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Role of belimumab in recurrent spontaneous abortions amongst patients with lymphocyte dysfunction: a retrospective case-control study

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Abstract

Objective In order to examine the impact of belimumab on recurrent spontaneous abortion (RSA) women exhibiting B lymphocyte dysfunction.

Methods This study conducted a retrospective case-control analysis of RSA patients with confirmed B lymphocyte dysfunction. The study included 102 women who had experienced at least two consecutive miscarriages and demonstrated elevated peripheral blood B cell percentages and/or counts. Participants were separated into two distinct groups: the belimumab group ($n=51$), which received basic treatment supplemented with belimumab (BENLYSTA) at a dosage of 10 mg/kg BW at 2-week intervals for the first 3 doses and at 4-week intervals thereafter, from the end of menstrual period until the 12th week of pregnancy, if necessary; and the control group ($n=51$), which received only standard treatment. Comparisons of Pregnancy outcomes, B cell percentage, B cell count and adverse reactions were made between 2 groups.

Results Healthy newborns were delivered by 45 participants (88.23%) in belimumab group and 36 participants (70.59%) in control group [$P=0.048$, odds ratio (OR) = 3.13; 95% confidence interval (CI) (1.10–8.87)]. The belimumab group exhibited significantly lower peripheral blood B cell percentage and B cell count compared to the control group during gestational weeks 2–12 ($P<0.05$).

Conclusion The findings suggest that belimumab is both safe and effective for treating RSA with lymphocyte dysfunction, indicating its potential as a therapeutic strategy for RSA.

Keywords Belimumab, Recurrent spontaneous abortion, B cells, Lymphocyte dysfunction

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Introduction

Recurrent spontaneous abortion (RSA) is defined as having 2 or more consecutive spontaneous abortions, with an incidence rate of about 5% among couples of childbearing age [1]. The risk of RSA increases with the number of miscarriages. It is reported that the probability of miscarriage in the first pregnancy is 11–13%,second pregnancy in 13–17% and third pregnancy in up to 80% [2]. For those with a history of four or more miscarriages, if not appropriately treated, most will experience subsequent miscarriages [3]. In recent years, the prevalence of recurrent miscarriage has been increasing, and women with multiple miscarriages face significant physical and emotional stress [4]. Therefore, investigating the etiology of RSA and implementing targeted and preventive treatments based on the underlying causes is crucial for managing and preventing RSA. Research into this condition is a current focus in the field of obstetrics and gynecology. Known causes of RSA include autoimmune diseases, chromosomal abnormalities, endocrine disorders, uterine abnormalities, infections, and immune system disorders [5]. Among these, about half of RSA cases are related to immune system disorders, primarily lymphocyte dysfunction [6].

Numerous foundational and clinical studies have established a link between immune cells and adverse pregnancy outcomes, particularly RSA [7–9]. Successful maintenance of immune tolerance to the fetus during pregnancy relies on the activation and balance of various immune cell types, including dendritic cells (DCs), natural killer (NK) cells, macrophages, T cells, and B cells [10]. Disruptions in the distribution, proportions, maturation, or function of these cells can negatively affect pregnancy outcomes, potentially leading to RSA [7, 11]. These findings underscore the important role of immune cells, especially lymphocytes, in the context of RSA [12], and B lymphocytes may play a significant role in this process.

Elevated B cells can promote the secretion of plasma cells, synthesize and secrete antibodies, and circulate in the blood, contributing to humoral immunity. B cells are also closely associated with conditions such as endometriosis, increased levels of autoantibodies, ovarian dysfunction, luteal phase insufficiency, and decreased progesterone synthesis. Additionally, activated B cells are capable of producing various cytokines, such as IL-4, IL-6, IL-17, and TNF-α, which participate in inflammatory cycles and immune regulation, inhibiting the proliferation and differentiation of trophoblast cells, ultimately leading to embryonic arrest [13].

Currently, treatments targeting lymphocyte dysfunction, such as cyclosporine and tacrolimus, are widely used for RSA management [6, 14, 15]. However, these treatments primarily focus on NK cells and T cells, with a lack of effective and safe therapies specifically targeting B cells for pregnant women. Since 2018, our hospital has treated RSA patients with documented lymphocyte dysfunction using a combination of aspirin, heparin, prednisone, cyclosporine, and intravenous immunoglobulin, achieving a success rate of approximately 75%. Nevertheless, about one-quarter of patients still experience treatment failure. For these patients, the primary reason for failure is believed to be the inadequacy of current traditional treatment regimens in reducing B cell levels to optimal levels, leading to pregnancy loss.

Belimumab is classified as a class C drug for pregnancy by the US Food and Drug Administration (FDA) [16]. Belimumab is a fully human monoclonal antibody which targets and suppresses the B lymphocyte activation factor. It is a specific inhibitor of the B lymphocyte stimulator (BlyS). By binding to excess BlyS, belimumab blocks the interaction between BlyS and its receptors on B cells, thereby inhibiting the survival of autoreactive B cells. This leads to an increased apoptosis of autoreactive B cells, consequently controlling the progression of the disease [17–20]. In 2011, belimumab became the first biological agent to be approved by the US FDA to cure adult systemic lupus erythematosus (SLE) [16]. Numerous real-world studies from countries such as the United States, Argentina, Germany, and Spain, along with extensive clinical data, have demonstrated the efficacy of belimumab. Additionally, some studies have reported the successful treatment of patients with antiphospholipid syndrome (APS) using belimumab [21–25]. Although some studies have indicated the safety of belimumab in women exhibiting pregnancy complicated by SLE or APS [26], there is still a lack of data on the therapeutic safety and efficacy of belimumab in women with recurrent RSA. Furthermore, the use of belimumab in the field of reproductive immunology lacks evidence-based medical support.

We hypothesize that belimumab may exert a role in preserving pregnancy by inhibiting B-cell activity, improving immune tolerance at the maternal-fetal interface, and reducing maternal immune rejection of the embryo. Therefore, we performed immunosuppressive treatment with belimumab in consenting RSA patients who did not respond to conventional treatments, including aspirin, low-molecular-weight heparin, prednisone and cyclosporine.

Methods and materials

Patients

A retrospective case-control analysis was carried out on 102 pregnant patients, split evenly with 51 participants in control group and 51 participants in belimumab group, all diagnosed as RSA in Qingdao Jinhua Gynecology Hospital from August 2021 to February 2024. All participants

in this study are Han ethnic. All pregnancy diagnosis were defined and diagnosed according to the guidelines of the Chinese Society of Obstetrics and Gynecology [27].

The inclusion criteria were:

1. Patients with two or more consecutive miscarriages and no history of a successful pregnancy.
2. Patients aged 39 years or younger.
3. No uterine abnormalities detected through uterine ultrasound examination or hysteroscopy.
4. Blood B cell percentage greater than 18.2% or B cell count exceeding 530/μl [28].
5. Failure of standard treatment in patients.
6. Husband's semen analysis is normal.

The exclusion criteria were:

1. Inability to rule out other RSA causes, including uterine defects, abnormal karyotypes, infectious diseases, endocrine disorders, thrombosis abnormalities or coagulation, and autoimmune deficiencies (including SLE and APS).
2. Abnormal semen analysis in the husband.
3. Patients undergoing infertility treatment.
4. Drug allergies.
5. Incomplete data.

Design of the study

All study participants were made aware of the potential impacts of this research on the fetus and the mother, including the possible risk of infection from belimumab. The belimumab group received belimumab plus standard treatment (aspirin, low-molecular-weight heparin, prednisone, cyclosporine), while the control group received a standard treatment. The 51 participants in the belimumab group were administered belimumab (BENLYSTA, GlaxoSmithKline Manufacturing S.P.A., Italy) intravenously at 10 mg/kg BW at 2-week intervals for the first 3 doses and at 4-week intervals thereafter, starting at the end of their menstrual period till the 12th week of pregnancy, if necessary.

During the treatment, belimumab was discontinued if the fetal growth was satisfactory without obvious gross anomalies, human chorionic gonadotropin (HCG) levels increased appropriately, and B cells count returned to normal. After discontinuation, B cell percentage and B cell count were measured every 2 weeks until 12 weeks gestation. The fetal growth was monitored via ultrasound and HCG levels were measured every 1 to 2 weeks. If any abnormalities were detected, the medication would be restarted, and continued until 12 weeks of gestation if necessary. Therefore, only very few participants used more than 3 doses in this study. Adverse reactions to the medication were monitored throughout the use of belimumab.

Except for belimumab, other drugs targeting B cells were not used. In addition, there was no difference in standard treatment (aspirin, low-molecular-weight heparin, prednisone, cyclosporine) between the two groups.

Observational indicators

The peripheral blood B cell percentage and B cell count were detected per 2 weeks from the end of menstruation to gestation week 12 in the two groups. The entire pregnancy period of all study participants was followed up throughout the study. From 4 to 12 weeks of pregnancy, transvaginal ultrasound examinations were conducted every 2 weeks to monitor embryo development or diagnose miscarriage (according to the criteria of the Chinese Society of Obstetrics and Gynecology). Detailed scan was carried out at 20–24 weeks of pregnancy to rule out fetal anomaly. To exclude congenital abnormalities, all newborns were examined by pediatricians. Gestational ages at which the miscarriage occurred were calculated based on the observed gestational sac size and crown-rump length during ultrasound examinations.

The primary outcome was the birth of a healthy baby free from congenital abnormalities. Secondary outcomes included neonatal weight, pregnancy complications (such as preterm birth, preeclampsia, gestational diabetes, bleeding and thrombosis, hypertensive disorders of pregnancy), and adverse reactions to the treatment.

Analyses of B cell percentage and B cell count in peripheral blood

The peripheral blood B cell percentage and the B cell count were measured using flow cytometry, following previously established protocols [29].

Statistical analyses

Statistical methods were conducted through SPSS version 23.0 (IBM, Armonk, NY, USA). Discrete variables were analyzed using Fisher's exact test and $\chi 2$ test, while continuous variables were evaluated through a two-tailed unpaired one-way ANOVA and Student's t-test. $P<0.05$ was regarded as statistically significant.

Results

Basic characteristics of the study participants in both groups

No statistically significant differences were observed between the two groups in terms of the number of consecutive miscarriages, age, gestational weeks at the time of miscarriage, and body mass index (BMI) before pregnancy (Table 1).

Table 1 Basic characteristics of study participants in both groups

	Belimumab	Control	*P* value
Number of patients	51	51	-
Age (years)	35.0 ± 3.0	34.4 ± 2.7	0.291
BMI	28.0 ± 1.8	27.6 ± 2.1	0.304
Number of consecutive miscarriages	3.0 ± 0.4	3.1 ± 0.3	0.157
Gestational age of last miscarriage (weeks)	6.2 ± 1.1	6.1 ± 1.2	0.662
Smoking history[#]	1	0	1.000

[#]More than 10 cigarettes per day

Table 2 Comparison of pregnancy and delivery data between the two groups

		Belimumab	Control	*P* value
Number of live births (%)		45(88.23)	36(70.59)	0.048
Number of abortions (%)		6(11.77)	15(29.41)	0.048
Gestational age of abortion (weeks, mean ± SD)		7.1 ± 1.3	7.3 ± 1.2	0.421
Neonate Apgar score (mean ± SD)	1 min	9.5 ± 0.6	9.6 ± 0.6	0.402
	5 min	9.8 ± 0.3	9.9 ± 0.4	0.157
Neonate weight (g, mean ± SD)		3059 ± 236	3118 ± 223	0.197
B cell percentage at 12 weeks		17.57 ± 0.40	21.23 ± 1.37	< 0.0001
B cell count at 12 weeks		512.60 ± 26.67	607.82 ± 52.43	< 0.0001
Therapy side effects	Rash	1	1	1.000
	Hypertension	1	4	0.362
	Maternal IgG at 12 weeks (g/L, mean ± SD)	9.4 ± 0.8	9.5 ± 0.7	0.503
	Neonatal white blood cell counts ($\times 10^9$/L, mean ± SD)	16.8 ± 1.8	17.5 ± 2.0	0.066

Primary and secondary outcomes

According to the data in Table 2, out of 51 participants in the belimumab group, 45 had live births (88.24%), whereas only 36 out of 51 participants in the control group had live births (70.59%). This difference is statistically significant [$P = 0.048$, $OR = 3.13$; 95% CI (1.10–8.87)]. The number of participants needed to be treated (NNT) to achieve one additional live birth is 5.67. No statistically significant differences were observed between two groups regarding gestational age at the time of miscarriage, neonatal weight, or adverse reactions to the treatment.

Both groups had one case of rash. In the belimumab group, one case (1.96%) of hypertensive disorders of pregnancy was observed, compared to four cases (7.84%) in the control group, with the control group having a higher incidence, though the difference was not statistically significant. None of the newborns had congenital defects or infections, and their perinatal development was also normal. The critical safety and immunological outcomes also have no differences between two groups, such as maternal infection (absent in both groups, 0 cases), maternal Immunoglobulin G (IgG), neonatal infection and neonatal white blood cell counts. Among 21 cases of miscarriage, chromosomal karyotyping of the embryonic tissue was performed in 12 cases, revealing chromosomal abnormalities in 3 cases: 1 from belimumab group (47 XY, +21) and 2 from control group (47 XX, +21 and 47 XY,+18, respectively).

Comparison of the B cell percentage and the B cell count in peripheral blood

Compared to control group, belimumab group exhibited a significant reduction in B cell percentage and B cell count of peripheral blood in gestation weeks 2–12 (Fig. 1, $P < 0.05$).

Discussion

In the present retrospective case-control study, belimumab demonstrated significant efficacy in women with RSA caused by lymphocyte dysfunction, markedly increasing live birth rates and reducing miscarriage rates. The NNT to achieve one additional live birth was 5.67, which is notably lower than the NNT for some traditional therapies, such as tacrolimus and lymphocyte immunotherapy, which have NNTs of 6.07 [6]and 10 [30], respectively.

However, the findings of the present retrospective case-control study may not generalize to all RSA patients due to limited sample volume and stringent inclusion and exclusion criteria. Currently, there are no large-scale clinical studies on the use of belimumab in the treatment of RSA. Previous studies on belimumab in pregnant populations were conducted in patients with SLE and only explored the safety of belimumab during pregnancy. This study is the first to apply belimumab in patients with RSA and found that belimumab treatment can significantly improve embryo survival rates in RSA patients, potentially reaching levels comparable to normal pregnancies. This suggests that belimumab could become a new treatment avenue for RSA.

Moreover, no significant fetal or maternal abnormalities were observed in patients using belimumab during pregnancy in this study. This provides new evidence supporting belimumab treatment among pregnant women and demonstrates the efficacy and safety in treating RSA secondary to lymphocyte dysfunction.

Belimumab is completely humanized IgG1 monoclonal antibodies that particularly targets BlyS, a member of the tumor necrosis factor (TNF) superfamily, which prevents B lymphocytes from maturing into plasma cells that produce autoantibodies [16]. The IgG antibodies of mothers are transferred through placentas in order to provide immune protection to fetus, whose own immune

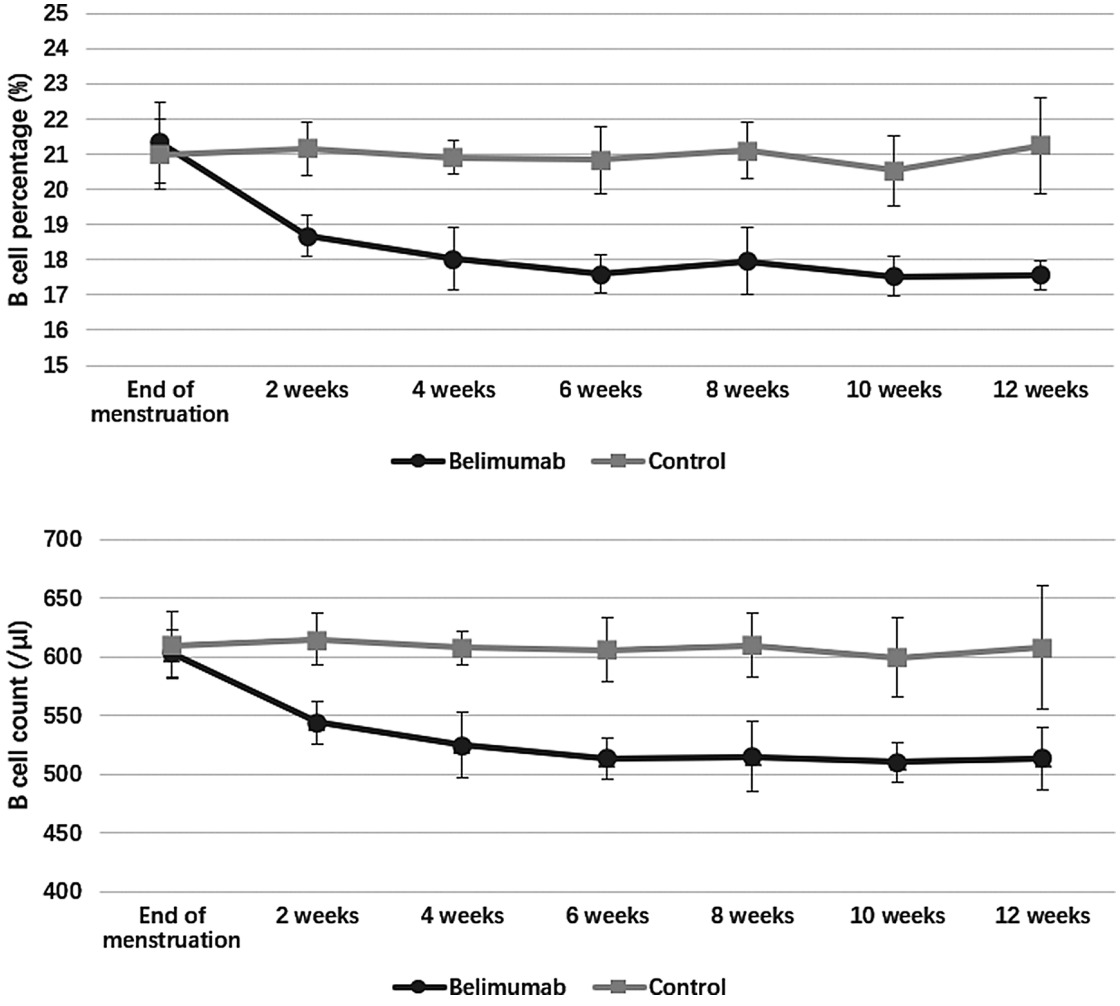

Fig. 1 B cell percentage and B cell count of the two groups

system is not fully functional. This transfer increases progressively, with infinitesimal transfer during first trimester, then peak transfer in third trimester. Although belimumab can cross the placenta in humans [31], it is unlikely to affect the fetus significantly, as this transfer typically begins around 15 weeks of gestation, similar to other immunoglobulin-based biologics [32]. Despite this, the absolute safety of belimumab during pregnancy is not fully established [33]. Consequently, the US FDA has classified belimumab as pregnancy category C [34]. In drug trials, there were 83 cases of unintended pregnancies. Among these, 42% resulted in live births, 24% in terminations, and 27.7% in miscarriages [35].

The safety of belimumab had been demonstrated in other studies whereby it was used from first trimester onwards [36–40]. Recently, a case series in Taiwan illustrated that 13 SLE patients were treated with belimumab through their pregnancies, and no fetal anomalies were observed [41]. European Alliance of Associations for Rheumatology (EULAR) advises considering an addition of belimumab in non-pregnant SLE patients with persistently active or flaring extrarenal disease [42]. It was noted that belimumab theoretically does not cross the placenta until around the gestation week 15, allowing its continued use throughout the first trimester of conception [43]. A 2023 study indicated that if SLE patients continue using belimumab after pregnancy, no cases of low birth weight (LBW) were reported. However, if belimumab is discontinued early in pregnancy, it may increase the risk of LBW (9 cases, 24.3%), possibly due to inadequate control of SLE [44]. In 2024, a recent study [45] reviewed reports on miscarriages and congenital abnormalities were collected from the belimumab pregnancy registry (BPR, NCT01532310), spontaneous /post-marketing data involving SLE patients who used belimumab during or before pregnancy, and all clinical trials of belimumab. The authors noted that due to data limitations, they could not offer definitive recommendations regarding using belimumab in pregnancy. Whereas, this research cannot identify an elevated risk of miscarriage

or congenital abnormalities in patients using belimumab [46]. Overall, analyses of results from registries and clinical trials, case series, and case studies indicate that belimumab exposure does not pose a risk for fetal malformations. The 2022 British Society for Rheumatology (BSR) guideline on prescribing drugs in pregnancy and breastfeeding [47] noted that while evidence is still insufficient to fully establish its safety in pregnancy, belimumab is not likely to cause harm when used in pregnancy. Consequently, it is likely to be thought about for managing serious maternal illness during pregnancy if not any other applicable treatments are available [46]. If belimumab is administered to cure serious maternal illness during the third trimester, it is advised to delay administering any living vaccines to the neonate till they are at least 6 months old [47].

Consistent with the aforementioned research, this study did not find any significant adverse reactions associated with belimumab. The incidence of adverse reactions was similar between the belimumab group and control group. Additionally, no statistical differences were observed between two groups regarding neonatal weight, congenital abnormalities, or Apgar scores, and no fetal adverse reactions were observed. However, this study did not evaluate the potential toxicity of belimumab during the mid and late stages of pregnancy.

Preeclampsia is a significant pregnancy-related disorder, and assessing whether Belimumab influences its risk is clinically relevant. In this study, we compared the incidence of hypertension between the two groups to evaluate the potential impact of Belimumab on preeclampsia risk. Although the difference was not statistically significant, the incidence was lower in the Belimumab group, suggesting a possible trend toward a protective effect. While further studies with larger sample sizes are needed to confirm this finding, our results indicate that Belimumab does not appear to increase the risk of preeclampsia and may even contribute to a reduction in its incidence.

B lymphocyte dysfunction can lead to RSA through mechanisms such as autoimmunity, immune regulation, and inflammatory responses [48]. This study evaluated peripheral blood B cells using two methods. The B-cell percentage reflects the relative proportion of B cells among lymphocytes, assessing the balance of the immune system and helping to understand the relative role of B cells in immune function. It is commonly used for evaluating immune function, autoimmune diseases, and immune system disorders. In contrast, B cell count directly reflects absolute number of the B cell and is often used for diagnosing and monitoring immune system diseases, hematological disorders, and infections. This is particularly useful for assessing changes in B cells when total lymphocyte counts are abnormal. The study found that after treatment with belimumab, both the B-cell percentage and count decreased significantly, and the live birth rate increased markedly. This suggests that belimumab may improve B lymphocyte dysfunction, enhance maternal-fetal immune tolerance, and reduce maternal immune rejection of the embryo, thereby improving pregnancy outcomes in RSA patients.

Limitations

Firstly, this study is a retrospective case-control analysis with issues related to data completeness and consistency, and the sample size is relatively small with strict inclusion criteria and exclusion criteria, which may limit the generalizability of the results. Therefore, larger and multicenter studies are needed in the future to confirm the safety and efficacy of belimumab in treating RSA. Secondly, the specific mechanisms of belimumab and B cells in RSA remain unclear. Research indicates that different subsets of B cells may play distinct roles [49], and further investigation is required. Thirdly, this study only assessed short-term pregnancy outcomes following belimumab treatment, and long-term maternal and infant health should be monitored in future follow-ups. Additionally, neonatal B-cell counts and IgG levels are unavailable in this study, which are important indicators of neonatal immune function and side effects of belimumab.

Conclusions

This study found that belimumab can improve B lymphocyte dysfunction, enhance maternal-fetal immune tolerance, and reduce maternal immune rejection of the embryo, thereby providing a protective effect and improving pregnancy outcomes in RSA patients. The study preliminarily demonstrates the safety and efficacy of belimumab for treating RSA, which means belimumab can be used with caution in patients with RSA. This not only provides new evidence for the use of belimumab in pregnant patients but also offers a new approach for treating RSA.

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Author contributions

LL, XM, JF, and LZ: conception and design, data analysis, and interpretation. LL and LZ: administrative support. XM, JF, JL, GY, and NL: provision of study materials or patients, collection, and assembly of the data. All authors wrote the manuscript and approved the final version of the manuscript.

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Data availability
The original contributions presented in the study can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
This retrospective case-control study was approved by the ethics committee of Qingdao Jinhua Gynecology Hospital. All subjects were treated with standard care without intervention from this study. All data were obtained via electronic medical records and a database review and were de-identified (all patients' name were replaced with an identification code, and all patients' private information were deleted before the analysis) to protect patient privacy, therefore all patients' informed consents are waived in accordance with national regulations, specifically the Measures for Ethical Review of Biomedical Research Involving Humans issued by the National Health Commission of China. Clinical trial number: not applicable.

Consent for publication
This study used de-identified patient data, and no individual identifiable details are presented. According to institutional guidelines, consent for publication was not required.

Competing interests
The authors declare no competing interests.

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