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Evaluation of the Efficacy of Aspirin and Low Molecular Weight Heparin in Patients with Unexplained Recurrent Spontaneous Abortions

J Zolghadri, F Ahmadpour*, M Momtahan, Z Tavana, L Foroughinia

Department of Obstetrics and Gynecology, Shiraz University of Medical Science, Shiraz, Iran

Abstract

Background: The roles of inflammatory cytokines and local placental thrombosis in patients with unexplained recurrent spontaneous abortion (URSA) have been shown. Since low molecular weight heparin (LMWH) and acetyl salicylic acid (ASA) have both anti-inflammatory and anti-coagulant effect, we evaluated their efficacy in patients with URSA.

Methods: One hundred patients with a history of URSA referring to Obstetrics Clinic affiliated to Shiraz University of Medical Sciences between 2004 and 2009 were randomly divided into two groups. Fifty patients in thromboprophylaxis group were treated with LMWH (5000 unit; twice a day), ASA (80 mg daily) and calcium supplement (500 mg daily) after detection of fetal heart beat. Another 50 patients received no thromboprophylaxis. Live birth rate, obstetrical complications, prenatal and neonatal complications and hemorrhagic side effects were recorded.

Results: Both groups were matched for mean age and mean number of pervious abortions. Thromboprophylaxis group had a higher rate of live birth (83.7%) in comparison to the control group (54%). No maternal or neonatal side effects were seen. There were no differences in obstetrical complications, prenatal and neonatal complications between the two groups.

Conclusion: Thromboprophylaxis with ASA and LMWH seems to be safe and effective in patients with URSA.

Keywords: Recurrent abortions; Thromboprophylaxis; Aspirin; Heparin

Introduction

Spontaneous abortion is still one of the most common admission causes in gynecologic wards necessitating surgical curettage to evacuate the possible retained gestational tissue in the uterine cavity for prevention of any complication.[1] Recurrent spontaneous abortion (RSA) with at least three consecutive miscarriages is a stressful experience with repeated cycles of hope and despair, which affects marital and social relations in addition to financial costs.[2] There is no valid estimates of the incidence of recurrent abortion but there are a few estimate of its prevalence between 1%-5%.[2-8] Considering such a high prevalence, it seems that recurrent abortion puts a great burden on the society.

Known etiologies for RSA are categorized into anatomical, immunological, hormonal, chromosomal, coagulopathy causes and infectious disease.[9] In 52-70% of women with pregnancy loss, none of the mentioned etiologies are found.[10,11] Among the postulated causes for unknown RSA, it seems that the role of inflammation and thrombosis is prominent. For example cell surface-associated membrane receptors rather than soluble factors (e.g., thrombophilic factors) are relevant to affect utero-placental circulation in patients with unknown RSA.[12]

Recent investigations provided information about new factors such as abnormal presentation of membrane hemostatic proteins (including tissue factor, endothelial protein C receptor on trophoblasts and thrombomodulin), circulating pro-coagulant micro particles, estrogen induced placental thrombosis, and

***Correspondence:** Fatemeh Ahmadpour, MD, Department of Obstetrics and Gynecology, Shiraz University of Medical Sciences, Shiraz, Iran. Tel/Fax: +98-711-2332365, e-mail: ahmadpour@sums.ac.ir
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cytokine release by progesterone and human chorionic gonadotropin (hCG) including interlukin4 (IL4), IL6 and tumor necrosing factor α (TNFα), which play a role in pregnancy loss.[8,12-16] Most of the mentioned factors promote two main pathogenic processes: hypercoagulable state and inflammation. Accordingly, for treatment of such complications, we need a strategy that covers recommended pathogenic processes. Low molecular weight heparin (LMWH) and Acetyl Salicylic Acid (ASA) are among medications that can inhibit both inflammation and hypercoagulation.[17,18] In addition, LMWH can improve trophoblasts invasion in patients with a history of miscarriage.[19] For these reasons, it is wise to consider these two agents as a potential treatment for unexplained RSA (URSA). Although a few studies have been conducted on this case-(URSA), none of them applied case-control investigation for combination therapy.[3,10,11,20-22] This study aims to evaluate efficacy of ASA and LMWH in URSA.

Material and Methods

One hundred patients with a history of unexplained recurrent abortion referring to Obstetrics Clinic affiliated to Shiraz University of Medical Sciences between 2004 and 2009 participated in our study. They were enrolled if all known causes of RSA were excluded.

They were with primary abortions (if all the pervious pregnancies had terminated as miscarriages) or with secondary abortions (if one or more of the pervious pregnancies had terminated as a live birth). This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. 87-4163). Each patient was asked to sign an informed consent before enrolment in the study. After computerized randomization, patients were allocated into two groups: thromboprophylaxis group, who received LMWH (fragmin-Caspian, Rasht, Iran, 5000 unit SQ, twice a day) and ASA (Pars Daru,Tehran, Iran, 80 mg PO daily) simultaneously, after detection of fetal heart beat (n=50) and control group who didn't receive anticoagulants (n=50).

The patients were informed about the method of subcutaneous self injection of LMWH, in the antrolateral sides of each arm. All the patients also received supplements of 1 mg folic acid till 20 weeks of pregnancies and 35 mg iron daily. Also, the patients in thromboprophylaxis group received 500 mg supplementary calcium daily in order to reduce the risk of LMWH-induced osteoporosis.[23]

Clotting tests and platelet count were performed before the start of medication, 5 days after initiation of treatment, and monthly afterwards until delivery. Prenatal visits were performed for both groups every 4 weeks till 28 weeks of pregnancy and every 2 weeks after it.Target sonographies for evaluation of fetal anomaly at 16-20 weeks and fetal growth assessment at 32-34 weeks were in our protocol. Completion of the treatment was at 36th week of pregnancy, but it has been interrupted if any sign of premature labor or abortion was observed. Pregnancy outcome, occurrence of obstetric complications and side effects of anti-platelet and anti-thrombotic drugs in both mother and fetus (such as bleeding tendency, allergies or thrombocytopenia in treatment group) were recorded during the follow up.

The e*xclusion criteria were* abnormal karyotyping of the couple, hysteroscopic findings for uterine anatomic anomalies, positive thrombophilia (protein C activity, protein S activity, factor V Leiden and factor II mutations), presence of autoimmune antibodies (anticardiolipin and lupus anticoagulant antibodies), endocrine diseases (TSH, FBS) and infections indicated by symptoms. In addition, we did not enroll patients who had co-morbid disorder or any history of taking medication.

Statistical analysis was performed using SPSS software (version 11.5, Chicago, IL, USA). The descriptive variables such as mean and standard deviations were determined. Chi Square (χ^2) was performed to compare data about the two groups of patients with pregnancy outcomes. T test was performed to determine the differences in relation to age and number of pervious abortions in both groups. The *p* value less than 0.05 was considered significant.

Results

Fifty patients were randomized to receive treatment and another 50, as the control group without thromboprophylaxis. The mean age of the patients was 36.3±5.2 in the thromboprophylaxis group and 34.6±4.7 in the control group with no significant difference (p=0.09). The mean number of pervious abortions in the thromboprophylaxis group (3.5±1.1) and control group (3.6±.9) was not significant (p=0.63). In thromboprophylaxis group, 11 patients, and in the control group, 8 patients had secondary abortions (p=0.44). The rate of successful pregnancy in those

with secondary abortions in thromboprophylaxis group (81.8%) was higher than the control group (0.25%) (p=0.02).

Forty one (83.7%) and 27 (54.0%) patients had successful pregnancy in the thromboprophylaxis and the control groups respectively. In thromboprophylaxis group, 9 patients and in the control group, 22 patients had early miscarriages. One patient in the control group had experienced intra uterine fetal death in the second trimester. The thromboprophylaxis group had a higher rate of live birth than the control group (p=0.001). The most neonatal and prenatal complication was preterm rupture of membrane in both groups (Table 1). No maternal or fetal side effect was seen.

Discussion

In our study, live birth rate was 83.7% after thromboprophylaxis which was significantly higher than that in the control group (54%) with 99% confidence interval. Comparing with the result of other studies, in our study, the combination therapy was not superior to other reports with LMWH alone,[20,21] showing no synergistic effect. Regarding the efficacy of ASA, the reports are different. So evaluation of a single agent of thromboprophylaxy versus combination therapy needs further investigations in cases with URSA.

Cell surface-associated membrane receptors rather than soluble factors (e.g., thrombophilic factors) are relevant to affect utero-placental circulation in patients with unknown RSA.[12] In addition, cytokine imbalances and placental inflammation have been described as the underlying cause; Also, we have some evidences regarding the role of these thrombolytic factors, including inhibition of TNF-α, decreasing vein wall permeability, limitation of neutrophil extravasation, modulation of local placental hemostasis and coagulation pathway, and improvement of trophoblasts invasion.[17-19,24-26]

As LMWH does not cross the placenta, no fetal or neonatal complication has been reported and recent studies have confirmed the safety of LMWH therapy during pregnancy and the low risk of potential side effects for both the mother and the neonate.[23] Also, studies have shown that ASA (with both anti-inflammatory and anti-coagulant effects) is a safe drug during pregnancy when administered at low dose (50-150 mg). The risk of cardiopathy which was hypothesized by some authors has never been definitively confirmed. As observed in our study, other studies have not also shown any increasing risk of hemorrhage for either the mother or the fetus.[25]

Besides, in secondary abortions, significant response to treatment was observed (81.8%) when compared with those not receiving any treatment (25%) (p=0.024) suggesting the presence of some unknown coagulopathic or inflammatory factors, but a definitive conclusion can not be described due to our small sample size. In our study, a higher response rate was visible to anti-coagulant agents which can be attributed to the exposure to some thrombogenic antigens in pervious full term pregnancies. Of course, further studies with a larger sample size are recommended to reach a more comprehensive conclusion.

There is no agreement on the exact time of commencement of treatment especially before or after the detection of the fetal heart, but considering that prothrombotic polymorphisms may contribute to thrombotic events in the placenta rather than to failure of implantation and in order to exclude cases with blighted ovum or ectopic pregnancy, it is safer to start it after live intrauterine pregnancy. Missing patients

Table 1: Prenatal and neonatal complications in both groups

Complication	Thromboprophylaxis group on thromboprophilaxies	Control group without treatment
Pre-eclampcia	1	1
Prolong preterm rupture of membrane	1	0
Preterm rupture of membrane	5	4
Intra-uterine growth retardation	1	0
Preterm labor pain	1	2
Intra-uterine fetal death	0	1
Poly-hydramnious associated with esophageal atresia	1	0

with implantation failure is a pitfall for our study. Therefore, future large scale investigations are required for choosing the best regimen of treatment or maybe other safer alternatives in patients with RSA. In this study, prevalence of prenatal, neonatal and obstetrical complications was not more than that in normal population.

We can conclude that thromboprophylaxis improves pregnancy outcome in patients with unexplained recurrent abortions when given early in pregnancy with few side effects for both mother and fetus.

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