Original Article

Uterine–umbilical artery Doppler velocimetry and pregnancy outcome in SLE patients: Relation to disease manifestations and activity

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KEYWORDS
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Doppler velocimetry;
Outcome

Abstract
Aim of the work: To evaluate the uterine–umbilical artery Doppler velocimetry and determine its relation to pregnancy outcome and disease manifestations in SLE patients.
Patients and methods: Blood flow velocity waveforms of the umbilical and uterine arteries were studied by color Doppler ultrasound in 36 pregnant SLE patients referred from the Rheumatology Department for follow up and delivery in the Obstetrics Department. Resistance index (RI) and pulsatility index (PI) were measured at the 1st week and then every 4 weeks from the 20th and 30th weeks till delivery.
Results: The mean age was 27.33 ± 4.03 years and disease duration of 5.72 ± 2.57 years. The nulliparity rate and history of previous abortions were higher in those with poor fetal outcome (50% and 62.5%, respectively). Lupus anticoagulants and anticardiolipin were obviously higher in those with a poor outcome (25% and 37.5%, respectively) with a higher association with APS in spite of anticoagulation. The SLEDAI was higher in those with a poor fetal outcome and the difference reached significance at the 24th week gestation (12.13). Eight (22.22%) of the patients had abnormal fetal outcome: 5 IUGR (13.89%), 1 IUFD (2.78%) and 2 (5.55%) with missed abortion. Uterine and umbilical artery Doppler abnormalities were higher in those with poor obstetric outcomes and were earlier revealed by the uterine.
1. Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune connective tissue disorder that primarily affects women of childbearing age. Pregnancy outcomes in women with SLE have significantly improved though a poor outcome is increased at least twofold compared with the normal population [1]. Pregnancy in SLE patients can be a concern, placing the mother and fetus at risk [2]. Most rheumatic diseases that are well controlled prior to pregnancy do not deteriorate in pregnancy, providing that the patient continues with appropriate disease-modifying therapy [3]. Patients with rheumatic diseases who become pregnant are justifiably categorized as having high-risk pregnancies. Utilizing a multidisciplinary approach successful pregnancies have become the rule rather than the exception. However, women with rheumatic disease are particularly prone to develop serious obstetric problems [4].

The most frequently observed autoimmune rheumatic disease during pregnancy is SLE where the immunoenocrine changes may influence its course [5]. Particular interest must be paid to the impact of SLE and its therapies on pregnancy and, conversely, the effect of pregnancy on the disease, which may have long-lasting implications for mothers and fetuses [6]. Adverse fetal outcomes, maternal disease flares, and drug potential teratogenic risk are the main reasons why pregnant SLE patients are considered a high-risk population [7].

The obstetric management of the pregnant SLE patients is largely dictated by the degree to which it is associated with adverse obstetric outcomes, maternal or fetal. A co-ordinated management effort on the part of obstetricians and rheumatologists will likely yield the optimal achievable results [8]. Intrauterine growth retardation (IUGR) is more likely in patients with active systemic disease, hypertension, a history of thrombosis and renal involvement [3]. Serial Doppler studies pregnant SLE patients showed that the absence of end-diastolic frequencies in the umbilical artery was a good predictor of the need for subsequent delivery by caesarian section [9].

Repeated Doppler umbilical artery velocimetry has been reported to be an effective way to follow pregnancies associated with APS and to indicate the timing of premature delivery. Color Doppler evaluation of the uterine artery RI was a good tool for early identification of pregnancies at major risk of having earlier delivery and lower birth weight and birth percentile. It provided a reliable method of studying blood flow in the uteroplacental circulation and strongly suggested impaired trophoblastic invasion of the placental bed, before any clinical sign of pre-eclampsia or IUGR [10]. Uterine artery Doppler velocimetry provides a non-invasive method to study the uteroplacental blood flow and impaired placentation perfusion and is a useful tool to identify antiphospholipid syndrome (APS) pregnancies at higher risk of poor outcome [11]. Abnormal resistance index of the uterine arteries at 18–24 weeks gestation predicted pregnancies at major risk for obstetric complications [10].

The aim of the present work was to determine fetal and maternal outcomes in pregnant SLE patients and detect the relation to disease manifestations, investigations and activity.

2. Patients and methods

2.1. Study population

Thirty-six pregnant SLE patients with a mean age of 27.33 ± 4.03 years, fulfilling the updated American College of Rheumatology (ACR) revised criteria for the classification of SLE [12] were recruited from the Rheumatology Department and outpatient clinic of Cairo University Hospitals during the year 2009. They were followed up till delivery in the Obstetrics Department.

Full history taking, thorough clinical examination and laboratory investigations were performed for all the patients and their current drug therapy was also reported. Disease activity and damage were assessed using the SLEDAI [13] and SLICC/ACR DI [14], respectively. An informed consent was obtained from all patients. CBC, ESR, liver and kidney function test in addition to C3 and C4 were measured. The ANA, anti-double-stranded DNA, Anti-Ro and Anti-La as well as anticardiolipin antibodies (IgG and IgM) were determined.

Blood flow velocity waveforms of the umbilical and uterine arteries were studied by color Doppler ultrasound. Resistance index (RI) and pulsatility index (PI) were measured at the first week and then every 4 weeks from the 20th and 30th week till delivery.

Ultrasound assessment of uterine artery Doppler velocimetry was performed by Accuvix machine (Medison, Seoul, Korea) using 3.5–5 MHz trans-abdominal probe and with interrogation of the main uterine artery at crossing with the iliac vessels. Doppler indices were taken (RI and PI). Both uterine arteries velocimetry were taken and the average indices were calculated. Umbilical artery velocimetry assessment was done using the same machine and the RI was measured 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). The 95th percentile for gestational age was used as the cutoff for abnormality. The study conforms to the ethics and standards currently applied in Cairo University Teaching Hospitals.

Statistical analysis, Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data was presented as mean ± SD. Mann–Whitney test was used for analysis of two quantitative data. One way ANOVA was used to compare more than two quantitative data. Pearson’s correlation was used for detection of the relation between two variables. p-Value was considered significant if \( p < 0.05 \).
3. Results

The study included 36 pregnant SLE patients with a mean age of 27.33 ± 4.03 years and disease duration of 5.72 ± 2.57 years. A quarter of the patients were nullipara being more in those with poor outcome (50%) compared to those with normal outcome (17.9%). Half of the patients had history of a previous abortion with a tendency to being higher in those with a poor outcome. Clinical manifestations are shown in Table 1. There was no significant difference between the patients with a normal or poor outcome as regards the age and disease duration. Those with poor fetal outcome had a significantly less mean offspring number (p 0.016) and there was a tendency for higher history of abortions in these patients.

The disease activity (SLEDAI) and damage index (SLICC) increased throughout pregnancy. The mean SLEDAI at the first week was 7.53 ± 2.31 and reached 8.6 ± 3.08 at the 24th week. Similarly, the SLICC was 0.61 ± 0.9 and became 0.78 ± 0.93. There was a higher SLEDAI and SLICC in those with a poor outcome and the difference reached significance for the disease activity at the 24th week (12.13 ± 3.27 and 7.57 ± 2.18, respectively, p 0.005).

The laboratory investigations of the studied SLE patients at the beginning of pregnancy were as follows: erythrocyte sedimentation rate (ESR) (63.5 ± 25.34 mm/1st hour), hemoglobin (Hb) (10.12 ± 1.01 g/dl), white blood cells (WBCs) (7.32 ± 3.29 × 10^9 mm⁻³), platelets (230.4 ± 64.1 × 10^9 mm⁻³), aspartate transaminase (AST) (25.44 ± 17.1 U/l), alanine transaminase (ALT) (37.9 ± 85.01 U/l), albumin (3.8 ± 0.49 g/dl), proteinuria (0.8 ± 0.95 g/24 h), creatinine (0.67 ± 0.34 mg/dl), Complement C3 (87.8 ± 25.7 g/l), C4 (16.75 ± 7.7 g/l). The antinuclear antibody (ANA) was positive in all patients, anti-dsDNA in 26 (72.2%) and the anticardiolipin (IgG and IgM) were positive in 10 (27.78%). There was a higher SLEDAI and SLICC in those with poor outcome (50%) compared to those with normal outcome (25 patients (100 mg/day) and hydroxychloroquine (HCQ) (400 mg/day) by 15.

Eight (22.22%) of the patients had abnormal fetal outcome: 5 with IUGR (13.89%) (one of them gave preterm labor at 34th week), 1 IUFD (2.78%) and 2 (5.55%) with missed abortion. All other patients (77.77%) delivered full-term and the fetuses were of good health and none had neonatal lupus. In the present study, two patients had pregnancy induced hypertension. Complement was consumed in one and the other had possible pre-eclampsia (2.78%) and the fetal outcome was good in both. Two patients with abnormal indices delivered by caesarian section, otherwise, all others had a normal vaginal delivery. The Doppler uterine and umbilical RI and PI in the studied patients according to the outcome are presented in Tables 2 and 3 and graphically presented in Fig. 1. Fig. 2 shows the abnormal uterine and umbilical arteries Doppler velocimetry.

The umbilical resistance index (RI) was significantly higher than the uterine through-out pregnancy. The difference became insignificant at the 40th week. Moreover, the umbilical pulsality index (PI) was higher than the uterine. However, the difference reached significance during the 1st, 28th, 30th and 38th weeks. During the first week, the uterine RI and PI were initially high. They were higher than the 95th percentile with notching, throughout pregnancy till delivery, in 8 patients. Starting from the 24th week, uterine RI and PI were significantly higher in those with poor fetal outcomes. Umbilical RI and PI were significantly higher in those with poor outcome starting from the 30th week till full term.

The uterine and umbilical RI and PI did not show a considerable correlation with the age or disease duration. The uterine RI significantly negatively correlated with the platelets, C3 and SLICC (R −0.44, p 0.008; R −0.38, p 0.02 and R −0.4, p 0.015, respectively) at the 1st week gestation and with the serum albumin at the 20th week (R −0.41, p 0.014). A significant positive correlation was present with the SLEDAI at the 24th week (R 0.34, p 0.04). The umbilical RI significantly negatively correlated with the steroid dose at the first and 30th week of gestation at (R −0.54, p 0.001 and R −0.4, p 0.017, respectively), with the C4 at the 40th week (R −0.51, p 0.002) and with SLICC at the 1st week (R −0.38, p 0.02).

The uterine PI at the 38th week significantly negatively correlated with the WBC count (R −0.4, p 0.015). Umbilical PI

Table 1  Clinical manifestations of the pregnant SLE patients.

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>All patients (36)</th>
<th>Poor outcome (8)</th>
<th>Normal outcome (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous</td>
<td>28 (77.78)</td>
<td>6 (75)</td>
<td>22 (78.6)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>15 (41.67)</td>
<td>5 (62.5)</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>24 (66.67)</td>
<td>5 (62.5)</td>
<td>19 (35.7)</td>
</tr>
<tr>
<td>Serositis</td>
<td>10 (27.8)</td>
<td>3 (37.5)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Hematological</td>
<td>10 (27.8)</td>
<td>3 (37.5)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Raynaud’s</td>
<td>4 (11.11)</td>
<td>0 (0)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>3 (8.33)</td>
<td>1 (12.5)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Myositis</td>
<td>3 (8.33)</td>
<td>0 (0)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>IPF</td>
<td>3 (8.33)</td>
<td>0 (0)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>APS</td>
<td>4 (11.11)</td>
<td>3 (37.5)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>AVN (hip)</td>
<td>2 (5.55)</td>
<td>0 (0)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>SLS</td>
<td>1 (2.78)</td>
<td>0 (0)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (5.55)</td>
<td>0 (0)</td>
<td>2 (7.1)</td>
</tr>
</tbody>
</table>

IPF: Interstitial pulmonary fibrosis; APS: anti-phospholipid syndrome; AVN: avascular necrosis; SLS: shrinking lung syndrome.
significantly negatively correlated with the platelets at the 24th and 40th weeks gestation ($R = -0.38$, $p = 0.02$ and $R = -0.34$, $p = 0.04$, respectively). A significant correlation was present with the ESR at the 1st week ($R = 0.39$, $p = 0.02$) and negatively with the hemoglobin level at 40th week ($R = -0.34$, $p = 0.04$). There was no other significance between the RI or PI with all the other studied laboratory parameters.

### 4. Discussion

Recent data demonstrated that advances in the management of pregnant patients with autoimmune diseases have improved the prognosis for mother and child. However, these patients are still classified as high risk because of the potential for ma-

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**Table 2** Doppler uterine resistance (RI) and pulsality (PI) index throughout pregnancy in SLE patients.

<table>
<thead>
<tr>
<th>Uterine Doppler (mean ± SD)</th>
<th>Resistance index (RI)</th>
<th>Pulsality index (PI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcome</td>
<td>Poor (8)</td>
<td>Normal (28)</td>
</tr>
<tr>
<td>First week</td>
<td>0.75 ± 0.07</td>
<td>0.70 ± 0.13</td>
</tr>
<tr>
<td>Week 20</td>
<td>0.64 ± 0.12</td>
<td>0.65 ± 0.04</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.70 ± 0.12</td>
<td>0.53 ± 0.04</td>
</tr>
<tr>
<td>Week 28</td>
<td>0.64 ± 0.1</td>
<td>0.54 ± 0.05</td>
</tr>
<tr>
<td>Week 30</td>
<td>0.58 ± 0.06</td>
<td>0.49 ± 0.12</td>
</tr>
<tr>
<td>Week 34</td>
<td>0.61 ± 0.04</td>
<td>0.59 ± 0.1</td>
</tr>
<tr>
<td>Week 38</td>
<td>0.54 ± 0.07</td>
<td>0.47 ± 0.05</td>
</tr>
<tr>
<td>Week 40</td>
<td>0.56 ± 0.09</td>
<td>0.54 ± 0.1</td>
</tr>
<tr>
<td>$p$ value</td>
<td><strong>0.000</strong></td>
<td><strong>0.000</strong></td>
</tr>
</tbody>
</table>

**Table 3** Doppler umbilical resistance (RI) and pulsality (PI) index throughout pregnancy in SLE patients.

<table>
<thead>
<tr>
<th>Umbilical Doppler (mean ± SD)</th>
<th>Resistance index (RI)</th>
<th>Pulsality index (PI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcome</td>
<td>Poor (8)</td>
<td>Normal (28)</td>
</tr>
<tr>
<td>First week</td>
<td>0.89 ± 0.08</td>
<td>0.88 ± 0.11</td>
</tr>
<tr>
<td>Week 20</td>
<td>0.77 ± 0.05</td>
<td>0.78 ± 0.06</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.63 ± 0.26</td>
<td>0.70 ± 0.04</td>
</tr>
<tr>
<td>Week 28</td>
<td>0.73 ± 0.04</td>
<td>0.70 ± 0.04</td>
</tr>
<tr>
<td>Week 30</td>
<td>0.71 ± 0.05</td>
<td>0.66 ± 0.04</td>
</tr>
<tr>
<td>Week 34</td>
<td>0.68 ± 0.08</td>
<td>0.60 ± 0.07</td>
</tr>
<tr>
<td>Week 38</td>
<td>0.70 ± 0.1</td>
<td>0.61 ± 0.05</td>
</tr>
<tr>
<td>Week 40</td>
<td>0.66 ± 0.13</td>
<td>0.53 ± 0.05</td>
</tr>
<tr>
<td>$p$ value</td>
<td><strong>0.002</strong></td>
<td><strong>0.000</strong></td>
</tr>
</tbody>
</table>

**Figure 1** Uterine and umbilical Doppler velocimetry; pulsality index (PI) and resistance index (RI) in SLE patients.
jor complications [15]. Abnormal fetal outcome was present in 22.22% of patients: 5 with IUGR (13.89%) and one of them gave preterm labor at 34th week, 1 IUFD (2.78%) and 2 (5.55%) with missed abortion. This was comparable to the results of another study that found women with rheumatologic diseases at increased risk of adverse obstetric outcomes and IUGR (8%) [16]. A recent study detected the fetal outcome of pregnant SLE patients to be stillbirth (7.1%), IUGR (14.3%), and pre-term delivery rates (23.1%) [17]. Furthermore, a significant risk of IUGR (28.5%) was present in pregnant SLE patients [18].

Pre-eclampsia was possibly present in (2.78%) and the fetal outcome was good which may be due to the proper management. Women with rheumatologic diseases were more likely to have pre-eclampsia [16]. However, in a similar study, the pre-eclampsia rate was 2.4% in pregnant SLE patients [17]. In the study of Roncoglia et al. [19], it was concluded that the later in pregnancy the abnormal uterine artery Doppler findings are observed, the greater the risk of pre-eclampsia. Normalization of uterine artery Doppler after 25 weeks reduces the risk of pre-eclampsia. In the normal population, poor outcomes are much less found as pre-eclampsia occurred in 1.2% and IUGR in 1.1% of 6035 pregnancies [20].

In this study, the skin and joints were more frequently affected (77.78% and 66.67%, respectively) and the renal involvement was 41.67%, being higher in those with a poor fetal outcome (62.5%). This is in agreement with the study of Ambrósio et al. [21], but the renal affection was only 14%. Antiphospholipid syndrome (APS) was present in 4 patients, 3 of them had a poor fetal outcome. Similarly, lupus anticoagulants (LA) and anticardiolipin (ACL) antibodies were obviously higher in those with a poor outcome (25% and 37.5%, respectively). In a similar study, LA and ACL IgG and IgM antibodies were present in 33%, 16.6% and 19%, respectively, of pregnant SLE patients but without any significant influence on poor obstetric outcome [17]. It was reported that prematurity and IUGR are common in SLE, but are not associated with APS [22]. Moreover, SLE patients with APS had a worse obstetric history, with no other significant differences in perinatal and obstetric outcome [23]. In the current study there was no significant correlation of the Doppler studies with the ACL and LA. Similarly, a poor correlation was found between antiphospholipid antibodies and Doppler results in pregnant SLE patients [24]. The RI was significantly lower in hypertensive pregnant APS patients with ACL treated with aspirin and low dose corticosteroids suggesting their beneficial effect on uterine perfusion [10]. In the present study, the SLEDAI became significantly higher starting from the 24th week gestation in those with a poor fetal outcome. In agreement with our results is the study of Gayed and Gordon [3] who found that IUGR is more likely in active systemic rheumatic disease patients.

In the current study, the number of live births was good (91.67%), still births (2.78%), no therapeutic abortions or perinatal deaths, premature delivery (2.78%), IUGR (7.9%) and only one patient had positive Anti-Ro/Anti-la antibodies and did not have neonatal lupus or any congenital anomalies. In a related study [25] the live births of SLE patients was less favorable (60.1%), stillbirths (2.2%), therapeutic abortions (14%), premature delivery (24.4%), IUGR (13.89%), neonatal lupus (3.5%) and congenital anomalies (2.3%). It is notable that 15 of the present SLE patients were receiving HCQ. In SLE mothers with Anti-Ro/Anti-La antibodies, exposure to HCQ during pregnancy may decrease the risk of fetal development of cardiac-neonatal lupus [26]. Anti-Ro antibody does not negatively influence the pregnancy outcome of SLE [27].

The SLEDAI was higher in those with a poor fetal outcome and the difference reached significance at the 24th week gestation to reach 12.13 (p 0.005). The pregnancy outcomes in SLE were related to disease activity during conception [28]. Disease flare during pregnancy consistently affects the outcome as premature labor and IUGR were more commonly found [30]. In the current study, a significant positive correlation was present between uterine RI and SLEDAI at the 24th week (R 0.34, p 0.04). In a similar study, all the patients with abnormal Doppler studies had SLE flare-ups [24]. Maternal renal disease...
was the only statistically significant predictor for fetal loss [25].
Active lupus nephritis during pregnancy is associated with a higher incidence of maternal and fetal complications [29].
However, in a recent study renal involvement did not have any significant influence on poor obstetric outcome [17].

The umbilical RI and PI were obviously higher than the uterine through-out pregnancy. During the first week, the Uterine RI and PI were initially high. They were higher than the 95th percentile with notching, throughout pregnancy till delivery, in 8 patients (22.22%). In agreement with this is the study that showed that uterine Doppler PI and notching obtained during the first trimester are significantly higher than those of the second in pregnant women with normal outcomes [31]. Starting from the 24th week gestation (uterine RI and PI) and from the 30th week onwards (umbilical RI and PI) were significantly higher in those with poor fetal outcomes. This may imply that uterine Doppler abnormalities are early predictor of adverse events before the umbilical. In agreement is the study that showed that including uterine artery Doppler might detect a group of pregnancies at high risk, even when the umbilical is normal [32].

Patients had the poorest outcome when a reduced flow velocity was noted in both uterine–umbilical vessels [24]. Cases with uterine artery Doppler abnormalities had significantly poorer obstetric outcomes [17,33]. Furthermore, abnormal umbilical artery flow velocity in pregnant SLE patients showed an increased risk of complications [34]. In the present study, Doppler velocimetry is suggested in pregnant SLE patients starting from the 24th week gestation. In another study, a single 20 weeks uterine Doppler assessment was recommended to detect pregnant women with a high risk for early-onset adverse outcomes [20]. An early observation (18–24 weeks) of the uterine RI would detect the relationship between an abnormal RI and adverse pregnancy outcome [10]. In the present study, longitudinal assessment of the Doppler findings suggested a trend toward reduction of the RI in pregnancies with an initial abnormal RI, similar to that observed in healthy pregnant women although at higher levels. This is in agreement with the study of Caruso et al. [10], as the reduction could be due to the beneficial effect of the treatment.

Uterine Doppler is a useful test in predicting high risk pregnancies secondary to uteroplacental insufficiency [35]. Although no present method to overcome IUUGR exists, umbilical velocimetry is expected to assist clinicians in predicting perinatal outcome and also formulating antenatal surveillance guidelines for such conditions [36]. Although pregnancy outcome in SLE is improving, it is still a concern. However, new strategies with respect to pregnancy timing and multidisciplinary care have improved maternal and fetal outcome in SLE [2,17].

Uterine artery Doppler seems to be a good prognostic factor for adverse obstetric outcomes [17].

It could be concluded that pregnancies in SLE are associated with important maternal and fetal morbidities. The ideal patients for pregnancy are those whose disease has been quiescent for several months before. A multidisciplinary management of pregnant SLE patients and the cooperation of the team players including the Obstetrician and Rheumatologist are central. Non-invasive color Doppler of the umbilical and uterine arteries during the late second and third trimesters can allow identification of at-risk pregnancies, allowing antepartum intensive care and optimal timing of delivery to early confirm a good pregnancy outcome and reduce the cost of prenatal care in SLE. Further study using a larger number of patients is recommended.

Conflicts of interest

The authors declare no conflicts of interest.

References

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