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Research Article

Autoimmune diseases in pregnancy: maternal and fetal outcomes

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ABSTRACT

Background: The aim of this study was to assess the impact of autoimmune connective tissue disorders on the outcomes of pregnancy and the influence of treatment on pregnancy.
Methods: Thirty-seven antenatal patients with autoimmune connective tissue diseases, comprising of Systemic Lupus Erythematosus (SLE), primary antiphospholipid antibody syndrome (APS), Mixed Connective Tissue Diseases (MCTD), ankylosing spondylitis and Takayasu arteritis were analysed.
Results: Multigravidas constituted 89.4% and were associated with bad obstetric history. Before diagnosis and treatment, serious maternal complications of eclampsia and thromboembolism were observed in patients with SLE and APS. The live birth rates were 9% and 2.4% respectively in patients with SLE and APS. With appropriate treatment- aspirin, heparin and immunosuppressant, the live birth rates were raised to 70% in SLE and 100% in APS patients. Investigation for autoimmune disease in recurrent pregnancy loss is important. A rare association between MCTD and congenital anomaly - Rhizomelic chondrodysplasia punctata was observed. Preeclampsia, gestational diabetes, fetal growth restriction and preterm labour were the common complications noted.
Conclusions: Active disease at onset of pregnancy, presence of Anti-ds DNA antibodies and secondary APS were strong predictors of poor pregnancy outcomes among patients with SLE. Vigilant monitoring during pregnancy is required for favourable outcomes.

Keywords: Autoimmune diseases, SLE in pregnancy, Antiphospholipid antibody syndrome, Mixed connective tissue diseases, Recurrent pregnancy loss

INTRODUCTION

Autoimmune diseases are chronic multi-system disorders, predominantly affecting females of child-bearing age. With improvements in diagnostic and treatment modalities, the survival and quality of life of these patients have been improving. Hence, pregnancy is becoming common among patients with autoimmune disorders. The hormonal alterations associated with pregnancy produce immunological variations in the course of the disease. Some conditions may improve while others remain relatively unchanged or may worsen during pregnancy. Nevertheless, the pregnancies in these women are particularly at high-risk because of the long lasting implications of these disorders on both the mother and fetus. Furthermore, pregnancy outcome may also be threatened by multiple organ involvement and the presence of auto-antibodies. Hence, pregnancy in autoimmune diseases was considered as a taboo in the past. The situation has undergone a dramatic change. Adequate preconceptional counselling, vigilant surveillance and interdisciplinary care during pregnancy, with the involvement of the obstetrician and rheumatologist are imperative for optimal management.

The aim of the present study was to assess the impact of autoimmune connective tissue disorders on maternal and fetal outcomes. The study has also intended to portray the

influence of treatment on the course of pregnancy in autoimmune diseases.

METHODS

We performed an observational analysis of thirty-eight antenatal patients with autoimmune connective tissue diseases, who were followed during their current pregnancies at the department of obstetrics and gynaecology in a tertiary care hospital. Patients with Systemic Lupus Erythematosus (SLE), primary antiphospholipid antibody syndrome (APS), Mixed Connective Tissue Diseases (MCTD), ankylosing spondylitis and Takayasu arteritis were included in the study.

RESULTS

Thirty-eight patients with autoimmune diseases were studied. The mean age of the patients was 29.3 ± 4.7 years and the mean age at the time of diagnosis was 26.9 ± 4.9 years. The mean duration of the disease prior to the current pregnancy was 4.8 ± 2.2 years. The demographic profile of the patients' is depicted in Table 1. Patients with first pregnancy were three (4/38=10.5%), those with second pregnancy were twelve (12/38=36.8%), with third pregnancy were fourteen (14/38=37.8%), with fourth and fifth pregnancy were five (5/38=13.1%) and two (2/38=5.3%) respectively. There was one patient with seventh pregnancy. It was not surprising to point out that all the multigravidas had bad obstetric outcomes in past.

Table 1: Patient characteristics.

Parameters	Systemic lupus erythematosus (n=11)	Primary antiphospholipid antibody syndrome (n=19)	Mixed connective tissue disease (n=5)	Ankylosing spondylitis (n=2)	Takayasu arteritis (n=1)
Age (years)	26.6 ± 4.5	30.5 ± 5.8	29.8 ± 4.5	30 ± 1.2	35
Age at diagnosis(years)	24.3 ± 6.2	28.6 ± 2.6	22.6 ±6.7	26.6 ± 4.5	30
Primigravida	1	-	3	-	-
Multigravida	10	19	2	2	1
Total pregnancies	23	41	4	4	1

Before diagnosis and treatment

Pregnancies had occurred in the thirty-eight, before the diagnosis of their specific autoimmune diseases. There were 23 pregnancies in the 10 patients with SLE. There were 41 pregnancies in the 19 patients who were later diagnosed with primary APS. There were 2 pregnancies, each in patients diagnosed with mixed connective tissue disease and ankylosing spondylitis, while 1 prior pregnancy in the patient with Takayasu arteritis.

Maternal complications

Medical and obstetric complications were frequently observed in patients with SLE and APS syndromes, while those with the other three disorders carried through pregnancy without developing any serious complications.

Recurrent pregnancy loss inclusive of fetal demise was observed in every other patient with SLE and APS. Preeclampsia was frequently observed among patients with SLE and Primary APS, which often progressed into severe sequelae such as, eclampsia and HELLP syndrome. Early onset eclampsia occurred in two SLE patients. Lupus nephritis and deep venous thrombosis during puerperium were among the other complications seen.

Favourable pregnancy outcomes were observed in 34 (89.4%) pregnancies. The mean birth weight of liveborn was 2535 ± 438g and the mean gestational age was 36.5 weeks (range: 32-39 weeks). The neonatal admission rate was 34.2% (13 out of 38) for prematurity and low birth weight.

Systemic lupus erythematosus

Prior to the diagnosis of SLE, there were eighteen gestations which were either lost or terminated in the first and second trimesters. Two pregnancies were terminated due to renal flare. Only four pregnancies reached the third trimester; early onset eclampsia occurred in two among them with only baby salvaged. The third had unexplained fetal demise at 30 weeks. The fourth was successful and delivered at term. Two patients developed deep venous thrombosis during puerperium.

With treatment, there was no first trimester loss, three second trimester losses ; one due to lupus flare. Eight pregnancies (72.7%) were successfully carried to the third trimester; preeclampsia and gestational diabetes mellitus, probably steroid induced were the most frequently noted maternal complications. There was no case of eclampsia or thromboembolism.

All the eight pregnancies had live births by Caesarean section; 2 (25%) patients had term delivery and 6 (75%) patients had preterm delivery. Among the patients who had preterm delivery, two patients presented with preterm prelabour rupture of membranes at 34 weeks each, two patients had fetal growth restriction with Doppler changes at 35 weeks and one patient had abruption at 30 weeks. All the babies born preterm, had survived, though three of them required neonatal intensive care for prematurity. Poor obstetric outcomes of intrauterine fetal demise and missed abortion were noted in 3 out of 23 pregnancies (13%).

We attempted to study the effects of known risk factors and associations that would adversely affect the outcome of pregnancy.

In our study, there were two patients with active lupus nephritis disease at the initiation of pregnancy. One among them had received pulse therapy of cyclophosphamide in the preceding 6 months of pregnancy. She presented to us only at 18 weeks and was on immunosuppressants but was not initiated on heparin or aspirin. She developed early onset fetal growth restriction followed by fetal demise. The other patient had active disease and received ten pulses of cyclophosphamide therapy. She conceived in the same cycle as the last dose. She was booked only at 12 weeks and started on aspirin and heparin immediately as she was positive for anti- phospholipid antibodies. She developed lupus flare during pregnancy and received pulse therapy with steroid. She had early onset preeclampsia and abruption at 30 weeks. The baby survived with prolonged neonatal care. Two more patients with nephritic renal changes but in remission were also enrolled in our study. They were followed from the beginning of their pregnancy and treated with aspirin and heparin. Both of them had favourable outcomes.

We sought to study the antibody pattern in clinical complications:

Anti-ds DNA antibodies were positive in seven (63.6%) out of eleven patients. It was analysed that only patients who had medium to high titres of Anti-ds DNA antibodies developed lupus flare during their past or present pregnancy. No instance of flare was seen in the absence of Anti-ds DNA antibody. Three patients with high titres of Anti-ds DNA antibodies had preterm prelabour rupture of membranes.

Anti-SSA (Ro) antibodies were noted in four patients. In three patients, they were associated with fetal demise, either second trimester missed abortion or intrauterine fetal death. No case of congenital heart block was seen.

We studied the significance of antiphospholipid antibodies (Secondary APS) in SLE patients. In our series, four among the eleven patients had APS antibodies and none carried their pregnancies up to term. Two pregnancies were terminated due to missed abortion; one among them had presented to us at 16 weeks with lupus flare and pregnancy culminated as missed abortion. Two patients, who had preterm delivery due to PPROM and preeclampsia with fetal growth restriction, associated with Doppler changes were booked with us and adequately treated. In contrast, SLE patients without associated APS antibodies had better fetal and neonatal outcomes. Two among them had thromboembolic manifestations in the puerperium during their previous pregnancies. These patients had no thromboembolic accidents in their current pregnancy as they received anticoagulants during antenatally and in the puerperium. No case of thrombosis was seen in SLE patients in the absence of secondary APS syndrome.

Hashimoto's thyroiditis was a common accompaniment, noted in four patients (33.4%).

Primary anti-phospholipid syndrome

Forty one pregnancies have occurred before the diagnosis. The first trimester and second trimester losses, either spontaneous or induced accounted for 78% (32/41). Among the remaining nine patients, who reached the third trimester, preeclampsia and its sequelae was the notable complication observed in five patients. There were eight perinatal losses, comprising of one stillbirth (pregnancy was terminated at 28 weeks due to HELLP) and seven intrauterine deaths; one was due to severe fetal growth restriction at 32 weeks, two were due to Abruptio placentae at 30 weeks each and one due to the same cause at 36 weeks. Three fetal demises were unexplained and occurred at 30, 35 and 36 weeks. There was only one live birth.

Table 2: Incidence of complications in patients with SLE and Primary APS in the present pregnancy.

Complications	SLE n (%)	Primary APS n (%)
Preeclampsia	7 (36.8)	6 (31.6)
Imminent eclampsia	Nil	1 (5.3)
Gestational Diabetes	4 (21.1)	3 (15.8)
Fetal growth restriction	3 (15.8)	4 (21.1)
Oligoamnios	Nil	3 (15.8)
Abruption	1 (5.3)	Nil
Preterm delivery	3 (15.8)	4 (21.1)
Anemia	4 (21.1)	4 (21.1)
Thrombocytopenia	2 (10.5)	6 (31.6)
Lupus flare	2 (10.5)	Nil

Following diagnosis and effective treatment, all the nineteen patients were successful to enter third trimester. None had eclampsia, abruption or thromboembolic accidents. All but four patients were delivered at term. The patients who had preterm delivery, one presented with preterm prelabour rupture of membranes, the other

two had fetal growth restriction with fetal distress and the last due to imminent eclampsia. Only three patients had vaginal delivery while the rest were delivered by caesarean.

A comparison of the maternal complications, developed in patients with SLE and APS are presented in Table 2.

Other autoimmune diseases

Three patients with mixed connective tissue disease had term deliveries, while one had preterm delivery due to PPROM. One patient was diagnosed with a rare congenital anomaly - Rhizomelic chondrodysplasia punctata and pregnancy was terminated at 18 weeks.

The three patients with ankylosing spondylitis and Takayasu arteritis had live babies, delivered at term.

It is noteworthy to point out that treatment from early gestation in patients with SLE and primary APS syndrome had dramatically improved the pregnancy outcomes. The rate of abortions had fallen by 6 times in SLE patients with effective treatment. There were no abortions or fetal demise among patients with primary APS. The live birth rate had increased to 70% and 100% in patients with SLE and Primary APS respectively, with treatment. The fetal outcomes of patients with SLE and APS are presented in Figures 1 & 2.

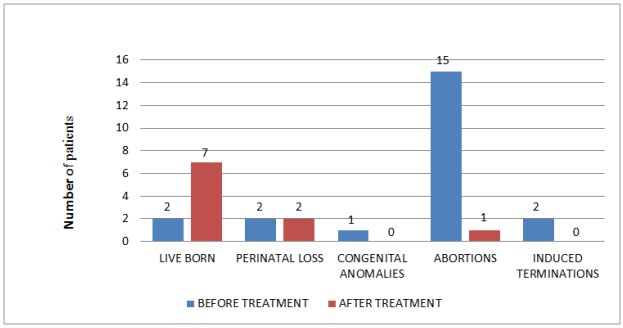

Figure 1: Comparison of fetal outcomes before and after the initiation of treatment in patients with SLE.

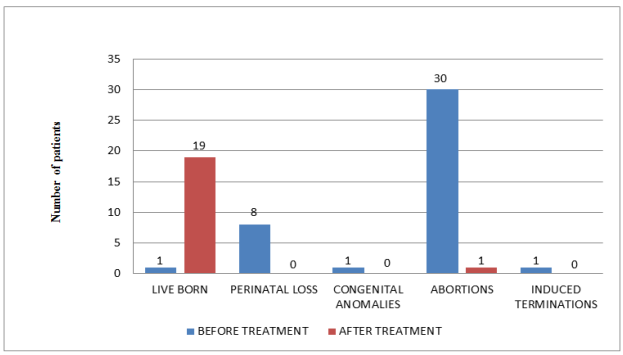

Figure 2: Comparison of fetal outcomes before and after the initiation of treatment in patients with primary APS.

DISCUSSION

Autoimmune disorders in pregnancy pose many difficult situations for the treating obstetrician during diagnosis and treatment.

Diagnosis of autoimmune conditions in pregnancy remains a challenging task due to common symptoms and signs of pregnancy masquerading the manifestations of diseases such as SLE. Generalized fatigue, weakness, skin changes, anemia and thrombocytopenia are common to both. Similarly, raised ESR and altered complement levels may add to the existing diagnostic confusion, finally leading to late diagnosis beyond irreparable damage or missed diagnosis. Reliable distinction between lupus flare and preeclampsia also becomes cumbersome since many features are common to both, such as thrombocytopenia.

Treatment likewise is not an easy task. Pregnancy influences the pharmacokinetics of drugs, causing unpredictable absorption due to delayed gastric emptying and vomiting, variable drug levels and increased renal clearance. The immunosuppressants may need to be modified in order to avoid the teratogenic risk to the fetus in early gestation. The disease per se is not stable during pregnancy and its course oscillates between exacerbation and remission due to the pregnancy induced influences on the immunology. Steroids, which are the cornerstone for management may aggravate maternal hypertension, diabetes and may even cause fetal growth restriction.

SLE Disease Activity Index scoring system, which identifies flare, is not applicable in pregnancy. A modification of the score was proposed by Buyon et al.,[3] which takes the physiological changes of pregnancy into consideration and is realistic.

Pregnancy in patients with autoimmune diseases is at high risk. Vigilant monitoring of antenatal patients averts many maternal and fetal complications. Close fetal surveillance improves outcome.

Women with SLE have more comorbid conditions such as pregestational diabetes, and hypertension,[4] as did the patients in our series. The routine use of prednisolone throughout pregnancy is controversial.[5] Pregnancy seemed to be associated with favourable outcomes, when SLE patients conceive while the disease is quiescent and live birth rates are reported tobe ranging from 65-85%.[6] An earlier study conducted in the Indian subcontinent on 31 patients with SLE compared the outcome among those with active and inactive disease. They noted live birth rates of 82.6% and 27.7% among those with inactive and active disease, suggesting that active disease is a predictor of worse pregnancy outcomes.[7]

The outcomes of 396 pregnancies in patients with SLE were studied in Saudi Arabia. The investigators had elucidated the live pregnancy rate 0f 70.2%, fetal death of 29.7% and preterm birth rate of 26.7%, which were

similar to the present study. They had concluded that active lupus nephritis, anti-Ro/SSA antibodies, aPL, hypertension, Raynaud's phenomenon, active disease at conception and SLE exacerbations were strong predictors of adverse pregnancy outcomes.[8]

SLE patients with secondary APLA are yet another subgroup, who need to be monitored more vigilantly. Prophylactic anticoagulation with a combination of heparin and low dose aspirin is the only undisputed therapy that has been noted to improve pregnancy outcomes in SLE patients in the setting of secondary APS.[9] In our series too, patients with secondary APS had better outcomes when treated with aspirin and Heparin compared to those who were not treated. A cross-sectional study, carried out in Iran and 100 patients with SLE were studied. Thirty- six percent were positive for Anti-cardiolipin antibody, as also in our study (40%). They noted a higher prevalence of recurrent abortions and thrombosis in ACL positive group than in non-ACL group.[10]

Literature quotes that in patients with antiphospholipid syndrome, the common fetal complications observed were miscarriage, fetal loss and premature birth, whereas the most common maternal manifestations were pre-eclampsia, followed by eclampsia and abruptio placentae.[11] In the present study, 48% and 20% of patients with APS had missed abortion and intrauterine fetal demise before diagnosis and treatment. The accepted recommendation and proven therapy for APS is low dose aspirin combined with heparin. Pre-conceptional initiation of Aspirin has been advocated. Heparin should be initiated as soon as the cardiac activity is demonstrated by ultrasound.[12]

Autoimmune diseases have been reported to be associated with congenital anomalies. Teratogenesis caused by the drugs could also possibly explain for anomalies. In our series, 3 cases were noted: anencephaly, spinabifida and Rhizomelic chondrodysplasia punctata; the first two unrelated to autoimmune pathology. The last mentioned anomaly was seen in a patient with MCTD. It is a rare anomaly caused due to the transplacental maternal antibodies that hamper the vitamin K metabolism and eventually arrests the development of bones.[13] Rhizomelic chondrodysplasia punctata of genetic origin is lethal while those due to autoimmune etiology, would survive with permanent shortening of limbs.

In a retrospective cohort of twelve pregnancies complicated with MCTD, most had favourable outcomes, although the reported preterm birth rate was 39%.[14]

The rates of caesarean deliveries are high in our series because of the high risk nature of the disease per se and the associated maternal and fetal complications.

In our series, no postnatal complication seemed to have occurred though the patients were monitored closely for infection, thromboembolism and lupus flare.

The study could not derive correlations between the clinico-serological parameters and the pregnancy outcomes due to the small sample size of patients studied.

CONCLUSIONS

The study suggests the active search for autoimmune diseases in young females, who present with hypertension, renal disease and thromboembolic events. The findings of our study also emphasizes the importance of incorporating autoimmune serological profile while investigating for recurrent pregnancy loss, unexplained fetal demise, early onset preeclampsia and eclampsia. Young women with SLE should be in remission before contemplating pregnancy to prevent poor obstetric outcomes. SLE with presence of antiphospholipid antibodies has adverse influences on pregnancy outcomes. Initiation of Heparin and Aspirin from early gestation in patients with autoimmune diseases has favourable outcomes.

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