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ASPIRIN AND CALHEPARIN IN UNEXPLAINED RECURRENT ABORTION

The role of prophylactic use of low dose aspirin and calheparin in patients with unexplained recurrent abortion

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Abstract

Objective: To study the effect of prophylactic use of low dose aspirin and heparin on patients with recurrent unexplained pregnancy loss.

Methods: Prospective case control study conducted on 180 pregnant women randomized into two equal groups. Group 1 received low-dose aspirin 75 mg and heparin 5000IU subcutaneous every 12 h. Group 2 received no treatment.

Results: There was a statistically significant difference between the two study groups regarding number of patients who completed their first trimester (66 versus 39) (p values 0.018). The outcome regarding completion of first trimester was not related to age, BMI or number of previous abortions in both the study groups. Complications of the use of aspirin calheparin occurred in 60% of the patients. The most common complication was bruising at injection site occurring in 60% of the patients followed by bleeding gums (14.4%), gastrointestinal troubles (12.2%), epistaxis (10%) and transient thrombocytopenia in only 2.22% of the patients (Table 4).

Conclusion: The use of prophylactic dose of calheparin and aspirin is associated with increased chance of passing 1st trimester safely regardless the age, body mass index or number of abortion in women with unexplained recurrent spontaneous abortion.

Keywords

Aspirin, Calheparin, unexplained recurrent abortion

Introduction

Recurrent spontaneous abortion is classically defined as three or more consecutive pregnancy losses at 20 weeks or less or with fetal weights less than 500 g [1]. Remarkably, the chance for successful pregnancy may approach 50% even after six losses [2]. The causes of recurrent miscarriage parallel those of sporadic miscarriage, although the relative incidence differs between the two categories [3]. The timing of the pregnancy losses may provide a clue to their cause. By way of another example, genetic factors most frequently result in early embryonic losses, whereas autoimmune or anatomical abnormalities are more likely to result in second-trimester losses [4].

Even after a thorough and systematic evaluation, well more than half of all women with recurrent pregnancy loss have no identified predisposing factors that can explain their poor reproductive history [5].

The evidence for pregnancy loss having a thrombotic basis is the widely reported association between antiphospholipid antibodies (aPL) and recurrent pregnancy loss. APL antibodies are believed to cause pregnancy loss by thrombosis in decidual vessels, impairing the blood supply to the fetus and thus leading to fetal death [6].

Patients with recurrent miscarriages have been successfully treated with aspirin and low-dose heparin with average to very high success rates, a treatment though confined only to those associated with antiphospholipid syndrome which does not represent more than 15% of all the cases [7].

In one study the use of low dose aspirin and enoxaparin on women with unexplained recurrent pregnancy loss was associated with a high live birth rate and few late pregnancy complications [8].

Aim of the work is to study the effect of prophylactic use of low-dose aspirin and heparin on patients with recurrent unexplained pregnancy loss.

Materials and methods

This study is a prospective case control study conducted on 180 pregnant women attending Kasr Al Ainy maternity hospital during the period from June 2011 and September 2013.

The study was approved by local ethics committee and informed consents about the study and expected value and outcome were obtained. All the participants were at 5–7 weeks of gestational age with history of three or more spontaneous abortions without an obvious cause. Gestational age was calculated based on regular last normal menstrual period then confirmed by ultrasound. Participants with documented cause of recurrent abortion as antiphospholipid syndrome, history of thrombo-embolic manifestations, medical disorder as diabetes or hypertension, chronic disorder like renal cardiac or liver disease and those with structural anomalies of the uterus were excluded.

The patients were subjected to history taking, including age, parity, menstrual history for verification of gestational age,
medical history, consanguinity, number and details of previous abortions, including timing, presence of fetal pulsations before abortion, need for surgical evacuation. Full examination including general and abdominal examination was done.

Investigations done included routine labs: complete blood count, liver and kidney functions, fasting and postprandial blood sugar, prothrombin time and concentration, and INR.

Other labs included TORCH screening, lupus anticoagulant, anticardiolipin, protein C, protein S, antithrombin III and karyotyping.

Follow-up every 2 weeks was done for all the participants till the end of first trimester. During follow-up visits measuring body weight, blood pressure and ultrasound evaluation of pregnancy were done.

The participants were randomized using automated web-based randomization system into two groups. Group 1 included 90 women received low dose aspirin 75 mg and heparin 5000 IU subcutaneous every 12 h. Group 2 included 90 women received no treatment.

The primary outcome parameter was continuation of pregnancy beyond first trimester. Secondary outcome parameter was occurrence of complications of treatment given.

Results are expressed as mean ± standard deviation (SD) or number (%). Comparison between the mean values of different variables in the two groups was performed using unpaired student t test.

Comparison between categorical data was performed using Chi square test. SPSS computer program (version 12 windows) was used for data analysis. p values less or equal to 0.05 was considered significant and less than 0.01 was considered highly significant.

**Discussion**

Recurrent pregnancy loss (RPL) is a common condition occurring in 1–2% of the women. Recurrent pregnancy loss is also associated with late pregnancy complications including intrauterine growth restriction, preterm labor and anomalies [9]. Approximately half of the couples with recurrent miscarriage will have no explanatory findings. Nevertheless, their prognosis is reasonable [1].

Our study concluded that combination of aspirin and calheparin is an effective treatment for women with unexplained recurrent spontaneous abortion helping these women to pass their first trimester safely without significant side effects of the treatment.

In our study 66 patients in the group taking aspocid and calheparin pass 1st trimester safely with incidence of 73.33% and 24 patients fail to pass 1st trimester with incidence of 26.67%.
While only 39 patients in the group with no treatment completed their 1st trimester with incidence of 43.33% (p values = 0.018).

These results are explained by the known fact that thrombosis in decidual vessels is believed to be one possible cause of recurrent miscarriage and late pregnancy complications. Moreover, heparin not only acts as an anticoagulant but also have immunomodulatory and anti-inflammatory effect. Heparin promotes the heparin-binding epidermal growth factor and improves the outcome in post-embryo transfer therapy [10].

Zolghadri and coworker held study in 2010 on 100 patients. Fifty patients were on prophylactic dose of LMWH and aspirid while other 50 patients were on no treatment. Among the group taking the treatment 41 patients with incidence 83.7% end in live birth and 9 patients end in abortion with incidence 16.3%. While in the group not on treatment 27 patients with incidence 54% end with live birth and 23 patients with incidence 46% end with abortion (p values = 0.001) [11].

Kaan and coworkers held study in 2009 in these study 91 patients were on prophylactic dose of LMWH and aspirid while 95 patients were on no treatment. Among the group on treatment 65 patients with incidence 71.4% end in live birth while 26 patients end in abortion with incidence 28.6%. In the other group 67 with incidence 70.5% end in live birth while 28 patients with incidence 29.5% end in abortion. In the previous study no difference in outcome was observed in the two groups [12].

Lazzarin and colleagues performed a prospective, randomized study to determine the effect of different therapeutic approaches on uterine artery blood flow in 60 women with recurrent miscarriage (RM) and impaired uterine perfusion.

The patients were randomly assigned to three different therapeutic regimens: 20 patients received a daily dose of 100 mg of aspirin (LDA); 20 patients were treated with omega-3 fatty acids (Ω3), 4 g daily; and 20 patients received LDA plus Ω3. They concluded that LDA and Ω3 are effective in improving uterine artery blood flow velocity in women with RM due to abnormal uterine perfusion. Further studies are needed to determine whether the improvement of uterine perfusion may lead to a better pregnancy outcome [13].

Dolitzky and colleagues performed a multicenter randomized comparative cohort study to compare the effect of aspirin and enoxaparin on live births in women with unexplained recurrent miscarriages, as well as secondary outcomes including birth weight, uterine and umbilical blood flows, and congenital malformations. They randomized 107 patients, 104 of them were available for analysis; 54 were randomized to enoxaparin and 50 to aspirin.

They found that both the groups had a similar live birth rate (relative risk = 0.92, 95% confidence interval: 0.58–1.46). In primary aborers, live births occurred in 17 of 18 (94%) enoxaparin-treated pregnancies compared to 18 of 22 (81%) aspirin-treated pregnancies. In the aspirin group, two pregnancies were terminated: for tricuspid insufficiency and for hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome. One enoxaparin-treated infant was growth restricted (2020 g) at 36 weeks. Preeclampsia was found in three aspirin-treated patients. Preterm delivery, placental Doppler blood flow, Apgar scores, and mean birth weights were similar in both the groups. In the aspirin group, one infant underwent orchidectomy after testicular torsion in utero, and one infant had hypoglycemia and convulsions. They concluded that both the regimens were associated with a high-live birth rate and few late pregnancy complications [8].

In our study there was no relation between successful pass of the first trimester and age, BMI or number of previous abortions in both the study groups (p > 0.05).

In our study we found that the side effects occurred in 60% of the patients in aspirin calheparin group with bruising at injection site occurred in 60% of the patients. Bleeding gums occurred in 14.4%, gastrointestinal troubles in 12.2%, epistaxis in 10% and transient thrombocytopenia in only 2.22% of the patients.

Our study showed a significant outcome as there were only a few studies evaluating role of thromboprophylaxis in women with unexplained recurrent spontaneous abortion and most of them had smaller sample size than our study.

The main limitation of our study was the inability to complete follow-up of patients till the end of pregnancy as most of them were lost after the first trimester.

We concluded that patients on prophylactic dose of calheparin and aspirid are associated with increased chance of passing first trimester safely regardless to age, body mass index or number of abortion if compared to those on no treatment.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References