ORIGINAL ARTICLE

ROLE OF ANTI-THROMBOTIC THERAPY FOR RECURRENT PREGNANCY LOSS DUE TO ANTI-PHOSPHOLIPID SYNDROME

Saadia Fawad

Department of Gynaecology, Aero Hospital, Air Weapon Complex Hassanabdal, Pakistan

Background: Recurrent pregnancy loss is a major health problem effecting 1–2% of women of reproductive age. Its causes range from chromosomal abnormalities to endocrinological factors and thrombophilia related factors. Treating thrombophilias especially antiphospholipid syndrome with low dose aspirin and low molecular weight heparin improves foetal outcome. This study will add local data to already existing knowledge. **Method**: Sixty selected patients from gynaecology OPD of Aero Hospital with clinical and/or serological findings of antiphospholipid syndrome from February 2009 to January 2011 were given aspirin 75 mg once daily and enoxaparine 40 mg subcutaneously once daily from 6–8 weeks to 35 and 37 weeks respectively. **Results**: Ninety-three percent of patients achieved live birth. Out of these 75% patients delivered at term and 18% had preterm delivered. Four (7%) had early pregnancy loss and only one had early neonatal death due to extreme prematurity. None of patients experienced any major hemorrhagic complications**. Conclusion**: Use of low dose aspirin and low molecular weight heparin is safe in pregnancy and improve foetal outcome in patients with recurrent pregnancy loss due to antiphospholipids syndrome.

Keywords: Recurrent pregnancy loss, Antiphospholipid syndrome, low molecular weight heparin

INTRODUCTION

Recurrent pregnancy loss (RPL) is a major problem affecting 1–2% of women of reproductive age. While Chromosomal aberrations, endocrinological dysfunction, uterine abnormalities are aetiological factors, until recently in most cases, a cause for RPL could not be identified.[1,2] Gestational outcome in women with inherited thrombophilias who present with RPL is poor with less than 25% of pregnancies resulting in live birth.[3] RPL is a well established finding in women with antiphospholipids syndrome (APS).[4] The APS was first described in 1986 by Highes Haris and Gharavi as a disorder in which antibodies are produced against a variety of phospholipids and phospholipids binding proteins.[5,6] Clinical manifestations may range from no symptoms to immediately life threatening catastrophic APS. As per 1999 Sapporo, International Consensus statement on preliminary criteria for classification of anti phospholipids syndrome, a patient with definite APS must have persistent high titres of antiphospholipid antibodies (aPL) associated with a history of arterial or venous thrombosis or both, or recurrent pregnancy morbidity.[7,8] Primary APS is defined as presence of aPL anti bodies in patient with idiopathic thrombosis but no evidence of autoimmune disease. Secondary APS is used when patients with a wide spectrum of autoimmune disorders (primarily SLE and rheumatoid arthritis and thrombosis are also found to have antiphospholipids antibodies.[9] Clinical manifestations of thrombosis are similar whether APS is primary or secondary. Probable APS is one in which there are typical clinical manifestations but without positive secological test of aPL. These are also called seronegative APS or pre APS.[10] APS is more common in females than males, 5:1 ratio.[11] The anti bodies detected for APS used in clinical practice are Anti-cardiolipin (aCL), Lupus anticoagulant (LA).

The biological effects medicated by human aPL antibodies include reactivity with endothelial structures, which disturbs the balance of prostaglandins E2 and thromboxane production, interaction with platelets with consequent up regulation of platelet aggregation, Disregulation of complement activation and interaction of aPL with phosphatidylserine exposed during trophoblast syncytium formation which causes the possibility of more direct effect of these auto antibodies on placental structure.[12]

Without treatment the miscarriage rate in a subsequent pregnancy in this condition is as high as 90%. It is widely accepted that treatment with low dose aspirin and heparin or low molecular weight heparin (LMWH) significantly improve out come as compared to previous untreated pregnancies.[13,14]

Use of low dose of aspirin and low molecular weight heparin (LMWH) Enoxaprin is safe in pregnancy and it improves foetal outcome.[15] Bleeding is a potential compilation of anti coagulant therapy, Heparin induced thrombocytopenia has been observed less commonly in patients treated with LMWH. LMWH do not cross placenta and therefore are not associated with bleeding in foetuses and have no teratogenic effects.[16] LMWH have higher specificity for Xa and have fewer effects on platelet activity. As a result LMWH may cause bleeding less often, while still retaining anticoagulant effects. The LMWH are associated with less risk of heparin induced osteoporosis.

Most of the research work carried out in this respect is international and local studies are lacking.

This study is conducted to add local data to already existing knowledge.

MATERIAL AND METHODS

It was retrospective study. Patients were selected from Gynaecology OPD of Aero Hospital from February 2009 to January 2011, aged between 20–35 years. All patients were interviewed about their medical, personal, family, obstetrical and thrombosis history. All patients included in study met strictly the clinical criteria for diagnosis of Antiphospholipid syndrome that is as following:

1. Vascular Thrombosis
   One or more episodes of arterial, venous or small vessel thrombosis occurring in any tissue or organ.
2. Pregnancy Morbidity
   a. One or more unexplained deaths of morphologically normal foetuses at or after 10 weeks of gestation with normal foetal morphology documented by ultrasound or direct foetal examination.
   b. One or more premature births of morphologically normal foetuses before 34 weeks of gestation because of:-
      i. Eclampsia or severe pre-eclampsia defined according to standard definitions
      or
      ii. Recognised feature of placental insufficiency.
   c. Three or more unexplained consecutive spontaneous abortions before10 weeks of gestation with maternal anatomic or hormonal abnormalities and parental chromosomal causes excluded.

Laboratory Criteria

1. Lupus anticoagulant (LA):
   In plasma, present on two or more occasions at least 6–12 weeks apart.
2. Anti cardiolipin (aCL) of IGg and/or IGM isotype: in serum or plasma present in medium or high tiers at least 6–12 weeks apart.

All patients were offered baseline tests including aCL, LA, Antinuclear antibodies (ANA) and repeated after 12 weeks before pregnancy and findings noted. All selected patients were in good general health without previous history of Diabetes Mellitus or thyroid dysfunction or cardiac disease. Patients with Thrombicytoperia $<100\times19^9$/litre, bleeding tendencies, ectopic pregnancy and multiple gestation were excluded from study.

Baseline blood complete picture, urine routine examination, blood sugar, blood grouping, Bleeding Time, Clotting Time, Prothrombin Time, Activated Partial Thromboplastin Time, Hepatitis B Surface Ag, Hepatitis C Virus screening were offered to all patients and findings noted as soon as they conceived. Anti Xa level were not tested.

All selected patients were given routine Folic Acid, Iron and Calcium supplementation orally daily during antenatal period (whether conceived spontaneously or with treatment). All were put on tab Aspirin 75 mg daily as soon as gestational sac was visible on ultrasound at around 6 weeks.

Patients were put on Inj. Enoxaparine 40 mg subcutaneous once a day when cardiac activity was seen on ultrasound (at around 7–8 weeks). Inj. Enoxaparine was given either into anterior abdominal wall or anterior aspect of thigh subcutaneously. Compliance as evidenced from patients' interview and marks of subcutaneous injection was excellent. No woman experienced any major hemorrhagic event during pregnancy labour or post partum. Two patients developed mild unexplained vaginal bleeding which settled by expectant management. Discontinuation of medicine was not required due to hemorrhagic problems. Patients were advised to visit fortnightly.

Foetal growth was monitored by fundal height measurement and serial ultrasounds. Doppler umbilical wave flow velocity was studied for foetuses with suspected intrauterine growth retardation.

All patients were given Aspirin 75 mg daily till 35 weeks completed. Aspirin was stopped to allow Ductus Arteriosis closure and prevent bleeding in labour. Inj. Enoxaparine was given till 37 weeks and stopped thereafter to reduce risk of epidural haematoma in case patient required anaesthesia for caesarean delivery. For some patients Aspirin and Enoxaparine were discontinued earlier due to abortion, preterm labour, intrauterine growth retardation, pre-eclampsia leading to premature delivery.

Data was analysed using SPSS-13.

RESULTS

Thirty-seven patients out of 60 (62%) had aCL antibody titres raised and only 3 patients (5%) has both aCL as well as LA positive reports. Two patients (3%) tested positive for ANA. Eighteen patients (30%) showed no positive test but had very strong obstetrical history of antiphospholipid related morbidity (Table-1). Out of 60 patients, 56 patients (93%) had live birth but 4 patients (7%) had early pregnancy loss at 10-12 weeks despite treatment (Table-2).

Fifty-six patients had live birth but out of these, 42 patients (75%) were delivered at term (completed 37 weeks). Fourteen patients (25%) had preterm delivery (36 weeks 6 days to 28 weeks). Twelve patients had iatrogenic preterm delivery due to oligohydramnios, severe intrauterine growth retardation, severe pre-eclampsia or abnormal foetal doppler flow velocity. Eight patients developed severe oligohydramnios of these one showed deranged doppler and four showed intrauterine growth retardation leading to iatrogenic preterm delivery between 34–36 weeks of

gestation. Four mothers developed pre eclampsia leading to iatrogenic preterm delivery of 2 more severly affected patients between 33 and 34 weeks and between 34–36 for 2 less severely affected mothers. Two patients went into spontaneous preterm labour at 34 and 35 weeks. Of these 14 foetuses, 2 were delivered between 28–34 weeks of gestation, both required NICU care, one survived other died of respiratory distress syndrome. Remaining 12 babies were born between 34–36 weeks 6 days gestation required no NICU care and discharged with mothers without any sequlae (Table-3).

Out of 56 patients, 49 delivered by Caesarean Section due to obstetrical causes as well as maternal preference. Remaining 7 patients delivered vaginally. None of these patients experienced major obstetrical haemorrhage or wound haematoma (Table-4).

Table-1: Serological status of patients (n=60)

Serological Test	Number	Percentage
aCL Positive	37	62%
LA Positive	-	-
aCL LA Positive	3	5%
ANA Positive	2	3%
Serologically Negative	18	30%

Table-2: Outcome of pregnancies (n=60)

	Number	Percentage
Early Pregnancy Loss	4	7%
Live birth at term (37 weeks or more)	42	75%
Preterm deliveries (28 to 36 weeks and 6 days)	14	18%

Table-3: Outcome of premature deliveries (n=14)

	Number	Required NICU Care	Peri-natal death
<28 weeks	0	-	-
28–34 weeks	2	2	1
34–36 weeks & 6 days	12	-	-

Table-4: Mode of delivery (n=56)

Mode of Delivery	Number	Percentage
Caesarean Section	49	84
Vaginal delivery	7	16

DISCUSSION

Out of 60 patients selected in our study achieved 93% live birth rate. Forty-two (75%) of these had delivery at term and 18% had preterm delivery. Forty-nine (84%) patients had caesarean section while 16% had vaginal delivery. There has been a trail by Brenner *et al*, that used aspirin 75 mg daily and Inj. Enoxaparine 40–80 mg subcutaneously once daily for solitary and combined defects respectively.[17] The study included patients not only with APS but also with other thrombophilias like V-Leiden mutations, protein C and S deficiency, Live birth rate achieved was 86%, 9% had preterm delivery, 77% were delivered at term, 72% were delivered vaginally and 28% by caesarean section. Two babies died due to pre-maturity and sepsis each.

In another study conducted at Department of Obstetrics and gynaecology, University of Sheffield, England. Enoxaparin was used in 20 mg subcutaneously dose with 80% live birth rate. Five percent underwent preterm delivery but no perinatal mortality was observed. All selected patients had positive serological tests of antiphospholipid syndrome.[12]

The difference in results when compared with these studies might be due to the fact that patient in my study were not strictly those with positive serological test but also those who strongly fulfilled the clinical criteria of APS (probable APS). Though live birth rate achieved is higher in my study but percentage of preterm deliveries is also high.

CONCLUSION

Use of low dose aspirin and enoxapirin 40 mg subcutaneously daily in patient with recurrent pregnancy loss due to antiphospholipid syndrome resulted in high live birth rates compared to their previous obstetrical outcomes.

REFERENCES

1. Clifford K, Rai R. Wason H, Regon L. An informative protocol for the investigation of recurrent miscarriage, preliminary experience of 500 consecutive cases. Human Reprod 1994;9:1328–32.
2. Hatasake HH. Recurrent miscarriage:epidemiologic factors, definitions and incidence. Clin Obstet Gynecol 1994;37:625–34.
3. Brenner B, Sarig Gy, Weiner Z, Younis J, Blumenfeld Z, Lanir N. Thrombophilic polymorphisms are common in women with fetal loss without apparent cause. Thromb Haemost 1999;82:6–9.
4. Triplett DA, Harris EN. Antiphopholipid Anti bodies and reproduction. Am J Reprod Immunol1989;21:123–31.
5. Levine JS, Branch DW, Raich J. The antilospholipid syndrome N Engl J Med 2002:346:752–63.
6. Roubey RAS. Immunology of Antiphospholipid syndrome. Arthritis Rheum1996;39:1444–54.
7. Wilson W, Gharavi A, Koike T, Lockshin MD, Branch DW, Piette JC, *et al*. International consenses statement on preliminary classification criteria for definite antiphospholipid syndrome: report on an international workshop. Arthritis Rheum 1999;42:1309-11.
8. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, *et al*. International Consenses statement on an update of classification criteria for definite anti phospholipid syndromes (APS). J Thromb Haemost 2006;4:295–306.
9. Baker WF Jr, Bick RL. The clinical spectrum of Antiphospholipid syndrome. Hematol Oncol Clin N Am 2008;22:35–52.
10. Hughes GR, Khamashta MA. Seronegative anti phospholipid syndrome. Ann Rheum Dis 2003;62:1127.
11. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al*. Anti phospholipid syndrome: clinical and immunologic manifestation and patterns of disease expression in a chort of 1000 patients. Arthritis Rheum 2002;46:1019–27.
12. Mo D, Saravelos S, Metwally M, Makris M, Li TC. Treatment of recurrent miscarriage and anti phospholipid syndrome with low dose Enoxaparin and Aspirin. Reprod Biomed online 2009;19:216–220.
13. Berg TG. Antiphospholipid antibody syndrome and pregnancy. 2009. Available from: http://emedicine.Medscape.Com/article/ 261691-print

14. Ensom MH, Stephenson MD. Pharmaco kinetics of low molecular weight Heparin and unfractionated Heparin in pregnancy. J Soc Gynocol Investig 2004;11:377–83.
15. Stephenson MD, Ballem PJ, T sang P, Purkiss S, Houlihan E, Enson MH. Treatment of Antiphospholipid antibody syndrome (APS) in pregnancy: a random pilot total comparing low molecular weight Heparin to unfractionated Heparin. J Obstet Gynacol Can 2004;26:729–34.
16. Shannon M. Bates, Ian A. Grear, Jack Hirsh, Jerry S. Ginsberg use of antithrombotic agents during pregnancy. Chest J 2004;126:627–44.
17. Brenner B, Hoffman R, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in Thrombophilic women with Recurrent Pregnancy loss Treated by Enoxaparin. Thromb Haemost 2000;83:693–7.

Address for Correspondence:

Dr. Saadia Fawad, Gynaecologist Aero Hospital, Air Weapon Complex, Hassan Abdal, Pakistan.
Email: saadia1997@gmail.com