INTRA-UTERINE GROWTH RESTRICTION IN PREGNANCIES COMPLICATED BY SYSTEMIC LUPUS ERYTHEMATOSIS

By

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ABSTRACT

Background: Compared with healthy pregnant women, pregnancy in women with systemic lupus erythematosus (SLE) is associated with a higher risk of complications including preterm labor, unplanned cesarean delivery, fetal growth restriction, preeclampsia, and eclampsia.

Objective: The aim of this work was to correlate the presence of lupus anticoagulant and anticardiolipin IgG, IgM with the incidence of intrauterine growth restriction in pregnancies complicated by systemic lupus erythematosus.

Subjects and methods: The current study was a prospective study included 56 pregnant patients with systemic lupus erythematosus coming for antenatal care, age ranged from 19 to 38 years, pregnant women at any gestational age, sure of their dates to confirm gestational age, previously known as systemic lupus erythematosus. Patients subjected to detailed history tacking, routine antenatal investigations, immunological tests, frequent u/s and doppler and birth weight.

Results: The current study was a prospective study conducted at the Department of Obstetrics and Gynecology, Sayed Galal University Hospital during the period from April 1st. to September 30th, 2019. It included 56 pregnant patients with systemic lupus erythematosus coming for antenatal care. Miscarriage occurred in 10.7%, preterm labor in 41.1%, fetal growth restriction in 21.4%, low birth weight (less than 2.5 kg) in 28.5% and 3 neonates were admitted to neonatal ICU. Among preterm deliveries, 7 cases were electively terminated between 34 and 36 weeks of gestation (5 cases had oligohydramnios and 2 cases had deteriorating doppler indices). There were no neonatal cases with congenital heart block. Also, there was no maternal mortality recorded.

Conclusion: Despite pregnancies complicated with systemic lupus erythematosus carry a high risk for both mother and fetus, there was a great improvement in the outcome of both. So it need more frequent antenatal care visits and frequent monitoring.

Keywords: Systemic lupus erythematosus, lupus anticoagulant, anticardiolipin antibodies, intrauterine growth restriction.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a potentially fatal, chronic autoimmune disorder with a prevalence that ranges from approximately 20-150 cases per 100,000 populations (Tsokos, 2011).

SLE is prevalent in women with an incidence peak in childbearing age (Mecacci et al., 2009).

Important factors for pregnancy outcome in patients with systemic lupus erythematosus include whether disease is active at the beginning of pregnancy, age and parity, coexistence of other medical or
obstetrical disorders, and whether antiphospholipid antibodies are detected (Zhao et al., 2013).

The presence of antiphospholipid antibodies has been associated with poor fetal outcomes.

The presence of a lupus anti-coagulant is associated with adverse fetal outcomes, with an overall live birth rate of 73% and a prematurity rate of 37%, despite the use of a number of treatment modalities (Smyth et al., 2010).

Adverse obstetrical outcomes including fetal growth restriction have been associated with three species of antiphospholipid antibodies: anticardiolipin antibodies, lupus anticoagulant and antibodies against β 2 glycoprotein I (Ginnakopoulos and Krilis, 2013).

Frequencies of spontaneous abortions and stillbirths are increased in women with lupus, with the stillbirth rate nearly 5 times greater than for non-lupus pregnancies.

Occurrence of preeclampsia/eclampsia is increased in lupus, and preeclampsia/Hemolysis, Elevated Liver, Low Platelet (HELLP) syndrome correlates with the presence of maternal antiphospholipid antibodies and thrombocytopenia.

It is recognized that pregnancy may exacerbate SLE, and the SLE may increase the pregnancy complications, including spontaneous abortion, premature delivery, intrauterine growth restriction (IUGR), and preeclampsia (Sun Ko, 2011).

The adverse perinatal outcomes resulting from SLE are believed to occur as a consequence of immunological alterations in the placenta. The histology of the placenta frequently reveals vascular abnormalities in the utero-placenta or alterations in coagulation.

Intrauterine growth restriction (IUGR) has been reported in 12–32% of lupus pregnancies, which was found to be higher than control populations.

Risk factors for intrauterine growth restriction (IUGR) in lupus pregnancies include hypertension, active lupus (particularly lupus nephritis) and the presence of antiphospholipid antibodies.

These pregnancies are usually monitored intensively by fetal ultrasound. The second trimester Doppler ultrasound examination may be useful as an indicator of IUGR and risk for pregnancy loss, and in particular, the last ultrasound within 5 weeks of delivery has been shown to best predict IUGR in lupus (Crow, 2013).

The present work aimed to correlate the presence of lupus anticoagulant and anticardiolipin IgG, IgM with the incidence of intrauterine growth restriction in pregnancies complicated by systemic lupus erythematosus (SLE).

**PATIENTS AND METHODS**

The current study was a prospective study included 56 pregnant patients with systemic lupus erythematosus (SLE) coming for antenatal care.

After approval of Institutional ethical committee and obtaining informed consents, patients were collected from the Department of Obstetrics and Gynecology, Sayed Galal University.
Hospital during the period from April 1st. to September 30th, 2019.

● Inclusion criteria:
  Age ranged from 19 to 38 years, pregnant women at any gestational age, sure of their dates to confirm gestational age, previously known as systemic lupus erythematosus.

● Patients were excluded if pregnant women have other medical disorders, (e.g.) diabetes mellitus, cardiac, pregnancy induced hypertension or the presence of fetal congenital anomalies or cases of intrauterine fetal death.

● Patients were subjected to:
  1. Detailed history taking with special concern to obstetric history, last menstrual period for calculation of gestational age, postpartum complications in previous pregnancies, history of lupus flare and timing of it.
  2. Routine antenatal investigations included:
     • Complete blood picture.
     • Random blood sugar.
     • Complete urine analysis.
     • Kidney function (urea, creatinine).
     • Liver function (SGOT, SGPT).
  3. Immunological tests included:
     • Lupus anticoagulant: measured by mixing patient’s plasma with normal pooled plasma and clotting was re-assessed.
     Reference range: (34.4-40.4 sec).
     • Anticardiolipin antibodies were measured using enzyme linked immunosorbant assay (ELISA).
     Reference range: IgM (<7 negative, ≥7 positive), IgG (<10 negative, ≥10 positive).
     • Anti ds DNA antibodies were measured using immunofluorescence technique.
     • Anti Ro and Anti La antibodies were measured using automated enzyme linked immunosorbant assay (ELISA).
     Reference range: (Normal <15, borderline 15-25, elevated >25).
     • Antinuclear antibodies were measured using immunofluorescent antinuclear antibody test.
     Reference range: (starting titer 1/40, significant titer >1/80).
     • C3 and C4 were measured using enzyme linked immunosorbant assay (ELISA).
     Reference range: (C3: 90-180, C4: 10-40).
  4. Frequent U/S and Doppler imaging throughout pregnancy till delivery include:
     • Fetal biometry for assessment of gestational age and the presence of IUGR (IUGR is below 5th percentile).
     • Amniotic fluid index measurement.
     • Doppler study: umbilical artery Doppler, to measure the mean systolic/diastolic ratio (S/D), resistance index (RI) and pulsatility index (PI).
     • Uterine artery Doppler.
  5. Birth weight (low birth weight (LBW) is less than 2.5 kg at birth).
Technique of ultrasound and Doppler examination

Trans-abdominal ultrasound was performed to all patients while in a slightly tilted position with the head of the bed raised 30 degrees and with a small pillow under the right loin. Using SONOACE SA-X6 ultrasound machine with Doppler unit and convex linear transducer 3.5 mHz.

● Umbilical Artery Doppler

All patients were placed in a semi-recumbent position with a left lateral tilt, and then the uterine contents are scanned to select an area of amniotic cavity with several loops of umbilical cord.

Then we used color and pulsed wave Doppler in a free-floating loop of the umbilical cord neither close to the placenta nor to the fetal abdomen during periods of fetal inactivity.

Random site for the umbilical artery was determined and the Doppler indices were taken (PI, RI). When the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and Doppler umbilical artery pulsatility index (UA-PI) was estimated. A minimum of 3 separate readings was averaged before the final values were obtained.

Doppler study was done at 32 weeks gestation and repeated at 36 weeks except in cases of IUGR and oligohydramnios Doppler was done whenever needed either weekly or every 48 hours till delivery.

● Amniotic Fluid Index (AFI)

a. The uterus is divided into four quadrants by using the umbilicus as one reference point dividing the uterus into upper and lower halves, and the linea nigra is then used to divide the uterus into right and left halves.

b. A linear transducer is then placed on the maternal abdomen along the longitudinal axis of the mother, with the transducer head being perpendicular to the floor in each of the four uterine quadrants.

c. The vertical diameter of the largest AF pocket (free of cord or limbs) is measured and the numbers obtained from each uterine quadrant are summed to represent the AFI.

d. AFI 0-5 was labeled as low AFV, while an AFI 5.1 to 20 cm was labeled as normal AFV and AFI more than 20 cm was labeled as abnormally high AFV.

Findings of ultrasound will be correlated with lupus anticoagulant anticardiolipin antibodies results to figure the relation between the presence of any of them and the presence of:

• Miscarriage.
• Intrauterine growth restriction.
• Low birth weight.

● Statistical methods

Data were statistically described in terms of mean ± standard deviation (SD), frequencies (number of cases) and percentages when appropriate.

All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).
RESULTS

The current study is a prospective study conducted at the department of Obstetrics and Gynecology, Sayed Galal University Hospital during the period from April 1st. to September 30th, 2019. The included patients’ age ranged between 19 and 38 years (Table1).

Table (1): Description of study group (No of cases: 56)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Range</th>
<th>Mean</th>
<th>±Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(19-38)</td>
<td>25.59</td>
<td>±4.459</td>
</tr>
<tr>
<td>Parity</td>
<td>(0-2)</td>
<td>0.66</td>
<td>±0.815</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>(0-6)</td>
<td>1.00</td>
<td>±1.427</td>
</tr>
<tr>
<td>Gestational age</td>
<td>(9-39)</td>
<td>33.59</td>
<td>±7.019</td>
</tr>
</tbody>
</table>

In our study, we recorded miscarriage in 10.7%, preterm labor in 41.1%, fetal growth restriction in 21.4%, low birth weight (less than 2.5 kg) in 28.5%, 5.4% neonates were admitted to neonatal ICU, and 5.4% with postpartum flare as nephritis but with no maternal mortality (Table 2).

Table (2): Pregnancy outcomes of the 56 pregnancies complicated with SLE (No of cases: 56)

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number</th>
<th>No. of pregnant patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriages</td>
<td>6</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>IUGR</td>
<td>12</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>Live births</td>
<td>50</td>
<td>89.3</td>
<td></td>
</tr>
<tr>
<td>IUFD</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Full term deliveries</td>
<td>27</td>
<td>48.2</td>
<td></td>
</tr>
<tr>
<td>Preterm deliveries</td>
<td>23</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>16</td>
<td>28.5</td>
<td></td>
</tr>
<tr>
<td>Neonatal ICU</td>
<td>3</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Postpartum flare</td>
<td>3</td>
<td>5.4</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

Systemic lupus erythematosus (SLE) predominantly affects women of childbearing age. Compared with healthy pregnant women, pregnancy in women with SLE is associated with a higher risk of complications, including a 2- to 4-fold increased rate of obstetric complications including preterm labor, unplanned cesarean delivery, fetal growth restriction, preeclampsia, and eclampsia.

Important factors for pregnancy outcome in patients with systemic lupus erythematosus include whether disease is active at the beginning of pregnancy, age and parity, coexistence of other medical or obstetrical disorders, and whether antiphospholipid antibodies are detected (Zhao et al., 2013).
In our study, we recorded intrauterine growth restriction (21.4%), miscarriage (10.7%), preterm delivery (41.1%) and low birth weight (28.5%).

Yelnik and Colleagues (2016), conducted a large multicenter, observational study of pregnancy outcomes (the PROMISSE Study) of the 44 antiphospholipid antibody positive patients, 13 were found to have adverse pregnancy outcomes, defined as fetal death after 12 weeks of gestation, neonatal death, delivery prior to 36 weeks of gestation due to pre-eclampsia or placental insufficiency, or small-for-gestational age (birth weight less than the fifth percentile). LAC was found in 69% of the patients with adverse pregnancy outcomes, compared to 27% of patients without adverse pregnancy outcomes.

In our study, lupus anticoagulant was found in 66.7% of intrauterine growth restriction, all cases of miscarriage and in 73.9% of preterm deliveries. Anticardiolipin antibodies were positive in 41.7% of intrauterine growth restriction, 83.3% of cases of miscarriage and in 26.1% of preterm deliveries. Patients with positive IgG anticardiolipin antibodies had a higher incidence of miscarriage compared to those with negative IgG anticardiolipin antibodies.

SLE pregnant patients carry a higher risk of IUGR when compared to normal females (28.5% vs. 17.5%) (Chen et al., 2010).

In our study, 41.1% had preterm deliveries mainly due to oligohydramnios or deteriorating Doppler indices.

Other several studies showed that pregnancy increased the incidence of SLE flares with rates up to 35% (Imbasciati et al., 2009). The difference in results is due to different number of cases and that they worked on cases with pre-existing biopsy proven Lupus Nephritis.

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 (Foocharoen et al., 2009).

In our study there were 5.4% with postpartum flare as (nephritis), but with no maternal mortality. C3 and C4 were 12.5%, 5.3% of them experienced postpartum flare (nephritis).

Hendawy et al (2011) stated that prematurity was the most common fetal complication followed by intrauterine growth restriction.

In a review of 13 studies with 17 maternal deaths attributable to SLE and lupus nephritis, all occurred in those with active disease (Ritchie et al., 2012).

In our study, we did not record any case of maternal or neonatal death.

The EUROAPS registry reported on the obstetrical results of 247 women recently. Recurrent first trimester miscarriage followed by fetal loss was the most common obstetric morbidities in this cohort. Prematurity was the most common finding (47%), followed by stillbirth and fetal loss (22.5%), miscarriage (16%), fetal growth restriction (14%). The presence of lupus anticoagulant (LAC), isolated or in combination with
anticardiolipin and/or anti-beta2-glycoprotein I was the strongest marker related to poor obstetric outcomes (De Jesus et al., 2015).

In another study, Imbasciati and Associates (2009) described outcomes in 113 pregnancies. After excluding 9 miscarriages, of the 104 remaining pregnancies, a third were delivered preterm, a third of infants weighed < 2500 gm, and the perinatal mortality rate was 6.

A meta-analysis included 37 studies with 2,751 pregnancies in 1,842 patients with SLE. Fetal complications included spontaneous abortion (16%), intrauterine growth retardation (12.7%), and stillbirth (3.6%). Among all live births the premature birth rate reached 39.4%. Neonatal deaths were reported at 2.5% (Smyth et al., 2010).

CONCLUSION

Despite pregnancies complicated with systemic lupus erythematosus carry a high risk for both mother and fetus there was a great improvement in the outcome of both. So it needs more frequent antenatal care visits and frequent monitoring.

REFERENCES


Timing of Pregnancy in 183 pregnancies in Korean Patients with SLE. International Journal of Medical Sciences, 8(7):577-583.


تقييم النمو داخل الرحم في حالات الحمل التي تضاعفت بالذينية

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خلفية البحث: الذينية الحمراء هو مرض غير متجانس أكلينيكي وهو عبارة عن حالة في المناعة الذاتية يتميز بوجود أجسام مضادة موجهة ضد المستضدات النووية، ويستند تشخيص الذينية الحمراء على النتائج الميزة للأعراض الإكلينيكية لإصابات الجلد والعظام والكلى والجهاز العصبي وكما ذلك على المعلومات المفصلية مثل الأجسام المضادة للنواة وخاصة الأجسام المضادة للحمض النووي.

هدف البحث: ربط وجود مضادات تختبر الذينية والأجسام المضادة للكارديوليبين مع حدوث نقص الوزن للطفل عند الولادة في حالات الحمل المعقدة بسبب الذينية الحمراء.

المريض وطريق البحث: إنتمت الدراسة على 56 مريضة تعاني من الذينية الحمراء في قسم النساء والتوليد مستشفى السيد جلال، جامعة الأزهر خلال الفترة من أبريل 2018 إلى سبتمبر 2019. وقد تم أخذ التاريخ المفصل والتحاليل الروتينية السابقة للولادة، والاختبارات المخبرية والإجراءات الفوقية السريرية والدموية قياس وزن الطفل عند الولادة.

نتائج البحث: في الدراسة الحالية سجلنا الإجهاض في 10.7٪، والولادة المبكرة في 41.1٪، ونقص نمو الجنين في 21.4٪، وانخفاض الوزن عند الولادة في 28.5٪. وكانت مضادات تختبر الذينية إيجابية في 100٪ من حالات الإجهاض، 73.9٪ من حالات الولادة المبكرة وفي 66.7٪ من حالات نقص نمو الجنين. حيث أن الأجسام المضادة للكارديوليبين كانت إيجابية في 83.3٪ من حالات الإجهاض، 26.1٪ من حالات الولادة المبكرة وفي 41.7٪ من حالات نقص نمو الجنين. وقد نقص مستوى C3 و C4 C3 كما وجد في 7 حالات بنسبة 12.5٪.
حالات منها شهدت حدوث إلتهاب حاد للكلية ما بعد الولادة، ولم تسجل أي حالة وفاة للأمهات أو الأطفال حديثي الولادة.

الاستنتاج: على الرغم من أن حالات الحمل المصحوبة بالذنبيه الحمراء تتضمن خطورة عالية على الأم والجنين، إلا أنه هناك تحسن كبير في النتائج لكليهما، لكنها تحتاج إلى المزيد من زيارات متابعة للحمل والرصد المتكرر لحالتها قبل الولادة.