ORIGINAL ARTICLE

Prevalence of Antiphospholipid Antibodies in Patients with Bad Obstetric History of unknown Etiology and Its Association with Clinical Parameters

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Abstract

Background: Antiphospholipid syndrome (APS) is one of the important treatable causes of bad obstetric history (BOH). The literature on the association between the presence of antiphospholipid antibodies (APLA) in patients with BOH and clinical parameters is limited.

Aims and objectives: (1) To estimate the prevalence of APLA in patients with BOH and (2) To determine the association of APLA with various clinical parameters in patients with BOH.

Materials and methods: A total of 80 patients with BOH of unknown etiology and 40 age-matched controls with at least 1 successful pregnancy outcome were clinically assessed and screened for the presence of APLA {anti-β2 glycoprotein-1-IgG (ABGP1-IgG); anticardiolipin IgG and IgM [anticardiolipin antibodies (ACLA), ACLA-IgG and -IgM)]; and lupus anticoagulant (LAC)}. The clinical parameters of APLA-positive and APLA-negative cases were compared.

Results: Antiphospholipid antibodies were detected in 12 of 80 cases (15%) compared with none among controls [odds ratio (OR) = 29.38; 95% confidence interval (CI) = 1.71–505.4; $p = 0.0199$]. The antibody ABGP1-IgG was the commonest one ($n = 7$, 58.33%) followed by LAC ($n = 4$, 33.33%) and ACLA-IgG and -IgM (1 each). Patients with APLA-positive BOH had significantly increased incidence of thrombotic episodes ($p = 0.01$), hypertension ($p = 0.05$), thrombocytopenia $p < 0.01$), and anemia (9.67 ± 1.75 vs 11.04 ± 1.37 gm/dL; $p < 0.01$). Second-trimester abortion was significantly higher ($p = 0.03$), and first-trimester abortions were significantly lesser ($p = 0.02$) compared with patients with APLA-negative BOH. Third-trimester adverse obstetric events were comparable between the two groups.

Conclusion: Antiphospholipid antibodies are present in 15% of patients with BOH of unknown etiology. History of thrombosis, hypertension, thrombocytopenia, anemia, and second-trimester abortions were significantly associated with the presence of APLA in BOH.

Clinical significance: The findings from this study will help in determining the subset of patients with BOH who have higher likelihood of presence of APLA and therefore increase the chances of treatment and a successful pregnancy outcome.

Keywords: Antiphospholipid antibodies, Bad obstetric history, Hypertension, Thrombocytopenia, Thrombosis.

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Introduction

The incidence of BOH has been reported to be 5.27% in a tertiary care hospital-based study from India.[1] Bad obstetric history may result from multiple causes which include genetic factors (3.5–5%), anatomic abnormalities (12–16%), endocrine problems (17–20%), infections (0.5–5%), immunological factors such as APS (20–50%), and miscellaneous factors (10%).[2] Antiphospholipid antibodies are a family of molecules directed against negatively charged phospholipid binding proteins. The most important APLA are ACLA, anti-β2 glycoprotein-1 antibody (AB2GP1), and LAC.[3] Complement-mediated injury, reduced proliferation, and syncytia formation, increased trophoblast apoptosis and reduced human chorionic gonadotropin are the important underlying mechanisms for APLA-related adverse pregnancy events.[3]

Despite the knowledge of APLA as an established risk factor of BOH, in a resource limited setting, most patients cannot afford screening for APLA. Therefore, in such a setting, the determination of clinical factors which are associated with APLA-related BOH will help in intelligent clinical decision making and selective screening of patients for APLA.

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This study was planned with the following objectives:

- Estimation of the prevalence of APLA: Anti-β2 glycoprotein-1 (ABGP1-IgG), ACLA (ACLA-IgG and IgM), and lupus LAC in patients with history of BOH of unknown etiology.
- Compare the clinical features of patients with APLA-positive vs APLA-negative BOH.

Material and Methods

This was a cross-sectional study conducted at the Department of Obstetrics and Gynaecology/Department Rheumatology, SCB Medical College, Cuttack, Odisha, India. The proposal and protocol were approved by the institutional ethics committee. Written informed consent was obtained from all participants. The study was ethically conducted in accordance with Declaration of Helsinki.

Female patients (18–45 years) attending both the Department of Obstetrics and Gynaecology and the Department of Rheumatology were screened for history of pregnancy outcomes. Patients were labeled to have BOH if they had experienced any of the following events on more than or equal to two occasions: (a) Consecutive, spontaneous abortions; (b) early neonatal deaths; (c) stillbirths; (d) intrauterine fetal deaths; (e) intrauterine growth retardation (IUGR); or (f) congenital anomalies in the fetus.[4] The patients detected to have an explainable etiology for BOH such as congenital uterine anomalies, irregular menstrual cycles, history of complicated labor, or induced abortions, infections [including toxoplasma, rubella, cytomegalovirus, and herpes simplex (TORCH) panel and Koch's], diabetes mellitus, thyroid dysfunction, chronic liver or kidney disorders, and autoimmune diseases such as systemic lupus erythematosus (SLE), severe obesity [body mass index (BMI) ≥ 30], smoking, alcohol, or substance abuse, were excluded. This group of patients with idiopathic BOH was labeled as group A ($n = 80$).

Age-matched healthy women with at least one successful pregnancy outcome and without any history of BOH were recruited as controls (group B: $n = 40$).

The observations from history, clinical and laboratory examination were recorded in a protocol. Patients were enquired for thrombotic history such as deep vein thrombosis, gangrene, cortical sinus venous thrombosis and any other site. The timing and type of BOH was documented.

Hemoglobin below 11 gm% was considered anemia during pregnancy, thrombocyte count below 1.5 lakh/cu mm was considered thrombocytopenia, and total leukocyte count below 4000/cu mm was considered leukopenia. Systolic blood pressure above 140 mm Hg and/or diastolic blood pressure above 90 mm Hg was used to define hypertension.

The serum samples of participants were assessed for the presence of APLA (ABGP1-IgG, ACLA-IgG, and IgM) using ELISA kits of EUROIMMUN, Germany. The cut-off values for ABGP1-IgG and ACLA-IgG were considered more than or equal to 40 GPL and ACLA IgM was considered more than or equal to 40 MPL based on the cut-off described in the modified Sapporo criteria for APS.[4] The plasma samples were used for estimation of LAC by diluted Russel Viper Venom Test (dRVVT) method. Fisher's exact test was used to compare nominal data. Two-way Student's *t*-test was used to compare continuous variables. *P*-values less than or equal to 0.05 were considered statistically significant. GraphPad Prism, v.9, was used for all statistical analysis.

Results

Demography and Clinical History

The demographic details of patients and controls are described in Table 1. The history of thrombotic events and hypertension

Table 1: Demographic profile of study participants

Parameters	*Cases*	*Controls*	*p-value*
Number of participants (*n*)	80	40	
Age (in years) (mean ± SD)	28.44 ± 3.9	27.03 ± 3.86	0.08
Past thrombotic event (*n*, %)	18, 22.5%	0, 0%	0.03[b]
Systolic BP[a] (mm Hg) (mean ± SD)	124.5 ± 20.1	116.6 ± 13.8	0.03[c]
Diastolic BP (mm Hg) (mean ± SD)	75.9 ± 10.9	72.9 ± 7.9	0.13
Hypertension (*n*, %)	27, 33.75%	5, 12.5%	0.02[d]
Hemoglobin (gm/dL)	10.8 ± 1.5	11.2 ± 1.2	0.25
Total leukocyte count (/cu mm)	7860 ± 1495	7715 ± 1488	0.61
Total platelet count (in lakhs/cu mm)	2.32 ± 0.99	2.46 ± 0.62	0.43
Fasting blood sugar (mg/dL) (mean ± SD)	80.5 ± 5.7	78.4 ± 6.2	0.59
Total bilirubin (mg/dL) (mean ± SD)	0.4 ± 0.3	0.5 ± 0.3	0.82
Serum alanine transaminase (U/L) (mean ± SD)	25.7 ± 3.7	28.3 ± 3.1	0.73
Serum aspartate transaminase (U/L) (mean ± SD)	28.9 ± 2.5	30.4 ± 3.5	0.56
Serum urea (mg/dL) (mean ± SD)	24.2 ± 2.6	21.5 ± 2.1	0.61
Serum creatinine (mg/dL) (mean ± SD)	0.6 ± 0.08	0.7 ± 0.09	0.83
Serum total protein (gm/dL) (mean ± SD)	6.3 ± 0.7	6.1 ± 0.6	0.91
Serum albumin (gm/dL) (mean ± SD)	3.9 ± 0.5	3.8 ± 0.45	0.89
Urine albumin	Not detected	Not detected	–

[a]BP, blood pressure
[b–d]Statistically significant

were more common in patients with BOH vs controls ($p = 0.03$ and $p = 0.02$, respectively). The systolic blood pressure was higher in patients with BOH (124.45 ± 20.15 mm Hg) compared with controls (116.55 ± 13.8 mm Hg) ($p = 0.03$) while the diastolic blood pressure was comparable between the two groups.

Bad Obstetric History

In the current study, there were 239 adverse pregnancy events in group A (Table 2). Spontaneous abortions were the most common type of BOH (n = 174, 72.8%) which included 95 (39.75%) first-trimester abortions and 79 (33.05%) second-trimester abortions. The other subtypes of BOH included 24 intra-uterine fetal deaths (10.04%) in 19 patients, 7 stillbirths (2.93%) in 6 patients, and 10 cases of IUGR (4.18%) in 9 patients. There were nine patients with history of babies with early neonatal deaths and seven babies with congenital birth anomalies. The cause of neonatal deaths could not be ascertained from history.

Table 2: Summary of BOH of study participants

Type of BOH	*Number of patients (n = 80)*	*Number of events (n = 239)*
First-trimester abortions	51 (63.75%)	95 (39.75%)
Second-trimester abortions	48 (60%)	79 (33.05%)
Third-trimester events	41 (51.25%)	49 (20.50%)
Intra-uterine death	19 (23.75%)	24 (10.04%)
Stillbirth (term delivery)	6 (7.5%)	7 (2.93%)
Intra-uterine growth retardation	9 (11.25%)	10 (4.18%)
Preterm delivery (live birth)	7 (8.75%)	8 (3.34%)
Neonatal death	9 (11.25%)	9 (3.77%)
Congenital birth anomalies	7 (8.75%)	7 (2.93%)

Prevalence of Antiphospholipid Antibody (APLA)

Out of the 80 cases with BOH, at least one APLA subtype was present in 12 (15%) cases while none among the controls (OR = 29.38; 95% CI = 1.71–505.4; $p = 0.0199$).

Furthermore, ABGP1-IgG was the commonest antibody ($n = 7$, 58.33%) followed by LAC ($n = 4$, 33.33%). Moreover, ACLA-IgG and -IgM antibodies were present in 1 (8.33%) case each. More than one subtype of APLA was present in one patient (combination of anticardiolipin-IgG and LAC). There were no patients with triple positive APLA (ABGP1, ACLA, and LAC).

Relationship between BOH and APLA

Among the patients with BOH positive for APLA, second-trimester abortion was the most common pregnancy related morbidity ($n = 11$, 91.66%) followed by first-trimester abortion ($n = 5$, 41.66%). Early neonatal death was seen in 3 (25%) cases while preterm intra-uterine deaths were seen in 2 (16.66%) cases. One patient with positive APLA had IUGR. None of the APLA positive cases had the history of babies with congenital birth defects.

Comparing the patients with "APLA-positive BOH" vs "APLA-negative BOH" (Table 3), a significantly increased incidence of thrombotic episodes ($p = 0.01$), hypertension ($p = 0.05$), higher systolic blood pressure ($p = 0.04$), diastolic blood pressure ($p = 0.05$), thrombocytopenia ($p < 0.01$), lower thrombocyte counts ($p < 0.01$) and hemoglobin ($p < 0.01$) was observed. An increased number of second-trimester pregnancy loss ($p = 0.03$) was recorded in cases with APLA-positive BOH. Interestingly, the number of patients with

Table 3: Comparison of clinical factors between APLA[a] positive cases and APLA negative cases with history of BOH ($n = 80$)

Clinical parameters	*APLA positive (n = 12)*	*APLA negative (n = 68)*	*p-value*
Age (years) (mean ± SD)	27.08 ± 2.79	28.68 ± 4.03	0.09
Past thrombotic history (*n*)	6 (50%)	12 (17.6%)	0.01[c]
Hypertension (*n*)	7 (58.3%)	20 (29.4%)	0.05[d]
Systolic blood pressure (mm Hg) (mean ± SD)	133.67 ± 23.38	122.82 ± 19.25	0.04[e]
Diastolic blood pressure (mm Hg) (mean ± SD)	80.5 ± 11.32	75.02 ± 10.71	0.05[f]
Hemoglobin (gm/dL) (mean ± SD)	9.67 ± 1.75	11.04 ± 1.37	<0.01[g]
Total leukocyte count (/cu mm) (mean ± SD)	7438 ± 1507	7935 ± 1492	0.15
Total platelet count (lakhs/cu mm) (mean ± SD)	1.7 ± 0.94	2.94 ± 0.94	<0.01[h]
Thrombocytopenia (*n*)	6 (50%)	10 (14.7%)	<0.01[i]
Number of patients with first-trimester pregnancy loss (*n*)	5 (41.7%)	46 (67.6%)	0.08
Number of first-trimester events per patient (mean ± SD)	0.5 ± 0.67	1.31 ± 1.19	0.02[j]
Number of patients with second-trimester pregnancy loss (*n*)	11 (91.7%)	48 (70.6%)	0.03[k]
Number of second-trimester events per patient (mean ± SD)	1.83 ± 0.94	0.84 ± 0.97	<0.01[l]
Number of patients with third trimester events[b] (*n*)	3 (25%)	32 (47.1%)	0.15
Number of third-trimester events per patient (mean ± SD)	0.25 ± 0.45	0.79 ± 0.91	0.11
Number of patients with history of early neonatal death	3 (25%)	9 (13.24%)	0.13
Number of patients with congenital birth defects	0	7 (100%)	0.59

[a]APLA, anti phospholipid antibodies
[b]Third-trimester events included intra-uterine preterm deaths, stillbirth, preterm live delivery, and intra-uterine growth retardation
[c-l]Statistically significant when $p \leq 0.05$ and $p > 0.01$

pregnancy loss in the first trimester was lower in patients with APLA-positive BOH *vis-à-vis* patients with APLA-negative BOH ($p = 0.02$ and $p = 0.03$, respectively).

Discussion

Most of the previous studies on APLA and pregnancy have tried to focus on the impact of presence of APLA on the pregnancy outcome. However, the current study tries to focus on how the history and clinical features of patients with BOH and positive APLA varies from patients with BOH without APLA.

This study demonstrates a prevalence of 15% of APLA in patients with idiopathic BOH. This is similar to the prevalence of APLA in the study by Rai et al. (15%) but much higher than detected by Bowman et al. (5.6%).[5,6] The literature available from India on prevalence of APS and/or APLA in patients with BOH is limited. Sharma et al. had described the prevalence of APS in BOH of 27.7% while Ghosh et al. had described prevalence of APLA (ACLA subtype only) in 27.7%.[7,8] The cut-off used in the present study for the antibodies (ACLA-IgG, -IgM, and anti-β2 glycoprotein-1 IgG) was 40 GPL/40 MPL. The previous studies had used a cut-off value of 18 GPL/18 MPL.[7,8] It has been demonstrated earlier that moderate to high titers of APLA (≥ 40 GPL/MPL) are clinically significant while lower titers may be detected incidentally.[4] Furthermore, in this study, the patients with SLE were excluded because it could be a confounding factor in assessing women with BOH due to presence of APLA in 30–40% of SLE patients.[9] Anti-β2 glycoprotein-1 IgG was the commonest antibody (58%) in the study cohort followed by LAC (33%) and ACLA (16.67%). Similarly, in the PREGNANTS multicentric study, anti-β2 glycoprotein antibodies were associated with the lowest live birth rate followed by ACLA and LAC.[10] Multiple Indian studies[7,8,11,12] have observed that ACLA (12–40%) is the most common subtype associated with APS related bad obstetric outcomes. However, Ghosh et al. and Chandran et al. had studied the prevalence of ACLA only.[8,11] Sharma et al. had described 27% BOH to have APS with ACLA (18%) as the most common APLA followed by LAC (10%) and ABGP1 (6.9%).[7] Kaneria and Vishwanathan had found isolated ACLA in 28%, isolated LAC in 12% and combination of ACLA and LAC in 3%.[12] The variation in antibody prevalence may be related to the racial, ethnic, and the environmental factors. In the BOH cohort, there were 239 events in 80 patients (Table 2). First- and second-trimester abortions were the most common adverse events (39.75 and 33.05%, respectively). In the APLA-positive BOH cohort ($n = 12$), the number of second-trimester abortions ($n = 22$, 64.71%) were much higher than the first-trimester abortions ($n = 6$, 17.64%). In addition, there were three early neonatal deaths, one IUGR, and two preterm intra-uterine deaths in the APLA-positive BOH group. In the Euro–Phospholipid project which included 1,000 patients (82% APLA positive), early fetal loss (<10 weeks of gestation) was noted in 35.4% and the late fetal losses (≥10 weeks) in 16.9% patients.[9] Prematurity was observed in 10.6%.[9] Thrombotic events were significantly higher in patients with BOH (22.5%) vs controls. Furthermore, thrombotic events were significantly higher in APLA-positive compared with APLA-negative BOH cases. The frequently hypothesized cause of unexplained recurrent pregnancy loss in APS is due to utero–placental thrombosis. Although we observed that 17.4% of APLA-negative BOH cases had past thrombotic events, they could neither be investigated for other causes of thrombophilia (deficiency of protein C and/or S, hyperhomocysteinemia) nor the non-criteria APLA (antiphosphatidyl serine, antiphosphatidyl choline, and antiphosphatidyl ethanolamine), which may also cause thrombosis and BOH.[13]

Hypertension was significantly more common in patients with BOH compared with controls. In addition, prevalence of hypertension as well as the mean systolic and diastolic blood pressures were significantly higher in APLA-positive BOH vs APLA-negative BOH. Similar observations of higher incidence of hypertension in patients with BOH and APLA (63.3%) has been demonstrated.[3] In a recent meta-analysis, Liu and Sun had confirmed significantly higher incidence of pregnancy induced hypertension in women with APS compared with healthy controls (RR = 1.81; 95% CI = 1.33–2.45; $p = 0.0002$).[14] Although the exact mechanism of hypertension in APS has not been established, renovascular hypertension due to microthrombi in renal circulation has been hypothesized. In a recent review by Turrent-Carriles et al., hypertension has been described as one of the most common presenting manifestations of renal involvement in APS.[15] Thrombocytopenia was significantly more prevalent in APLA-positive BOH cases compared with APLA-negative BOH cases and controls. In addition, the mean total platelet count was significantly lower in APLA-positive BOH vs APLA-negative BOH. Thrombocytopenia is a common associated clinical condition with APLA syndrome.[4]

The various adverse pregnancy events were compared between APLA-positive and APLA-negative BOH patients. It was observed that the first-trimester events were lower in APLA-positive compared to APLA-negative patients. Although three consecutive pregnancy losses below 10 weeks is considered as one of the obstetric APS criteria, there are other important etiologies for the first-trimester abortions; for example, maternal and paternal chromosomal abnormalities, anatomical, and hormonal causes.[16] The genetic testing of parents could not be done due to financial constraints. The mechanism of increased first-trimester abortions in APLA-negative individuals could not be analyzed.

On the other hand, the second-trimester events were significantly higher in APLA-positive patients. The third-trimester events (preterm IUD, IUGR, stillbirth at term, and preterm live delivery) and postpartum events (early neonatal deaths and congenital birth defects) were comparable between the two groups. However, Out et al. had demonstrated that presence of ACLA could predict low birth weight in a newborn.[17]

Limitations

The study was a cross-sectional study focusing on patients with BOH of unknown etiology. The lack of genetic testing of parents was a limitation in the evaluation of the etiology of BOH, especially the first-trimester fetal loss. Due to financial constraints, the repeat screening of APLA at 12 weeks could not be performed as required by the modified Sapporo criteria to establish the diagnosis of APS. As the number of patients with positive APLA was small, comparison of clinical parameters between individual subtypes of APLA could not be performed.

Conclusion

The presence of antiphospholipid antibody is an important cause of idiopathic BOH. Antiphospholipid antibodies is present in 15% of patients with BOH of unknown etiology after ruling out anatomic, hormonal, infective, and other chronic illnesses. History of thrombosis, hypertension, thrombocytopenia, anemia, and the second-trimester abortions were significantly associated with presence of APLA in BOH.

Clinical Significance

With treatment, the patients with APLA-positive BOH increase the chance of a successful pregnancy outcome. On the other hand, screening all patients with BOH for APLA carries the issue of affordability in a resource limited setting like India. This study will guide in conducting future prospective studies to validate the clinical predictors of APLA in a patient with BOH. The results will help the clinician and the patient make a shared decision when to undertake a screening for APLA in a setting for BOH.

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References

1. Singh G, Sidhu K. Bad obstetric history: A prospective study. Med J Armed Forces India 2010;66(2):117–1120. DOI: 10.1016/S0377-1237(10)80121-2.
2. Lathi RB, Schust DJ. Recurrent pregnancy loss. In: Berek JS, editor. Berek and Novak's Gynecology. Philadelphia: Lippincott Wilkins and Williams; 2012. pp.2636–2734.
3. Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. N Engl J Med 2018;378(21):2010–2021. DOI: 10.1056/NEJMra1705454.
4. Qi Y, Zhu S, Li C, et al. Seroepidemiology of TORCH antibodies in the reproductive-aged women in China. Eur J Obstet Gynecol Reprod Biol 2020;254:114–118. DOI: 10.1016/j.ejogrb.2020.09.010. DOI: 10.1016/j.ejogrb.2020.09.010.
5. Rai RS, Regan L, Clifford K, et al. Antiphospholipid antibodies and β2-glycoprotein-I in 500 women with recurrent miscarriage. Results of a comprehensive screening approach. Hum Reprod 1995;10:2001–2005. DOI: 10.1093/oxfordjournals.humrep.a136224.
6. Bowman ZS, Wunsche V, Porter TF, et al. Prevalence of antiphospholipid antibodies and risk of subsequent adverse obstetric outcomes in women with prior pregnancy loss. J Reprod Immunol 2015;107:59–63. DOI: 10.1016/j.jri.2014.09.052.
7. Sharma A, Yadav S, Yadav P. Study of antiphospholipid syndrome in patients with bad obstetric history: A cross-sectional study. Int J Clin Obstet Gynaecol 2018;2(2):24–28. https://www.gynaecologyjournal.com/articles/53/2-1-23-570.pdf.
8. Ghosh A, Ghosh M, Bhattacharya SM. Antiphospholipid antibodies as a cause of recurrent pregnancy loss: a study in Calcutta, India. J Obstet Gynaecol 2006;26(5):407–410. DOI: 10.1080/01443610600719974.
9. Cervera R, Boffa MC, Khamashta MA, et al. The Euro–Phospholipid project: Epidemiology of the antiphospholipid syndrome in Europe. Lupus. 2009;18:889–893. DOI: 10.1177/0961203309106832.
10. Saccone G, Berghella V, Maruotti GM, et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: The PREGNANTS study. Am J Obstet Gynecol 2017;216(5):525.e1–525.e12. DOI: 10.1016/j.ajog.2017.01.026.
11. Chandran V, Aggarwal A, Misra R. Active disease during pregnancy is associated with poor foetal outcome in Indian patients with systemic lupus erythematosus. Rheumatol Int 2005;26(2):152–156. DOI: 10.1007/s00296-004-0540-3.
12. Kaneria MV, Vishwanathan C. A preliminary study of antiphospholipid antibodies in 50 cases of bad obstetric history. J Assoc Physicians India 1999;47(7):669–672. PMID: 10778583.
13. Pignatelli P, Ettorre E, Menichelli D, et al. Seronegative antiphospholipid syndrome: refining the value of "non-criteria" antibodies for diagnosis and clinical management. Haematologica 2020;105(3):562–572. DOI: 10.3324/haematol.2019.221945.
14. Liu L, Sun D. Pregnancy outcomes in patients with primary antiphospholipid syndrome: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(20):e15733. DOI: 10.1097/MD.0000000000015733.
15. Turrent-Carriles A, Herrera-Félix JP, Amigo MC. Renal involvement in antiphospholipid syndrome. Front Immunol 2018;9:1008. DOI: 10.3389/fimmu.2018.01008.
16. Allison JL, Schust DJ. Recurrent first trimester pregnancy loss: revised definitions and novel causes. Curr Opin Endocrinol Diabetes Obes 2009;16:446–450. DOI: 10.1097/MED.0b013e3283327fc5.
17. Out HJ, Bruinse HW, Christiaens GCML, et al. A prospective, controlled multicenter study on the obstetric risks of pregnant women with antiphospholipid antibodies. Am J Obstet Gynecol 1992;167(1):26–32. DOI: 10.1016/s0002-9378(11)91619-6.