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CLINICAL ARTICLE

Prothrombotic state of patients with unexplained recurrent spontaneous abortion

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ABSTRACT

Objective: To determine the effect of aspirin and low-molecular-weight heparin (LMWH) for women affected by recurrent spontaneous abortion (RSA). **Methods:** The present prospective observational study included women with RSA (≥ 2 previous spontaneous abortions) and those without a history of RSA attending Ren Ji Hospital, Shanghai, China, between March 2011 and March 2014. D-dimer levels, auto-antibodies, and platelet aggregation in response to arachidonic acid (AA) and adenosine diphosphate (ADP) were monitored before pregnancy. Women with unexplained RSA and increased platelet aggregation received low-dose aspirin, and those with elevated D-dimer levels (>0.75 $\mu\text{g/mL}$) received LMWH. Platelet aggregation in response to AA and ADP, and D-dimer levels were monitored during pregnancy. **Results:** Among 517 participants with RSA, 325 had unexplained RSA. Compared with 63 control patients, those with unexplained RSA and two, three, four, or at least five previous spontaneous abortions had increased platelet aggregation in response to AA ($P < 0.05$ for all comparisons) but not to ADP. Among 37 women with unexplained RSA who became pregnant, aspirin reduced platelet aggregation in response to AA ($P < 0.001$). LMWH reduced D-dimer levels during pregnancy ($P < 0.001$). Among 37 women with unexplained RSA who became pregnant and completed the study, 33 (89.2%) had a live birth. **Conclusion:** Aspirin and LMWH maintained a lower thrombotic state and led to a high live birth rate among patients with unexplained RSA.

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1. Introduction

Approximately 5% of all women are affected by recurrent spontaneous abortion (RSA), which is defined as two or more previous spontaneous abortions [1]. For more than half these patients, the underlying cause of RSA cannot be identified [2]. Although various interventions have been suggested to improve the live birth rate among women with RSA, no effective treatment has been identified.

The combined use of low-molecular-weight heparin (LMWH) and aspirin for patients with RSA who test positive for antiphospholipid antibodies has become routine practice [3,4]. The use of this therapy is guided by the hypothesis that patients with unexplained RSA are in a prothrombotic state. Investigations have supported this notion by demonstrating that women with RSA have thrombosis in decidual vessels and circulating procoagulant microparticles [5,6]. Moreover, using thromboelastography, Rai et al. [7] showed that a subgroup of women with recurrent RSA were in a prothrombotic state before pregnancy. Women in this state were found to be at increased risk of

spontaneous abortion in future untreated pregnancies [7]. Therefore, it is often concluded that there is a subgroup of women affected by RSA who are in a prothrombotic state, and for whom antithrombotic treatment might improve the live birth rate.

Nevertheless, the benefit of this approach for treating unexplained RSA is controversial. To address this issue, Dolitzky et al. [8] conducted a multicenter clinical trial among patients with unexplained RSA, and observed good outcomes with respect to live birth rates and late pregnancy complications for women treated with either aspirin or enoxaparin. Kaandorp et al. [9] found that, as compared with placebo, the administration of aspirin, either alone or combined with nadroparin, from 6 weeks of pregnancy improved the live birth rate among women with RSA.

In many of the previous studies, the patients with RSA received aspirin and/or LMWH therapy during pregnancy. By contrast, there are limited data demonstrating the effect of therapy before pregnancy. The aim of the present study was to assess whether women affected by RSA would maintain a lower thrombotic state and achieve a successful birth outcome after receiving aspirin and/or LMWH.

2. Materials and methods

The present prospective observational study included women presenting at the outpatient clinic at Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, between

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March 1, 2011, and March 31, 2014. Women presenting with RSA (≥ 2 previous spontaneous abortions) and a control group of women without a history of RSA were enrolled. Women in the control group had presented to the outpatient clinic for any reason related to fertility, had a history of 0 or 1 spontaneous abortions, and were negative for auto-antibodies, including anti-extractable nuclear antigens (anti-ENA) antibody, antinuclear antibodies (ANAs), anticardiolipin antibody (ACA), lupus anticoagulant (LA), anti- $\beta 2$ glycoprotein-1 (anti- $\beta 2$ GP-1) IgG, and anti- $\beta 2$ GP-1 IgM. Participants could not be pregnant at enrollment. The local ethics committee approved the study. All participants received a briefing of the study and provided informed consent.

Parental karyotype screening and pelvic ultrasonography were performed after enrollment. Individuals were excluded from analyses on the basis of an abnormal finding in either test (e.g. uterine myoma, uterine septum, or saddle-shaped uterus).

Platelet aggregation in response to arachidonic acid (AA) and adenosine diphosphate (ADP), D-dimer levels, and auto-antibody levels were monitored three times per month while the patients were not pregnant. Platelet aggregation in response to AA and ADP, and D-dimer levels were monitored every 2 weeks during any subsequent pregnancy. The rate of platelet aggregation induced by AA and ADP was measured by the turbidimetric method. Quantitative determination of D-dimer in human citrated plasma was performed via an automated latex enhanced immunoassay. D-dimer was detected by using a HemoSIL D-dimer kit (Instrumentation Laboratory Company, Bedford, MA, USA) in accordance with the manufacturer's protocol.

Women with antiphospholipid antibody syndrome (APS) were diagnosed using the Sydney criteria for APS [10]. To determine the presence of LA, clotting assays for LA were performed in accordance with the guidelines of the International Society on Thrombosis and Haemostasis [11]. A HemosIL DRVVT Screen and HemosIL dRVVT confirm assay (Instrumentation Laboratory Company) were used to measure LA via the diluted Russels Viper Venom method. Serum levels of ACA and anti- $\beta 2$ GP-1 antibody were measured by enzyme linked immunosorbent assay (ELISA). ACA isotype G (IgG), ACA IgM, anti- $\beta 2$ GP-1 IgG, and anti- $\beta 2$ GP-1 IgM ELISA kits were purchased from Euroimmun (Lübeck, Germany) and used in accordance with the manufacturer's protocols.

Anti-ENA antibody was detected using a Euroassay kit for anti-ENA IgG (Euroimmun) in accordance with the manufacturer's protocol. Antinuclear antibodies (ANAs) were detected by indirect immunofluorescence using a Fluoro Hepana Test (Medical & Biological Laboratories, Nagoya, Japan) performed in accordance with the manufacturer's protocol.

As a prophylactic measure, women with unexplained RSA (i.e. neither diagnosed with APS nor positive for any auto-antibody tested) and high platelet aggregation in response to AA ($> 80\%$) were given low-dose aspirin therapy (≥ 25 mg per day) from 2 months before they were ready for pregnancy to 37 weeks of pregnancy. The dose of aspirin was adjusted according to the level of platelet aggregation in response to AA every 2 weeks. Simultaneously, platelet aggregation in response to ADP and the levels of D-dimer were monitored every 2 weeks. Women with elevated D-dimer levels (> 0.75 $\mu\text{g/mL}$) during pregnancy were given supplementary LMWH therapy (subcutaneous injection; ≥ 4100 IU per day).

OriginPro version 7.5 (Microcal Software, Northampton, MA, USA) software was used for data analyses. An unpaired two-tailed *t* test with Welch correction was applied to compare data between groups. $P < 0.05$ was considered to be significant.

3. Results

In total, 570 women with RSA were enrolled, of whom 50 were excluded because of an abnormal parental karyotype and three were

excluded because of an abnormal pelvic ultrasonography examination. Therefore, 517 women with a history of RSA were included in the analyses. On enrollment, levels of ACA IgG and IgM, anti- $\beta 2$ GP-1 IgG and IgM, and auto-antibodies (including anti-ANA and anti-ENA) were examined (Table 1). Only 83 (16.1%) women had APS and could be treated with a combination of aspirin and LMWH. Approximately 5% of women with RSA had APS and also tested positive for auto-antibodies. By contrast, 325 (62.9%) of the patients tested were negative for both antiphospholipid antibody and auto-antibodies, and so were deemed to have unexplained RSA. Among the women with unexplained RSA, most had had two or three previous spontaneous abortions (Table 1).

Seventy women were screened for inclusion in the control group, of whom five were positive for auto-antibodies. Additionally, an abnormal parental karyotype was recorded for one woman, and one had an abnormal pelvic ultrasonography result (uterine myoma). Therefore, 63 women in the control group were included in analyses.

Platelet aggregation in response to AA and ADP was compared between the control women and the 325 patients with unexplained RSA before any subsequent pregnancies. The mean level of platelet aggregation in response to AA was significantly lower among women with 0–1 previous spontaneous abortions ($68.3\% \pm 21.7\%$) than among those with two ($84.8\% \pm 11.7\%$; $P < 0.001$), three ($85.7\% \pm 8.6\%$; $P < 0.001$), four ($86.1\% \pm 6.7\%$; $P < 0.001$), or at least five spontaneous abortions ($78.8\% \pm 15.6\%$; $P = 0.0275$) (Fig. 1A). Among the 325 women with unexplained RSA, 246 (75.7%) had high platelet aggregation in response to AA and so received low-dose aspirin.

The mean level of platelet aggregation in response to ADP in the control group (0–1 spontaneous abortions) was 74.3%. Among the women with unexplained RSA, mean platelet aggregation in response to ADP for women with two, three, four, and five or more spontaneous abortions was 76.7%, 76.8%, 76.6%, and 75.0%, respectively. There was no significant difference in platelet aggregation in response to ADP between the patients with unexplained RSA and the control women (Fig. 1B). Levels of D-dimer, a clinical indicator of thrombin generation, among women with unexplained RSA were lower than control levels before pregnancy, but were within the normal range (Fig. 1C).

Among the 325 women with unexplained RSA, 37 subsequently became pregnant and completed the study (i.e. the outcome of their pregnancy was known) and 240 did not become pregnant; information about any subsequent pregnancies were not available for 48. Among the 37 women who became pregnant and completed the study, 16 showed higher platelet aggregation in response to AA ($> 80\%$) and received low-dose aspirin. Aspirin administration led to patients with unexplained RSA showing lower levels of platelet aggregation in response to AA (88.6% before treatment vs 52.5% after; $P < 0.001$) (Fig. 2A). However, aspirin had no effect on platelet aggregation in response to ADP (60.6% before treatment vs 57.1% after; $P = 0.7950$) (Fig. 2B). Overall, platelet aggregation in response to AA fell below 80% among 36 of the 37 patients with unexplained RSA before and during their subsequent pregnancy, 15 of whom had received aspirin (data not shown).

Table 1
Results of antibody tests among patients with RSA ($n = 517$).^a

No. of RSAs	Negative for all antibodies tested	Positive for other auto-antibodies ^b	APS	APS plus positive for other auto-antibodies
2	154 (29.8)	46 (8.9)	50 (9.6)	17 (3.3)
3	108 (20.9)	27 (5.2)	20 (3.9)	3 (0.6)
4	45 (8.7)	4 (0.8)	9 (1.7)	5 (1.0)
≥ 5	18 (3.5)	7 (1.4)	4 (0.7)	0
Total	325 (62.9)	84 (16.2)	83 (16.1)	25 (4.8)

Abbreviations: RSA, recurrent spontaneous abortion; APS, antiphospholipid antibody syndrome.

^a Values are given as number (percentage).

^b Positive for auto-antibodies, but negative for anticardiolipin and anti- $\beta 2$ GP1 antibodies.

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