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Case Reports

Antiphospholipid Syndrome as a Cause of Recurrent Pregnancy Loss: 3 Case Reports and Successful Outcome

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Abstract:

Recurrent pregnancy loss is common problem now a days and is commonly found in our daily practice.There are so many causes that are established as causative factors for recurrent pregnancy loss. Among them systemic causes includes uncontrolled diebetes mellitus, uncontrolled chronic hypertension, hypothyroidism and local causes includes uterine polyp, uterine fibroid, cervical incompetency etc.

Anti-phospholipid syndrome has recently been found to be one of the causes for recurrent pregnancy loss and we have not yet enough study in our country regarding this problem that causes recurrent pregnancy loss.

Pregnancy with Anti-phospholipid Syndrome (APS) is rare and it is one of the important factor that causes recurrent pregnancy loss at any trimester of pregnancy. Early diagnosis and pre-conceptional precaution for prevention of recurrent pregnancy loss is essential to deliver a healthy fetus in a diagnosed case of APS.

Three cases of anti-phospholipid syndrome (APS) are reported here who have successfully deliverd healthy baby. All the cases were presented with the complaints of recurrent pregnancy loss.

Introduction:

Anti-phospholipid syndrome (APS) or anti-phospholipid antibody syndrome or Hughes syndrome, is an autoimmune, hypercoagulable state caused by anti-phospholipid antibodies. APS provokes blood clots (thrombosis) in both arteries and veins as well as pregnancy related complications such as miscarriage, preterm delivery, severe pre-eclampsia or stillbirth.The diagnostic criteria requires one clinical event, i.e. thrombosis or pregnancy complication, and two positive blood tests for antibody spaced at least 3 months apart. These antibiodies are: lupus anticoagulant, anti-cardiolipin antibody and anti-â$_2$-glycoprotein-I antibody[1].

"Primary anti-phospholipid syndrome" is used when APS occurs in the absence of any other related disease and "Secondary antiphospholipid syndrome" is used when APS occurs in the context of other autoimmune diseases, such as systemic lupus erythematosus (SLE). In rare cases, APS leads to rapid organ failure due to generalized thrombosis; this is termed "catastrophic anti-phospholipid

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syndrome" (CAPS) and is associated with a high risk of deathIn pregnant women affected by APS, miscarriage can occur prior to 20 weeks of gestation, while pre-eclampsia is reported to occur after that time. Placental infarctions, early deliveries and stillbirth are also reported in women with APS.The anti-phospholipid syndrome responsible for most of the miscarriages in later trimesters is seen in concomitant systemic lupus erythematosus and pregnancy[2].This disease is treated by giving aspirin to inhibit platelet activation, and/or warfarin as an anticoagulant. The goal of the prophylactic treatment with warfarin is to maintain the patient's INR between 2.0 and 3.0[3]

Anticoagulation appears to prevent miscarriage in pregnant women[4]. In pregnancy, low molecular weight heparin and low-dose aspirin are used instead of warfarin because of warfarin's teratogenicity. Women with recurrent miscarriage are often advised to take aspirin and to start low molecular weight heparin treatment after missing a menstrual cycle. In refractory cases plasmapheresis may be used[4].Three cases of anti-phospholipid syndrome are reported here who have successfully delivered healthy babies. All three cases presented with the complaints of history of recurrent pregnancy loss.

Case – 1:

Mrs. Humaira Binte Bashar, 32 yrs, G3P2 with 1 neonatal death, was a diagnosed case of Anti-phospholipid syndrome after her 1st pregnancy in Japan. She had history of previous 2 preterm deliveries by LSCS and one neonatal death. Her 1st baby was delivered at 32wks of gestation due to IUGR and birth weight of the baby was only 775 gm and baby died on 2nd postoperative day. She was then screened for auto-immune disease and was found that she has Antiphospholipid syndrome. She was under preconceptional counseling prior to subsequent pregnancies.

During her current pregnancy she was under joint consultation of Gynecologist and Rheumatologist. From the beginning of the pregnancy she was treated with Tab. Aspirin 75mg daily. During 1st trimester her anti-nuclear antibody was negative, anti-phospholipid antibody and anti-DSDNA antibody were positive, complement-3, complement-4 were normal, Hb conc. - 9.3gm%, glucose challenge test was normal, activated partial thromboplastin time (APTT) was 35.4 sec , prothombin time (PT), thyroid stimulating hormone, creatinine were within normal range and USG showed normal pregnancy profile with bilateral small ovarian cyst. At the beginning of 12 wks of gestation Injection low moleculer weight heparin (LMWH) was started at a dose of 60units subcutaneously daily. She was routinely monitored with the estimation of coagulation profile; APTT, PT, bleeding Time (BT) , clotting Time (CT) and complete blood count (CBC). At her 30 wks of gestation UGS reveals single live pregnancy of 29 wks 04 days with cephalic presentation with normal doppler study of uteroplacental and midcerebral arteries of the fetus.

During her 34+wks pregnancy, ultrasonogram reveals moderately low amniotic fluid index but no IUGR of the baby. She was advised to be hospitalized for better monitoring of herself and her baby. Throughout the pregnancy period she was given progesterone in oral form to prevent preterm labour as she had history of previous 2 preterm labour. After getting admission in hospital she was monitored daily with CTG and Doppler Ultrasonogram at 3 days interval. Injection LMWH was stopped on 23rd September. She underwent LSCS on 24th September due to the diagnosis of *3rd gravida with 35 wks pregnancy with APS with moderate oligohydramnios with history of previous 2 LSCS*. A male baby of 2120 gm was delivered. Apgar score of the baby was 8 in 1st minute and 9 in 5th minute. Her postoperative period was uneventful. She was treated with injectable antibiotics and analgesics. Injection LMWH was started from 1st postoperative day. Patient was discharged on her 5th postoperative day along with oral antibiotics, analgesics, anticoagulant and corticosteroids. Injectable Low molecular weight heparin was given throughout the puerperium.

Case – 2:

Mrs. Tahmina khatun, 32yrs, G2P1 with 1 neonatal death, was presented at her 13 weeks of pregnancy as a diagnosed case of pregnancy with APS. She developed eclampsia during her previous pregnancy and had to be delivered a premature baby by LSCS. The baby died due to prematurity. She was under preconceptional counseling and was screened for autoimmune disease to find out the cause of development of sudden rise of blood pressure and eclampsia. At that time it was found that her Anti – DS DNA was positive. But anti-phospholipid antibody and anti-cardiolipin abtibody were negative.

At the beginning of 2^{nd} trimester of her current pregnancy her blood pressure began to rise and she had to start antihypertensive, Tab. Labetolol 200 mg 8 hourly. At that period her Hb conc. was 9.6gm%, APTT was slightly raised 32.9 sec, serum creatinine was 1.2 mg/dl, C3 and C4 were within normal range, ultrasonogram reveals 12-13 weeks single live pregnancy with fibroid uterus and normal bilateral renal vascular flow. As she had history of preterm delivery her pregnancy was supported by oral progesterone. She was treated with injection LMWH 60 units subcutaneously daily from her 12 weeks of gestation. She was monitored routinely with coagulation profile and routine sonographic monitoring to see the fetal wellbeing.

During her 30 weeks of gestation her blood pressure was difficult to control and was treated with maximum doses of combination of antihypertensive drugs like Labetolol, calcium channel blocker and alpha methyldopa. At that time her Hb conc. was 10.7gm%, serum uric acid was 7.0 mg/dl (increased), serum thyroid stimulating hormone was 0.7microIU/ml, APTT was 30.8 second (increased), ultrasonogram revealed 28 weeks single live pregnancy with mild placental insufficiency. Her pregnancy was monitored with serial ultrasonogram.

During her 34 weeks of gestation she developed placental insufficiency and IUGR. She was advised to be hospitalized for better monitoring. After hospitalization corticosteroid was administered for foetal lung maturation and injection LMWH was stopped. At last her LSCS was done on 10^{th} December for non-reactive CTG and fetal hypoxia with history of previous 1 LSCS. A baby girl of 1.8 kg was delivered. Though the baby had IUGR yet she didn't require neonatal intensive care unit support as her reflexes were good. Patient was managed with injectable antibiotics and analgesics. Anticoagulant was administered during her 1^{st} postoperative period. Her post operative days were uneventfull and she was discharged at her 4^{th} postoperative day.

Case – 3:

Mrs. Salma, 29yrs, P0+3, at first visited for preconceptional counseling. She gave history of 3 conseceutive unexplained fetal loss. Among them two were in 1^{st} trimester and 1 was in 2^{nd} trimester. She said that she was normotensive and non diabetic during her previous pregnancies. During her investigation she was diagnosed as a case of Anti-phospholipid syndrome. Her anti-phopspholipid antibody and anti-cardiolipin antibody were positive and ANA was negative. Other antenatal investigations were found normal. At that time her coagulation profile was done and was found within normal limit.

She became pregnant after preconceptional check up. From the 7 wks of gestation her pregnancy was protected by oral and injectable progesterone and injectable LMWH and oral tab, Asprin 75mg daily. She was monitored by routine antenatal investigations along with coagulation profile and routine ultrasonogram. During her 2^{nd} trimester she developed pregnancy induced hypertension and tablet methyldopa 250 mg 8 hourly was added. Her pregnancy was uneventful with this dose of antihypertensive. At the beginning of 33wks of gestation her Doppler ultrasonogram reveals mild placental insufficiency with mild oligohydramnios. She was advised to be hospitalized for better monitoring of the foetus and the mother. But patient refused to be admitted.

During 33 wks 04 days she came with the complain of less fetal movement and got admitted herself. Injection LMWH was stopped and steroid was administered for fetal wellbeing. She was monitored with daily CTG and fetal kick count chart. Doppler ultrasonogram was done at 3 days interval. On 34 wks gestation her Doppler UGS reveals placental insufficiency. Her LSCS was done during her 34 wks 02days of gestation due to non-reactive CTG and placental insufficiency. A baby boy of 2 kg was delivered. Apgar score was 7 in 1^{st} minute and 9 in 5^{th} minute. Her postoperative period was uneventful. She was given oral Aspirin from her 2^{nd} postoperative day. Baby developed jaundice and required neonatal intensive care unit support. She was discharged at her 7^{th} postoperative day.

Discussion:

All these cases presented here were managed in a private hospital. During the period of management it was found that anti-coagulants play an important role for continuation of pregnancy in patients with Anti-phospholipid syndrome.

Anticardiolipin antibodies are associated with thrombosis at moderate to high titres (>40 GPLU or MPLU). Patients with both Lupus anticoagulant antibodies and moderate / high titre anticardiolipin antibodies show a greater risk of thrombosis than with one alone.

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder defined by the occurrence of venous and arterial thrombosis, often multiple, and pregnancy morbidity in the presence of antiphospholipid antibodies (APL) is obvious. Prematurity may also be due to the presence of APL ; however, APL do not generally display any thrombotic events on neonates. In addition, behavior and neuropsychological outcomes have also been a matter of interest, but is currently few data available. Beyond the biological influence of both maternal disease and autoimmune background, it is important to focus on the possible influence of maternal chronic illness on the neuropsychological development of her children. Whether APL exposure could have a direct effect on brain development is still being debated. In children of mothers with APS, language delays have been noted and learning disabilities were described with a higher rate than the general age-school population. Several studies were performed on children born to lupus mothers, even if maternal lupus does not seem to impair intelligence levels, it may increase the occurrence of learning disabilities and particularly dyslexia in male children.

Pregnant women with APS are an extremely high risk group for adverse maternal & fetal outcome. Treatments can improve the pregnancy outcome. Antibody titers three times the upper limit of normal and low level complement 4 may be the risk factors for pregnancy failure and treatment may be a protective factor for successful pregnancy outcome[5].

A study was conducted by Department of Rheumatology and Immunology, Peking University Third Hospital, Beijing 100191. China Study was conducted upon the clinical characteristics, laboratory profiles and the outcomes of delivery of 54 APS patients from January 2000 to March 2013, they investigated retrospectively to summarize the maternal / fetal outcome in antiphospholipid syndrome (APS) patients to evaluate the influence of treatment and to investigate the possible clinical predictors of unsuccessful pregnancy. In that study they found that , 17 pregnancies (31.4%) resulted in full term delivery, 7 (12.9%) in stillbirth, 16 (29.6%) in spontaneous abortion, 10 (18.5%) in premature birth due to eclampsia or severe preeclampsia or signs of placental insufficiency, 4 (7.4%) received therapeutic termination of pregnancy due to eclampsia or severe preeclampsia. In 27 live birth cases, 8 (29.6%) had fetal growth restriction, 4 (14.8%) were low birth weight infants, and 3 (11.1%) were very low birth weight infants. Twenty four (24) APS patients were given the treatment of aspirin or aspirin combined with low molecular weight heparin, and 30 patients received no treatment. Compared with the untreated group, the treated group had lower rate of fetal loss, higher rate of full-term delivery, increased gestational age and birth weight, decreased incidence of preeclampsia / eclampsia and thrombocytopenia. There was a significant difference between the two groups ($P<0.05$)[5].

Predictors of Pregnancy outcome in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) (PROMISSE) study[6-11] was conducted at New York. The PROMISSE study is an observational study of 700 pregnant patients, enrolled at nine major clinical centers. The purpose of the study is 1) To determine whether certain proteins (called complement split products) that can injure the healthy organs can be used to predict poor pregnancy outcome in patients with systemic lupus erythematosus (SLE) and anti-phospholipid syndrome (APS), and 2) to determine whether elevated levels of circulating antiangiogenic factors predict pregnancy complications in patients with aPL antibodies and / or SLE.

Here three cases are presented considering as rare cases with successful pregnancy outcome rather than study on a selective group of pregnant patient of anti-phospholipid syndrome. All three cases that are presented here had history of either neonatal death or still birth or unknown intrauterine fetal death or history of pre- eclampsia or eclampsia. Among these cases anti-phospholipid antibody were positive in case 1 and case 3 but anti-phospholipid antibody was negative in case 2. Anti-cardiolipin antibody was positive in case 3, but was absent in case 1 and 2. Anti-nuclear antibody was absent in all three case but Anti-DS DNA antibody was positive in case 1 only. None of these three cases were complicated with gestational diabetes mellitus. No one was presented as hypertensive patient during their preconceptional counseling period.

We consider successful pregnancy outcome in pregnant patients with anti-phospholipid syndrome as we had no foetal loss in current pregnancies. But utero-placental insufficiency develops after 34 wks of gestation in case – 2 and 3. Among these cases only in case 2 foetus developed intrauterine growth restrictions and in case- 3 baby required neonatal intensive care unit for hyperbilirubinaemia. But all the presented cases had successful pregnancy outcome irrespective of high risk pregnancies.

Conclusion:

Antiphospholipid syndrome is an important cause of recurrent pregnancy loss. So patients with history of recurrent pregnancy loss should be investigated for APS. preconceptional counseling along with prophylactic anticoagulant therapy can prevent fetal loss, maternal morbidity and provokes successful pregnancy outcome.

References:

1. “Aps | Action”. Apsaction.org. Retrieved 2013-11-06.
2. Lupus and Pregnancy by Michelle Petri. The Johns Hopkins Lupus Center. Retrieved May 2011
3. Horton JD, Bushwick BM. “Warfarin therapy: evolving strategies in anticoagulation”. *American Family Physician* 1999;59(3): 635–46.
4. De Jong, P. G.; Goddijn, M.; Middeldorp, S. “Antithrombotic therapy for pregnancy loss”.*Human Reproduction Update* 2013;19(6): 656–673.
5. Zheng XJ, Deng XL, Liu XY. Pregnancy outcome in 54 patients with antiphospholipid syndrome: a retrospective clinical study. Journal of Peking University. Health Science. 2014;46(2):323-328
6. Lockshin MD, Kim M, Laskin CA, Guerra M, Branch DW, Merrill J, Petri M, Porter TF, Sammaritano L, Stephenson MD, Buyon J, Salmon JE. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum. 2012;64(7):2311-8. doi: 10.1002/art.34402.
7. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004;10(11):1222-6. Epub 2004 Oct 17.
8. Girardi G, Berman J, Redecha P, Spruce L, Thurman JM, Kraus D, Hollmann TJ, Casali P, Caroll MC, Wetsel RA, Lambris JD, Holers VM, Salmon JE. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest. 2003;112(11):1644-54.
9. Holers VM, Girardi G, Mo L, Guthridge JM, Molina H, Pierangeli SS, Espinola R, Xiaowei LE, Mao D, Vialpando CG, Salmon JE. Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. J Exp Med. 2002;195(2):211-20.
10. Michael D Lockshin, Cohn E, Aslam A, Buyon JP, Salmon JE. Sex ratios among children of lupus pregnancies. Arthritis Rheum. 2013;65(1):282. doi: 10.1002/art.37718.
11. Salmon JE, Heuser C, Triebwasser M, Liszewski MK, Kavanagh D, Roumenina L, Branch DW, Goodship T, Fremeaux-Bacchi V, Atkinson JP. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. PLoS Med. 2011 Mar;8(3):e1001013. doi: 10.1371/journal.pmed.1001013. Epub 2011 Mar 22.