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Role of Low Dose Aspirin with Low Molecular Weight Heparin (LMWH) in the Management of Recurrent Missed Abortion: A Non-Randomized Clinical Trial

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Abstract

Background: Management of recurrent missed abortion is very crucial. **Objective:** The aim of this study was to explore the outcome of combined treatment of low dose aspirin with low molecular weight heparin (LMWH) in recurrent missed abortion cases. **Methodology:** This non-randomized clinical trial was performed in the Department of Obstetrics & Gynaecology at Mugda Medical College Hospital, Dhaka, Bangladesh between January 2018 and December 2019. The samples were collected from Central Police Hospital, Dhaka, Bangladesh and in a private hospital in Dhaka city. The patients who were able to give clear history of missed abortion, who had no endocrine and hypertensive disorders and who conceived spontaneously or after fertility treatment were selected as study population. After positive pregnancy test all patients started taking oral progesterone (Allylstrenol 5 mg TDS), folic acid and aspirin 75 mg daily. Patients were advised to come for ultrasonography at 6 weeks of pregnancy. After confirming intrauterine viable pregnancy by ultrasonography we started injection enoxaparin (LMWH) 40 mg subcutaneous daily to all patients and continued till 34 completed weeks. The primary end point was the live birth rate and secondary end points were the side effects, late pregnancy complications and neonatal outcome in the study population. **Results:** Fifteen (50.4%) patients had antiphospholipid syndrome. Among them antiphospholipid subgroup antibody found in 40.4% cases, ACLA found in 27.5% cases, LA found in 18.3% cases and both ACLA and LA found in 13.8% cases. Antinuclear antibody was positive in 10% cases. No abnormality was identified in 40.1% cases. Pregnancy continued successfully in 97.0% cases. There were no maternal and foetal complications. Except failed cases there was no need to discontinue the treatment. **Conclusion:** In conclusion it has found a satisfactory outcome with low dose heparin therapy. Large, well-designed randomized trials are needed to establish the heparin therapy in recurrent missed abortion. *[Journal of National Institute of Neurosciences Bangladesh, January 2024;10(1):57-63]*

Keywords: LMWH; missed abortion; live birth

Introduction

Recurrent pregnancy loss (RPL) is a common and frustrating obstetric problem affecting 0.5% to 5.0% women in different population[1-2]. Approximately 15.0% to 20.0% of clinically recognized pregnancies are generally subjected to spontaneous abortion, mostly during first trimester[3]. Most of these abortions are early missed abortions. Missed abortion may be either embryonic (preclinical) or fetal miscarriage. Embryonic miscarriage is defined as an embryo with crown rump length of more than or equal to 5cm without cardiac activity, fetal miscarriage is defined as a fetus of 7 to 20 weeks' size with negative cardiac activity[4].

Genetic factors including chromosomal disorders, single gene defects, and multifactorial factors account for 3.5% of the causes of recurrent missed abortion[5]. There is a big volume of literature describing that cytogenetic abnormality is detected in 31.0% of early missed abortion[6-7]. Other studies showed that foetal chromosomal abnormalities account for about 50.0% of first trimester and near 30.0% of second trimester pregnancy losses[8-9]. Studies revealed that maternal

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insertional translocation associated with recurrent missed abortion[10-15].

Though chromosomal aberration of the embryo is responsible for most of the first trimester pregnancy loss, thrombotic defect of uterine and placental vasculature plays a major role in RPL. Foetal wastage in women with thrombotic defect results from thrombosis of early placental vessels, which peaks in the early trimester but may also occur in the 2nd and 3rd trimester[16-34]. In early weeks of pregnancy, the placental vessels are smaller, undergo partial or total occlusion by thrombus formation. This thrombotic occlusion of placental vessels, both venous and arterial preclude adequate blood supply with nutrition leads to foetal death[16-17].

Thrombophilia either hereditary or acquired have been found in a significant number of women with RPL without apparent cause. The thrombotic hemostatic defects associated with RPL include the following Antiphospholipid syndrome, Factor XII deficiency, protein C deficiency, protein S deficiency, Antithrombin deficiency, Heparin cofactor II deficiency, Dysfibrinogenemias associated with thrombosis, Fibrinolytic defects associated with thrombosis - Plasminogen deficiency, tissue plasminogen activator [tPA] deficiency, elevated plasminogen activator inhibitor type 1 [PAI-1], and PAI-1 polymorphisms, Sticky platelet syndrome, Factor V Leiden, 5,10-methyltetrahydrofolate reductase (5,10-MTHFR) mutations, Prothrombin G20210A gene mutation), Hyperhomocysteinemia, Lipoprotein (a) elevation and Immune vasculitis[8-11].

This ever ending list has the common phenomenon of RPL by thrombosis of uterine and placental vasculature leading to impaired blood supply to foetus causing death. Most common cause for recurrent missed abortion is chromosomal defect[6-9], which is not preventable by any means. But abortions due to thrombotic mechanism can be prevented by antithrombotic drugs. Many researchers consider APLS are the most common prothrombotic disorder causing RPL[16,17,35-41]. Other substances like cytokine, microparticles, hormonesoestrogen, progesterone, hCG - all have thrombogenic effect, may lead to thrombosis of placental vasculature. According to some authors thrombophilic markers are not the only criteria for the initiation of thromboprophylactic treatment[17-18]. The fact that thrombosis at placental level is a common finding whether antiphosholipid antibody are present or not, suggest that other pathologic mechanisms are also involved leading to same outcome, that is the fetal loss[19].

Whatever may be the cause of thrombosis the treatment by anticoagulant and thromboprophylaxis might help in evident or unseen and undiagnosed cases of thrombophilia. Therefore, the purpose of this present study was to observe whether thromboprophylaxis by low molecular weight heparin (LMWH) can prevent foetal wastage in patients with history of recurrent missed abortion.

Methodology

Study Settings and Population: This non-randomized clinical trial was performed in the Department of Obstetrics & Gynaecology at Mugda Medical College Hospital, Dhaka, Bangladesh between January 2018 and December 2019. The samples were collected from Central Police Hospital, Dhaka, Bangladesh and in a private hospital in Dhaka city. The patients who were able to give clear history of missed abortion, who had no endocrine and hypertensive disorders and who conceived spontaneously or after fertility treatment were the target population for this study. Nine (09) patients had history of infertility and others had no problem with getting pregnancy. Patients having diabetes, hypo or hyperthyroidism and hyperprolactinaemia were excluded. The best available data suggest that the risk of miscarriage in subsequent pregnancies is 30.0% after 2 losses, compared with 33.0% after 3 losses among patients without a history of a live birth. This strongly suggests a role for evaluation after just 2 losses in patients with no prior live births42. So in this study we defined recurrent missed abortion with history of at least two previous abortions.

Patients Preparation: Patients, who conceived spontaneously were evaluated by transvaginal ultrasonography, routine blood test, blood sugar, TSH, prolactin, antiphospholipid antibodies subgroups, lupus anticoagulant (LA), anticardiolipin antibody (ACLA) and antinuclear antibody testing. Those who needed treatment for infertility were evaluated in same manner along with other infertility work up. All patients were advised to do pregnancy test by beta hCG or by pregnancy test kit after missed period. After positive pregnancy test all patients started taking oral progesterone (Allylestrenol 5 mg TDS), folic acid and aspirin 75 mg daily. Patients were advised to come for ultrasonography at 6 weeks of pregnancy.

Allocation: After confirming intrauterine viable pregnancy by ultrasonography we started injection enoxaparin (LMWH) 40 mg subcutaneous daily to all patients irrespective of positive or negative

antiphospholipid antibody (LA and/ or ACLA), and antinuclear antibody testing and continued till 34 completed weeks.

Follow Up and Outcome Measures: Patients were under regular antenatal checkup with following follow up with complete blood cell (CBC) with platelet monthly to term, Sonogram at 20 weeks for diagnosis of foetal anomaly and for biophysical profile at 32, 36 and in between if indicated, Daily Fetal movement count chart, starting at 28 weeks, PT, APTT and INR were assessed in every trimester. Pregnancy was terminated by elective caesarean section at 37 completed weeks or before if any emergency occurred. The primary end point was the live birth rate and secondary end points were the side effects, late pregnancy complications and neonatal outcome in the study population.

Statistical Analysis: Statistical analysis was performed by Windows based software named as Statistical Package for Social Science (SPSS), versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data were expressed as mean, standard deviation, minimum and maximum. Categorical data were summarized in terms of frequency counts and percentages. Chi-square test was used for comparison of categorical variables and Student t test was applied for continuous variables. Every effort was made to obtain missing data. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Differences between case and control were tested.

Ethical Consideration: All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration 2013) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the local ethics committee. Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and were analyzed using the coding system.

Results

Twenty-two (22) patients had no children and eight (8) patients had one child with history of recurrent missed abortions. Majority (60.0%) had 2 to 3 recurrent missed abortions and 40.0% cases had more than 3 abortions. Most of the foetal death took place during first trimester and range of gestational age was 7 to 18 weeks. Fifteen (50.39%) patients had antiphospholipid syndrome. Among them antiphospholipid subgroup antibody found in 39.36% cases, ACLA found in 28.55% cases, LA found in 19.3% cases and both ACLA and LA found in 12.77% cases. Antinuclear antibody was positive in 10% cases. No abnormality identified in 40.09% cases. (Table 1).

Table 1: Baseline Patients Characteristics

Characteristics	Values
Age (Mean± SD)	26.10± 4.20
Parity	
0	22(73.33%)
1	8(26.67%)
Previous Abortions	
2	9(30.0%)
3	8(26.7%)
4	6(20.0%)
5	4(13.3%)
6	3(10.0%)
Gestational age of previous abortions (Range in weeks)	7-18
Total abortions (n)	104
6 to 8 Weeks	62(59.6%)
9 to 12 Weeks	37(35.6%)
13 to 18 Weeks	5(4.8%)
Antiphospholipid syndrome (APLS)	15(50.4%)
Antiphospholipid antibody subgroups positive	11(39.4%)
Anticardiolipin antibody positive (ACLA)	9(28.6%)
Lupus Antibody positve (LA)	6(19.3%)
ACLA+LA	4(12.8%)
Antinuclear antibody positive	3(10.0%)
No identifiable causes	12(40.1%)
Spontaneous pregnancy	21(70.0%)
Pregnancy after fertility treatment	9(30.0%)

Pregnancy continued successfully in 97.0% cases. Three patients had failed to respond the treatment with

Table 2: Outcome of Treatment

Outcome of Treatment	Value
Successful Continuation of Pregnancy and Live Birth	29 (97.0%)
Failed	1(3.0%)
Complication of Treatment	Nil
Withdrawal of Treatment	Nil
Gestational age Mean ± SD (Weeks)	36.7± 3.21
Congenital Anomaly of Babies	Nil
Birth weight of Babies Mean ± SD (gm)	2628.0±202.15
Birth Asphyxia	Nil

this therapy but subsequently with same treatment they became successful to deliver full term baby. Among 3 cases 2 had APLS and 1 had no identifiable factors. There were no maternal and foetal complications. Except failed cases there was no need to discontinue the treatment (Table 2).

Discussion

Recurrent pregnancy loss is classically defined as 3 or more consecutive losses, though some feel that 2 rather than 3 losses are sufficient to define recurrent pregnancy loss, especially if they have preceded by infertility treatment. Diagnosis of recurrent pregnancy loss often remains the enigma even after exclusion of hormonal, immunological, infectious, genetic defects and uterine abnormalities. There is a strong association of thrombophilia (either hereditary or acquired) and recurrent pregnancy loss without any apparent cause. The most common hemostasis related cause is a thrombotic disorder, of which the most common is antiphospholipid syndrome (APS) and accounts for 55 to 62% cases[16]. Antiphospholipid antibodies (APL) are thought to cause pregnancy loss by thrombosis in decidua vessels, impairing the blood supply to the fetus and leading to fetal death. As APL induces thrombosis causing pregnancy loss, it has been assumed that any prothrombotic state may also increases the chance of pregnancy loss due to thrombotic mechanism. Recent understanding is that APL impairs signal transduction mechanisms controlling endometrial cell decidualization, increases trophoblast apoptosis, decreases trophoblast fusion and impairs trophoblast invasion. In vitro study shows that the effects of APL on trophoblast function can be reversed by low molecular weight heparin. Besides APS hereditary thrombophilias have been reported to be associated with recurrent pregnancy loss include anti-thrombin, protein C and protein S deficiencies, factor V Leiden (FVL), the G20210A mutation in the factor II (FII) gene and homozygocity for the thermolabile variant of methyletetrahydrofolate reductase (MTHFR C677T). This hereditary thrombophilia has been suggested to be a cause for microembolism in the placenta resulting in abortion or adverse outcome of pregnancy[43]. Not only these hereditary thrombophilias are responsible, APL also plays role in this thrombophlic mechanism. APL induce acquired activated protein C resistance (APC-R)[44] interferes the function of prothrombin (factor II), protein C and protein S, tissue factor, factor XI[45] and the tissue factor/tissue factor pathway inhibitor (TF/TFPI) system[46]. APLAs also harbor antibodies to prothrombin, protein C, and protein S[47] and may also develop antibodies to "thromboplastin" and thrombin[48].

Pregnancy is a hypercoagulable state secondary to both an increase in the levels of certain coagulation factors and simultaneous decrease in both the levels of anticoagulant proteins and fibrinolysis. Some cases of recurrent miscarriage and later pregnancy complications are due to an exaggerated haemostatic response during pregnancy leading to thrombosis of the uteroplacental vasculature and subsequent foetal demise.

Therefore, whatever may be the aetiology of thrombosis, if it could be prevented by anticoagulant help to restore optimum placental circulation. Considering this we used low molecular weight heparin along with low dose aspirin in recurrent missed abortion cases. We evaluated 30 patients who had recurrent missed abortions and found antiphospholipid antibodies in a significant number (50.39%) of cases. In 40.09% cases we did not find any causes. We did not investigate hereditary thrombophilia factors like antithrombin, protein C, protein S, factor V Leiden (FVL), G20210A mutation in the factor II (FII) gene and methyle-tetrahydrofolate reductase (MTHFR C677T). So among these (40.09%) some might be thrombophilia cases.

APL and thrombophilic factors are not the only factors involved in thrombotic mechanism. Tissue factors (TF) also play role in thrombotic mechanism. Tissue factors is a glycoprotein and membrane receptor that plays an important role in mediating the cellular initiation of the extrinsic pathway of coagulation through the activation of factor VII, which is the main coagulation pathway in the placenta[49]. This increase may contribute to the formation of fibrin deposition and occlusive injuries and may participate in the thrombotic complications[50]. The placenta is a major source of tissue factors, as it has been possible to find high levels of this protein in extracts of placental tissue and amniotic fluid[51]. Increased tissue factors mRNA and protein stimulate thrombin generation. Thrombin exacerbates this process by generating greater tissue factors expression, thus promoting uteroplacental thrombosis and inducing the production of inflammatory cytokines and abnormal angiogenesis, which ultimately lead to foetal loss[52].

Mousa and Alfirevic[53] found placental infarction and thrombosis in 50.0% cases of missed abortion. These

thrombosis was found in both women with and women without thrombophilia. As so many causes are involved in thrombus formation in placental vessels so we gave thromboprophylaxis in all recurrent missed abortion cases irrespective of test findings. We found that 97.0% patients continued pregnancy successfully to term and gave birth healthy babies. Only seven cases (3.0%) had same event in-spite of getting LMWH. Out of three cases, two had APL positive and one had no identifiable causes. These patients' embryos might have some chromosomal defect. Subsequently we treated those patients with same regime and pregnancy continued to term successfully. A multicenter study shows that there is no difference in outcome of pregnancy when they compared between two doses of LMWH: 40 mg/day and 40mg twice daily. They found LMWH (40 or 80 mg/day) is safe and effective for improving pregnancy outcome and reducing late pregnancy complications in thrombophilic women with a history of pregnancy loss. They also concluded that it reduces late pregnancy complications like preeclampsia, abruptio placenta, IUGR[54]. In our study there was no IUGR and no abruptio placenta and 3(10.0%) had preeclampsia in mild form and 5(16.7%) had preterm delivery.

There was no complication of the treatment in our series except slight bruise on the injection site and itching in some cases. The need for monitoring of LMWH therapy in pregnancy is debatable. However, consensus conferences such as the ACCP suggest that changes in pharmacokinetics and pharmacodynamics properties during pregnancy may require monitoring[55]. We monitored by PT, APTT and INR and we did not find any abnormalities throughout the treatment. Though there is no utility in checking APTT as drug has wide therapeutic window and APTT does not correlate with anticoagulant effect. APTT is already prolonged in APLS. Therefore, after heparin therapy measurement of APTT does not reflect much in patients with APLS. Moreover, with good renal clearance there is little need of monitoring of LMWH therapy.

In this series all patients got low dose aspirin and different studies showed higher live birth rate in combined low dose aspirin and LMWH therapy[56-57]. All patients also got oral progesterone till 20 weeks of pregnancy. Progesterone has got both thrombotic and antithrombotic effects. It upregulates TF expression[58] and also induces the production of cytokines such as IL-4, which upregulates protein S, which inhibits coagulation. Progesterone allylstrenol inhibits production of TNF-á (prothrombotic), but increases the levels of IL-4 (antithrombotic) and slight IL-6 (prothrombotic)[59]. So more pronounced action may be antithrombiotic.

Heparin-induced osteoporosis (1.0% to 2.0%) and thrombocytopenia, mild to moderate alopecia, skin allergic reaction, bleeding, eosinophilia occurs in some cases of heparin therapy. But in our series except some allergic reaction no complication developed.

Limitation of the study is that we could not do all necessary investigations to declare some cases as unexplained RPL. There might be more causative factors in those cases where we did not find any abnormality. Absence of controlled arm in study design is another important limitation of this study to draw conclusion of efficacy of heparin therapy. Yet result of LMWH and aspirin therapy was found satisfactory in these recurrent missed abortion cases. Large, well designed randomized trials are needed to establish the heparin therapy in recurrent missed abortion.

Conclusion

In conclusion it has found a satisfactory outcome with low dose heparin therapy. Large, well-designed randomized trials are needed to establish the heparin therapy in recurrent missed abortion. Pregnancy has continued successfully in majority cases. The patients have failed to respond the treatment with this therapy but subsequently with same treatment they became successful to deliver full term baby. There were no maternal and foetal complications. Except failed cases there was no need to discontinue the treatment.

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Conflict of interest: Other than technical and logistic support
None.

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Contribution to authors: Sultana N, Tariquzzaman M conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript. Tariquzzaman M, Kutubi S, Tariq NSB involved in the manuscript review and editing. All authors read and approved the final manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

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