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A successful pregnancy following 11 miscarriages in an unexplained recurrent pregnancy loss patient with thrombophilia: a case report and literature review

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Summary

Objective: To highlight the benefit of thrombophilia screening and antithrombotic therapy in consecutive unexplained pregnancy losses. *Case Report:* The authors presented a detailed description and follow-up of a 37-year-old patient with a history of 11 miscarriages between the sixth and eighth weeks of gestation. In her eighth pregnancy, she was considered as unexplained recurrent pregnancy loss (RPL) and received lymphocyte immunization. However, the patient still experienced subsequent four spontaneous abortions at the similar gestational age. In the outpatient departments, she was diagnosed as thrombophilia and then she received low molecular weight heparin (LMWH) subcutaneous daily injection after ovulation and 50 mg aspirin daily orally started two months before pregnancy until the 32nd week of gestation. At 36+2 gestational weeks, a male infant was born in good condition with weight of 3,410 grams. *Conclusion:* Early start of LMWH and aspirin decreases the incidence of miscarriage in women with unexplained RPL.

Key words: Aspirin; Low molecular weight heparin; Unexplained recurrent pregnancy loss.

Introduction

Recurrent pregnancy loss (RPL) is a relevant public health problem, which affects up to 15% of the reproducing couples and recurs in 2% to 3% of them [1]. Despite extensive investigations, a significant proportion of cases remain unexplained. Women with unexplained RPL have routinely received lymphocyte immunization [2]. However, some patients still experienced spontaneous abortions subsequently, which implied that other pathologic mechanisms might also involved.

A state of thrombophilia, due to an increase of pro-coagulant factors and a decrease in physiological anticoagulants, is a common finding in normal pregnancy [3]. If risk factors for thrombophilia are present before pregnancy, a further imbalance of the pro-thrombotic process existed in pregnancy, and moreover, leading to adverse pregnancy outcomes [4]. Recently, thrombophilia has been frequently associated to unexplained RPL [5]. D'Uva *et al.* showed a strong association, reaching nearly 78%, of one or more thrombophilic defects in women with RPL if other common causes of miscarriage are excluded. From these views, thrombophilia examination should be advised for patients with unexplained RPL, and low molecular weight heparin (LMWH) and aspirin are used as it should be. Other investigators, however suggested not to treat unexplained miscarriage without evidenced antiphospholipid syndrome (APS) with heparin or aspirin for lack of evidence of any benefit and potential risks [6]. So, it still remains unclear if routine testing and treatment for thrombophilia in patients with unexplained RPL should be advised or not? The patient in the present case had a successful pregnancy following 11 miscarriages in an unexplained RPL with thrombophilia when she initiated aspirin and LMWH before pregnancy until the 32nd gestational week. The case presented that active screening for thrombophilia should be performed in unexplained RPL. Also, the role of anticoagulants for women with unexplained RPL was recommended before pregnancy.

Case Report

A 37-year-old woman with a history of previous 11 spontaneous abortions was referred to Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai JiaoTong University, Shanghai, China. Her first pregnancy was in 2001. On the sixth weeks of gestation, cesarean section was performed due to inevitable abortion. She underwent subsequent consecutive six spontaneous abortions between sixth and eighth weeks of gestation. In her eighth pregnancy, she was considered as unexplained RPL and received lymphocyte immunizations. However, the patient still experienced subsequent consecutive four spontaneous abortions at the similar gestational age.

The patient was referred to Ren Ji hospital. Her personal and family history showed no obvious abnormalities. She was administered karyotype study in order to detect if several chromo-

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Table 1. — *Mean values of screening for thrombophilia before pregnancy.*

	Fibrinolytic activity						Placental function		Anticogulant protein			Acquired thrombophilia	
D-D [a]	FDP[a]	TT[a]	APTT[a]	PT[a]	Fg[a]	INR[a]	AA[a]	ADP[a]	PS[a]	PC[a]	AT-III[a]	APS[a]	Hcy[a]
0-0.5 ug/ml	0-5 ug/ml	14-21 s	20-40 s	9.4-12.5 s	2-4 g/l	0.8-1.15 R	60-80 %	45-78 %	76-135 %	70-140	75-125 %		3.0-17.0 umol/L
0.25	1.06	15.4	29.4	9.8	2.08	0.89	92.0	85.4	73.7	147.2	104	-	7.9

[a]*D-D, D-dimer; FDP, fibrin degradation product; TT, thrombin time; APTT, activated partial thromboplastin time; PT, prothrombin time; Fg, fibrinogen; INR, International Nornalized Ratio; AA, arachidonic acid; ADP, adenosine diphosphate; PS, protein S; PC, protein C; AT-III, antithrombin; APS, antiphospholipid antibody syndrome; Hcy, homocysteine.*

Table 2. — *Mean values of the impendence to uterine perfusion in the early, middle and late stage of gestation.*

	Early stage (10w)			Middle stage (20w)			Late stage (30w)		
mean value	PI[a]	RI[a]	S/D[a]	PI	RI	S/D	PI	RI	S/D
Normal people	1.56	0.71	3.65	1.09	0.59	2.55	0.78	0.48	1.99
The patient	1.34	0.66	3.00	1.03	0.60	2.59	0.79	0.51	2.04

[a] *PI, pulsatility index; RI, resistance index; S/D, systolic/diastolic ratio.*

Table 3. — *Mean value for umbilical artery flow in late stage of gestation.*

	Late stage					
	28 gestational weeks			34 gestational weeks		
Mean value	PI[a]	RI[a]	S/D[a]	PI	RI	S/D
Normal people	0.95	0.63	3.59	0.9	0.58	3.08
The patient	0.812	0.563	2.25	0.96	0.66	2.96

[a]*PI, pulsatility index; RI, resistance index; S/D, systolic/diastolic ratio.*

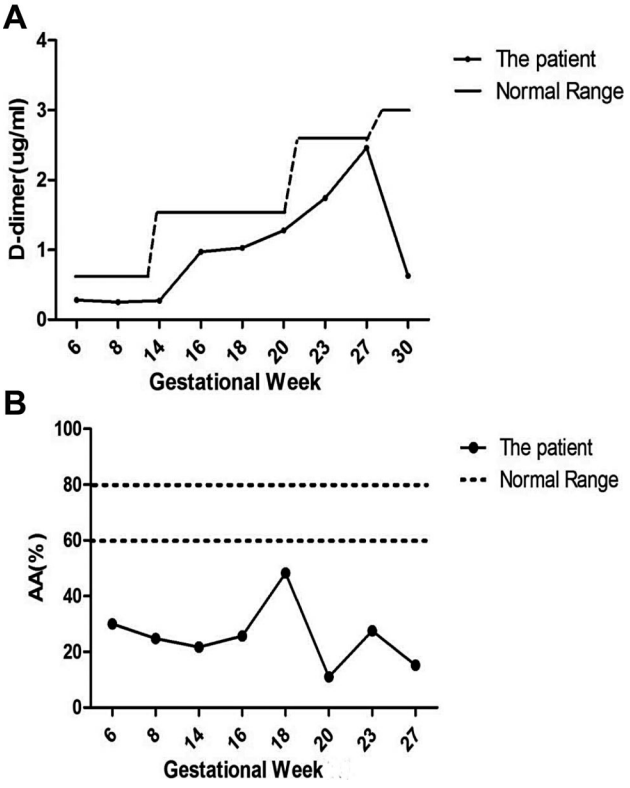

Figure 1A. — D-dimer levels during the gestation.
Figure 1B. — The levels of platelet aggregation in response to arachidonic acid (AA) during the gestation.

some are aberrations or balanced translocations. The uterine cavity was evaluated anatomically by transvaginal ultrasound. Endocrinological assessment included screening for diabetes, hypothyroidism, hypopituitarism, hyperprolactinemia, luteal insufficiency, and polycystic ovarian syndrome (PCOS). Autoimmune antibodies (anti-extractable nuclear antigens (anti-ENA) antibody, antinuclear antibodies (ANAs) and dsDNA), coagulation and fibrinolytic activity (PT, APTT, TT, Fg, FDP, D-dimer), anticoagulation systems (protein C, protein S, antithrombin III), platelet function (platelet aggregation rate (PAgT)), antiphospholipid antibodies and plasma homocysteine level were examined. APS was diagnosed according to the Sydney criteria. In addition, the patient was tested for mixed lymphocyte cells test (MLCT). The basic laboratory data were obtained when the patient was not pregnant.

After a thorough examination, the patient showed negative screening for routine RPL evaluations, such as uterine anomalies, parental chromosomal abnormalities, and autoimmune diseases. She therefore was considered as unexplained RPL. The diagnosis was supported by the absence of blocking factors in MLCT test. She received two donor lymphocyte immunizations within a three-week interval before pregnancy and two boosters in the first month of gestation. In addition, the thrombophilia examination of the patient revealed that ADP levels (85.4%) were higher than the normal. AA levels increased to 92% compared to normal (60-80%). Protein S activity (73.7%) decreased (normal range 76-135%). These results are shown in Table 1. She was considered to have thrombophilia. Low dose aspirin (LDA) was administrated orally from post-menstrual to one week before the probable date of delivery and LMWH (nadroparin calcium, 4,100 units, subcutaneous) was introduced until 48 hours before delivery. During her pregnancy, AA and D-dimer were monitored every two weeks. The dosage of aspirin was adjusted based on AA value. Simutaneously, the amount of LMWH was controlled regularly by D-dimer. During her whole pregnancy, AA and D-dimer levels were under the normal range. These results are shown in Figures 1A and 1B.

Maternal uterine artery perfusion and fetal umbilical artery flow were determined by transvaginal sonographic Doppler. Peak systolic to lowest diastolic velocity ratio (S/D), pulsatility index (PI), and resistance index (RI) were calculated. PI, RI, and S/D indexes of uterine arteries tended to be normal after she received LDA and LMWH. The similar magnitude was observed in umbilical artery. These results are shown in Table 2. In the entire pregnancy, the use of LMWH appears to be safe for mother and fetal. Maternal bleed-

ing, venous/arterial thrombotic episodes or heparin induced thrombocytopenia were not observed.

On 36+2 weeks of gestation, the patient delivered a baby boy after performing caesarean section due to premature rupture of membranes. The healthy boy weighted 3,410 grams and Apgar score was 10 pts.

Discussion

The patient in the present case showed negative screening for routine RPL evaluations, such as uterine anomalies, parental chromosomal abnormalities, and autoimmune diseases. The patient was therefore generally considered as unexplained RPL. The majority of cases of unexplained RPL is found to be associated with decreased production of alloimmune antibodies termed as mixed lymphocyte reaction blocking factor (MLR-Bf). Lymphocyte immunization used to be considered the conventional treatment for unexplained RPL [7]. However, the patient in the present case still experienced four subsequent times of fetal losses after immunotherapy. The present authors consider that the alloimmune dysfunction may not be the only cause for her consecutive fetal losses and other pathologic mechanisms are also involved leading to same outcome. There are reports that unexplained RPL are often associated with uteroplacental thrombosis and the classical thrombophilia markers account for a certain fraction of these patients [8]. Therefore, the present authors had undertaken to see whether thrombophilia may have had a role to play in the case. Tests revealed the increase of platelet aggregation in response to AA (92%) and the decrease of protein S activity (73.7%) in the patient. The authors concluded that thrombophilia examination should be recommended in particular if several routine causes potentially responsible of RPL have been already excluded.

Thrombophilia is a diverse group of coagulation-anticoagulation disorders associated with a predisposition to thrombosis. Platelets are one of the major cellular elements involved in coagulation. Patients with a background history of unexplained RPL demonstrate reduced platelet function if they have a subsequent miscarriage compared to those who go on to have a successful pregnancy [9]. AA levels were abnormal in the patient presented before pregnancy. Therefore, LDA might be necessary before pregnancy begins and maintains the whole pregnancy. The present authors found that platelet aggregation in response to AA was a sensitive indicator for aspirin therapy [6]. The dose of LDA was adjusted according to AA levels in the pregnancy. It is important to mention that the patient maintained a lower AA levels in the whole pregnancy.

Protein S is a Vitamin K-dependent plasma protein cofactor that is necessary along with activated protein C cofactor to inactivate factors Va/VIIIa and control the balance between coagulation and anticoagulation [10]. A meta-analysis published by Rey *et al.* showed that protein S deficiency was associated with 14.72-fold risk for unexplained RPL (<13 weeks), but it did not reach statistical significance (95% CI: 0.99-218.01). The patient of this case had reduced protein S activity [11].

So far, there is no equivocal opinion about the prophylactic dose of LMWH in pregnancies complicated with anticoagulation dysfunction. There is no consensus in the literature concerning the appropriate dose of LMWH during pregnancy because evidence-based data are missing in this field. High-risk patients were advised to require at least intermediate-dose LMWH prophylaxis and LMWH 2,500 to 5,000 U/d is an effective alternative for obstetric thromboprophylaxis [12]. In this case, the authors chose 4,100U LMWH and the dose of LMWH was adjusted according to D-dimer levels during the whole pregnancy. Significantly, the patient maintained a lower thrombotic state as normal D-dimer levels in the whole pregnancy. The present treatment is supported by some literatures that a modest improvement occurs in outcomes, as reducing early and late spontaneous abortions for women with unexplained RPL treated with LMWH over no treatment (live birth risk ratio 1.07, 95% CI 1.00–1.14) [13]. A multicenter randomized controlled trial of LMWH and LDA plus intensive pregnancy surveillance resulted in a 22%-miscarriage rate in women with RPL versus 20% in the group receiving intensive surveillance alone [14]. Therefore, it can be concluded the initiation of thromboprophylactic treatment can benefit the RPL patients.

A successful pregnancy outcomes is highly dependent on satisfactory and sustained placental function. In the present case, the authors performed a Doppler flow examination to determine the effect of prophylactic therapy on fetal and maternal circulation parameters and found that the use of LDA plus LMWH significantly improved the maternal uterine artery perfusion and fetal umbilical artery flow. Thrombophilia may indicate that disturbances in hemostasis led to a prothrombotic state and may predispose affected individuals to decreased placental perfusion later in pregnancy [15]. Prophylactic therapy promoted the establishment of an adequate fetomaternal circulatory system.

In conclusion, thrombophilia should be evaluated soon if patients affected by RPL do not show other causes of miscarriage. Because such patients may show an asymptomatic hypercoagulable state. Early antithrombotic treatment (ie, before the beginning of pregnancy) should be recommended based on aspirin and/or low-molecular-weight heparin.

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