Efficacy of Different Treatment Regimens for Antiphospholipid Syndrome-related Recurrent Spontaneous Abortion

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Abstract

Background: Antiphospholipid syndrome (APS)-related immune factors are considered as an important cause of recurrent spontaneous abortion (RSA). Anticoagulant and anti-inflammatory treatments are believed to effectively improve adverse pregnancy outcomes by affecting the abnormal autoimmune response of the maternal-fetal interface. The aim of this study was to observe the clinical characteristics and treatment outcomes of anticoagulant regimens and anti-inflammatory plus anticoagulation regimens for APS-related RSA.

Methods: APS-related RSA cases from September 2011 to September 2016 at Peking University Third Hospital were retrospectively analyzed. The patients were assigned to study group (anti-inflammation plus anticoagulation) and control group (simple anticoagulation). The incidence of repeat abortion, the incidence of placental dysfunction, the gestational weeks of pregnancy, and the mean weight of the fetus were observed.

Results: The pregnancy and neonatal outcome indicators of the repeat pregnancy loss rate (11.11% vs. 22.70%), placental dysfunction-related diseases (6.35% vs. 15.60%), the mean birth weight of infants born after 24 weeks gestation (3152.41 ± 844.67 g vs. 2765.76 ± 816.40 g), full-term delivery weight (3456.28 ± 419.79 g vs. 3076.18 ± 518.79 g), the proportions of low birth weight infants (12.70% vs. 21.98%), and small for gestational age (6.35% vs. 14.18%) differed significantly between the study and control groups (all $P < 0.05$). The incidence of preterm delivery, term delivery, and stillbirth was not significantly different between the two groups, and there was no significant difference between the study and control groups in gestational age at birth (37.6 ± 3.3 weeks vs. 36.9 ± 3.2 weeks; $P > 0.05$).

Conclusion: The anti-inflammatory and anticoagulation regimen is more effective than the simple anticoagulation regimen in the treatment of APS recurrent abortion.

Key words: Anticoagulant Therapy; Anti-inflammatory Therapy; Antiphospholipid Syndrome; Recurrent Spontaneous Abortion

Introduction

The incidence of recurrent spontaneous abortion (RSA) is approximately 2–4%,[1] and 65–70% of RSA cases are complicated by abnormal immune factors.[2] Antiphospholipid syndrome (APS) is a group of diseases characterized by RSA, stillbirth, premature birth, and serum antiphospholipid antibodies (APL). APS is the most common cause of immune-related RSA; nearly 7–25% of RSA patients have APS.[3]

In our previous work, RSA patients with APS were treated according to the relevant guidelines with low-dose aspirin (LDA) and low-molecular-weight heparin (LMWH) combination therapy.[4,5] In practice, there is still a high rate of repeat abortion among those patients.[6,7] To reduce the rate of repeat abortion and improve the mother-fetus outcomes of subsequent pregnancies and based on previous guidelines and our experience with the diagnosis and treatment of RSA, we developed a treatment regimen of giving prednisolone + hydroxychloroquine (HCQ) + LDA before pregnancy and introducing LMWH at the beginning of pregnancy as an anti-inflammatory–anticoagulant treatment regimen. The anti-inflammatory–anticoagulant treatment

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regimen improves the success rate of APS-related RSA pregnancy and pregnancy outcomes. Therefore, we conducted a retrospective study of our hospital's APS-related RSA cases using the anticoagulant therapy group as a control group to observe the case characteristics and clinical outcomes of patients treated with anti-inflammatory and anticoagulant therapy and to explore the clinical value and feasibility of the anti-inflammatory and anticoagulant regimen.

Methods

Ethical approval

The study design was approved by the Peking University Ethics Committee (No. 2016_261_01). Informed consent was obtained from all the research participants.

Patients

APS-related RSA patients who underwent regular prenatal examinations and delivered at Peking University Third Hospital between September 2011 and September 2016 were included in this study. The inclusion criteria were as follows: naturally conceived singleton pregnancy; pregnancy without hypertension or diabetes; normal thyroid function before pregnancy; and no other autoimmune diseases. The exclusion criteria were as follows: embryonic chromosomal abnormalities; abnormal fetal development and infectious abortion cases. All the enrolled patients took oral dydrogesterone from the beginning of pregnancy to 11 weeks of gestation. Regarding the determination of gestational age, although a pregnancy with a prenatal period of 28 weeks is considered viable, recent improvements in neonatal diagnosis and treatment have made it possible for even younger preterm babies to survive. In this study, we included newborns with various birth weights and gestational ages of more than 24 weeks.[8] In recent years, some scholars have proposed the concept of atypical obstetric APS, characterized as patients who are: (1) APL-positive but with atypical clinical manifestations (such as two unexplained abortions at <10 weeks of pregnancy or three or more abortions of nonsequential pregnancies); (2) have typical clinical manifestations of APS but are intermittently APL positive; and (3) have APL laboratory indicators that do not meet the high titre for positivity (>99th percentile) but are low-titer positive (95th–99th percentile). Research has shown that anticoagulant therapy can also improve pregnancy outcomes for women with atypical APS.[9] In this study, the APS cases included both typical and atypical APS patients.

In the retrospective study, the cases were divided according to the different treatment regimens into the study group (anti-inflammation plus anticoagulant therapy) and the control group (anticoagulation therapy). From September 2011 to March 2014, we performed standard anticoagulation treatment regimen for APS-related RSA, and then we changed regimen to anti-inflammation plus anticoagulant therapy from April 2014 to September 2011. The observation indicators were the repeat pregnancy loss rate, the incidence of placental dysfunction-related diseases (early onset preeclampsia, placental abruption), the average birth weight, the term birth weight, the average gestational age, and other factors.

Treatment methods

Treatment methods were as followed. In the study group, prednisone (10 mg/d) + HCQ (0.2 g bid) + LDA (75 mg/d) were taken from the 6th day of the menstrual cycle. Subcutaneous injection of LWMH (5000 U/d) was taken in determining the intrauterine pregnancy. During the pregnancy, prednisone was discontinued in 14 weeks, LDA was stopped in 36 weeks, and LMWH was stopped in 24 h before delivery and re-taken from 24 h after labor to 6 weeks postpartum. However, if the pregnancy failed in the menstrual cycle, drug treatment would be stopped 14 days after ovulation, and started again on the 6th day of the next menstrual cycle. In control group, only LDA and LMWH were taken with the same usage as former.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0, New York, USA). Continuous data were presented as a mean ± standard deviation (SD), and compared by independent Student's *t*-test between two groups. Categorical variables were expressed as *n* (%), and compared using Chi-square test or Fisher's exact test. The value of $P < 0.05$ (two-sided) was considered statistically significant.

Results

During the study, 267 RSA cases were collected. The study group comprised 126 patients and the control group comprised 141 patients. The two groups did not differ significantly in terms of age, history of abnormal pregnancy, and other basic information [Table 1].

The observation indicators for pregnancy and neonatal outcomes in the study group and control group were the repeat pregnancy loss rate (11.11% vs. 22.70%), the incidence of placental dysfunction-related diseases (6.35% vs. 15.60%), average birth weight after 24 weeks of gestation (3152.41 ± 844.67 g vs. 2765.76 ± 816.40 g), term birth weight (3456.28 ± 419.79 g vs. 3076.18 ± 518.79 g), the incidence of low birth weight (12.70% vs. 21.98%), the incidence of small for gestational age (6.35% vs. 14.18%), all of which differed significantly between the two groups (all $P < 0.05$). The mean gestational age (37.6 ± 3.3 weeks vs. 36.9 ± 3.2 weeks), the incidence of preterm and term birth, and the incidence of stillbirth did not differ significantly between the two groups [Tables 2 and 3]. No cases of fetal or neonatal malformations occurred.

Discussion

Previous studies on the pathogenesis of RAS caused by APS are not entirely clear. However, the following consensus has been reached. Approximately 15% of females with RSA were persistently positive for APL. In early pregnancy, APL combines with autoantigens on the trophoblast cells of the maternal-fetal interface. With the mutual reactions of endothelial cells, trophoblast cells, and

Table 1: Basic characteristics of APS-related RSA patients in the two groups

Characteristics	Study group (n = 126)	Control group (n = 141)	Statistics	P
Age (years)	32.3 ± 4.3	32.2 ± 5.0	0.161*	0.872
>3 pregnancy losses	10 (7.94)	13 (9.22)	0.139†	0.709
Gestational diabetes mellitus	14 (11.11)	16 (11.34)	0.004†	0.951
Pregnancy with thyroid disease	10 (7.94)	12 (8.51)	0.029†	0.865
Early onset preeclampsia- eclampsia	6 (4.76)	17 (12.06)	4.498†	0.034

Data are shown as mean±SD or n (%). *t values; †χ^2 values. APS: Antiphospholipid syndrome; RSA: Recurrent spontaneous abortion ; SD: Standard deviation.

Table 2: Comparison of the pregnancy outcomes of APS-related RSA patients in the two groups

Outcomes	Study group (n = 126)	Control group (n = 141)	Statistics	P
Repeat pregnancy loss	14 (11.11)	32 (22.70)	6.261†	0.012
Abortion within 10 weeks	9 (7.14)	25 (17.73)	6.712†	0.010
Pregnancy longer than 24 weeks	116 (92.06)	113 (80.14)	7.747†	0.005
Premature delivery	18 (14.30)	20 (14.18)	0.001†	0.981
Term delivery	94 (74.60)	90 (63.83)	3.605†	0.058
Placental dysfunction-related diseases	8 (6.35)	22 (15.60)	5.713†	0.017
Gestational age of pregnancy termination* (weeks)	37.6 ± 3.3	36.9 ± 3.2	1.640‡	0.102

Data are shown as n (%) or mean±SD. *To pregnancy longer than 24 weeks; †χ^2 values; ‡t values. APS: Antiphospholipid syndrome; RSA: Recurrent spontaneous abortion; SD: Standard deviation.

Table 3: Comparison of the neonatal outcomes of APS-related RSA patients in the two groups

Outcomes	Study group (n = 126)	Control group (n = 141)	Statistics	P
Birth weight of infant born after 24 weeks (g)	3152.41 ± 844.67	2765.76 ± 816.40	3.504*	0.001
Full-term birth weight (g)	3456.28 ± 419.79	3076.18 ± 518.79	5.462*	<0.001
Low birth weight	16 (12.70)	31 (21.98)	3.957†	0.047
Small for gestational age	8 (6.35)	20 (14.18)	4.352†	0.037
Stillbirth	4 (3.17)	4 (2.84)	<0.001†	>0.999

Data are shown as mean±SD or n (%). *t values; †χ^2 values. APS: Antiphospholipid syndrome; RSA: recurrent spontaneous abortion; SD: Standard deviation.

natural killer (NK) cells, the cross-immunity responses from the antigen-antibody complexes can activate the complement system, inducing inflammation reactions, hindering trophoblast growth and development, and causing venous thrombosis. Autoantibody can also directly damage the placenta, disturbing trophoblastic layer fusion, invasion, and proliferation and resulting in placental dysfunction. These factors eventually lead to abortion, placental disease, fetal growth restriction, and other adverse pregnancy outcomes.[10-13]

Placental-trophoblastic dysfunction might be the core pathological mechanism of RAS-related adverse pregnancy outcomes. Both autoimmune-induced inflammatory factors and thrombosis factors impact pregnancy outcomes throughout the entire pregnancy. In early pregnancy, trophoblast cell implantation and infiltration are impacted; next, placental implantation and placenta dysfunction develop; and in the late stages of pregnancy, complications such as placental abruption and fetal growth restriction emerge.

Compared with the simple anticoagulation group, the anti-inflammatory and anticoagulant treatment group showed a clear decrease in the incidence of repeat pregnancy loss, miscarriage, and placental dysfunction-related diseases and a significant increase in pregnancies lasting longer than 24 weeks. Early anti-inflammatory and anticoagulant treatment could inhibit the autoimmune inflammatory responses on the trophectoderm of the maternal-fetal interface, thus improving trophoblastic and placental function, which could decrease adverse pregnancy outcomes.

In the study group, the birth weights of the infants born after 24 weeks and those born at term were significantly higher than those of the control group. The incidence of infants who were small for gestational age was significantly lower than that of the control group. The placental pathology of the APS patients showed that with the progression of pregnancy, the placenta presented more infarcts and villus aging, villus trophoblast surface fibrin and/or fibrin-like substance deposition; the maternal-fetal interface spiral vascular wall had a vague structure; and the vascular lumen narrowed or even disappeared. Therefore, compared with anticoagulation, anticoagulation combined with anti-inflammatory therapy in late pregnancy can inhibit maternal-fetal interface inflammation, reduce placental and trophoblastic damage, improve placental function, and, to some extent, improve fetal growth.

Although the new treatment regimen reduced the incidence of recurrent miscarriage, the incidence of low neonatal birth

weight remained high in both groups. Neonatal birth weight is co-determined by gestational age and the intrauterine growth rate. Anti-inflammatory plus anticoagulant therapy may partly improve the function of the placenta, which could improve intrauterine fetal growth. In this study, the rates of term delivery and premature birth did not differ significantly between the groups, indicating that the new therapy did not decrease the occurrence of preterm delivery. Other than the placental factors, low birth weight might be caused by premature birth, although it is not clear whether there are other APS-related mechanisms involved in premature birth.

APS is usually considered as a thrombotic disease, so it has primarily been treated with aspirin + LMWH combined with an anticoagulant. However, in recent years, animal models of APS have shown that the incidence of obstetric complications associated with APS is due not only to thrombosis but also to the APL-mediated immune inflammatory response.[14-16] To this end, the enhancement of anticoagulant therapy with anti-inflammatory therapy could further improve the outcomes of RSA pregnancies.

Glucocorticoids and HCQ, which are routinely used in rheumatology, play a role in anti-inflammatory and immune regulation. A large amount of gestational lactation exposure data has fully confirmed the safety of these two drugs for maternal use.[17] Previous studies have found that the use of low-dose prednisone in anticoagulant therapy during early pregnancy improves the pregnancy outcomes of patients with RSA.[18] In addition, the anti-malarial drug HCQ inhibits the release of inflammatory cytokines, interfere with the toll-like receptor mediated innate immune response, prevent the antigen presentation process, and inhibit platelet aggregation and activation;[19] HCQ inhibits complement activation, improve placental dysfunction and promote the normal development of the fetal brain.[20] HCQ is known as "the most promising treatment among APL-related RSA drugs".[21]

Based on the pathogenesis of RSA and the functional characteristics of prednisone + HCQ, in this study, the anti-inflammatory (prednisone + HCQ) plus anticoagulant therapy (LDA + LMWH) regimen was applied for the therapeutic observation of APS-related RSA. Multi-national guidelines recommend the use of these drugs because aspirin provides an anticoagulant effect and HCQ plays an immunomodulatory role that could inhibit the toxicity of NK cells and the bond of interferon γ with decidual cells.[22]

In this study, the drug regimen (prednisone + HCQ + LDA + LMWH) had the following advantages compared with the recommended domestic and foreign regimen (LDA + LMWH). (1) A focus on the importance of anti-inflammation in pathogenesis. In recent years, increasing studies have shown that anti-phospholipid antibody-mediated RSA is not a simple thrombotic disease but an immune inflammatory disease.[23] Inflammatory reactions occur mainly at the maternal-fetal interface; during early pregnancy, this is the peak of the inflammatory response, and during late pregnancy, it is inflammatory reaction-mediated thrombosis. HCQ is currently used to treat anti-phospholipid antibody-mediated RSA;[24] a small study also suggested that LDA + LMWH beginning 14 weeks before pregnancy plus prednisone could improve refractory RSA pregnancy outcomes.[25] In this study, the trial program for the prepregnancy initiation of prednisone + HCQ + LDA enhanced the anti-inflammatory treatment immediately after the addition of LMWH until the inflammation gradually subsided at 14 weeks of pregnancy, when prednisone was discontinued and HCQ + LDA + LMWH anti-inflammatory + anticoagulant therapy was continued. (2) An emphasis on the importance of preventive medication. Multi-national guidelines recommend the early initiation of LDA + LMWH anticoagulation in patients with RSA, and our experimental drug regimen requires prophylactic anticoagulation with prednisolone + HCQ and prophylactic anticoagulation with LDA, which reflects the importance of prophylactic drug use before pregnancy.

The British Rheumatology Society in 2016 issued the latest recommendations for drug safety during pregnancy. The guidelines indicated that the use of prednisone, HCQ, LDA, and LMWH in pregnant women is safe.[17,26] The dose of prednisone used in this protocol was ≤10 mg/d, and the use time was <14 weeks. Compared with the previous high-dosage regimen (40–60 mg/d), this low-dose could reduce the risk of premature delivery, gestational diabetes mellitus, and congenital malformation.

In recent years, there has been increasing evidence that APS-related RSA is both a thrombotic disease and an immune inflammatory disease. A larger study of the effect of intensive anti-inflammatory (prednisone + HCQ) and intensive anticoagulant (LDA + LMWH) regimens on the outcome of APS-related RSA is needed.

The limitations of our study are that it is nonrandomized and retrospective. A prospective randomized control study with a larger sample size will be necessary to confirm the effects of anti-inflammation plus anticoagulant therapy regimen on APS-related RSA patients. In addition, basic research on trophoblastic cellular and related molecular signaling mechanisms will provide more support for the results of this study.

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Conflicts of interest

There are no conflicts of interest.

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