no treatment) (5 & 45 cases respectively).

The primary outcome of this study was the achievement of live term birth. The live birth was 37 out of 50 patients in group A (74%) versus 31 out of 50 patients in group B (62%); this means that drug treatment carries a little bit increase in the incidence of live birth rate (statistically non significant difference). The secondary outcomes of our study were pregnancy complication as miscarriage, preterm delivery, IUGR, IUFD, and obstetric hemorrhage. As regards miscarriage, the total number of patients who experienced miscarriage were 13 out of 50 in group A (one patient in the group of patients with antiphospholipid syndrome and 12 in the patients with unexplained recurrent miscarriage) the incidence was 26.7% and 20% in patients with unexplained recurrent miscarriage and patients with APS respectively versus 19 out of 50 in group B (15 out of 45 in patient with unexplained recurrent miscarriage and 4 out of 5 in APS) the incidence was 33.3% and 80% in patients with unexplained miscarriage and patients with APS respectively. The incidence of preterm delivery in our study was 10.5% in group A versus 29% in group B and p-value was 0.111 of no significant value. Regarding IUFD, the incidence was 5.3% in group A versus 12.9% in group B the p-value was 0.490 of no significant value. As regard IUGR the incidence was 5.3% in group A versus 19.4% in group B with p-value 0.129 still of no significance. In the current study, there were 3 patients developed PE in group A versus 7 in group B with p-value 0.142. Obstetric hemorrhage was experienced in 2 patients in group A versus one in group B and the p-value was 0.821. The results of our work are similar to that obtained by Stef et al. [20] who reported that neither aspirin combined with nadroprin nor aspirin alone improved the live birth rate as compared with placebo among women with unexplained recurrent miscarriage.

Similarly, Robert [21] concluded that LMWH did not have an incremental benefits compared with low dose aspirin alone. In the study done by Triolo et al. [22] showed that treatment with LMWH plus low dose aspirin should be considered as standard therapy of recurrent miscarriage due to antiphospholipid. In our study there was improvement in the incidence of miscarriage but still of no significant value which may be due to small sample size, as compared to study done by Triolo et al. who examined 40 patients with positive results of anticardiolipin and lupus anticoagulant.

Recently in two randomized trials investigators assessed the benefits of low molecular weight heparin in women with recurrent miscarriage. In one trial done by Fawazy et al. [23] involving 170 women with unexplained recurrent miscarriage live birth rate were significantly higher among women who received enoxaparin than among the patients who receive placebo (81% versus 48%).

In another trial done by Badaway et al. [24] involving 340 women who received enoxaparin or no treatment, the reported miscarriage rate were 5% and 11% respectively. However the difference in the methodology and the characters of the patients and sample size in those studies make it difficult to compare the results of these studies to our study. Finally, we concluded that the use of daily low dose Aspirin plus low molecular weight heparin may increase the birth rate and decrease pregnancy complication yet the difference is not statistically significant, another studies of large number of patients may be needed.

References
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