Systemic Lupus Erythematosus Versus IgA Nephropathy with Mild Proteinuria During Pregnancy

SAAD ALSHOHOHAIB, M.D.
The Department of Internal Medicine, Faculty of Medicine, King Abdullah University, Jeddah Saudi Arabia.

Abstract

Objective: To assess the outcome of pregnancies in patients with inactive systemic lupus erythematosus (SLE) compared to IgA nephropathy (IgAN) who has mild proteinuria and normal serum creatinine.

Methods: A prospective study of 32 female patients with a mean age of 28.58 ± 3.55 Vs 27.2 ± 5.58 years for renal vs SLE in King Abdul Aziz University Hospital, in Jeddah, Saudi Arabia was conducted between 1998 and 2008. Before each pregnancy all the patients had their blood pressure, serum creatinine, creatinine clearance and 24-hour urine protein excretion measured. Followed by monthly measurements of blood pressure, serum creatinine, creatinine clearance, a complete blood count (CBC), liver function tests (LFTs) and serology for lupus. All SLE patients had Class IV lupus nephritis and proteinuria of less than 1 g/day, but none of them had renal impairment or hypertension. Statistical analysis for proteinuria measurements during pregnancy was performed using the Wilcoxon signed-rank test. A \( p \) value <0.05 was considered statistically significant.

Results: Even though all of the SLE patients reached the third trimester and were antinuclear antibody (ANA) negative, significant complications were observed during pregnancy. The daily proteinuria during 34-36 weeks’ gestation was significantly higher (\( p < 0.05 \)) than during 32 weeks. One had a stillbirth, 2 required a terminations of the pregnancy; 1 due to severe hypertension and 1 due to renal impairment. One patient developed haemolysis and elevated liver enzymes, due to HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. Two patients had abortions, 14 patients had a successful pregnancy and 4 of them required a caesarian section.

In IgAN group one patient (8.3%) developed hemolysis, elevated liver enzymes and low platelets HELLP syndrome. Two patients, one with preeclampsia and the other with the HELLP syndrome required cesarean section.

Conclusion: Although no clinical evidence of lupus disease activity was demonstrated pre-conception and there was minimal proteinuria, serious complications for both mother and foetus developed as proteinuria significantly increased during pregnancy. SLE is a serious complication during pregnancy. IgAN has also serious complications for both mother and foetus and therefore close monitoring and multi-disciplinary care are essential during the pregnancy and post-partum period. The study was limited due to the small sample size and meta-analysis is recommended to further investigations in both groups.

Key Words: Systemic lupus erythematosis (SLE) – Proteinuria during pregnancy.

Introduction

SLE and IgAN are relatively common problems in Saudi Arabia [1] and we have encountered some patients with such diseases who are willing to become pregnant, regardless of the risks for both the foetus and the mother. These problems can be a challenge to a physician and become more evident when the patient has active SLE, gross proteinuria or severe hypertension.

SLE is an autoimmune disease that primarily affects young females of childbearing age. For social reasons, the Kingdom of Saudi Arabia has one of the highest rates of pregnancy and childbirth. Therefore, we see many patients with lupus in Saudi Arabia and it’s essential that the right advice is given to those who are willing to become pregnant.

We have seen patients initially diagnosed with lupus during pregnancy or in their post-partum period. The data on pregnancy and lupus is variable and the recommendations about pregnancy differ between studies. Some studies have recommended that it’s safe to proceed with pregnancy if the lupus is inactive for at least 6 months, but most people would agree that pregnancy is unsafe in the presence of severe renal impairment or uncontrolled hypertension. To have a proper comparison we compared SLE to IgAN patients. The IgA group has minimal proteinuria and normal serum creatinine. The aim of this study was to see the outcome in both groups.
Patients and Methods

All patients are recruited in King Abdul Aziz University Hospital, in Jeddah, Saudi Arabia between 1998 and 2008.

SLE Group:

This is a group of 20 female SLE patients between 18 and 38 years of age, with a mean age of 27.2 ± 5.57 years [mean ± SD] with SLE. All of them had kidney biopsies, that confirmed the presence of Class IV lupus nephritis, but none of them had renal impairment and all of them had proteinuria of less than 1g/day. All of the biopsies showed mild interstitial fibrosis.

Eight patients were primigravida and 12 were multigravida who had uncomplicated previous pregnancies. Prior to each pregnancy, all the patients had their blood pressure, serum creatinine, creatinine clearance and 24-hour urine protein excretion measured. Each patient was closely monitored and received a monthly measurement of blood pressure, serum creatinine, creatinine clearance, as well as a CBC, LFTs and serology for lupus. The mean systolic blood pressure was 127.3 mmHg and the diastolic was 78 mmHg. None of them were receiving anti-hypertensive medication and the pre-conception creatinine clearance was 89.2 ml/min.

IgAN Group:

The IgAN patients are 12 female between 23 and 35 years of age, with a mean of 28.58 ± 3.55 years [mean ± SD]. All the patients had kidney biopsies confirming the diagnosis of IgA nephropathy with minimal findings. Confirmation was based on light microscopy, immunofluorescence and electron microscopy. All patients had mild glomerular changes and mild to moderate interstitial fibrosis on microscopic examination.

Results

Both groups look very similar in age with clear differences in their disease manifestations.

Table (2): Urinary protein excretion, renal function and haemoglobin levels during pregnancy.

<table>
<thead>
<tr>
<th>SLE Group</th>
<th>24-hour urine protein (mg)</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Serum Creatinine (µmol/l)</th>
<th>Haemoglobin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32</td>
<td>34-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>354.7 ± 121.73</td>
<td>1531.3 ± 2013.13</td>
<td>79.85 ± 4.47</td>
<td>83 ± 7.26</td>
</tr>
<tr>
<td>Median</td>
<td>357.5</td>
<td>1150</td>
<td>80</td>
<td>81.5</td>
</tr>
<tr>
<td>Range</td>
<td>211-615</td>
<td>101-10011</td>
<td>69-90</td>
<td>70-100</td>
</tr>
</tbody>
</table>

All of the patients were ANA negative.

The results in Table (2) show that daily proteinuria during 34-36 weeks of gestation was significantly higher (p < 0.05) than at 32 weeks. The mean creatinine clearance was 79.85 ± 4.47 ml/min and the serum creatinine was 83 ± 7.26 µmol/l. The mean haemoglobin level was 10.59 ± 0.41 g/dl, ranging from 10 to 11.02 g/dl.

The normality tests used were the Shapiro-Wilk, Anderson-Darling, Martinez-Iglewicz, Kolmogorov-Smirnov, D’Agostino Skewness, D’Agostino Kurtosis and D’Agostino Omnibus tests.

It should be noted that non-normality is difficult to detect even when it is present when using these normality tests with small samples.

For all of the normality tests used, the age, the 24-h urine protein during 32 weeks of gestation, the creatinine clearance and the serum creatinine data could not reject the null hypothesis that the
data came from a normal distribution. However, normality was rejected for the haemoglobin data using the Shapiro-Wilk, Anderson-Darling, Kolmogorov-Smirnov, D’Agostino Kurtosis and D’Agostino Skewness tests. Although normality could not be rejected using the Martinez-Iglewicz and D’Agostino Omnibus tests. Normality was also rejected for the 24-h urine protein data collected between 34-36 weeks of gestation for all the normality tests used.

All of the patients reached the third trimester and were ANA negative. One had a stillbirth, one required a termination of the pregnancy due to severe hypertension and one due to renal impairment. One patient developed haemolysis and elevated liver enzymes, due to HELLP syndrome. Two patients had abortions, fourteen patients had a successful pregnancy and four of them required a caesarian section.

During pregnancy, all IgA nephropathy patients (100%) developed hypertension-requiring treatment and 3 of them (25%) developed preeclampsia. One patient (8.3%) had HELLP syndrome. All patients had worsening of their proteinuria during pregnancy from 535.2 (101.4) mg/24 hours to 2179.2 (636.6) mg/24 hours \( (p < 0.01) \) with a decrease in creatinine clearance from 88.6 (7.6) mls/min to 77.4 (5.9) mls/min \( (p < 0.05) \). No foetal complication was observed.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD) at conception</th>
<th>Mean (SD) at 3rd trimester</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine (µmol/L)</td>
<td>87.2 (4.3)</td>
<td>84.3 (5.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>88.6 (7.6)</td>
<td>77.4 (5.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>128.2 (7.6)</td>
<td>163.7 (8.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>82.1 (4.2)</td>
<td>90.3 (3.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24 hour urine protein (mg)</td>
<td>535.2 (101.4)</td>
<td>2179.2 (636.6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

For renal patients we used methyldopa (dose ranging from 250mg bid to 500mg qid) for all our patients except for one who required hydralazine drip. Three patients (25%) were eventually diagnosed with preeclampsia, based on the triad of hypertension, severe edema and heavy proteinuria. Only one patient (8.3%) developed hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Two patients, one with preeclampsia (number 11) and the other with the HELLP syndrome (number 6) required cesarean section.

**Discussion**

In pregnant women daily proteinuria in excess of 300mg at any time during gestation is considered abnormal [2]. The increase of the mean daily proteinuria from 354.7 ± 121.73mg to 1531.3 ± 2013.13mg observed from 32 weeks to 34-36 weeks of gestation respectively, could indicate a lupus flare [3]. Pregnancy can increase the possibility of a lupus flare [4] although there seems to be a lack of consistency in the literature, with some studies indicating an increase in lupus flare with pregnancy, while others show no increase in flares [5]. Also, diagnosis of a lupus flare in pregnancy may be difficult as normal physiological changes or pregnancy related complications such as pre-eclampsia can mimic a lupus flare. However, overall many studies confirm lupus flares are common in pregnancy [6-8].

In pregnant women creatinine clearance is usually more than 100ml/min and a serum creatinine level greater than 0.8mg/dl (70.72 µmol/l) is indicative of renal impairment [4]. Therefore a creatinine clearance level reduction from the preconception level of 89.2ml/min to 79.85 ± 4.47ml/min, together with a mean serum creatinine level of 83±7.26 µmol/l, would suggest renal impairment [4].

Haematological abnormalities are common in patients with SLE and about 50% of them are usually anaemic [5] defined as haemoglobin of 12g/dl or less for women [6]. However, during normal pregnancy the plasma volume increases [4] causing haemodilution which can give an artificially low haemoglobin level. Nevertheless, in this study 65% (13/20) of patients had an abnormally low haemoglobin level of less than 11g/dl [7].

Lupus is a very common problem in Saudi Arabia, but it’s unusual for Nephrologists and Obstetricians to see a pregnant patient with lupus. Even though all our patients had inactive lupus, there were still significant complications for both the mother and the foetus. Therefore before embarking on a pregnancy it’s essential that severe hypertension, proteinuria and renal impairment are ruled out.

There is a vast amount of literature on SLE and pregnancy outcome and the results of this study are generally comparable to those of many other studies. Although, our results show that inactive
SLE in pregnant patients still gave rise to serious complications for both mother and foetus. It is noteworthy, that had they had active SLE at the onset of the pregnancy, it is likely they may have had a worse outcome. Active lupus nephritis patients are generally advised against pregnancy, and a more favourable pregnancy outcome is usually observed in patients with inactive SLE at conception and during the gestation. In general, lupus flares occur with greater frequency in SLE patients with active disease at conception. In agreement with the literature, our study supports the prediction of an adverse foetal outcome if the SLE patients have a history of nephritis. Proteinuria >0.5g/day was also associated with complications during pregnancy. Furthermore, many studies confirm SLE pregnancies have a greater foetal loss and preterm births when compared to the general population. Although all 20 patients in this study reached the third trimester [8]. It’s important to understand the pregnancy-lupus interaction, because many potential complications during pregnancy can be confused as symptoms of lupus disease activity, which is challenging for both diagnosis and treatment.

Despite the improvements in obstetrical care, complications still exist for mother and baby as lupus reactivations are common during pregnancy. Therefore, pregnancy in SLE patients is considered a high-risk pregnancy. For optimal pregnancy outcome it is advisable to plan conception when SLE is inactive. In the last decade maternal and foetal outcome have improved in pregnant patients with SLE. In part, this is due to improvements in obstetrical care. Other possible reasons for improvement of pregnancy outcomes over time include: Conception counselling to advise timing of pregnancy when SLE is inactive; better multidisciplinary care and more patients with mild SLE being diagnosed [8].

IgA Nephropathy affects all ages but is most common in the second and third decades of life. Eighty percent (80%) of patients are aged 16-35 years at the time of diagnosis [9]. During this period women are at the peak of their reproductive life. The rates of pregnancy and child birth are among the highest in Saudi Arabia for social and cultural reasons [9-11]. This fact plus the fact that IgAN is a common form of glomerulonephritis in Saudi Arabia renders the possibility of pregnancy in females with IgAN as being high [13].

Although in our series of 12 patients, there was what could be termed a mild form of IgAN (pre-conception normotension, less than one gram per day-proteinuria, normal renal function and no requirement for immunosuppression), the findings during pregnancies were disturbing. Indeed, by the end of each pregnancy, there was clear deterioration in renal function. Not only that, but all patients developed significant hypertension requiring treatments and many-fold increase in the rate of protein excretion. We noticed that renal parameters were similar in both groups while not all the SLE group had successful complete pregnancy.

Conclusion:

Despite the numerous studies evaluating the effect of pregnancy on SLE activity, the exact consequence of pregnancy on the course of SLE is not completely understood. Historically, the medical community advised against pregnancy in SLE patients. However over time this view has changed and SLE is no longer a contraindication to pregnancy. In summary, although women with SLE face significant risks during pregnancy, a successful outcome for both mother and baby is possible if lupus is inactive at conception and there is proper management and close monitoring from pre-conception to post-partum.

In the IgAN group, we observed an increased risk of uncontrolled hypertension, proteinuria and preeclampsia. We recommend close clinical and laboratory monitoring, before, during and after conception and delivery, to address any potential complication that might occur to the mother or to her unborn child.

Limitations of the study relate to the small sample size, nevertheless although generalizations cannot be made, it is possible for women with SLE to become pregnant and reach the third trimester, even if there are still serious complications which need to be addressed. The results of this study show that not all pregnancies in SLE patients fail and 70% (14/20) had a successful pregnancy. However, the small sample size of the study is a limitation which may be addressed by using meta-analysis in order to provide a detailed guide for SLE in pregnancy.

We feel that pregnancy should be monitored in these groups even if the clinical findings are not alarming or impressive. More caution should be taken in patients with SLE.

References


