Role of foetal umbilical artery Doppler on prediction of adverse pregnancy outcomes in patients with systemic lupus erythematosus

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Abstract

Objective

To investigate the foetal outcomes and examine the predictive value of the third-trimester umbilical artery Doppler in systemic lupus erythematosus (SLE) pregnancies.

Methods

Data of 180 pregnancies in 175 SLE patients from Jan 2007 to Jan 2017 were analysed retrospectively. Pulsatility index (PI), resistance index (RI), and systolic/diastolic ratio (S/D) of the umbilical artery flow velocity data were monitored by Doppler ultrasound.

Results

One or more composite adverse pregnancy outcomes (APOs) occurred in 46.7% of patients with SLE. A total of 62 (34.4%) pregnancies were pre-term birth, and 34 (18.9%) newborns were small for gestational age (SGA). Twenty-two of pregnancies (12.2%) resulted in foetal distress. In multivariate analysis, predictors of composite APOs included positive anti-Ro (OR 5.5, 95% CI 1.7–18.2, p=0.005) and low complement (OR 3.9, 95% CI 1.1–13.6, p=0.04). Doppler PI, RI, and S/D were significantly higher in the pre-term birth, SGA, and composite APO groups than in the patients without APOs. RI with cut-off values of 0.57 and 0.70 indicated the highest risk of pre-term birth and composite APOs, with sensitivities of 50.0% and 21.4%, as well as specificities of 59.6% and 97.7%, respectively. PI emerged as the best predictor of SGA. The optimal cutoff value for PI was 0.77, at which sensitivity (90.9%) and specificity (49.2%) had the best combination.

Conclusion

Pregnancies in lupus still had an increased risk of APOs in terms of pre-term birth. Third-trimester umbilical artery Doppler was useful in predicting pre-term birth, SGA, and composite APOs in lupus pregnancies.

Key words

umbilical artery Doppler, systemic lupus erythematosus, adverse pregnancy outcomes, pre-term birth, small for gestational age

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that mainly affects women of reproductive age. SLE could cause placental vascular inflammatory injury (1), resulting in an increased risk of placenta-mediated complications, such as small for gestational age (SGA) babies and foetal distress, as well as an increased risk of adverse pregnancy outcomes (APO) including pre-term births (2, 3). The above pregnancy complications lead to worse perinatal outcome and long-term neurodevelopment. Therefore, the important task of the late pregnancy (at 28 gestational weeks later) is to prenatally identify at-risk babies and, through close surveillance, to define the best time, place and mode of delivery. An important method for achieving this objective is Doppler assessment of impedance to flow in the umbilical artery (UA). Umbilical artery is the last vessel upstream of the placenta and is particularly important for placental perfusion and foetal development (4). Increased umbilical artery resistance could be traced by Doppler velocimetry, which is frequently related to pre-eclampsia, SGA, and foetal distress (5-7). Umbilical artery Doppler is used as a screening tool for placenta-related diseases in the general population. However, the predictive value in complications of lupus pregnancies has not been widely assessed.

We, therefore, conducted a retrospective study based on a large number of patients. The objectives of this study were as follows: (1) explore the frequency of placenta-mediated complications and other APOs in the third trimester in Chinese patients with SLE; and (2) ascertain the association of foetal umbilical artery Doppler and foetal outcomes in the third trimester of SLE.

Materials and methods

Study design and patients

Consecutive SLE patients, who gave birth in the First Affiliated Hospital of Sun Yat-Sen University from Jan 2007 to Jan 2017, were included in this study. Women with SLE fulfilled the 1997 American College of Rheumatology revised criteria for SLE (8). Patients with incomplete medical records were excluded. In this study, all pregnant women received umbilical artery Doppler examinations during 28-34 gestational weeks to monitor foetal growth and development. Doppler ultrasound data and clinical records of SLE pregnancies were retrospectively analysed. Moreover, the outcomes of the pregnancies were systematically checked. The study was reviewed and approved by Medical Ethical Committee of the First Affiliated Hospital of Sun Yat-Sun University. The Ethics Committee approved that the research be performed based on record review, without contacting the patients, given that this study was retrospective. Support letter was obtained from the medical director's office of the hospital to retrieve retrospective data from the database and records.

Data collection

Information was obtained from the recorded data of the patients, including demographic data, lupus activity during the late pregnancy, laboratory data, treatment during late pregnancy, and pregnancy outcomes. Laboratory data included complete blood count, urinalysis, serum creatinine, serum albumin, complement C_3 and C_4, CH50, antinuclear antibody (ANA), anti-dsDNA antibody, anti-SSA/Ro, and anti-SSB/La. Tests for antiphospholipid (aPL) antibodies included anticardiolipin antibodies (aCL, aCL-IgG, and aCL-IgM), anti-β_2-glycoprotein I antibodies, and lupus anticoagulants.

The third trimester was defined as 28^{th}–40^{th} week of gestation. Hypoalbuminaemia was defined as serum albumin less than 35 g/L. The disease activity of SLE during the third trimester was assessed by SLE pregnancy disease activity index (SLEPADI) (9), and active SLE was considered when the scores were more than 4. We defined hypocomplementaemia as the state in which at least one of the following was lower than the lower limit of the normal range: complement 3 (C_3) (normal range 80–120mg/dL), complement 4 (C_4) (normal range 17–35mg/dL), or total complement activity (CH50) (normal range 25–48 ug/mL). Active lupus nephritis: proteinuria ≥0.5 g/day or estimated creatinine clearance <60 ml/

min/1.73 m^2 with active urinary sediment. Diagnosis of antiphospholipid syndrome (APS) was based on the 2006 revised APS classification criteria (10).

Doppler ultrasound examinations of foetal umbilical artery

All patients between 28 and 34 weeks' gestation received umbilical artery Doppler examination, using Voluson E8 (GE Kretztechnik, USA) machine equipped with a 4–8 MHz transabdominal probe. Pregnant patients were placed in a semi-recumbent position with a left lateral tilt. Measurements were performed in the absence of foetal movements. Then, using a pulsed wave Doppler on a free loop of the cord, the characteristic sound and shape of the umbilical artery were identified. When the screen showed at least three consecutive wave forms of similar height, the image was frozen, and the Doppler index of the umbilical artery was estimated. A minimum of three separate readings was averaged before the final values were calculated. Pulsatility index (PI), resistance index (RI), and peak velocity of the umbilical arteries at end-systole (v_{max}, also abbreviated as S), or end-diastole (v_{min}, also abbreviated as D) were measured and calculated. S/D value was estimated by: $S/D = v_{max/} v_{min}$.

APOs

Pre-term birth is defined as live birth before 37 weeks of gestation. SGA newborn is defined as having a birth-weight below the fifth percentile without anatomical or chromosomal abnormalities. Foetal distress refers to foetal hypoxia and acidosis, which could endanger the health of the foetus. Composite APO was defined as the development of pre-term birth and/or an SGA baby and/or foetal distress at any gestation. Severe APOs included pre-term delivery <34 week of gestation and very small birth weight (WG) <1500g.

Statistical analysis

Quantitative variables were shown as mean ± standard deviations. Categorical variables were described as numbers and proportions. Student's *t*-test was used to compare continuous variables, and chi-square test or Fisher exact test, as appropriate, for categorical variables. A multivariate logistic model was used to determine an optimal set of parameters to predict APOs. Only those variables at $p<0.10$ in the univariate model were stepped into the multivariate regression model. Receiver operating characteristic (ROC) curves were plotted to evaluate the diagnostic power of Doppler values by measuring the area under the curve (AUC). Sensitivity, specificity, positive predictive values and negative of Doppler were calculated. Statistical significance was defined as $p<0.05$. All analysis was performed with SPSS v. 20.0 software (SPSS Inc., Chicago IL, USA).

Table I. Comparison of characteristics between SLE patients with and without APOs in the third trimester during pregnancy

Characteristics	Total	With APOs	Without APOs	*p*-value
n	180	84	96	-
Medical history (n, %)				
Stable disease >6 months	136	52 (61.9)	84 (87.5)	**0.02**
Clinical manifestation during pregnancy (n, %)				
SLEPDAI>4 during pregnancy	68 (37.8)	46 (54.8)	22 (22.9)	**<0.001**
Leukopenia	8 (4.4)	4 (4.8)	4 (4.2)	0.8
Thrombocytopenia	28 (15.6)	20 (23.8)	8 (8.3)	**0.004**
Anaemia	50 (27.8)	34 (40.5)	16 (16.7)	**<0.001**
Active lupus nephritis	56 (31.1)	34 (40.5)	22 (22.9)	**0.01**
Skin rash	22 (12.2)	20 (23.8)	2 (2.1)	**<0.001**
Joint involvement	10 (5.6)	10 (11.9)	0 (0)	**<0.001**
Antiphospholipid syndrome	12 (6.7)	8 (9.5)	4 (4.2)	0.2
Lab data (n, %)				
ANA positivity	166 (92.2)	80 (95.2)	86 (89.6)	0.2
Anti-dsDNA antibody positivity	108 (60.0)	58 (69.0)	50 (52.1)	**0.02**
Anti-Ro antibody positivity	83 (46.1)	48 (57.1)	35 (36.5)	**0.007**
Anti-La antibody positivity	33 (18.3)	24 (28.6)	9 (9.4)	**0.002**
Antiphospholipid antibodies positivity	36 (20.0)	25 (29.8)	11 (11.5)	**<0.001**
Hypoalbuminaemia	78 (43.3)	54 (64.3)	24 (25.0)	**<0.001**
Hypocomplementaemia	40 (22.2)	32 (38.1)	8 (8.3)	**<0.001**
Medication during pregnancy (n, %)				
Isodose of prednisone >10mg/d	19 (10.6)	14 (16.7)	5 (5.2)	**0.006**
Hydroxychloroquine	84 (46.7)	24 (28.6)	60 (62.5)	**0.007**
Aspirin	24 (13.3)	16 (19.0)	8 (8.3)	0.2
Low molecular weight heparin	12 (6.7)	8 (9.5)	4 (4.2)	0.2
Azathioprine	9 (5.0)	4 (4.8)	5 (5.2)	0.8

Significant values are in bold face. SLE: systemic lupus erythematosus; APOs: adverse pregnancy outcomes; SLEPDAI: systemic lupus erythematosus pregnancy disease activity index.

Results

Clinical characteristics

Clinical records for 175 SLE patients with 180 pregnancies were reviewed. The sample had a mean age of 29.4±3.5 (20–37 yrs.) yrs. at pregnancy. Among all pregnancies, 68 (37.8%) had active diseases during pregnancy. The most common complication was lupus nephritis, which was identified in 31.1%, followed by anaemia in 27.8%, thrombocytopenia in 15.6%, skin rash in 12.2%, and joint involvements in 5.6%. A total of 12 patients had APS (6.7%). Among the 180 pregnancies, 19 (10.6%) were on >10 mg/d prednisone treatment during pregnancy. Moreover, hydroxychloroquine (HCQ) and azathioprine were administered in 84 (46.7%) and 9 (5.0%) patients, respectively. A total of 18 patients received aspirin alone during pregnancy, and 12 patients were treated with aspirin and low molecular weight heparin (Table I).

Foetal and maternal outcomes

Among the 180 pregnancies, 84 (46.7%) had one or more APOs. Sixty-two (34.4%) pregnancies were born prematurely, with 26 at gestational age <34 weeks (41.9%) and 36 at 33-36^{+6} weeks (58.1%). A total of 34 (18.9%) newborns were SGA at birth and 22 (12.2%) had foetal distress. No fetuses developed atrioventricular block (AVB) and inter uterine foetal death (IUFD) in our study. The average birth weight (BW) of the babies in our study

Table II. Comparison of characteristics between SLE patients with and without severe APOs in the third trimester during pregnancy.

Characteristics	Live birth <34 weeks	Live birth ≥34 weeks	*p*-value	BW<1500g	BW≥1500g	*p*-value
n	26	154	-	14	166	-
Stable disease >6 months	6 (23.1)	130 (84.4)	**<0.001**	0 (0)	136 (81.9)	**<0.001**
SLEPDAI >4 during pregnancy	22 (84.6)	46 (29.9)	**<0.001**	13 (92.9)	55 (33.1)	**<0.001**
Leukopenia	0 (0)	8 (5.2)	0.6	0 (0)	8 (4.8)	0.4
Thrombocytopenia	6 (23.1)	22 (14.3)	0.3	4 (28.6)	24 (14.5)	0.2
Anaemia	18 (69.2)	32 (20.8)	**<0.001**	10 (71.4)	40 (24.1)	**0.001**
Active lupus nephritis	22 (84.6)	34 (22.1)	**<0.001**	13 (92.9)	43 (25.9)	**<0.001**
Skin rash	6 (23.1)	16 (10.4)	0.09	3 (21.4)	19 (11.4)	0.4
Joint involvement	6 (23.1)	4 (2.6)	**0.001**	4 (28.6)	6 (3.6)	**0.004**
Antiphospholipid syndrome	2 (7.7)	10 (6.5)	0.7	0 (0)	12 (7.2)	0.6
ANA positivity	26 (100.0)	140 (90.9)	0.2	14 (100.0)	152 (91.6)	0.2
Anti-dsDNA antibody positivity	22 (84.6)	86 (55.8)	**0.006**	12 (85.7)	96 (57.8)	**0.04**
Anti-Ro antibody positivity	16 (61.5)	67 (43.5)	0.09	9 (64.3)	74 (44.6)	0.2
Anti-La antibody positivity	8 (30.8)	25 (16.2)	0.1	4 (28.6)	29 (17.5)	0.3
Antiphospholipid antibodies positivity	8 (30.8)	28 (18.2)	0.1	4 (28.6)	32 (19.3)	0.5
Hypoalbuminaemia	26 (100.0)	52 (33.8)	**<0.001**	13 (92.9)	65 (39.2)	**<0.001**
Hypocomplementaemia	24 (92.3)	16 (10.4)	**<0.001**	13 (92.9)	27 (16.3)	**<0.001**

Significant values are in bold face. SLE: systemic lupus erythematosus; APOs: adverse pregnancy outcomes; SLEPDAI: systemic lupus erythematosus pregnancy disease activity index; BW: Birth weight.

was 2509.1±647.5g (700~3800.0 g). All but 14 babies had a BW below 1500 g. In this study, pregnancy induced hypertension occurred in 23 cases, of which, 2 cases were gestational hypertension and 21 were preeclampsia. There was no eclampsia and HELLP symptoms occurred.

Associated clinical factors of foetal APOs

Compared with mothers with APOs, those without APOs were more likely to have a stable disease for more than six months before conception. The proportions of active disease as well as new or worsening disease manifestations during pregnancy (lupus nephritis, thrombocytopenia, anaemia, skin rash, and joint involvements) were significantly high in patients with composite APOs. Moreover, those with composite APOs had lower serum albumin and complementary level than those without. Mothers with APOs were highly likely to be positive in anti-dsDNA, anti-Ro, anti-La, and aPL antibodies. Rates of use of prednisone >10 mg/d and antimalarial medications differed between those with and without APOs (Table I). According to multivariate regression analysis, variables that were independently predictive of APOs included anti-Ro positive (OR 5.5, 95% CI 1.7–18.2, p=0.005) and hypocomplementaemia (OR 3.9, 95% CI 1.1–13.6, p=0.04).

The comparison of patients with and without severe APOs was listed in Table II. Predictors for pre-term birth <34 weeks included hypocomplementaemia (OR 72.2, 95% CI 15.2–361.7, p<0.001) and active lupus during pregnancy (OR 6.8, 95% CI 1.8–26.5, p=0.005). Factors associated with BW <1500g were active lupus nephritis (OR 16.4, 95% CI 1.9–140.1, p=0.01) and hypocomplementaemia (OR 35.0, 95% CI 4.2–291.7, p=0.001).

Foetal umbilical artery Doppler results in the third trimester

The mean gestational age at examination had no significant statistical differences between the two groups (with APOs: 32.5±2.0 gestational weeks; without APOs: 33.0±1.4 gestational weeks; p=0.07). Representative images of the umbilical artery Doppler are shown in Figure 1. Table III shows the difference of umbilical artery Doppler index among patients with and without pre-term birth, pre-term delivery <34 weeks, SGA newborns, BW below 1500g, foetal distress, and the composite APOs. The pre-term birth and SGA groups exhibited significantly high values of PI, RI, and S/D. All Doppler values in the composite APOs patients were significantly higher than those of patients without APOs. No significant difference was observed between the Doppler indices in the foetal distress and non-foetal distress groups.

Doppler analysis for the prediction of APOs

ROC curves were plotted to assess the potential role of Doppler values in predicting APOs onset in SLE patients. Table IV provided the AUC^{ROC} and 95% CI for each index of Doppler examination to predict variable adverse outcomes. The largest AUC for pre-term birth was found for the RI, with an optimal cut-off value of 0.57, at which sensitivity (50.0%) and specificity (59.6%) had the best combination; whereas the positive and negative predictive values were 67.7% and 75.6%, respectively. Umbilical artery PI emerged as the best predictor of late SGA newborns among all indices. The optimal cut-off value of PI to predict SGA at birth was 0.77, and the sensitivity and specificity of PI were 90.9% and 49.2%, respectively. At this cut-off, the positive and negative predictive values were 96.9% and 75.0%, respectively. RI was the best indicator of the composite APOs. RI at 0.70 showed the best combination of the sensitivity (21.4%) and specificity (97.7%) (Fig. 2). Apart from SGA, the S/D value was less predictive of pre-term birth and composite APOs.

Discussion

To the best of our knowledge, this study aimed at investigating the value of the third-trimester umbilical artery Doppler in predicting APOs in SLE pregnancies. Moreover, we retrospec-

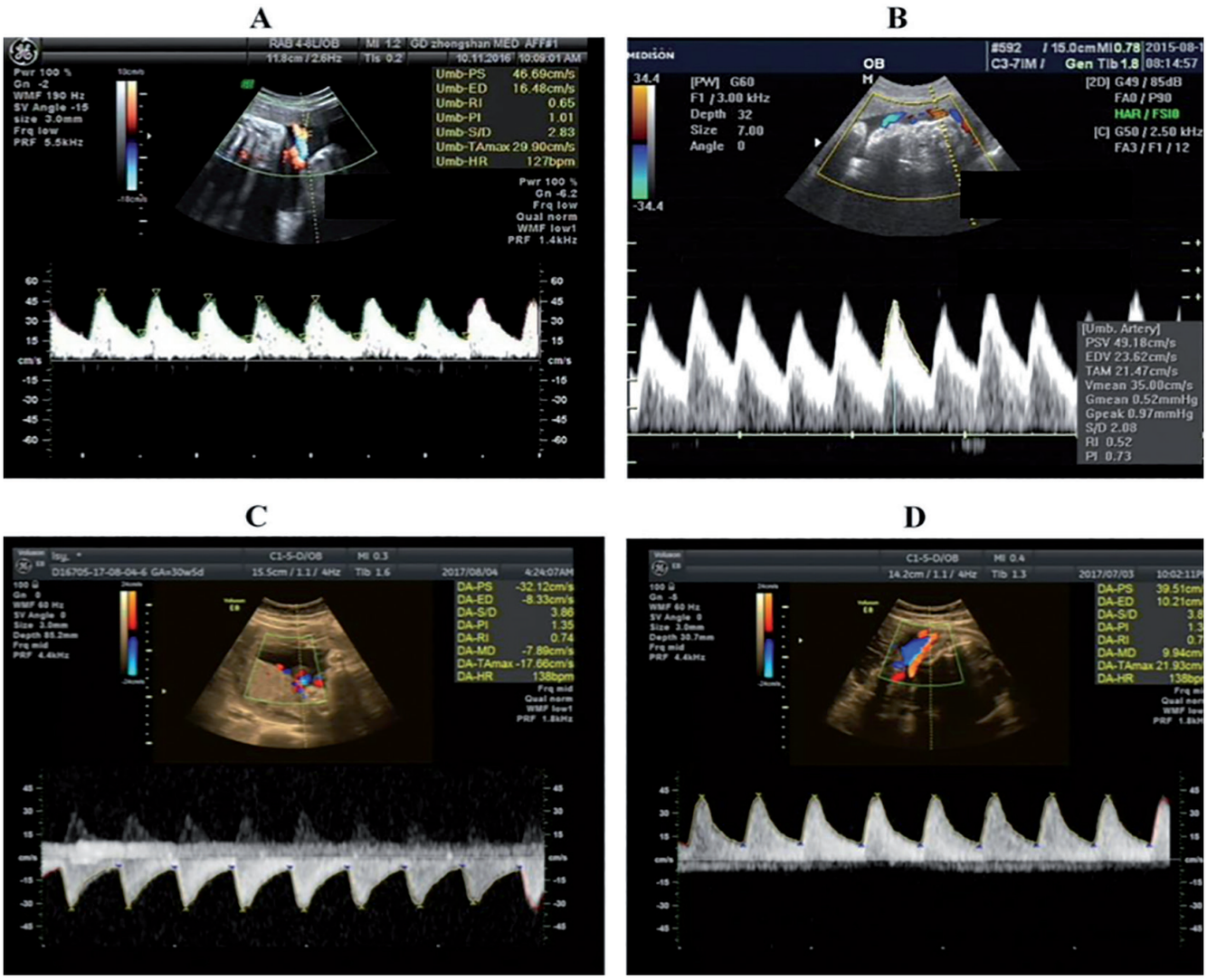

Fig. 1. Representative umbilical artery Doppler images in the third trimester of pregnancy.
A-B: Normal umbilical artery Doppler. The patient was with stable disease before and during pregnancy, who delivered a normal newborn. A: 31 gestational weeks PI=1.01, RI=0.65, S/D=2.83. B: 36 gestational weeks PI=0.73, RI=0.52, S/D=2.08. C-D: Abnormal umbilical artery. C: 30^{+5} gestational weeks, PI=1.35, RI=0.70, S/D=3.86. The patient delivered a SGA pre-term newborn. D: 31 gestational weeks, PI=1.34, RI=0.74, S/D=3.87. The patient was with stable disease before and during pregnancy, who delivered a full-term newborn with SGA, interuterine foetal distress, and polydactylyl.

tively analysed the foetal complications in SLE.

A number of studies have shown that pregnancy outcomes had improved dramatically over time (11, 12). The risk of foetal loss has decreased over the past 40 years (13). However, lupus still remains complicated with an increased risk of stillbirths, foetal distress, pre-term births, and SGA in newborn. Patients participated in this study only after 28 weeks of gestation, and for this reason, foetal loss was not taken into account. In our cohort, we found a quite higher rate of pre-term delivery (34.3%) than the rates from recent prospective studies. For example, pre-term delivery rate was 28.4% in Italy (14), 20.5% in Germany (15), and 9.0% in North America (16). The rate of SGA newborns was similar to previous reports. A large multicentre and multiracial study (PROMISSE study) prospectively found that SGA occurred in 10% of newborns (16). The similar rate of SGA newborns (12.7%) was observed in a meta-analysis, in which 37 studies with 1,842 patients and 2,751 pregnancies were included (17). Foetal distress increased the possibility of cesarean section and was a common cause of perinatal mortality. Cortes *et al*. reported a prospective study of 103 lupus pregnancies with a foetal distress rate of 12.0% (18). In our study, the foetal distress rate was as high as 12.2%. Overall, these data suggested that lupus during pregnancy still hold an increase in risk of APOs, especially pre-term births.

Our data indicated that the hypocomplementaemia and positive anti-Ro were independent risk factors predisposing to composite APOs. This study also demonstrated that serologic activity (low complement level) and active disease were predictors for severe APOs including pre-term birth <34 and BW <1500g. Physicians often use complement levels to anticipate clinical outcomes of lupus. A retrospective

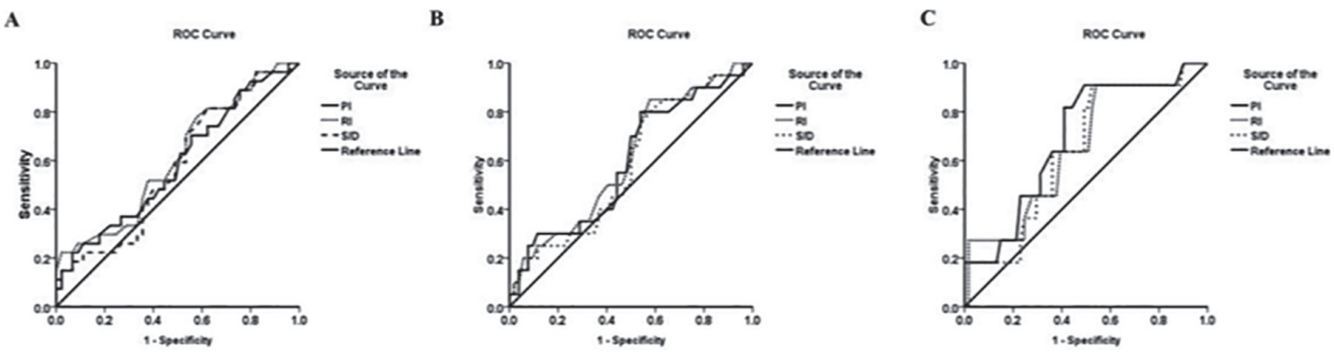

Fig. 2. Receiver Operating Characteristic (ROC) curves of umbilical artery Doppler in the prediction of for composite APOs (**A**), pre-term birth (**B**) and SGA newborns (**C**).

Table III. Comparison of foetal umbilical artery Doppler index between patients with and without APOs (mean ± SD).

	PI	RI	S/D
Premature birth			
Yes (n=62)	0.87 ± 0.24	0.64 ± 0.26	2.75 ± 0.92
No (n=118)	0.79 ± 0.18	0.56 ± 0.17	2.35 ± 0.60
p-value	0.02	0.04	0.001
Live birth<34 weeks			
Yes (n=26)	1.03 ± 0.32	0.80 ± 0.44	3.06 ± 1.13
No (n=154)	0.79 ± 0.18	0.56 ± 0.15	2.39 ± 0.61
p-value	<0.001	<0.001	<0.001
SGA			
Yes (n=34)	0.95 ± 0.27	0.69 ± 0.31	3.02 ± 1.18
No (n=146)	0.79 ± 0.18	0.56 ± 0.17	2.36 ± 0.54
p-value	<0.001	0.005	<0.001
BW			
<1500g (n=14)	1.22 ± 0.42	0.73 ± 0.18	3.56 ± 1.28
≥1500g (n=166)	0.80 ± 0.18	0.58 ± 0.20	2.40 ± 0.61
p-value	<0.001	0.1	<0.001
Foetal distress			
Yes (n=22)	0.84 ± 0.22	0.66 ± 0.34	2.54 ± 0.83
No (n=158)	0.81 ± 0.20	0.57 ± 0.17	2.48 ± 0.74
p-value	0.6	0.07	0.7
Composite APOs			
Yes (n=84)	0.86 ± 0.24	0.65 ± 0.29	2.72 ± 0.89
No (n=96)	0.78 ± 0.17	0.54 ± 0.09	2.29 ± 0.51
p-value	0.01	0.001	<0.001

PI: pulsatility index; RI: resistance index; S/D: systolic/diastolic ratio; SGA: small for gestational age; APOs: adverse pregnancy outcomes.

study of 267 SLE pregnancies indicated that hypocomplementaemia was predictive of APOs, even in those with low clinical activity (19). Our finding was comparable to the results by Watson *et al*. and Arfaj *et al*., showing that patients with positive anti-Ro have an increased risk for pregnancy loss and pre-term deliveries (20,21). However, other studies showed that anti-Ro antibodies did not adversely affect pregnancy outcomes (22, 23). The controversial results might be related with significant variation with respect to study design, definitions of APOs, statistical methods, and the bias of control group selection. More evidence was required to provide conclusions. The proportion of APS was higher in patients with composite APOs than that without (9.5% *vs*. 4.2%), while due to the small number, there was no significance in the statistical analysis. A large research was needed to explore the association between APS and the APOs in lupus in the future. A recent multicentre prospective study demonstrated

Table IV. Sensitivity, specificity, positive predictive value and negative predictive value of the ultrasound index for prediction APOs in the third trimester (%).

	Index	AUC^{ROC} (95%CI)	*p*-value	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Pre-term birth	PI	0.59 (0.49~0.70)	0.09	0.74	80.0	46.2	36.4	85.7
	RI	0.61 (0.51~0.71)	0.04	0.57	50.0	59.6	67.7	75.6
	S/D	0.58 (0.48~0.68)	0.1	3.10	25.8	89.8	42.9	69.7
SGA at birth	PI	0.69 (0.59~0.80)	0.004	0.77	90.9	49.2	96.9	75.0
	RI	0.66 (0.53~0.78)	0.02	0.60	45.4	27.9	77.3	88.0
	S/D	0.65 (0.53~0.76)	0.03	3.30	29.4	91.8	45.5	84.8
Composite APOs	PI	0.59 (0.49~0.68)	0.08	0.88	23.8	75.0	45.5	52.9
	RI	0.61 (0.51~0.70)	0.03	0.70	21.4	97.7	85.7	66.2
	S/D	0.57 (0.48~0.67)	0.2	2.73	68.2	60.3	35.7	85.4

PI: pulsatility index; RI: resistance index; S/D: systolic/diastolic ratio; SGA: small for gestational age; APOs: adverse pregnancy outcomes

that the use of HCQ could reduce the rate of cardiac complications related to anti-Ro antibodies (24). A normal complement level at conception must be maintained to reduce the risks of APOs. HCQ should not be discontinued during pregnancy because it decreases the risks of anti-Ro antibody related cardiac complications (24).

In the present study, high umbilical PI, RI, and S/D values were correlated with a high risk of pre-term birth, SGA, and composite APOs. The Doppler indices were not associated with foetal distress. All Doppler indices showed a similar trend on their association with the perinatal outcomes. In particular, the RI should be extremely similar to the S/D values given that both include the peak systolic and the end diastolic velocities. Additionally, PI provided an improved analysis of all velocities during the cardiac cycle. Studies on umbilical Doppler in SLE pregnancies were limited. A study from France found that an abnormal umbilical artery waveform in second trimester was the best predictor for APOs in SLE and/or APS (25). In 77 APS pregnancies, Carmona *et al*. found that adverse foetal outcomes were correlated with abnormal umbilical Doppler examination at 23–26 weeks (26). Our data showed that the third-trimester umbilical Doppler would enable clinicians to identify women at high risk of developing pre-term birth, SGA newborns, and composite APOs, and initiate intensive monitoring or intrauterus management or end pregnancy for the maintenance of foetal and neonatal well-being. This was comparable to the research by Martínez-Sánchez (27).

Pre-term birth and SGA, as a consequence of chronic uteroplacental insufficiency, are the main causes of perinatal mortality and long-term morbidity (28, 29). The present results showed that in the third trimester, the umbilical artery blood velocity indices RI and PI were the best predictors of pre-term birth, SGA newborns, and composite APOs. RI offered the largest AUC for prediction of pre-term birth. The sensitivity and specificity of RI in predicting pre-term birth were moderate. The umbilical artery RI also had the largest AUC^{ROC} for composite APOs, which had high specificity and low sensitivity. Clinicians must be aware of the possibility of not identifying high-risk women given the low sensitivity. PI has high sensitivity in predicting SGA. The cut-off of PI >0.77 may screen the subgroup of lupus patients, who require intensive monitoring for SGA occurrence. The optimal cut-off values provided by the ROC analysis could be used to stratify the standard of care in pregnancy with SLE. Women with Doppler index less than cut-offs could undergo less intensive monitoring; whereas women with Doppler index more than cut-offs should start strict monitoring to rapidly identify and treat obstetric complications. However, the findings should be assessed in large prospective studies.

In conclusion, most lupus pregnancies may be successful, but still hold an increased risk of foetal complications. Hypocomplementaemia and positive anti-Ro are independent factors for composite APOs. The third-trimester umbilical artery Doppler is a meaningful and noninvasive method to predict late pre-term birth, SGA, and the composite APOs. The present study indicated that the PI and RI were the most important indices in predicting APOs. The level of antenatal surveillance could be modified by the Doppler result. Intensive monitoring was recommended for SLE patients with greater cut-off offered by the ROC analysis.

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