Pregnancy Outcome in Patients with Systemic Lupus Erythematosus: Study of Pregnancy Outcome of 23 Patients with SLE at High Risk Unit, Kasr El-Aini Hospital

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Abstract

Background: Systemic lupus Erythematosus (SLE) is an autoimmune multi-system disease of unknown etiology mostly affecting females in child bearing age. Offering the patients adequate obstetrical care will improve both maternal & fetal outcome.

Aim of the Work: To study the effect of SLE on pregnancy by evaluating maternal & fetal outcome & to study the effect of pregnancy on SLE flares.

Material and Methods: Twenty three SLE pregnant patients were followed at the antenatal care clinic at High Risk Unit at Kasr El-Aini Hospital. The pregnancy outcome was evaluated, recording any maternal & fetal complications.

Results: All 23 patients were at remission at onset of pregnancy. Predinisolone was used by [14 patients], [19 patients] treated with low dose acetylsalicylic acid, Hydroxychloroquine [13 patients], and low molecular weight heparin [13 patients] Azathioprine [4 patients]. Prematurity was 13% [3 patients], IUGR [4 patients] maternal renal involvement [5 patients], Arthritis [7 patients], Skin rash [4 patients], Hematological abnormalities [2 patients], pulmonary embolism [1 patients], with one maternal mortality.

Conclusion: Although improvement in pregnancy outcome in SLE patients, SLE still carries a risk for the mother and fetus and careful follow-up should be done during pregnancy.

Key Words: Pregnancy outcome – Systemic lupus erythematosus.

Introduction

SLE is most commonly diagnosed between 20 and 40 years, it is the connective tissue disease that is mostly associated with pregnancy and puerperium [1].

Historically, fetal and maternal well being of SLE patients was compromised to the extent that the medical community recommended against pregnancy in SLE patients [2]. With better control of disease activity, there is improvement in pregnancy outcome of SLE patients, but still there is fetal and maternal complications Careful planning of pregnancy coupled with monitoring and treatment substantially decreases the risks for the mother and the infant [3].

Studies of the impact of SLE on pregnancy and of pregnancy on maternal lupus showed variable results. Some studies indicated that there is an increase in SLE flares during pregnancy [4] while others found no difference in flares between pregnant and non-pregnant patients with SLE [5].

Pregnancies for patients with lupus have a greater risk of fetal loss, intrauterine growth restriction IUGR, prematurity, pre-eclampsia and neonatal lupus syndrome [6].

Remission of the disease around the time of conception is related to favorable pregnancy outcome. On the other hand, a diagnosis of SLE during pregnancy and flare-up around the time of conception or during pregnancy are related to poor prognosis for both the pregnancy and the course of the disease [1].

Material and Methods

This is an observational study which included 23 pregnant patients with SLE attending the antenatal clinic at High Risk Unit and rheumatology clinic at Kasr El-Aini Hospital, Cairo University from October 2010 to January 2012. All the patients were followed to delivery.
Patients:

Inclusion criteria:

All patients were diagnosed as SLE before the start of pregnancy. All SLE patients fulfilled at least 4 of the 11 criteria of American College of Rheumatology ACR [7] which include:

- Malar Rash.
- Discoid Rash [Also subacute cutaneous lesions].
- Photosensitivity.
- Oral Ulcers.
- Arthritis (Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion).
- Serositis (pleuritis or pericarditis).
- Renal Disorder (persistent Proteinuria greater than 0.5 grams per day or cellular casts).
- Neurological disorder (seizures or psychosis).
- Hematologic disorder (hemolytic anemia, Leukopenia or lymphopenia on two or more occasions, thrombocytopenia).
- Immunologic disorder:
  a) Anti-ds-DNA: Antibody to native DNA in abnormal titer, OR.
  b) Anti-Sm: Presence of antibody to Sm nuclear antigen, OR.
  c) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.
  d) Positive finding of antiphospholipid antibodies based on: Abnormal serum level of IgG or IgM anticyclic cardiolipin antibodies.
- An abnormal titre of Anti-nuclear antibodies[ANA] at any point in time and in the absence of drugs known to cause an elevated ANA (drug induced lupus)

Exclusion criteria:

Other medical disorders as Diabetes, hypertension, cardiac diseases as mitral and aortic valve disease and renal diseases.

All patients were subjected to:

- Personal, obstetric, medical, & past history
- Clinical examination of the current condition
- Base-line laboratory investigations:
  - Complete blood picture [hemoglobin, red, white, and platelet count].
  - Erythrocyte sedimentation rate.
  - Kidney functions [serum level of creatinine] & liver functions.
- Urine analysis & 24-h urine collection for total proteinuria.
- Immunological evaluation:
  - Antinuclear antibodies (ANA).
  - Anti -double stranded (ds) DNA antibodies.
  - Anti-Ro/SSA antibodies, anti-La/SSB antibodies.
  - Anticardiolipin antibodies (via immunoglobulin G and immunoglobulin M determination) and/or lupus anticoagulant.
  - Complements C3 and C4.
- Serial ultrasounds With Doppler were done for ante-natal care, every 2 weeks in first and second trimester, then weekly starting from 36 weeks. Pregnancies complicated with IUGR, decreased amniotic fluid, or hypertension or lupus nephritis were followed twice weekly by Doppler evaluation & GTG.

All 23 patients included in the study were managed according to a specific protocol by both an obstetric and a rheumatology team. Nephrology consultation was needed if kidneys were involved. Pregnancy was planned after at least 6 months remission of SLE. Frequent consultation of rheumatology was done to detect any SLE activity especially mild flares as arthritis and skin rash that may be found in normal pregnancy or severe activity as nephritis hemolytic anemia, low platelet count [less than 60,000], myositis, central nervous system disease.

Neonatal assessment:

Fetal outcomes for live births including birth weight, prematurity [less than 37 weeks of gestation], 1-and 5-min Apgar scores, admission to neonatal intensive care unit were recorded.

Statistical analysis:

Data are statistically described in terms of range, mean±standard deviation (X±SD), frequencies and percentages. For comparing categorical data, Chi square test was performed. A probability value [p-value] less than 0.05 was considered statistically significant. Statistical calculations done using computer program SPSS [Statistical Package for the Social Science; SPSS] version 15 for Microsoft Windows.

Results

A total of 23 SLE pregnant patients were followed up in High Risk antenatal clinic & in the rheumatology clinic during the study period from October 2010 to January 2012. SLE was diagnosed
in all patients before pregnancy whom were in a state of remission at time of pregnancy [at least 6 months]. All 23 patients were delivered at our department.

Patient characteristics:

The mean age of the patients was 28.4 years ± 5.4 (range: 18-38 years). Mean number of pregnancies per patient is 3.08 pregnancies. The patients had between one and 11 pregnancies, including the current one.

History of recurrent abortion was present in 10 cases [43.5%], while 13 [56.5%] cases didn’t have any miscarriages. Mean number of abortions was 1.1 per patient.

Table (1): Distribution of Drugs among SLE patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Yes</th>
<th>%</th>
<th>No</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>14</td>
<td>60.8</td>
<td>9</td>
<td>39.14</td>
<td>23</td>
</tr>
<tr>
<td>LMW heparin</td>
<td>13</td>
<td>56.5</td>
<td>10</td>
<td>43.5</td>
<td>23</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>19</td>
<td>82.6</td>
<td>4</td>
<td>17.4</td>
<td>23</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>13</td>
<td>56.5</td>
<td>10</td>
<td>43.5</td>
<td>23</td>
</tr>
<tr>
<td>Azathioprin</td>
<td>4</td>
<td>17.4</td>
<td>19</td>
<td>82.6</td>
<td>23</td>
</tr>
</tbody>
</table>

Acetylsalicylic acid (75-150mg) was the most commonly used drug, 19 cases (82.6%) followed by Prednisolone (at doses of 5 to 20mg/day) was used by 14 patients [60.8%], while 9 patients (39.14%) did not use the drug. Low molecular weight heparin LM 1 mg/kg body weight was received by 13 patients (56.5%).

Hydroxychloroquine with doses of 100-200mg was received by 13 (56.5%) patients. Patients taking Hydroxychloroquine suffered no complications in pregnancy. Azathioprine was used by 4 patients (17.3%).

Autoantibodies were positive as follows: ANA in all 23 patients, Anti-DNA antibodies was positive in 16 out of 23 cases (69.6%). Anticardiolipin antibodies (ACL) (immunoglobulin G and M determination) in 8 cases only (34.7%) and lupus anticoagulant (LAC) positive in 20 cases [86.9%]. Anti-Ro antibodies was positive in 9 patients (39.1%). Anti-La found in 5 patients (21.7%) Low Complement level, C3 in 4 patients (17.4%), while C4 was low in 5 patients (20.8%).

Table (2): Immunological investigations of SLE patients.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
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</tr>
<tr>
<td>Anti-DNA</td>
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<td>7</td>
</tr>
<tr>
<td>ACL</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>LAC</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Anti-Ro</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Anti-La</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>

Pregnancy outcome:

According to mode of delivery 16 (69.6%) patients had cesarean section, while 7 (30.4%) had vaginal delivery. Indications for CS were prematurity, fetal distress, previous section & breech presentation.

The pregnancy outcome was 24 live births as there was one twin pregnancy. There were no cases of still birth or abortions in the study. The mean birth weight of neonates was 2.05 kg ± 0.81 range (1.1-3kg). There were 3 cases of neonatal ICU admission (due prematurity) & one neonatal death after 20 days.

Intrauterine growth retardation IUGR, oligohydraminos & worsening of Doppler flow were diagnosed in 4 out of 23 patients (17.4%). IUGR was significantly more in patients with worsening of renal functions & proteinuria above 3gm% (3 cases). p-value was significant (less than 0.05).

Prematurity rate was 13% (3 cases), two cases with renal flares, IUGR & oligohydraminos, elective CS was done in two cases before 34 weeks. There was one case that developed severe pre-eclampsia (defined as the raising of blood pressure after 20th week of pregnancy plus proteinuria above 300mg over a 24-hour period), CS done at 28 weeks.

There was one maternal mortality that occurred immediately after cesarean section, she developed lupus activity in form of DVT in lower limbs, pulmonary hypertension, pulmonary embolism, died at ICU after a week from delivery.

SLE pregnancy associated flares:

Mild symptoms of SLE activity during pregnancy as arthritis especially of small joints was found in 30.4% (7 cases), skin rash 17.39% (4 cases), discoid malar rash 8.69% (2 patients). None of the patients suffered from oral ulcers or hair loss & alopecia.

Table (3): Systems involved in SLE flares.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>7</td>
<td>30.4</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>4</td>
<td>17.3</td>
</tr>
<tr>
<td>Disoid Rash</td>
<td>2</td>
<td>8.6</td>
</tr>
<tr>
<td>Lupus nephropathy</td>
<td>5</td>
<td>21.7</td>
</tr>
<tr>
<td>Hematological Abnormalities</td>
<td>2</td>
<td>8.6</td>
</tr>
<tr>
<td>Pulmonary embolism&amp;DVT</td>
<td>1</td>
<td>4.3</td>
</tr>
</tbody>
</table>
Severe SLE activity including renal flares & hematological abnormalities were recorded. Five patients (21.7%) developed lupus nephropathy with aggressive renal disease, deterioration of renal functions, rise of creatinine levels & proteinuria more than 3gm%. From those 5 patients with nephropathy three had IUGR (60%). There was significant relation between deterioration of renal function & lupus nephropathy with development of IUGR ($p$-value less than 0.05).

Blood abnormality in form of normocytic anemia was present in 2 patients, hemoglobin level dropped below 6gm%. Both of which received blood transfusion before delivery & were followed post partum.

### Discussion

Although advances in the improvement of management of SLE with pregnancy & the better pregnancy outcomes achieved, SLE can still cause adverse pregnancy outcomes. Conversely, pregnancy can cause flares of lupus disease activity.

Abortion, intrauterine growth restriction, prematurity, and perinatal morbidity and mortality are among the most common adverse perinatal outcomes in pregnant lupus patients. Flare-ups, nephritis and arterial hypertension are factors that increase the risk of perinatal complications [8].

In the study pregnancies complicated with IUGR was 17.4% (4 cases). SLE complicated with aggressive renal disease, hypertension, preeclampsia or IUGR, are at risk of iatrogenic preterm delivery [9]. Prematurity rate in SLE pregnancies is between 17-54% [10]. In this study the rate of preterm birth rate was 13% (3 cases). Prematurity was more frequent in lupus nephritis patients (2 cases), one case of pre-eclampsia.

Flare-up rates during pregnancy have a wide range from 13 to 60%. Flare-ups during pregnancy are defined as the presence of any: Hematological, immunological, renal, cutaneous, constitutional or osteoarticular alterations, or serositis. However these indices do not focus specifically on pregnant lupus patients and this makes their application in pregnancy difficult, since many of the above can be present in normal pregnancy [11].

SLE flares during pregnancy ranged from mild manifestations in form of skin rash (4cases) and arthritis (7 cases), discoid malar rash (2 cases). severe flares including nephrotic syndrome and worsening of renal disease, pulmonary hypertension & DVT.

Several studies suggested that nephritis may contribute to Unfavorable pregnancy outcome [12]. Our results support this finding, as in our study 5 patients developed active renal disease, 3 (60%) of them developed IUGR. Lupus nephritis diagnosed by urinary proteins more than 3gm, deterioration of renal functions We also found significant relationship between IUGR &active renal disease ($p$-value less than 0.05). SLE patients with quiescent renal disease usually do not have adverse pregnancy outcomes [13].

It is difficult to differentiate between renal flares and pre-eclampsia in clinical practice. Pre-eclampsia occurs in about 13% of SLE pregnant patients [14]. In pre-eclampsia there is isolated proteinuria. Features that suggest renal flares include increased anti-DNA antibody titers, low or dropping complement levels abnormal urinary sedimentation with the presence of cellular casts. Despite these indicators, it is sometimes difficult to differentiate between lupus nephritis & preeclampsia [15]. The treatment is different in both conditions, as pre-eclampsia will require delivery of fetus, but active lupus nephritis will require immunosupression.

Neonatal lupus syndrome is associated with maternal anti-Ro/SS-A and anti-La/SS-B antibodies, even if the mother is asymptomatic. Congenital
heart block occurs from 18 to 30 weeks, in 2% of fetuses of women with the anti-Ro antibody, with a recurrence rate of 16% in subsequent pregnancies [16]. Fetal echocardiography should be performed over this period to enable early detection. Also, cholestatic hepatitis, cytopenias, and photosensitive rash are grouped under “neonatal lupus syndrome”. They are usually transient, also linked to anti-Ro antibodies [17].

As for medical therapy, cyclophosphamide, and methotrexate are totally contraindicated in pregnancy and lactation because of their teratogenicity. Azathioprine may be continued in pregnancy on the basis of recent data. Hydroxychloroquine should not be stopped in early pregnancy because this could precipitate a flare. The dose of prednisolone should be kept at 10mg daily or less because of increased risk of hypertension, gestational diabetes, and infection [18]. It is recommended by some authors the routine use of prednisone for all pregnant lupus patients [19], but this is refused also by many authors [17].

Conclusion:

Although improvement in pregnancy outcome in SLE patients, SLE still carries a risk for the mother and fetus especially those with renal flares. Management of SLE with pregnancy requires the involvement of an obstetrician, rheumatologist and a nephrologist if renal status.

References
