

## Pregnancy Related Complications in Patients with Systemic Lupus Erythematosus, An Egyptian Experience

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### Abstract:

**Background:** Systemic Lupus Erythematosus (SLE) has a tendency to occur in women in their reproductive years, causing complications during pregnancy and labour. Conversely, pregnancy can cause flares of disease activity, often necessitating immediate intervention.

**Aim of study:** to study pregnancy related complications in patients with SLE.

**Patients and methods:** The study included 48 SLE pregnant females. 27 patients with 38 pregnancies, their data viewed retrospectively from medical records, and 21 patients with 21 pregnancies followed up prospectively. The laboratory data included ANA, DNA, APL antibodies and anti Ro/SSA. The disease activity was calculated according to the Systemic Lupus Activity Measure. Ultrasound was performed to confirm gestational age and assess for the presence of any congenital fetal malformations, and then repeated monthly to detect any abnormality including intrauterine growth restriction. At 30 weeks gestation and onwards, assessment of fetal wellbeing including daily fetal kick chart and once weekly non stress test was performed. Doppler blood flow velocimetry was done for those with abnormal fetal heart rate pattern. After labour, the neonate was examined for complications including complete heart block and neonatal lupus.

**Results:** Anti dsDNA was found in 95% of the patients, anti Ro/SSA in 6% and anti APL in 30%. 57% of the patients followed up prospectively had active disease in the 1st trimester, 24% in the 2nd and 62% in the 3rd trimester. The most common maternal complication was preeclampsia 33%, followed by spontaneous abortion 20%. Prematurity was the most common fetal complication 37%, followed by intrauterine growth restriction 29%. 2 neonates were born with congenital heart block and 1 with neonatal lupus.

**Conclusion:** Pregnancy in SLE patients is associated with a higher risk of obstetric complications affecting both the mother and the fetus. Preeclampsia was the most common complication followed by prematurity. Preeclampsia was significantly associated with third trimester disease activity.

**Keywords:** SLE, pregnancy complications

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## Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune chronic disease involving multiple organs, particularly joints, skin, heart, lungs, nervous system and kidneys. SLE has a tendency to occur in women in their reproductive years and causes numerous health complications during pregnancy and labour. Lupus flares occur during each trimester of pregnancy and also in the postpartum period.<sup>1</sup>

Pregnancy is an important clinical setting for disease management in SLE patients. Complications of pregnancy, particularly preeclampsia, can be difficult to distinguish from symptoms of SLE, making diagnosis and treatment challenging. SLE can be detrimental to the pregnancy and may cause adverse fetal outcomes. Conversely, pregnancy can cause flares of disease activity, often necessitating immediate intervention.<sup>2</sup>

Among the reported complications are a greater number of abortions, fetal loss and preterm deliveries. Moreover, the newborn may be affected with neonatal SLE, usually manifested as a skin or blood disease, or by the presence of congenital heart block (CHB). Neonatal SLE is intimately associated with the presence of anti Ro/SSA.<sup>3</sup>

Advances in the understanding of the pregnancy-lupus interaction have resulted in better methods of monitoring and treating these patients, resulting in an improvement in maternal and fetal outcomes over the last few decades.<sup>2</sup>

## The Aim of this Work

The aim of this work was to study pregnancy related complications in patients with SLE by a retrospective study of previously pregnant SLE patients and a prospective follow up of recently pregnant SLE patients.

## Patients and Methods

The current study included 48 pregnant SLE patients who were selected from the rheumatology inpatient ward and outpatient clinic of internal medicine department and the ante-natal outpatient clinic of the Obstetrics and Gynecology Department at Ain Shams University Hospital. All the selected patients satisfied the American College of Rheumatology revised classification criteria for SLE diagnosis.<sup>4</sup> An informed consent was obtained from all participants and the

study was approved by the Ain Shams Medical Ethics Committee.

The retrospective group included 27 patients with 38 pregnancies documented in medical records. The prospective group included 21 patients with 21 pregnancies. The age of the patients ranged between 20–35 years. All were singleton, sure of their dates and all of them started their ante-natal care during their first trimester. Any patient with a medical condition other than SLE was excluded from the study including diabetes mellitus, hypertension, thyroid dysfunction and other autoimmune disorder including rheumatoid arthritis and systemic sclerosis.

For the retrospective group the following was reviewed from medical records

**I. Medical history:** with special attention to the obstetric history and associated complications and neonatal outcome.

**II. Laboratory investigations:** including ANA and Anti dsDNA, Anti RO/SSA antibody and APL antibodies.

For the prospective group the following was done

**I. Full medical history:** repeated each trimester (1st trimester till 13 weeks; 2nd trimester till 27 weeks and 3rd trimester till delivery) with special emphasis on flares that were recorded throughout pregnancy.

**II. Thorough clinical examination:** with detailed musculoskeletal examination and assessment of disease activity with special emphasis on disease flares using the Systemic Lupus Activity Measure (SLAM)<sup>5</sup> with a score of: <6 represents mild disease activity, 6–12 represents moderate disease activity, >12 represents severe disease activity. Flares defined as: **Joint flare:** the presence of definite arthritis in more than one joint. **Skin flare:** the presence of malar rash and/or photosensitivity. **Renal flare:** the presence of proteinuria >500 mg/day (in absence of preeclampsia or eclampsia) or cellular casts. **Neurological flare:** the presence of psychosis or convulsions (in absence of eclampsia). **Cardiopulmonary flare:** the presence of pleurisy and/or pleural effusion and/or pericardial effusion and/or pericarditis. **Hematological flare:** the presence of leucopenia (<4000 mm<sup>3</sup>), or Coombs positive autoimmune hemolytic anemia, or thrombocytopenia (<100,000 mm<sup>3</sup>).



### III. Laboratory investigation:

- Investigations recorded once throughout pregnancy (in the 1st ante-natal care visit):
  1. ABO, Rh blood group and Coombs test.
  2. ANA (Antinuclear Antibodies).
  3. Anti-dsDNA (Anti double stranded DNA).
  4. Anti-RO/SSA antibody.
  5. Anti-phospholipid antibodies (APL).
- Investigations recorded at the beginning of each trimester:
  1. Complete blood count.
  2. Erythrocyte Sedimentation Rate.
  3. Blood sugar and oral glucose tolerance test.
  4. C3 and C4.
  5. Hepatic trans-aminases and Serum bilirubin.
  6. Serum creatinine and creatinine clearance.
  7. Urine analysis and total urinary protein in 24 hour urine collection.

**IV. Obstetric management:** all patients attended the outpatient ante-natal care clinic starting from their 1st trimester. Visits were scheduled every two weeks till 28 weeks then weekly till end of pregnancy. In their first visit, all patients received a full obstetric history with thorough general and abdominal examination with determination of exact gestational age and expected date of delivery. In subsequent visits, thorough examinations were carried out with emphasis on blood pressure, lower limb edema and weight gain, also protein in urine was assessed. At 18–20 weeks gestation, a detailed ultrasound was performed to confirm gestational age and assess for the presence of any congenital fetal malformations, then monthly to detect any abnormality including growth retardation and oligohydramnios. At 30 weeks gestation and onwards, assessment of fetal well being including daily fetal kick chart and once weekly ante-partum fetal heart testing using non stress test was started. Doppler blood flow velocimetry was done for those with abnormal fetal heart rate pattern. Time and mode of delivery was individualized, depending on gestational age, fetal condition and maternal condition.

After labour, the neonate was examined carefully for complications including complete heart block, neonatal lupus and prematurity.

The following definitions were used in this study<sup>6</sup>

**Spontaneous abortion:** Spontaneous loss of a fetus before 20 weeks gestation.

**Therapeutic abortion:** Termination of pregnancy for medical indications.

**Gestational hypertension:** Defined as either a systolic blood pressure  $\geq 140$  mm Hg or a diastolic blood pressure  $\geq 90$  mm Hg on at least two occasions, at least 6 hours apart after 20 weeks gestation.

**Oligohydramnios:** Decrease amniotic fluid volume with amniotic fluid index  $< 10$ .

**Preeclampsia:** Onset of hypertension after 20 weeks gestation as manifested by elevated blood pressures  $\geq 140/90$  mm Hg on two occasions, at least 6 hours apart, in previously normotensive patients, accompanied by new-onset proteinuria  $\geq 300$  mg/day, in patients without proteinuria at baseline and/or edema. Other criteria supporting a diagnosis of preeclampsia included an elevated serum alanine aminotransferase (ALT) concentration ( $> 70$  units/L), increasing proteinuria in patients with pre-existing renal disease, persistent severe headaches, or epigastric pain.

**Eclampsia:** Generalized convulsions and/or coma in the setting of preeclampsia, and in the absence of other neurological conditions.

**HELLP:** Syndrome of hemolysis, elevated liver enzymes, and low platelet count (thrombocytopenia) during pregnancy.

**Intrauterine growth restriction (IUGR):** Estimated birth weight less than 10th percentile for gestational age.

**Prematurity:** Live birth before 37 weeks gestation.

**Intrauterine fetal death (IUFD):** Intrauterine fetal demise at  $\geq 20$  weeks of gestation.

**Neonatal death:** Death of a neonate before 28 days following birth.

### Statistical analysis

Statistical analysis was done using a personal computer software package (Statistical version 5, Stat Soft inc. USA 1995). The data obtained were expressed as descriptive statistics (mean  $\pm$  standard deviation, number and percent). Statistics included independent sample t-test for comparison between two parametric groups. Chi-Square test ( $\chi^2$ ) was used to compare qualitative variables.  $P > 0.05$  was considered non significant,  $P < 0.05$  was considered significant and  $P < 0.01$  was considered highly significant.

## Results

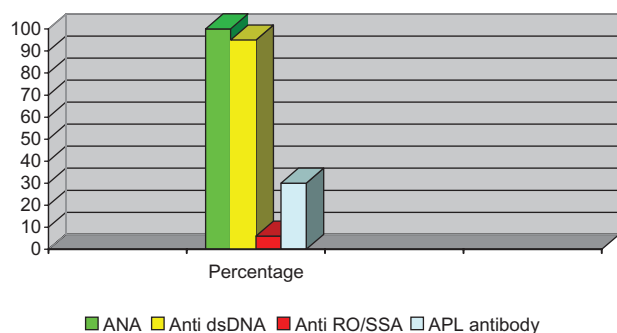
This study included 48 SLE patients with 38 pregnancies in the retrospective group and 21 pregnancies in the prospective group. There was no significant difference between both groups as regards age (mean  $\pm$  SD of  $28.3 \pm 5.23$ ,  $27.5 \pm 6.28$  years) or disease duration (mean  $\pm$  SD of  $64.3 \pm 5.08$ ,  $63.9 \pm 7.3$  months) with  $P > 0.05$ .

The most frequent autoantibody detected was ANA, present in 100% of the patients followed by anti dsDNA, in 95% of patients. Anti Ro/SSA was present in 6% and APL in 30% of all patients (Fig. 1).

The disease activity was recorded for the 21 patients in the prospective group in each trimester. 57% of the patients had active disease in the 1st trimester, 24% in the 2nd and 62% in the 3rd trimester. Most of the disease activity was mild in all three trimesters (Table 1). The frequency of SLE flares in all the 59 pregnancies was recorded (Table 2). Joint flares were the most common (80%), followed by skin flares (75%).

Maternal, fetal and neonatal complications were recorded in all pregnancies (Tables 3 and 4). The most common maternal complication was preeclampsia (33%), followed by spontaneous abortion (20%). Prematurity was the most common fetal complication (37%) followed by intra uterine growth restriction (IUGR) (29%).

The relation between different qualitative disease parameters and different pregnancy outcome parameters was done (Table 5). There was a significant relation between 3rd trimester disease activity and preeclampsia ( $P < 0.05$ ).



**Figure 1.** The percentage of auto-antibodies in all 48 patients.

**Table 1.** Disease activity in the prospective group (21 patients).

Disease activity	1st trimester		2nd trimester		3rd trimester	
	No	%	No	%	No	%
Total	12	57	5	24	13	62
Mild	7	58	4	80	9	69
Moderate	5	42	1	20	1	8
Severe	0	0	0	0	3	23

Correlation between different autoantibodies and various clinical features was addressed in Table 6.

## Discussion

Systemic Lupus Erythematosus (SLE) is mainly a disease of women in the childbearing period and the coexistence of pregnancy is not a rare event. Disease flare during pregnancy consistently affects pregnancy outcome.<sup>7</sup>

Although the outcome of pregnancy in patients with SLE has improved progressively with time, nevertheless the rate of spontaneous abortion and preterm delivery still remains higher in patients with SLE than in normal pregnancies.<sup>8</sup>

This study was conducted on 48 SLE patients, all were ANA antibodies positive, anti dsDNA were detected in 95%, anti Ro/SSA in 6% and APL antibodies in 30%.

According to the Systemic Lupus Activity Measure (SLAM) score, in the 21 patients followed up prospectively, 57% of the patients had active disease in the 1st trimester, 24% in the 2nd and 62% in the 3rd trimester. Most of the disease activity was mild in all three trimesters.

It has been reported in various studies that SLE flares might occur in any trimester or during the post-partum period. Usually the severity of the flare is mild, with arthritis, constitutional and cutaneous manifestations being the most common. However, more serious problems affecting the kidneys and central nervous system have been reported.<sup>8</sup> In this study the highest incidence of flare was joint, followed by skin flares. Renal flares occurred in 31% and no neurological flares were recorded.

Diagnosis of a lupus flare in pregnancy may be difficult; normal physiological changes dur-

**Table 2.** Frequency of SLE flares in all 59 pregnancies.

Flare	Total pregnancies (59)		Prospective pregnancies (21)		Retrospective pregnancies (38)	
	No	%	No	%	No	%
Joint	47	80	18	86	29	76
Skin	44	75	13	61	31	82
Renal	18	31	9	43	9	24
Neurological	0	0	0	0	0	0
Cardiopulmonary	4	7	2	10	2	5
Haematological	20	34	8	38	12	32

ing pregnancy and related complications such as preeclampsia can mimic a flare. However, although an increased frequency of flares has been reported in pregnant SLE patients, some studies have found similar frequencies in non-pregnant SLE patients.<sup>10</sup>

Several factors can affect pregnancy or neonatal outcome in SLE, for example repeated spontaneous pregnancy losses are frequently related to APL antibodies. Neonatal lupus and congenital heart block (CHB) are linked to trans-placental passage of anti Ro/SSA antibodies. The disease activity itself can affect the mother and the fetal outcome.<sup>11</sup>

In this study, the most common maternal complication was preeclampsia followed by spontaneous abortion. Oligohydramnios were recorded in 12% of the patients and gestational hypertension in 7%. Prematurity was the most common fetal complication followed by intrauterine growth restriction (IUGR). Intrauterine fetal Death (IUFD) was recorded in 8%. There were five neonatal deaths, one neonatal lupus and two neonates with CHB.

Similar studies have shown preeclampsia to be the most common maternal complication and higher

rates of complications occurred with active disease. Predictors of poor pregnancy outcome included flare-up of the disease, renal involvement and hypertension.<sup>12</sup> In accordance with them this study showed a significant relation between preeclampsia and third trimester disease activity.

Other studies have detected 20% exacerbations of the disease during pregnancy, with most flares being mild. The most common obstetric complication was gestational hypertension. Preeclampsia occurred in 11% and 46% of pregnancies ended in preterm delivery.<sup>13</sup>

Different study designs have yielded different results on the effect of SLE pregnancies on fetal and neonatal outcome. In SLE pregnancies followed prospectively at one center, preterm birth was the most frequent adverse event. Active SLE contributed to both preterm birth and to pregnancy loss. In addition, the lupus anticoagulant was associated with an increased risk of pregnancy loss.<sup>14</sup>

SLE is associated with an increased rate of prematurity. Studies have shown variable frequencies of prematurity in SLE pregnancies ranging from

**Table 3.** Maternal complications in all 59 pregnancies.

Maternal complication	Total pregnancies (59)		Prospective pregnancies (21)		Retrospective pregnancies (38)	
	No	%	No	%	No	%
Spontaneous abortions	12	20	4	19	8	21
Therapeutic abortion	1	2	0	0	1	3
Gestational HTN	4	7	1	5	3	8
Oligohydramnios	7	12	3	14	4	11
Preeclampsia	20	33	11	52	9	24
Eclampsia	0	0	0	0	0	0
HELLP syndrome	0	0	0	0	0	0

**Table 4.** Fetal and neonatal complications in all 59 pregnancies.

Fetal and neonatal complication	Total pregnancies (59)		Prospective pregnancies (21)		Retrospective pregnancies (38)	
	No	%	No	%	No	%
IUGR	17	29	8	38	9	24
Prematurity	22	37	8	38	14	37
IUFD	5	8	1	5	4	11
Neonatal death	5	8	3	14	2	5
CHB	2	3	1	5	1	3
Neonatal lupus	1	2	2	5	0	0

4% to 62%.<sup>15</sup> In this study prematurity was the most common fetal complication. This discrepancy in the frequency of prematurity might be due to the fact that preterm birth in SLE has multiple causes including preeclampsia, APL antibodies, placental insufficiency and an increased prevalence of premature rupture of membranes.<sup>16</sup>

On the other hand, other studies have reported an overall live-birth of 72.7% in SLE pregnancies and pregnancy loss was attributed mainly to spontaneous abortion and IUFD,<sup>17</sup> although one study did report that pregnancy outcomes such as miscarriage, therapeutic abortion, stillbirth and neonatal death rate in SLE patients were similar to controls.<sup>18</sup> This study showed 20% spontaneous abortion, ranking second to preeclampsia as a maternal complication, however IUFD only constituted 8% of all pregnancies.

IUFD has been reported with a frequency ranging from 4%–43% in SLE patients. Studies have shown fetal prognosis to depend mostly on disease activity, with fetal loss ranging from 25%–52% in patients with active SLE compared to 8%–12% in patients with inactive SLE.<sup>19</sup> Other studies have

**Table 5.** Relation between 3rd trimester disease activity and preeclampsia in the prospective group.

3rd trimester disease activity	Preeclampsia (positive)		Preeclampsia (negative)	
	No	%	No	%
Mild (9)	6	66	3	34
Moderate (1)	1	100	0	0
Severe (3)	2	66	1	34

Notes:  $\chi^2 = 3.6$ ;  $P < 0.05$ .

shown the presence of APL antibodies as the main predictor of fetal death in SLE.<sup>20</sup>

Various studies have detected APL antibodies in 35%–40% of pregnant SLE patients. The association between APL antibodies and fetal loss has been well demonstrated. In addition, APL antibodies were found to be more prevalent in patients with recurrent miscarriages.<sup>21</sup> Mechanisms could include failure of implantation, placental vasoconstriction and thrombosis leading to either fetal growth restriction or death. The presence of these antibodies was associated with an approximately two-fold increase in fetal loss.<sup>22</sup> In the present study APL antibodies were also detected in 30% of the patients, however there was an insufficient percent of IUFD (8%) to find any significant relation between both, but there was a significant positive relation between APL antibodies and both of spontaneous abortion and preeclampsia.

IUGR was found to occur in 15%–20% of SLE pregnancies. The main factors contributing to the increased rate of growth restriction was APL antibodies and preeclampsia.<sup>23,24</sup>

**Table 6.** Correlation between autoantibodies and various clinical features.

	R	P	Sig
<b>Anti dsDNA</b>			
Disease activity	0.435	<0.05	S
<b>APL Ab</b>			
Spontaneous abortion	0.413	<0.05	S
Preeclampsia	0.382	<0.05	S
<b>Anti RO/SSA</b>			
Neonatal lupus	0.521	<0.05	S



One study including 47 pregnancies in 31 SLE patients recorded 13% flares, all mild. Twelve women developed preeclampsia and one experienced an intrauterine death. 14% experienced IUGR. There were 77% live births of which two experienced CHB and one had a neonatal lupus rash.<sup>25</sup> The present study recorded a higher frequency of IUGR 29%, although APL antibodies were present in similar frequencies to other studies, highlighting the fact that APL antibodies may not be the only contributing factor to the increase rate of IUGR in SLE pregnancies.

It is well known that anti Ro/SSA antibodies have been found to be linked to the development of CHB in-utero and to other clinical manifestations in newborns such as skin rash, liver abnormalities and thrombocytopenia.<sup>26</sup> In this study anti Ro/SSA was detected in three patients two of which gave birth to neonates with CHB and the third delivered a newborn with neonatal lupus and a significant positive correlation was detected between Anti Ro/SSA and neonatal lupus.

In conclusion, despite the recent progress in obstetrical care maternal and fetal complications still exist in SLE pregnancies. Pregnancy in SLE patients should be considered as a high risk pregnancy and conception should be planned, if possible, during a quiescent period. Close monitoring for optimal disease control and multidisciplinary obstetrical care is necessary throughout the gestation period to increase the chances of a successful pregnancy.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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