

Incidence of Intrauterine Growth Restriction among Pregnancies Complicated by Systemic Lupus Erythematosus

NAHLA H. AHMED, M.Sc.*; MOHAMED H. SHEHATA, M.D.*; EMAN A. HUSSEIN, M.D.* and DALIA G. AMIN, M.D.**

The Departments of Obstetrics & Gynecology and Clinical & Chemical Pathology**, Kasr El-Eini Hospital, Cairo University*

Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies directed against nuclear antigens. It is a multisystem disease, and patients can present in many different ways. Women with systemic lupus erythematosus maintain fertility, although once they become pregnant, they have an increased frequency of adverse pregnancy outcomes including intrauterine growth restriction.

Aim of Study: To correlate the presence of lupus anticoagulant and anticardiolipin antibodies with the incidence of intrauterine growth restriction in pregnancies complicated by systemic lupus erythematosus.

Patients and Methods: We included 56 pregnant patients with systemic lupus erythematosus coming for antenatal care at any gestational age during the period from June 2015 to June 2016 at Kasr El-Eini Hospital, Cairo University. We correlated the presence of lupus anticoagulant and anticardiolipin antibodies with the incidence of intrauterine growth restriction among the study group.

Results: Among the included 56 pregnant patients, 50 patients had live births (89.3%) and 6 patients had abortions (10.7%). Also we recorded abortion in 10.7%, preterm labor in 41.1%, fetal growth restriction in 21.4%, low birth weight (less than 2.5kg) in 28.5% and 3 neonates were admitted to neonatal ICU.

There is significant relation between the presence of anticardiolipin IgG antibodies and the presence of current abortion (p -value 0.008). There is no significant relation between the presence of lupus anticoagulant (LAC) and the presence of intrauterine growth restriction or current abortion.

Conclusion: Despite that pregnancies complicated with systemic lupus erythematosus carry a high risk for both mother and fetus there is a great improvement in the outcome of both.

Key Words: *Systemic lupus erythematosus – Lupus anticoagulant – Anticardiolipin antibodies – Intrauterine growth restriction.*

Correspondence to: Dr. Nahla H. Ahmed, The Department of Obstetrics & Gynecology, Kasr El-Eini Hospital, Cairo University

Introduction

SYSTEMIC lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies directed against nuclear antigens. It is a multisystem disease, and patients can present in many different ways [1].

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 fetal growth restriction [2].

Important factors for pregnancy outcome in patients with systemic lupus erythematosus include age, parity, coexistence of other medical or obstetrical disorders, and whether antiphospholipid antibodies are detected [3].

Diagnosis of SLE is based on characteristic clinical findings of skin, joints, kidneys, and the central nervous system, as well as on serological parameters [4].

Several blood tests can be performed to detect specific auto-antibodies and help make the diagnosis of lupus. These blood tests are not conclusive by themselves, but combining the tests with certain physical findings can help to corroborate a diagnosis [5].

Lupus anticoagulants (LAC) are a heterogeneous class of immunoglobulins that may develop spontaneously or as a consequence of autoimmune diseases [6].

Once the patient has been identified as positive for LAC, it is imperative that testing be repeated on a 2nd occasion 12 weeks later [7].

Tests for lupus anticoagulant are nonspecific coagulation tests. The partial thromboplastin time is generally prolonged because the anticoagulant interferes with conversion of prothrombin to thrombin in vitro [8].

Phospholipids are the main lipid constituents of cell and organelle membrane. Antiphospholipid antibodies are directed against these phospholipids or phospholipid binding proteins [9].

This antibody group may be of IgG, IgM and IgA classes, alone or in combination [8]. IgG is the anticardiolipin antibody type most associated with complications [10]. Approximately 50% of people with lupus possess these antibodies [10].

In women with high levels of anticardiolipin antibodies and especially when lupus anticoagulant is identified, there are increased risks of decidual vasculopathy, placental infarction, fetal growth restriction, early onset preeclampsia and recurrent fetal death [8,11].

The aim of this study is to correlate the presence of lupus anticoagulant and anticardiolipin antibodies with the incidence of intrauterine growth restriction in pregnancies complicated by systemic lupus erythematosus.

Patients and Methods

The current study was a prospective study included 56 pregnant patients with systemic lupus erythematosus coming for antenatal care collected during the period from June 2015 to June 2016.

All patients were followed by team of obstetricians, chemical pathologists and rheumatologists during antenatal care and neonatologists at delivery.

Patients included in the study were pregnant women at any gestational age ranging from 19 to 38 years, previously known as systemic lupus erythematosus and sure of their dates to confirm gestational age.

- Gestational age was confirmed either by dates or early ultrasound.
- All patients were on remission throughout the whole pregnancy.

Patients were excluded if:

- Pregnant women with other medical disorders (e.g.: Diabetes mellitus, cardiac, pregnancy induced hypertension).
- The presence of fetal congenital anomalies.
- Cases of intrauterine fetal death.

- Cases of twin pregnancy.

• 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 include: Complete blood picture, random blood sugar, complete urine analysis, kidney function (urea, creatinine), liver function (SGOT, SGPT).

3- Immunological tests include:

Anticardiolipin ELISA is the test done to detect the antiphospholipid antibodies. The test results are reported by the specific isotype (IgG and IgM) and their levels in serum [12].

- Lupus anticoagulant: Measured by mixing patient's plasma with normal pooled plasma and clotting is re-assessed. Reference range: (34.4-40.4 sec).

- Anticardiolipin antibodies: Measured using enzyme linked immunosorbant assay (ELISA). Reference range: IgM (<7 negative, ≥7 positive), IgG (<10 negative, ≥ 10 positive).

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).

5- Birth weight (low birth weight (LBW) is less than 2.5kg at birth).

Every patient was seen monthly till seventh month then every 2 weeks till ninth month then weekly till delivery.

Statistical methods:

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

Comparison of numerical variables between the study groups was done using Student's *t*-test for independent samples in comparing normally distributed data and Mann Whitney U test for

independent samples in comparing non-normal data.

For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5.

p-values less than 0.05 was considered statistically significant. 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

This study included 56 pregnant patients with systemic lupus erythematosus coming for antenatal care at the department of high risk pregnancy of Kasr El-Eini Hospital, Cairo University during the period from June 2015 to June 2016.

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

	Range	Mean	±Standard deviation
Age (years)	(19-38)	25.59	±4.459
Parity	(0-2)	0.66	±0.815
Gestational age (wks)	(9-39)	33.59	±7.019

Analysis of the study group:

First clinical manifestations of systemic lupus erythematosus among the study group were arthritis in 22 cases (39%), nephritis in 21 cases (38%), skin rash in 9 cases (16%), photo sensitivity in 3 cases (5%) and neurological symptoms in one case (2%).

The study recorded lupus anticoagulant (LAC) positive in 41 cases (73.2%), Anticardiolipin IgG antibodies were positive in 17 cases (30.4%) and Anticardiolipin IgM antibodies were positive in 7 cases (12.5%).

Table (2): Relation between IUGR and presence of lupus anticoagulant (LAC), anticardiolipin IgG or IgM antibodies (No of pregnant cases: 56).

	IUGR (No. 12)	No IUGR (No. 44)	<i>p</i> -value
LAC (positive)	8 (4.3%)	33 (58.9%)	0.715
LAC (negative)	4 (7.1%)	11 (19.7%)	
IgG (positive)	5 (8.9%)	12 (21.4%)	0.480
IgG (negative)	7 (12.5%)	32 (57.2%)	
IgM (positive)	2 (3.6%)	5 (8.9%)	0.637
IgM (negative)	10 (17.8%)	39 (69.7%)	

This study showed abortion in 10.7%, preterm labor in 41.1%, fetal growth restriction in 21.4% and low birth weight (less than 2.5 kg) in 28.5%.

Among 12 cases (21.4%) complicated with IUGR, 8 had positive lupus anticoagulant (66.7%), 5 cases (41.7%) had positive anticardiolipin IgG antibodies and 2 cases (16.7%) had positive anticardiolipin IgM antibodies.

Table (3): Relation between current abortion and presence of lupus anticoagulant (LAC), anticardiolipin IgG or IgM antibodies (No of pregnant cases: 56).

	Current abortion (No. 6)	No abortion (No. 50)	<i>p</i> -value
LAC (positive)	6 (10.7%)	35 (62.5%)	0.177
LAC (negative)	0	15 (26.8%)	
IgG (positive)	5 (8.9%)	12 (21.4%)	0.008
IgG (negative)	1 (1.8%)	38 (67.9%)	
IgM (positive)	2 (3.6%)	5 (8.9%)	0.117
IgM (negative)	4 (7.1%)	45 (80.4%)	

6 cases had abortions (10.7%) 2 cases of them had first trimester abortion and 4 cases had second trimester abortion with lupus anticoagulant positive in all cases.

There is significant relation between the presence of anticardiolipin IgG antibodies and the presence of current abortion (*p*-value 0.008). [Significant *p*-value is (<0.05)].

Discussion

Studies have shown that women with systemic lupus erythematosus maintain fertility, although once they become pregnant, they have an increased frequency of adverse pregnancy outcomes including intrauterine growth restrictions, pregnancy losses and preterm births [13].

Intrauterine growth restriction (IUGR) has been reported in 12-32% of lupus pregnancies, which was found to be higher than control populations [14].

Frequent complications in a cohort study of women with SLE during pregnancy show fetal growth restriction in 5.6% [11].

In another study intrauterine growth restriction occurs in 14.8% ±2% of SLE pregnancies. The main factors contributing to the increased rate of growth restriction are hypertension, corticosteroids, antiphospholipid antibodies and preeclampsia [15].

A recent 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% [16].

SLE pregnant patients carry a higher risk of IUGR when compared to normal females (28.5% vs. 17.5%) [17].

The presence of lupus anticoagulant (LAC) isolated or in combination with anticardiolipin antibodies was the strongest marker related to poor obstetric outcomes [18].

In the current study we recorded 12 cases had intrauterine growth restriction (21.4%), 6 cases of abortion (10.7%), 23 cases had preterm delivery (41.1%) and 16 cases had low birth weight (28.5%).

In this study preterm deliveries (41.1 %) were mainly due to oligohydramnios or deteriorating Doppler indices.

In our study lupus anticoagulant was found in 66.7% of intrauterine growth restriction, all cases of abortion and in 73.9% of preterm deliveries.

Anticardiolipin IgG antibodies were positive in 41.7% of intrauterine growth restriction, 83.3% of cases of abortion and in 26.1 % of preterm deliveries.

Anticardiolipin IgM antibodies were positive in 16.7% of intrauterine growth restriction, 33.3% of cases of abortion and in 4.3% of preterm deliveries.

Conclusion and Recommendations:

Despite pregnancies complicated with systemic lupus erythematosus carry a high risk for both mother and fetus there is a great improvement in the outcome of both.

So it needs more frequent antenatal care visits and frequent monitoring.

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معدل حدوث تأخر نمو الجنين داخل الرحم في الحوامل اللآتى تعانين من الذئبة الحمراء

الذئبة الحمراء هو مرض غير متجانس إكلينيكيًا وهو عبارة عن خلل في المناعة الذاتية ويتميز بوجود أجسام مضادة موجهة ضد المستضدات النووية. ويمكن تعريفه بأنه مرض يصيب أجهزة متعددة ويمكن للمرضى الإصابة بأعراض مختلفة إلى حد كبير.

وقد أظهرت الدراسات أن النساء المصابات بالذئبة قادرات على الحفاظ على الخصوبة، على الرغم من ذلك بمجرد أن تصبح حاملًا، تعاني من زيادة في معدل حدوث مشاكل الحمل والتي تتضمن فقد الحمل، نقص نمو الجنين والولادة المبكرة.

أن الهدف من هذا العمل هو ربط وجود مضادات تخثر الذئبة والأجسام المضادة للكارديوليبين مع حدوث نقص الوزن للطفل عند الولادة في حالات الحمل المعقدة بسبب الذئبة الحمراء.

اشتملت هذه الدراسة على ٥٦ مريضة حامل تعانى من الذئبة الحمراء قادمة للحصول على الرعاية السابقة للولادة تم جمعها من قسم الحمل الحرج بمستشفى القصر العيني، جامعة القاهرة خلال الفترة من يونيو ٢٠١٥ إلى يونيو ٢٠١٦.

تعرضت كل مريضة لأخذ التاريخ المفصل، التحاليل الروتينية السابقة للولادة، والاختبارات المناعية والموجات فوق الصوتية والديولر وقياس وزن الطفل عند الولادة.

نتائج الدراسة: ١٢ حالة عانت من نقص نمو الجنين بنسبة ٢١.٤٪ منهم ٨ حالات بنسبة ٦٦.٧٪ تحتوي على مضادات تخثر الذئبة و ٥ حالات احتوت على الأجسام المضادة للكارديوليبين بنسبة (٤١.٧٪).

في الدراسة الحالية سجلنا الإجهاض في ١٠.٧٪ من الحالات، الولادة المبكرة في ٤١.١٪، ونقص نمو الجنين في ٢١.٤٪، وانخفاض الوزن عند الولادة في ٢٨.٥٪.

مضادات تخثر الذئبة كانت إيجابية في ١٠.٠٪ من حالات الإجهاض، ٧٣.٩٪ من حالات الولادة المبكرة وفي ٦٦.٧٪ من حالات نقص نمو الجنين في حين أن الأجسام المضادة للكارديوليبين كانت إيجابية في ٨٢.٣٪ من حالات الإجهاض، ٢٦.١٪ من حالات الولادة المبكرة وفي ٤١.٧٪ من حالات نقص نمو الجنين.

لم تكن هناك علاقة ذات أهمية إحصائية بين وجود مضادات تخثر الذئبة ونقص نمو الجنين أو حدوث الإجهاض لدى حالات الدراسة.

الاستنتاج: على الرغم من أن حالات الحمل في النساء اللآتى تعانين من الذئبة الحمراء تحمل خطورة عالية إلا أن نتائج الحمل للأم والطفل قد تحسنت تحسن هائل ولهذا فإن الحامل تحتاج لزيادة معدل الزيارات أثناء الحمل وذلك لضمان أفضل النتائج.