

Role of Low Molecular Weight Heparin (LMWH) in the Treatment of Recurrent Missed Abortion

MOSAMMAT RASHIDA BEGUM¹, MARIYA EHSAN², NAZIA EHSAN³, IFTEKHAR AMIN⁴, FARHANA SHARMIN⁵, ASHIK AHMED CHOWDHURY⁶, FARZANA KHAN⁷, MOSAMMAT SHAHINA BEGUM SANTA⁸

Abstract:

Objective (s): The aim of this study was to explore the outcome of treatment of low molecular weight heparin (LMWH) in recurrent missed abortion cases.

Method: This prospective observational study was done between January 2005 and July 2014 in Infertility Care and Research Center, Dhaka, Bangladesh. Two hundred and ten (210) 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. After positive pregnancy test all patients started taking oral progesterone (Dydrogesterone 10 mg bd), 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 sc 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: One hundred and nine (52.39%) patients had antiphospholipid syndrome. Among them antiphospholipid subgroup antibody found in 40.37% cases, ACLA found in 27.52% cases, LA found in 18.34% cases and both ACLA and LA found in 13.77% cases. Antinuclear antibody was positive in 10% cases. No abnormality was identified in 38.09% cases. Pregnancy continued successfully in 96.66% cases. There were no maternal and foetal complications. Except failed cases there was no need to discontinue the treatment.

Conclusion: This observational study dealt only with recurrent missed abortion and found satisfactory outcome with low dose heparin therapy. Large, well-designed randomized trials are needed to establish the heparin therapy in recurrent missed abortion.

Key Words: LMWH, Missed abortion, Live birth

Introduction:

Recurrent pregnancy loss (RPL) is a common and frustrating obstetric problem affecting 0.5% - 5% women in different population^{1,2}. Approximately 15-20% of clinically recognized pregnancies are generally subjected to spontaneous abortion, mostly during first trimester³. 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 7-20 weeks size with negative cardiac activity⁴.

Genetic factors including chromosomal disorders, single gene defects, and multifactorial factors account for 3.5-5% of the causes of recurrent missed abortion⁵. There is a big volume of literature describing that cytogenetic abnormality is detected in 31% of early missed abortion^{6,7}. Other studies showed that foetal chromosomal abnormalities account for about 50% of first trimester and near 30% of second trimester pregnancy losses^{8,9}. Studies revealed that maternal insertional translocation associated with recurrent missed abortion¹⁰⁻¹⁵.

1. Chief Consultant, Infertility Care and Research Center
2. Medical Officer, fertility Care and Research Center
3. Medical Officer, Infertility Care and Research Center
4. Medical Officer, Infertility Care and Research Center
5. Medical Officer, Infertility Care and Research Center
6. Ex Medical Officer, Infertility Care and Research Center
7. Senior Medical Officer, Infertility Care and Research Center
8. Consultant, Infertility Care and Research Center

Though chromosomal aberration of the embryo is responsible for most of the first trimester pregnancy loss, thrombotic defect of uterine and placental vasculature play 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 trimester¹⁶⁻³⁴. 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.

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 defect⁶⁻⁹, 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, hormones- oestrogen, 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 antiphospholipid antibody are present or not, suggest that other pathologic mechanisms are also involved leading to same outcome, that is the fetal loss¹⁹.

Whatever may be the cause of thrombosis the treatment by anticoagulant and thromboprophylaxis might help in evident or unseen and undiagnosed cases of thrombophilia. So purpose of this study was to observe whether thromboprophylaxis by low

molecular weight heparin (LMWH) can prevent foetal wastage in patients with history of recurrent missed abortion.

Materials and methods:

This prospective observational study was done between January 2005 and July 2014 in Infertility Care and Research Center, Dhaka, Bangladesh. Two hundred and ten (210) 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. Ninety-eight (98) patients had history of infertility and others had no problem with getting pregnancy. The best available data suggest that the risk of miscarriage in subsequent pregnancies is 30% after 2 losses, compared with 33% 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, 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. Patients having diabetes, hypo or hyperthyroidism and hyperprolactinaemia were excluded. 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 (Dydrogesterone 10 mg bd), 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 sc daily to all patients irrespective of positive or negative antiphospholipid antibody (LA and/or ACLA), and antineuclear antibody testing and continued till 34 completed weeks.

Patients were under regular antenatal checkup with following follow up

- Complete blood cell (CBC), 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.
- Fetal activity chart daily, 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.

Results:

One hundred and seventy two patients had no children and 38 patients had one child with history of recurrent missed abortions. Majority (58.57%) had 2-3 recurrent missed abortions and 41.43% had more than 3 abortions. Most of the foetal death took place during first trimester and range of gestational age was 7-21 weeks. (Table 1)

One hundred and nine (52.39%) patients had antiphospholipid syndrome. Among them antiphospholipid subgroup antibody found in 40.37% cases, ACLA found in 27.52% cases, LA found in 18.34% cases and both ACLA and LA found in 13.77% cases. Antinuclear antibody was positive in 10% cases. No abnormality identified in 38.09% cases. (Table1). Pregnancy continued successfully in 96.66% cases. Seven patients had failed to respond the treatment with this therapy but subsequently with same treatment they became successful to deliver full term baby. Among 7 cases 4 had APLS and 3 had no identifiable factors. There were no maternal and foetal complications. Except failed cases there was no need to discontinue the treatment (Table 2).

Table-I
Patients Characteristics

Characteristics	Mean	±SD
Age: Mean	28.10	± 4.20
Parity :	N	%
0	172	81.90
1	38	18.10
Previous abortions:		
2	58	27.61
3	65	30.96
4	35	16.67
5	30	14.29
6	10	4.77
7	07	3.33
8	05	2.39
Gestational age of previous abortions (Range in weeks)	7-21	
Total abortions: n	750	
	N	%
6-8 weeks	440	58.67
9-12 weeks	280	37.33
13-21 weeks	30	04
Antiphospholipid syndrome (APLS)	109	52.39
Antiphospholipid antibody subgroups positive	44	40.37
Anticardiolipin antibody positive (ACLA)	30	27.52
Lupus antibody positive (LA)	20	18.34
ACLA+LA	15	13.77
Antinuclear antibody positive	21	10
No identifiable causes	80	38.09
Spontaneous pregnancy	112	53.33
Pregnancy after fertility treatment	98	46.67

Table-II
Outcome of treatment

Outcome	
Successful continuation of pregnancy and live birth: N (%)	203 (96.67)
Failed: N (%)	07 (3.33)
Complication of treatment: N	Nil
Withdrawal of treatment: N	Nil
Gestational age: Mean \pm SD (Weeks)	36.67 \pm 3.21
Congenital anomaly of the babies: N	Nil
Birth weight of the babies: Mean \pm SD (gm)	2728 \pm 202.15
Birth Asphyxia: N	Nil

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 55-62%¹⁶. Antiphospholipid antibodies (APL) are thought to cause pregnancy loss by thrombosis in decidual vessels, impairing the blood supply to the foetus and leading to foetal death. As APL induces thrombosis causing pregnancy loss, it has been assumed that any prothrombotic state may also increase 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 antithrombin, protein C and protein S deficiencies, factor V Leiden (FVL), the G20210A mutation in the factor II (FII) gene and homozygosity for the thermolabile variant of methylenetetrahydrofolate reductase (MTHFR C677T). These hereditary thrombophilia have been suggested to be a cause for microembolism in the placenta resulting in abortion

or adverse outcome of pregnancy⁴³. Not only these hereditary thrombophilias are responsible, APL also plays role in this thrombophilic 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) system⁴⁶. APLAs also harbor antibodies to prothrombin, protein C, and protein S⁴⁷ and may also develop antibodies to "thromboplastin" and thrombin⁴⁸

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 .

So, 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 210 patients who had recurrent missed abortions and found antiphospholipid antibodies in a significant number (52.39%) of cases. In 38.09% 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 methylenetetrahydrofolate reductase (MTHFR C677T). So among these (38.09%) some might be thrombophilia cases.

But APL and thrombophilic factors are not the only factors involved in thrombotic mechanism. Tissue

factors (TF) also play role in thrombotic mechanism. TF 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 placenta⁴⁹. This increase may contribute to the formation of fibrin deposition and occlusive injuries and may participate in the thrombotic complications⁵⁰. The placenta is a major source of TF, as it has been possible to find high levels of this protein in extracts of placental tissue and amniotic fluid⁵¹. Increased TF mRNA and protein stimulate thrombin generation. Thrombin exacerbates this process by generating greater TF expression, thus promoting uteroplacental thrombosis and inducing the production of inflammatory cytokines and abnormal angiogenesis, which ultimately lead to foetal loss⁵².

Mousa and Alfirevic found placental infarction and thrombosis in 50% cases of missed abortion. These thrombosis was found in both women with and women without thrombophilia⁵³. 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 96.67% patients continued pregnancy successfully to term and gave birth healthy babies. Only seven cases (3.33%) had same event in spite of getting LMWH. Out of seven cases, three had APL positive and 4 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, IUGR⁵⁴. In our study there was no IUGR and no abruptio placenta and only 3 (1.42%) had pre-eclampsia in mild form and 35 (16.66%) 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 monitoring⁵⁵. 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. So 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 expression⁵⁸ and also induces the production of cytokines such as IL-4, which upregulates protein S, which inhibits coagulation. Progesterone dydrogesterone inhibits production of TNF- α (prothrombotic), but increases the levels of IL-4 (antithrombotic) and slight IL-6 (prothrombotic)⁵⁹. So more pronounced action may be antithrombotic.

Heparin-induced osteoporosis (1-2%) 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.

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