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ORIGINAL ARTICLE

Hypertensive disorders of pregnancy associated with adverse pregnant outcomes in patients with systemic lupus erythematosus: a multicenter retrospective study

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Abstract

Background Hypertension disorders in pregnancy (HDP) were common complications in women with systemic lupus erythematosus (SLE). However, the impact of HDP and the measures to prevent HDP-related fetal adverse pregnancy outcomes (APOs) remained to be explored.

Methods A multicenter retrospective study of 342 pregnant women with SLE was performed. Variables related to SLE and APOs were recorded. Fetal development was evaluated by umbilical artery Doppler ultrasonography.

Results HDP was diagnosed in 45 (13.2%) patients, including pre-eclampsia in 42 and gestational hypertension in 3. Patients with HDP had higher incidence of preterm birth (71.1% vs 20.9%, $P < 0.001$), intrauterine growth retardation (IUGR) (37.8% vs 11.8%, $P < 0.001$), low-birth-weight infants (62.2% vs 17.2%, $P < 0.001$), and very-low-birth-weight infants (37.8% vs 2.7%, $P < 0.001$), compared with lupus patients without HDP. A total of 35 (77.8%) HDP patients had disease activation during pregnancy. All the events occurred during the second and third trimesters, mainly presenting as moderate-to-high activity (65.7%). Active disease [odds ratios (OR) = 3.9, 95% confidential interval (CI) 1.5–9.7, $P = 0.004$] and positive anticardiolipin (aCL) antibody (OR = 7.6, 95% CI 2.7–18.6, $P < 0.001$) were independent risk factors for HDP in lupus patients. Doppler RI and S/D ratio predicted APOs in patients with HDP. The optimal cut-off values for RI and S/D ratio were 0.7 (sensitivity 48.1%, specificity 53.3%) and 3.4 (sensitivity 66.7%, specificity 100%), respectively.

Conclusions HDP was a common pregnant complication and caused various fetal and maternal adverse outcomes in patients with SLE. Umbilical artery Doppler ultrasonography was effective in predicting fetal APOs in lupus patients with HDP.

Key Points
- *HDP induced preterm birth, IUGR, low-birth-weight infants, and very-low-birth-weight infants in patients with SLE.*
- *HDP led to lupus activation during the second and third trimesters.*
- *Disease activation and aCL positivity were predictors for HDP.*
- *RI and S/D ratio from umbilical artery Doppler predicted APOs in patients with HDP.*

Keywords Hypertension · Pregnancy · Systemic lupus erythematosus · Umbilical artery Doppler

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease mainly affecting women at their child-bearing age. The survival of SLE has plateaued, and 15-year pooled survival estimate is approximately 0.8 after a period of major improvement [1]. In recent years, pregnancy and family planning provoke a myriad of concerns. Women with SLE are likely to complicate with adverse pregnant outcomes (APOs) due to the dysregulation of immune system [2]. The overall incidence rate of APOs was reported to be 19.0%, nearly 2-fold over the non-SLE population [3].

Hypertensive disorders of pregnancy (HDP) remains a leading cause for perinatal mortality and morbidity [4, 5]. The incidence rate of HDP was reported to be 14.1% in lupus patients, compared to 5–10% in the general population [6–8]. HDP was associated with various fetal adverse outcomes, including pregnancy loss and preterm birth [9]. Eclampsia is a severe complication that threatened the mothers' lives. SLE, per se, is predisposed to cardiovascular dysfunction due to the inflammation storm [10]. Activation of the lymphocytes contributes to the development of pregnancy-induced hypertension [11]. Until recently, the impact of HDP on pregnant women with SLE is not well-elucidated.

Umbilical artery is an important conduit to supply oxygen and nutrients for fetal development. The increasing blood resistance of the umbilical artery usually suggested the insufficiency of placenta function and was associated with the subsequent outcomes, such as HDP, intrauterine growth retardation (IUGR), and low-birth-weight infants [12]. Our previous research indicated that umbilical artery Doppler ultrasonography has a role in predicting preterm birth, IUGR, and the overall fetal APOs in lupus patients [13]. Doppler indices of the umbilical artery provide clues of pregnancy complications [14]. Timing for delivery is critical in patients with HDP. Pregnancy should be terminated in the presence of intrauterine distress. Therefore, to find out a non-invasive method to monitor fetal development in patients with HDP is of great importance.

Herein, we leveraged a multicenter retrospective study, aiming to explore the impact of HDP on maternal and fetal outcomes and to evaluate the use of Doppler ultrasonography as a non-invasive method to predict fetal outcomes in lupus patients with HDP.

Patients and materials

Patient selection

A total of 342 pregnant women with SLE from three tertiary hospitals in Guangzhou from 2008 to 2017 were included. To be specific, 258 pregnancies from the First Affiliated Hospital of Sun Yat-sen University were collected from 2008 to 2017, 50 pregnancies from the Guangzhou First People's Hospital were collected from 2012 to 2017, and 34 pregnancies from the First Affiliated Hospital of Guangzhou Medical University were collected from 2012 to 2017. Only one pregnancy from each patient was included. All patients fulfilled the 1997 ACR diagnostic criteria for SLE [15]. A common follow-up procedure was conducted in all the three centers. Pregnant patients were visited every four weeks up to 28 weeks of gestation and every two weeks from the 28th week up to delivery. During each visit, all the patients received antenatal examination and blood test for SLE activity evaluation. Fetal ultrasonography was conducted according to Chinese recommendations for perinatal care in women with SLE [16]. Patients who were not followed regularly or without complete records were excluded. Ethics committee of the First Affiliated Hospital of Sun Yat-sen University approved the research. Considering the retrospective nature of this study, no informed consent was required. This work was conducted in compliance with the Declaration of Helsinki principles.

Clinical data

Regular obstetric practice, blood pressure, fetal heartbeat, clinical symptoms of lupus, laboratory test, including complete blood count, routine urine test, blood biochemical test, complement C3 and C4, anti-dsDNA antibodies, anti-SSA/Ro antibodies, anti-SSB/La antibodies, anticardiolipin (aCL) antibody IgM, aCL antibody IgG, and lupus anticoagulants (LAC), and medical treatment were recorded. Positivity of anti-phospholipid (aPL) antibodies was defined as positive twice in blood test of LAC or aCL-IgG/aCL-IgM or anti-β2GPI antibodies at medium to high titers (> 40 units), measured at least 12 weeks apart. Anti-phospholipid syndrome (APS) was diagnosed if the patient presented clinical symptoms of thrombotic or obstetric complications with aPL positive. SLE activity was measured by the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) at the first, second, and third trimesters [17]. The highest score was used in statistical analysis.

Umbilical artery Doppler ultrasonography was performed by a Voluson E8 (GE Kretztechnik, USA) ultrasound machine equipped with a 3–5-MHz trans-abdominal probe during 28 to 34 weeks of gestation. Measurements were performed according to the manufacturer's instructions, as described in previous reports, in all the three centers [13]. Umbilical artery hemodynamics were assessed by peak velocity of the umbilical arteries at end-systole (Vmax, abbreviated as S), peak velocity of the umbilical arteries at end-diastole (Vmin, abbreviated as D), pulsatility index (PI), and resistance index (RI). The peak S/D (Vmax/Vmin) ratio was estimated and recorded.

Definition of APOs

Fetal APOs include the following: (1) Pregnancy loss, including spontaneous abortion (termination of pregnancy before 20 weeks of gestation caused by natural factors), therapeutic abortion (artificial termination of pregnancy because of life-threatening progression of lupus or obstetric complications), and fetal death (intrauterine fetal demise after 20 weeks of gestation unexplained by chromosomal abnormalities, anatomic malformation, or congenital infection); neonatal death referred to the death of a live infant within 28 days after birth. (2) Preterm birth (live birth before 37 weeks of gestation); (3) IUGR (birth weight below the 10th percentile of Chinese population according to gestational week at delivery and fetal gender). (4) Fetal distress referring to fetus hypoxia and acidosis, which could endanger the health of the fetus. (5) Low-birth-weight infant (infant with birth weight < 2500 g). (6) Very-low-birth-weight infant (infant with birth weight < 1500 g).

Maternal APOs include the following: (1) Disease activation was defined according to the International Consensus for disease flare in lupus, namely new-onset or worsening of specific and associated cutaneous manifestations of SLE, arthritis, one or more hemocytopenia not attributed to immunosuppressive drugs, neurological, cardiopulmonary, and renal manifestations, elevated serum creatinine in association with low serum complement and/or elevated titers of anti-dsDNA antibodies [18]. Mild disease activity was defined as SLEPDAI score 5 to 9, moderate disease activity as SLEPDAI score 10 to 14, and high disease activity as SLEPDAI score ≥ 15. Active lupus nephritis: proteinuria > 0.5 g/24 h, active urinary sediment (> 3 red blood cells/high power field (HPF) or > 5 white blood cells/HPF or cellular casts), or estimated creatinine clearance (Cr.Cl) < 60 ml/min/1.73 m^2 with active urinary sediment. (2) HDP includes the following four categories: chronic hypertension, preeclampsia–eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension [19]. Hypertension was diagnosed by systolic blood pressure (SBP) > = 140 mmHg and/or diastolic blood pressure (DBP) > = 90 mmHg in sitting position in at least two consecutive measurements. Chronic hypertension was defined as hypertension that emerges before 20 weeks of gestation or persists beyond the 42nd postpartum day. Gestational hypertension was diagnosed if hypertension develops beyond 20 weeks of gestation, with or without proteinuria, in the absence of preeclampsia/eclampsia characteristics, and resolves within 42 days postpartum. Preeclampsia was defined as new onset of hypertension with or without proteinuria after 20 weeks of gestation in a previously normotensive woman. Proteinuria was defined as 300 mg protein per 24-h urine collection, or a urinary protein-to-creatinine ratio greater than 0.3, or a urine dipstick protein grade of 1+ or greater if other methods were unavailable. In the absence of proteinuria, new-onset hypertension with one of the following abnormalities: (a) platelet count < 100,000/μl; (b) serum creatinine concentration of 1.1 mg/dl; or doubling of the serum creatinine concentration in the absence of other renal disease; (c) elevated liver transaminases to twice the normal concentration; (d) pulmonary edema; (e) cerebral or visual symptoms; was considered as preeclampsia. Any of BP of 160/110 mmHg or greater with multi-organ involvement denotes severe preeclampsia. Eclampsia was the occurrence of seizures in a pregnant woman with preeclampsia. Preeclampsia/eclampsia superimposed on chronic hypertension was established if the onset of preeclampsia/eclampsia in a woman with chronic hypertension was beyond 20 weeks of gestation.

Statistical analysis

Software SPSS 20.0 was used for data analysis. Quantitative variables were recorded as mean ± standard deviation (SD) and compared by Student's *t* test. Categorical variables were described as frequency and percentage and compared by chi-squared test. Factors related to APOs at $P < 0.10$ in univariate logistic regression analyses were included into multivariate logistic models. A $P<0.05$ was considered as statistically significantly. The receiver-operating characteristic curve (ROC) curves and area under the curve (AUC) measurements were derived to determine the discriminative power of different parameters obtained from Doppler ultrasonography to identify HDP. The cut-off value for each parameter was selected according to the maximal Youden index.

Results

Demographics

A total of 342 pregnant women with SLE were enrolled. The mean (SD) age was 28.9 ± 3.9 years (range 18–41). HDP was diagnosed in 45 (13.2%) patients. In particular, preeclampsia was diagnosed in 42 (93.3%) and gestational hypertension in 3 (6.7%). Six (13.3%) patients were complicated with severe preeclampsia. No patient developed eclampsia. Among lupus patients with HDP, 26 were primigravidae and 19 were multiparae. Thirteen patients had experienced at least one episode of APOs, including spontaneous abortion ($n = 6$), low-birth-weight infants ($n = 5$), preterm birth ($n = 5$), IUGR ($n = 3$), preeclampsia ($n = 2$), and therapeutic abortion ($n = 1$).

Fetal outcomes

Among 45 patients with HDP, 32 (71.1%) were complicated with preterm birth, 17 (37.8%) with IUGR, 6 (13.3%) with fetal distress, and 5 (11.1%) with pregnancy loss. Nineteen (19/41, 46.3%) pregnancies ended with normal delivery, and

22 (22/41, 53.7%) patients received cesarean. Causes for pregnancy loss included stillbirth (2/5, 40.0%), induced labor due to high lupus activity (2/5, 40.0%), and newborn deaths (1/5, 20.0%). Twenty-eight (62.2%) low-birth-weight infants and 17 (37.8%) very-low-birth-weight infants were born. The average (SD) birth weight (BW) was 1938.2 ± 748.0 g (range 790.0–3400.0). The average (SD) BW of preterm birth was 1777.0 ± 710.8 g (range 790.0–3400.0). Eighteen (56.3%) preterm infants were born before 34 weeks of gestation, while 14 (43.8%) were born after that. The average (SD) gestational weeks of preterm infants was 33.0 ± 2.9 weeks (range 28.0–36.0). Therapeutic premature delivery (19/32, 59.3%) was the primary cause for preterm birth, followed by spontaneous premature delivery (8/32, 25%), and preterm premature rupture of membranes (PPROM) (5/32, 15.6). Reasons for therapeutic premature delivery included moderate-to-high disease activity (13/19, 68.4%), preeclampsia (10/19, 52.6%), fetal distress (3/19, 15.8%), placenta previa (2/19, 10.5%), and placental abruption (1/19, 5.3%). Patients with HDP had higher incidence of preterm birth (71.1% vs 20.9%, $P < 0.001$), IUGR (37.8% vs 11.8%, $P < 0.001$), low-birth-weight infants (62.2% vs 17.2%, $P < 0.001$), and very-low-birth-weight infants (37.8% vs 2.7%, $P < 0.001$), compared with lupus patients without HDP (Table 1). The newborn death was caused by respiratory distress. Three infants developed neonatal lupus erythomatosus (NLE). In particular, one infant presented cutaneous lupus erythomatosus, one presented anemia and sinus bradycardia, and one presented QT prolongation.

Maternal outcomes

Among patients with HDP, 10 (22.2%) maintained stable disease activity during pregnancy and 35 (77.8%) experienced mild (12/35, 34.3%), moderate (8/35, 22.9%), or severe (15/35, 42.9%) disease activation. Eighteen (51.4%) patients with HDP had disease activation during the second trimester and 17 (48.6%) during the third trimester. Active nephritis (30/35, 85.7%) and thrombocytopenia (12/35, 34.3%) were the major manifestations. The incidence of cutaneous disease (11/35, 31.4%) and arthritis (7/35, 20.0%) was relatively low. Four patients developed APS during pregnancy, two of them presented as stillbirth, and the rest were complicated with deep venous thrombosis (DVT).

Treatments

Lupus patients with stable disease were treated with prednisolone 5–10 mg daily. Patients with mild activity received prednisolone 10–15 mg daily. An escalated dose of 15–30 mg of prednisolone per day was given to patients with moderate activity. High disease activity normally required prednisolone over 30 mg per day. Hydroxychloroquine (HCQ) was prescribed to 14 (31.1%) patients with a dose of 200–400 mg daily. Immunosuppressants were considered only in patients with active disease. One out of 12 (8.3%) patients with mild disease activity received azathioprine (AZA). Among 8 patients with moderate activity, 2 (25.0%) received AZA and 1 (12.5%) received tacrolimus. Among 15 patients with severe lupus activation, 2 (13.3%) were treated with cyclophosphamide (CYC) after induced labor, 6 (40.0%) with AZA, and 1 (6.7%) with cyclosporin A (CsA). Aspirin and low molecular weight heparin (LMWH) were given to 5 (11.1%) and 2 (4.4%) patients, respectively. Antihypertension drugs, including labetalol, nifedipine, and nitroglycerin, were given to 33 (73.3%) patients. Overall, blood pressure was under control in 19 (42.2%) patients, among which 9 (47.4%) pregnancies ended with full-term birth and 10 (52.6%) with preterm birth. Uncontrolled hypertension persisted in 26 (57.8%) patients despite of intensive therapy. Two (7.8%) patients received induced labor due to disease activation, and two (7.8%) had stillbirth. A total of 22 (84.6%) preterm infants were born, including one newborn death.

Risk factors

A comparison between patients with and without HDP was shown in Table 2. The prevalence of active disease (77.8% vs 49.2%, $P < 0.001$), active lupus nephritis (LN) (66.7% vs 38.7%, $P < 0.001$), anti-dsDNA positivity (77.8% vs 51.9%, $P = 0.001$), hypoalbuminemia (77.8% vs 51.9%, $P = 0.001$), and aCL positivity (40.0% vs 13.8%, $P < 0.001$) was higher in patients with HDP than those without. In order to evaluate whether disease remission reduced HDP development, we excluded 83 patients who developed new-onset SLE during pregnancy and further analyzed the rest 259 pregnancies. We found that patients with active disease had a higher rate of HDP than those with stable disease > 6 months prior to pregnancy (9/46, 19.6% vs 27/213, 12.7%, $P < 0.001$). Multivariate regression analysis revealed that SLEPDAI > 4 (OR = 3.9, 95% CI 1.5–9.7, $P = 0.004$) and aCL positivity (OR = 7.6, 95% CI 2.7–18.6, $P < 0.001$) were independent risk factors for HDP in lupus patients. Further analysis evaluating the impact of disease activation on fetal outcomes in HDP patients was performed. As shown in Table 3, patients with active disease had higher risk of preterm birth (82.9% vs 30.0%, $P = 0.003$), especially preterm birth before 34 weeks of gestation (51.4% vs 0%, $P = 0.003$).

Umbilical artery Doppler ultrasonography

Umbilical artery Doppler ultrasonography was performed in 41 patients with HDP and 191 patients without HDP during the third trimester. The average (SD) checking time was 31.0 ± 2.2 weeks of gestation in patients with HDP and 32.7 ± 2.2 weeks of gestation in patients without HDP ($P > 0.50$).

Table 1 Fetal outcomes in pregnant women with SLE

Fetal adverse events	Total ($n = 342$)	With HDP ($n = 45$)	Without HDP ($n = 297$)	P value
Pregnancy loss, n (%)	78 (22.8)	5 (11.1)	73 (24.6)	0.05
Preterm birth, n (%)	94 (27.5)	32 (71.1)	62 (20.9)	**< 0.001**
IUGR, n (%)	52 (15.2)	17 (37.8)	35 (11.8)	**< 0.001**
Fetal distress, n (%)	36 (10.5)	6 (13.3)	30 (10.1)	0.45
BW < 2500 g, n (%)	79 (23.1)	28 (62.2)	51 (17.2)	**< 0.001**
BW < 1500 g, n (%)	25 (7.3)	17 (37.8)	8 (2.7)	**< 0.001**

BW, birth weight; HDP, hypertension disorders in pregnancy; IUGR, intrauterine growth retardation; SLE, systemic lupus erythematosus

PI (1.0 ± 0.2 vs 0.9 ± 0.2, $P = 0.004$), RI (0.7 ± 0.1 vs 0.6 ± 0.1, $P < 0.001$), and S/D ratio (3.1 ± 0.8 vs 2.5 ± 0.5, $P < 0.001$) were remarkably higher in patients with HDP than those without. PI (1.1 ± 0.2 vs 0.9 ± 0.2, $P = 0.003$), RI (0.7 ± 0.1 vs 0.6 ± 0.1, $P = 0.003$), and S/D ratio (3.3 ± 0.7 vs 2.6 ± 0.5, $P = 0.001$) persisted to increase in HDP patients who developed fetal APOs (Table 4).

Predictive value of umbilical artery Doppler ultrasonography

Diagnostic test was conducted to evaluate the predictive value of umbilical artery Doppler ultrasonography for HDP with APOs. Results of the ROC curve were shown in Fig. 1. In HDP patients with APOs, AUC^{ROC} of RI and S/D ratio were

Table 2 Comparison between SLE patients with and without HDP

	With HDP ($n = 45$)	Without HDP ($n = 297$)	P value
Basic characteristics			
Age, years, mean ± SD	28.3 ± 3.6	29.0 ± 4.0	0.27
Disease duration, years, mean ± SD	4.6 ± 4.1	4.6 ± 4.2	1.00
Clinical manifestations during pregnancy			
SLEPDAI > 4 during pregnancy, n (%)	35 (77.8)	146 (49.2)	**< 0.001**
Leukopenia, n (%)	0 (0)	22 (7.4)	0.09
Thrombocytopenia, n (%)	12 (26.7)	47 (15.8)	0.07
Anemia, n (%)	24 (53.3)	112 (37.7)	0.05
Active lupus nephritis, n (%)	30 (66.7)	115 (38.7)	**< 0.001**
Skin rash, n (%)	11 (24.4)	41 (13.8)	0.06
Joint involvement, n (%)	7 (15.6)	21 (7.1)	0.07
Anti-phospholipid syndrome, n (%)	4 (8.9)	18 (6.1)	0.50
Laboratory data			
Anti-dsDNA antibody positivity, n (%)	35 (77.8)	154 (51.9)	**0.001**
Anti-Ro antibody positivity, n (%)	17 (37.8)	135 (45.5)	0.33
Anti-La antibody positivity, n (%)	9 (20.0)	51 (17.2)	0.64
Hypoalbuminemia, n (%)	35 (77.8)	154 (51.9)	**0.001**
Low serum level of C3, n (%)	20 (44.4)	107 (36.0)	0.28
Low serum level of C4, n (%)	33 (73.3)	199 (67.0)	0.40
aCL-IgG positivity, n (%)	16 (35.6)	19 (6.4)	**< 0.001**
aCL-IgM positivity, n (%)	8 (17.8)	19 (6.4)	**0.02**
Anti-β2GP-I positivity, n (%)	7 (15.6)	23 (7.7)	0.09
LAC positivity, n (%)	6 (13.3)	22 (7.4)	0.38
Medication prior to pregnancy			
Isodose of prednisone > 10 mg/d, n (%)	7 (15.6)	22 (7.4)	0.08
Hydroxychloroquine, n (%)	14 (31.1)	99 (33.3)	0.77

aCL, anti-cardiolipin; β2GP, β2 glycoprotein; HDP, hypertension disorders in pregnancy; LAC, lupus anticoagulants; SD, standard deviation; SLE, systemic lupus erythematosus; SLEPDAI, Systemic Lupus Erythematosus Pregnancy Disease Activity Index

Table 3 Fetal outcomes in SLE patients with or without active disease

	Active ($n = 35$)	Inactive ($n = 10$)	P value
Pregnancy loss, n (%)	5 (14.3)	0 (0)	0.57
Preterm birth, n (%)	29 (82.9)	3 (30.0)	**0.003**
< 34 weeks, n (%)	18 (51.4)	0 (0)	**0.003**
≥ 34 weeks, n (%)	11 (31.4)	3 (30.0)	1.00
IUGR, n (%)	13 (37.1)	5 (50.0)	0.49
Fetal distress, n (%)	3 (8.6)	3 (30.0)	0.11
BW < 2500 g, n (%)	24 (69.6)	4 (40.0)	0.14

BW, birth weight; IUGR, intrauterine growth retardation; SLE, systemic lupus erythematosus

0.8 [95% confidential interval (CI) 0.6–0.9, $P = 0.01$] and 0.9 (95% CI 0.7–1.0, $P < 0.001$), respectively. The optimal cut-off value of RI was 0.7 (sensitivity 48.1%, specificity 53.3%). S/D ratio over 3.4 was a favorable predictor for APOs in patients with HDP (sensitivity 66.7%, specificity 100%) (Table 5).

Discussion

In this research, we found that HDP was a common complication in pregnant women with SLE. HDP increased the risk of various fetal and maternal adverse outcomes. Patients with active disease or aCL positivity predisposed to develop HDP. Umbilical artery Doppler ultrasonography was an effective method to monitor fetal development in patients with HDP. To the best of our knowledge, this is the first research exploring the impact of HDP on pregnancy outcomes in patients with SLE intensively.

HDP is a common complication in patients with SLE [20, 21] and is associated with various APOs [22, 23]. A multicenter prospective study suggested that arterial hypertension increased the probability of preterm birth to 18-fold [9]. HDP was an additional risk factor for pregnancy loss, IUGR, and low-birth-weight infants [24–26]. In consistence with previous research, our results suggested that lupus patients with HDP experienced high risk of various fetal APOs, including preterm birth, IUGR, low-birth-weight infants, and very-low-birth-weight infants.

HDP increased the risk of disease activation during pregnancy [27]. The development of HDP involves immunological dysfunction. Imbalance of Th1/Th2 with a shift towards Th1 response and the release of abundant cytokines, such as TNF-α, could reactivate lupus disease [28–30]. The impact of HDP on SLE development could even persist for more than five years after child birth [31]. Our previous study investigating the overall impact of pregnancy on SLE found that most of the disease flares during pregnancy was mild [32]. However, in the current research, moderate-to-high disease activity was commonly induced by HDP during the second and third trimesters. These results implied that patients with HDP could bear higher risk of severe disease activation compared to those with other complications.

Many factors, including active disease, lupus nephritis, and aPL, anti-Ro, and anti-La antibodies, were identified as predictors of maternal and fetal APOs [33]. However, their roles in predicting HDP were not well-defined. In our research, multivariate regression analysis revealed that active disease and aCL positivity were independent predictors for HDP. The generation of agonistic autoantibodies to angiotensin II type-1 receptor (AT1-AA) due to miscellaneous activation of lymphocytes causes hypertension by inducing oxidative stress, promoting the production of anti-angiogenic factors, and activating complement component C3 in endothelial cells, vascular smooth muscle cells, and mesangial cells [34, 35]. aCL exerts an effect on endothelial cell activation and vasoconstriction which leads to hypertension [36–39]. Therefore, surveillance and disease control are necessary to improve pregnant outcomes. Anticoagulants should be initiated in HDP patients with aCL positive. The presence of anti-Ro/La antibodies was considered to be associated with NLE or congenital atrioventricular block. Its relation with HDP in lupus patients remained to be explored.

Induced by HDP, lupus activation increased the likelihood of APOs, especially of preterm birth before 34 weeks of gestation in our research. Our previous research indicated that active disease during pregnancy was responsible for preterm birth in patients with SLE [32]. Conversely, patients in SLE remission or with cutaneous lupus only were reported to be

Table 4 Doppler parameters in SLE patients with HDP and HDP complicated with fetal APOs

	With HDP ($n = 41$)	Without HDP ($n = 191$)	P value	HDP with fetal APOs ($n = 25$)	HDP without fetal APOs ($n = 16$)	P value
PI, mean ± SD	1.0 ± 0.2	0.9 ± 0.2	**0.004**	1.1 ± 0.2	0.9 ± 0.2	**0.003**
RI, mean ± SD	0.7 ± 0.1	0.6 ± 0.1	**< 0.001**	0.7 ± 0.1	0.6 ± 0.1	**0.003**
S/D ratio, mean ± SD	3.1 ± 0.8	2.5 ± 0.5	**< 0.001**	3.3 ± 0.7	2.6 ± 0.5	**0.001**

APOs, adverse pregnancy outcomes; HDP, hypertension disorders in pregnancy; PI, pulsatility index; RI, resistance index; SD, standard deviation; S/D, systolic/diastolic; SLE, systemic lupus erythematosus

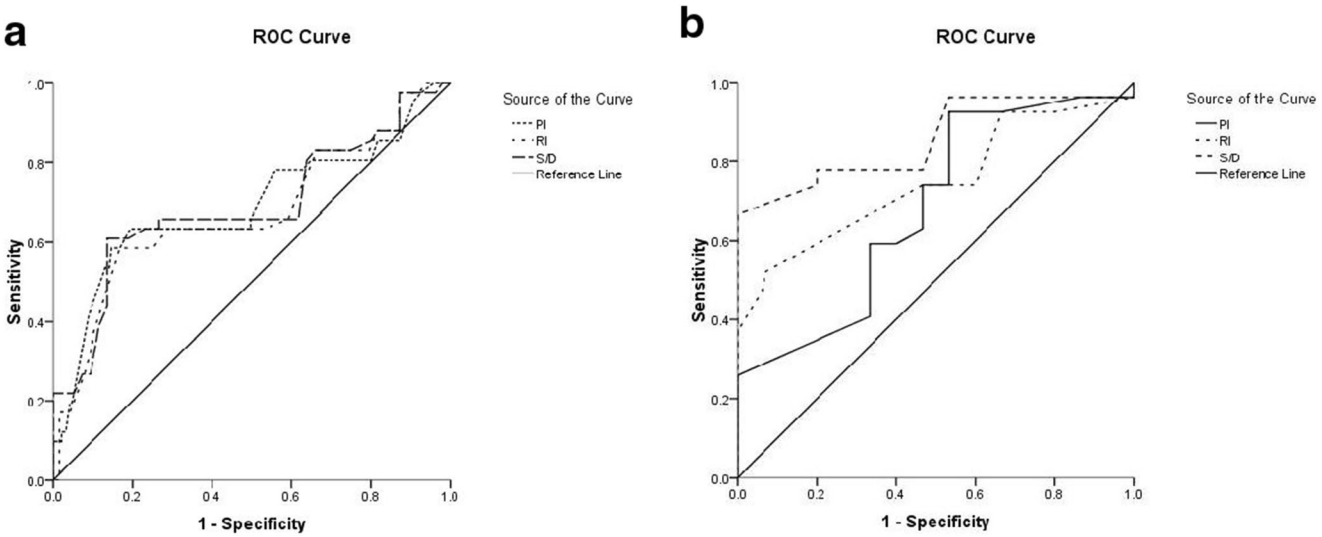

Fig. 1 ROC curve for PI, RI, and S/D ratio. (**a**) ROC curve in patients with HDP but no APOs. (**b**) ROC curve in patients with HDP and APOs. APOs, adverse pregnancy outcomes; HDP, hypertension disorders in pregnancy; PI, pulsatility index; RI, resistance index; ROC, receiver-operating characteristic curve; S/D, systolic/diastolic

more likely to have a normal pregnancy comparable to the general population [40, 41]. Previous findings and ours indicated that strict control of blood pressure improved the outcomes of pregnancy in lupus patients.

Umbilical cord is a conduit connecting the fetus and the placenta for oxygen and nutrient exchange. Hypertension, by inducing vasculitis and promoting embolism in placental vessels, impairs placenta function and leads to intrauterine distress and fetal growth restriction [21, 42]. A prospective study enrolling 116 pregnancies found that abnormal end-diastolic umbilical flow during the second trimester was an independent risk factor for fetal APOs in patients with SLE and/or anti-phospholipid syndrome (APS) [43]. Our research found that RI and S/D ratio were effective to predict APOs in patients with HDP and guide the strategy of pregnancy termination. Selective delivery should be considered in patients with increased blood resistance and IUGR. Otherwise, prolonging gestation with intensive surveillance until full term is suggested in patients with HDP but without IUGR.

Our research has some drawbacks. Treatment algorithm has been improving based on the increasing knowledge over time. For example, the protective effect of hydrochloroquine (HCQ) against endothelial dysfunction and preeclampsia was reported in experimental and clinical research [44, 45]. However, in China, HCQ was not regularly prescribed to pregnant women with SLE until the recommendations of pregnancy management were released in 2017 [46]. The advantage of HCQ could be overlooked due to the retrospective nature of the study that included data from the past 10 years. The benefit of HCQ in Chinese pregnant women with SLE and HDP needs to be re-evaluated in the future. Besides, patients were selected only from three tertiary hospitals from

Table 5 Predictive value of Doppler ultrasonography for HDP and HDP complicated with fetal APOs

	HDP			HDP with fetal APOs		
	PI	RI	S/D	PI	RI	S/D
AUC^{ROC}	0.7	0.7	0.7	0.7	0.8	0.9
95% CI of AUC	0.6–0.8	0.6–0.8	0.6–0.8	0.5–0.9	0.6–0.9	0.7–1.0
P value	**< 0.001**	**0.001**	**< 0.001**	0.05	**0.01**	**< 0.001**
Cut-off value	1.1	0.7	3.3	0.9	0.7	3.4
Sensitivity (%)	54.5	61.9	56.8	74.1	48.1	66.7
Specificity (%)	85.9	83.2	86.4	53.3	53.3	100.0
NPV (%)	47.1	44.8	49.0	74.1	92.9	100.0
PPV (%)	89.1	90.9	89.7	53.3	50.0	62.5

APO, adverse pregnancy outcome; AUC, area under the curve; CI, confidential interval; HDP, hypertension disorders in pregnancy; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value; RI, resistance index; ROC, receiver-operating characteristic curve; S/D, systolic/diastolic

China. The interpretation of the results to the general SLE population needs to be cautious due to selection bias. Additionally, PI was reported to be a good predictor for fetal complications in lupus patients [47]. However, its role to predict APOs in lupus patients with HDP was ambiguous in our research. Further studies enrolling a larger number of candidates are needed to verify the value of PI for HDP evaluation.

Conclusions

HDP was a common pregnant complication and induced various fetal APOs, including preterm birth, IUGR, low-birth-weight infants, and very-low-birth-weight infants in patients with SLE. Disease activation during the second and third trimesters was the major maternal APO. Disease activation and aCL positivity were predictors for HDP. Abnormal hemodynamics of the umbilical artery predicted fetal development in lupus patients with HDP.

Compliance with ethical standards

Disclosures None.

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