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Case Report

Successful pregnancy outcome in grade IV lupus nephritis and secondary antiphospholipid antibody syndrome with recurrent pregnancy failures - challenging achievement of motherhood

Kaliki Hymavathi Reddy*, Kolla Praveen Kumar, Surekha Tadisetti, Divya Pusarla

Department of Obstetrics and Gynaecology, Narayana Medical College and Hospital, Nellore, Andhra Pradesh, India

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***Correspondence:**
Dr. Kaliki Hymavathi Reddy,
E-mail: dr.hymakrreddy@gmail.com

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that occurs predominantly in women of childbearing age. The risk of complications and adverse fetal outcomes in pregnant women with lupus is high viz., increased risks of preterm birth, hypertensive diseases of pregnancy and lupus flares both during pregnancy and in the postpartum period. An additional association with Antiphospholipid antibody (APLA) syndrome is expected to multiply the pregnancy complications. Though improved understanding of the disease nature and greater number of therapeutic options in the treatment of SLE, made the medical community regard these patients with less trepidation, the risk of significant morbidity to both the mother and the fetus still exist. We report an interesting case of grade IV Lupus nephritis (LN) with secondary APLA syndrome and h/o recurrent pregnancy failures for twenty times but had a successful pregnancy and delivery in the 21st attempt though pregnancy was absolutely contraindicated in view of her medical illness. Many complications were encountered during her pregnancy which could be successfully tackled and a live male baby was delivered by Caesarean section.

Keywords: Grade IV lupus nephritis, Recurrent pregnancy failure, Secondary antiphospholipid antibody syndrome

INTRODUCTION

An autoimmune disease occurs when a sustained, specific, adapture immune response is generated against self-components and results in tissue damage or dysfunction.[1] Systemic lupus erythematosus is one such autoimmune disease in which organs, tissues and cells undergo damage mediated by tissue-binding auto antibodies and immune complexes.[2] Here is an interesting rare case of grade IV LN with secondary APLA syndrome with innumerable number of pregnancy failures (20 times) but had a live baby through her 21st pregnancy!!

CASE REPORT

Mrs. X, a 38 year old lady, housewife belonging to lower middle class has attended the antenatal out-patient department of Narayana Medical College and Hospital (NMCH) - a tertiary care center, Nellore, Andhra Pradesh, India with c/o 2 months amenorrhea and history of irregular periods. Pregnancy was suspected and confirmed by pregnancy test.

She is a known case of Grade IV LN with secondary APLA syndrome and was advised both by her Obstetrician and Nephrologist not to conceive as pregnancy will be detrimental to her life due to her medical illness. She also gave a history of being non-compliant with her treatment.

Past obstetric history: She got married at 15 years of age (third degree consanguinity). She is G21 P6D6A14L0. All were spontaneous conceptions.

1st and 2nd pregnancies: H/o intrauterine deaths (IUD) at 7 and 7 ½ months gestation and vaginal delivery of dead babies at a rural hospital near her village.

3rd to 16th pregnancies: H/o early miscarriages at 3rd and 4th months of gestation with an exception of 5th, 8th, 13th and 14th pregnancies which were IUDs at around 6 to 7 months of gestation. H/o all pregnancies being confirmed by pregnancy test and Ultrasonogram (USG). Fetal cardiac activity noticed initially, became absent in some of the pregnancies (missed abortions), others being spontaneous miscarriages. For all these she attended to different rural hospitals near her village. She was not investigated for these repeat miscarriages or IUDs. Evacuation of retained products of conception (ERPC) was done only in four instances as per her history.

17th pregnancy: She had vaginal spotting and fever at 4th month of gestation for which she was taken to a tertiary care hospital in Chennai. Having got investigated there, she was diagnosed as a case of? Advanced kidney disease and the couple were also made aware of the absolute need for termination of that pregnancy. With a strong desire to continue the pregnancy she left the hospital against medical advice and was later brought to the emergency department of NMCH with high fever and in a morbid state. There were no authentic medical reports available with her. As she was pregnant with vaginal spotting, case was referred to the Obstetrician and was admitted as a case of threatened abortion in the Obstetric intensive care unit. Specific investigations for bad obstetric history (BOH) revealed positive Antiphospholipid antibodies (APLAs), Anti double stranded DNA (anti dS-DNA) and antinuclear antibodies (ANA) in addition to abnormal renal function tests. Case was referred to the Nephrologist and fever could be controlled only after administration of parenteral steroids in addition to antibiotics. During this fever episode itself she had a spontaneous miscarriage of this pregnancy also. After her condition was reasonably stabilized, renal biopsy was performed and a final diagnosis of grade IV LN with secondary APLA syndrome was made and was under the care of Nephrologist for her medical condition.

18th and 19th pregnancies: She attended to NMCH during her 3rd month of these pregnancies and the same terminated with a diagnosis of missed abortions. She was also found to have elevated renal parameters and significant proteinuria. The couple was again counselled about vasectomy or tubectomy stressing that pregnancy would be harmful to her life.

During her subsequent follow ups she was found to be compliant with the treatment and was in remission.

21st pregnancy: She landed up with history of 2 months amenorrhea and a positive pregnancy test report. She gave history of another spontaneous miscarriage (i.e., 20th pregnancy) at 3rd month of gestation prior to the index pregnancy about 8 months back. Due to her existing medical problems, the couple was again counselled about the risks involved in continuation of pregnancy and advised termination. At this juncture, her husband has expressed his family's (including him) wish for his second marriage to have children for which she was very much against and she expressed her strong desire to continue this pregnancy despite the fact that it might lead to a fatal maternal outcome following which she was registered as a high risk pregnancy (Antenatal booking).

Family history: She is born to parents of second degree consanguineous marriage. Father has ?kidney disease. She is the third in the family and other two siblings are healthy. Personal history: Nil relevant

On clinical examination: She was moderately built and nourished. Vitals: within normal limits (WNL). P/A: nil relevant. Blood investigations: Routine antenatal investigations along with glucose challenge test (GCT), Thyroid profile were WNL but for mild anemia (Hb-9 g/dl). Blood Group and typing - "B" Rh Positive. Serum Creatinine (S.Cr)- 1.4 mg/dl, Platelet count - 1.5 Lakhs / cumm, Coagulation Profile: PT - 18.9 sec (control 13.2 sec), INR- 1.40, APTT- 50.7 sec (control 30.8 sec), APLA Screening- positive, anti-ds-DNA-positive, ANA-Positive. Urine: Proteinuria 1 +, 24 hrs urine protein-460mg. Obstetric scan: Single live intrauterine fetus - 6 weeks gestation, fetal cardiac activity present.

She was started on Tab. Folic acid 5mg/day. Inj. Human Chorionic Gonadotropin (HCG) 5000IU IM twice weekly, Inj. Heparin 5000 IU SC BD and Tab. Ecosprin 75mg/day. She was also kept on immunomodulator Tab. Azathioprine (50mg/day) and Tab. Prednisolone (10mg/day) following Nephrology referral.

At 13 weeks of pregnancy markers for Down's syndrome were normal. As she was anemic (Hb-6g/dl), two units of compatible packed cells were transfused followed by oral Iron therapy and dietary advice. At 16 weeks of pregnancy there was not much of improvement in her Hb% (8g/dl) despite her good compliance with medication. Therefore Hb electrophoresis was done and hemoglobinopathies were excluded. It was then decided to give parenteral Iron sucrose and implemented.

At 17 weeks gestation she suddenly started c/o back pain. Ultrasonogram (USG) was done to look for any cervical insufficiency. There was evidence of cervical shortening (2cm) and positive beaking sign. Clinical examination confirmed the scan findings and cervical Cerclage (Mc Donalds) done. Inj. Proluton depot 500mg IM given fortnightly thereafter stopping the HCG injections. Another two units of packed cells were transfused as her Hb was only 7g/dl.

At 20 weeks, anomaly scan revealed to be normal.

At 22 weeks she developed pregnancy induced hypertension (PIH) with blood pressure of 150/100mm

Hg. Renal function tests were found to be impaired as evidenced by elevated S.Cr-3.8mg/dl and elevated proteinuria (1.2g/day). Coagulation profile deranged. Then treatment was started with the well tried drug Tab Methyldopa 500mg twice daily. Two units of packed cells were transfused during this visit as her Hb was 7.2gm%.

At 25 weeks of gestation, she had an attack of Varicella Zoster for which she was started on Tab. Acyclovir 400mg BD for one week.

At 29 weeks, there was clinical suspicion of fetal intrauterine growth restriction (IUGR) and was confirmed by USG. There was a growth lag of 2-3 weeks with amniotic fluid index (AFI) of 8 cms. Doppler study was found to be WNL. Since her blood pressure was persistently high Tab Labetolol 100 mg BD was started along with Methyldopa 500mg TID. At this juncture, coagulation profile which is getting done periodically showed elevated APTT (64/30.8) and low platelet count (90,000cells/cumm) which could be attributed to Heparin administration. Due to the alteration in the coagulation profile, we intensified monitoring these parameters so as to reduce Heparin dose if situation demands. Rest of the treatment was continued as before.

At 30 weeks gestation her repeat Hb was found to be very much lowered (6 gm%) and urine examination showed plenty of pus cells, bacteriuria with microscopic haematuria for which she was started on oral antibiotic guided by culture sensitivity report and 3 units of compatible packed cells transfused.

At 32 weeks, she developed severe hypoalbuminemia with facial puffiness for which she received 2 units of human albumin infusions.

At 33 weeks gestation, fetal Doppler velocimetry was found to be abnormal. Coagulation profile was same as before with increased APTT (67/30.8) with further reduced platelet count (70,000 cells/cumm) but without bleeding manifestations. Betamethasone injections were given anticipating the need for pregnancy termination. Since her Hb was still found to be very low, again 2 units of packed cells were transfused. Likewise a total of 11 units of packed cells were transfused during pregnancy in an attempt to improve her anemia.

At 33weeks 6 days gestation Doppler study revealed absent end diastolic flow waves in the umbilical artery. AFI was 5 cm with reactive non stress test (NST). Coagulation profile was still showing raised APTT with low platelet count (55,000 cells/cumm). Since it was decided to terminate her pregnancy (i/v/o her Doppler findings and decreased AFI), Heparin and Aspirin were withheld and case referred to Anaesthetist for surgical fitness. Anaesthesiologist opined that case could be taken up for surgery once coagulation profile becomes near normal. Since there is an impending need for delivery, three units of fresh frozen plasma (FFP) were transfused. 36 hours after the transfusion of FFPs, APTT (52/30.8) and platelet levels (75,000cells/cumm) became satisfactory. Case was posted for Caesarian section and a live male baby (Berth weigh 2 kg) with Apgar score of 6 delivered. There were no notable adverse intra-operative events. Post operatively she was kept in high dependency unit and 4 units of FFP were transfused in the immediate post op period to maintain the coagulation profile. In the postpartum period patient had a lupus flare with significant proteinuria and elevated renal parameters. She was started on Acitrom 2mg/day, mycophenolate mofetil (MMF) 360mg BD and Telmisartan 40 mg/day additionally. Mother and baby discharged in good condition.

This is no doubt a challenging case of pregnancy to the attending clinician - grade IV LN and secondary APLA syndrome with recurrent pregnancy failures. Apart from the existing medical problem many other complications were encountered during her pregnancy like preeclampsia, severe IUGR, varicella infection, altered coagulation profile, anemia, hypoalbuminemia and severe UTI. All these have been successfully managed making her a blissful mother.

DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic multi-organ autoimmune disease with a predilection for women of reproductive age. Pregnancy and its outcome is a major concern to most SLE patients requiring a multidisciplinary approach.

Lupus nephritis (LN) is classified into 6 grades[3] according to International Society of Nephrology/ Renal Pathology Society (ISN/RPS) as follows:

Grade I - Minimal mesangial lupus nephritis

Grade II - Mesangial proliferative lupus nephritis

Grade III - Focal lupus nephritis

Grade IV - Diffuse segmental (IV-S) or global (IV-G) lupus nephritis.

Grade V - Membranous lupus nephritis

Grade VI - Advanced sclerosing lupus nephritis.

Classes I, II, V are known to have low activity and chronicity indices whereas classes III and IV tend to be more aggressive and are associated with increased incidence of LN flares (WHO and ISN/RPS classification).[4,5] In our patient renal biopsy revealed grade IV LN involving >50% glomeruli showing segmental or global proliferation.

The Antiphospholipid syndrome is defined by the presence of antiphospholipid antibodies (APLA) in association with vascular thrombosis (arterial/venous) and/or recurrent abortions in women. APLAs can be present in people with or without autoimmune disorders and referred to as secondary or primary APLA syndrome respectively. In our case APLA test is found to be positive and as it is associated with LN, considered as secondary APLA syndrome.

Fecundity in SLE remains undiminished with the exception of patients having APLA syndrome or advanced renal insufficiency (i.e., creatinine >3 mg/dl) or those treated with cytotoxic alkylating agents.[6] In our case fertility potential is not affected at all, despite having advanced grade IV LN with secondary APLA syndrome as all her pregnancies were spontaneous conceptions.

Table 1: Gist of investigations (preconception to postpartum).

	Pre-conception	6 wks	17 wks	22 wks	29 wks	33 wks	postpartum
CUE	Albumin: trace	1+	1+	2+	2+	2+	Trace
	RBC's: 1-2	4-6	4-6	6-8	8-10	8-10	occasional
Hb %	10gm%	9gm%	8gm%	8.8gm%	8 gm%	7gm%	8.7gm%
S. creatinine (mg/dl)	1.3	1.4	1.9	3.8	2.4	2.0	1.62
APTT	42/30.8	50.7/30.8	52/30.8	56/30.8	64/30.8	67/30.8	56.2/30.8
Platelet count (per cu mm)	2,15,000	1,50,000	1,50,000	1,20,000	90,000	70,000	1,20,000
24 hr. urine protein	180 mg/day	460mg/day	640mg/day	1.2gm/day	1.4gm/day	1.8gm/day	1.2 gm/day
ANA	Positive	-	-	Positive	-	-	-

The prognosis for both mother and child is best when SLE has been quiescent and when renal disease in remission for at least six months prior to the pregnancy.[7] In our case, may be due to her noncompliance with prescribed treatment it appears that the disease was never quiescent for a considerable time, thus may be contributory to the repeated pregnancy failures.

Patients with Anticardiolipin's and/or a positive Lupus anticoagulant are at increased risk for flares.[8,9] Hence a comprehensive pre-pregnancy screen should include lupus serology, serum complement levels, APLAs and anti-Ro/SSA as well as anti-La/SSB antibodies. Though our patient had come after the confirmation of index pregnancy still all tests viz., APLA screening, anti-dS-DNA and ANA tests were done and found positive. Serum complement levels (C3, C4) were low and anti-Ro/SSA, anti-La/SSB antibodies were negative. Our patient also has encountered flares in the current pregnancy despite the fact that she has been on immunomodulator - Azathioprine from the early weeks of gestation.

Lupus pregnancy is associated with high rate of obstetrical and fetal complications. These include hypertensive disorders of pregnancy, spontaneous abortions, late miscarriages, IUGR, preterm delivery, prematurity and IUD with overall fetal loss of 50% in unplanned vs. 13% in planned pregnancies[10]. APLAs also confer increased risk of thrombosis (placental vasculopathy) in the mother and severe early onset of pre-eclampsia leading to fetal intrauterine growth restriction and death.[11-13] Extra renal manifestations of lupus will also affect pregnancy outcomes.[14] In our case, excluding the index pregnancy outcome, the fetal loss is almost 100%. In the present pregnancy also she developed severe PIH (with BP-160/110) and late onset IUGR (28 weeks) despite the preventive measures being taken from early pregnancy itself but could be successfully managed.

In SLE, pregnancy outcome is influenced by various factors viz., pre-conceptional lupus activity, the severity of renal involvement, relapse of SLE during pregnancy and presence of APLAs with resultant placental dysfunction. A previously complicated pregnancy by itself is an important adverse prognostic variable[15.] In our case the innumerable number of previous pregnancy mishaps and her present renal and hematological parameters made us anticipate a probable impending adverse prognosis of the index pregnancy also thus creating a real dilemma about the case management.

Chronic renal failure is also associated with hypertensive disorders and miscarriages, the risk of which increases sharply in women with serum creatinine levels of over 3mg/dl.[16] In our case also, though initially her S. Cr was around 1.4-1.8 mg/dl the levels have increased to 3.8mg/dl in mid pregnancy with the onset of

preeclampsia but no renal failure has sent in may be due to adequate precautions and treatment.

As mentioned before, pre-eclampsia is more likely in patients with APLA syndrome and steroids also will typically aggravate pre-eclampsia.[17] Many studies reported that antiplatelet agents, especially low to moderate doses of Aspirin, were used to prevent pre-eclampsia in high-risk patients.[18] Our patient was also started on a low dose of Aspirin (75mg/dl) as a preventive measure immediately after noting the fetal cardiac activity by USG but even then she developed PIH (probably due to the oral steroids) and thus started on anti-hypertensives.

It is important to rule out APLA syndrome in any case with recurrent pregnancy failures as this diagnosis would alter pregnancy care as well as be an indication for Heparin use. With the use of low-dose Aspirin and Heparin live birth rates have found to be almost doubled. Along with LN, since our patient was also found to have secondary APLA syndrome Heparin was started from early pregnancy itself.

In these cases availability of renal biopsy report may facilitate the initiation of disease-specific treatment, rather than empirical treatment, which can be advanced postpartum to include immunosuppressive agents that are otherwise contraindicated during pregnancy.[19] In our case definitive diagnosis of grade IV LN was already made by renal biopsy. The advantage of having a pre-pregnancy (index pregnancy) renal biopsy report could be made useful in starting specific treatment with Aspirin, Heparin and Azathioprine in early pregnancy itself with an intention to evade the expected adverse outcomes.

Decision regarding the timing and mode of delivery should be made in conjunction with an Obstetrician with experience in managing labor in the setting of renal disease. Delivery may be best in a tertiary care centre where Neonatologists are available, particularly if a patient is likely to deliver before 37 weeks of gestation. Caesarean section should be reserved for obstetrical indications. In our case, she was delivered by elective Caesarean section (33 weeks) in a tertiary care centre (NMCH) where expertise is available in all the concerned fields.

If the patient is breastfeeding, consideration should be given to the safety of immunosuppressive medications for the infant. The patient should be followed postpartum with regular visits, because LN flares may occur. Since our patient had a lupus flare in the postpartum period with significant proteinuria and elevated renal parameters she was started on MMF, Acitrom and Telmisartan.

Fetal and neonatal morbidity and mortality may also be increased in pregnancies complicated by LN and APLA syndrome. Children born to mothers positive for anti-SSA/Ro and anti-SSB/La antibodies are at risk for congenital heart blocks. These pregnancies should be monitored by fetal cardiac auscultation, echocardiography and neonatal electrocardiography after delivery.[20] In our case, the above said antibodies were found to be negative in the antenatal investigations. Even then during pregnancy and after delivery fetal Echocardiography done to rule out the above mentioned congenital heart blocks and not found to have any such.

CONCLUSIONS

Pregnancy with severe grades of LN continues to pose a major challenge to the attending clinicians. With the technological advancements in the monitoring and the treatments, attaining motherhood in such women can become a dream come true. Close surveillance throughout pregnancy with a mind on the anticipated problems, their prevention, detection and treatment in the appropriate time may result in fruitful maternal and fetal outcome.

The goals of therapy should be to maintain the mother in disease remission, provide prophylaxis against the APLA associated thrombotic complications, prevent and treat hypertension and pre-eclampsia as well as optimize fetal growth and wellbeing.

Indeed weighing the potential benefits of treating active disease against the risks of therapy induced side effects often represents the greatest dilemma. Under the watchful eye of the Obstetrician in collaboration with the Nephrologist, these women can successfully have children and fulfil their maternal desire.

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