Original Article
The clinical significance of prethrombotic state t-PA, PAI-1, and D-dimer data in the diagnosis and treatment of recurrent abortion in pregnant Chinese women

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Abstract: Objective: This study aimed to investigate the clinical significance of prethrombotic state t-PA, PAI-1, and D-dimer data in the diagnosis and treatment of recurrent abortion in pregnant Chinese women. Methods: The terms “recurrent spontaneous abortion”, “pregnancy”, “hemodynamics”, “D-Dimer”, “antithrombin”, “tissue plasminogen activator”, “plasminogen activator inhibitor-1”, “hematology index”, and “fibrinolysis dynamic” were selected as search terms in the PubMed, CNKI, Wangfang Data Journal Resources, and Springer databases. The relevant, retrospective cohort research literature was searched from January 1979 to January 2019. The prethrombotic state and hematologic index between the recurrent abortion group (RAG) and the non-abortion pregnancy group (NAPG) were statistically analyzed and compared. The quality of data was assessed in accordance with the criteria in the Cochrane system assessment manual. The results in the retrospective cohort study reports (D-Dimer, AT-III, t-PA, PAI-1, F1+2, TAT, and LA) were analyzed with Review Manager (5.1.0). Results: 13 clinical retrospective cohort studies were ultimately included. The analysis showed that prethrombotic state can be used as a predictor of recurrent spontaneous abortion. The mean D-dimer of the pre-thrombotic state-related indicators was compared between the recurrent abortion group and the non-abortion pregnancy group (Z = 23.18, 95% CI = 24.21-28.68, P < 0.00001), t-PA mean Z = 15.01, 95% CI = 0.04-0.06, P < 0.00001), mean AT-III (Z = 12.36, 95% CI = 0.03-0.05, P < 0.00001), mean PAI-1 (Z = 53.07, 95% CI = 26.65-28.69, P < 0.00001), mean F1+2 (Z = 10.30, 95% CI = 26.71-39.28, P < 0.00001), TAT mean (Z = 136.65, 95% CI = 0.15-0.16, P < 0.00001) and the LA positive rate (Z = 7.47, 95% CI = 12.33-73.54, P < 0.0001), and the difference is statistically significant, so the above indicators can be used as predictors of recurrent spontaneous abortion. Conclusions: Our meta-analysis shows that the determination of prethrombotic state related indexes can be used as a basis for predicting recurrent spontaneous abortion in pregnant Chinese women. It provides a theoretical basis and a foundation for the prevention of recurrent spontaneous abortion and related mechanisms.

Keywords: Pregnant Chinese women, recurrent spontaneous abortion, D-dimer, prethrombotic state

Introduction
Recurrent spontaneous abortion (RSA) means the loss of pregnancy products or fetuses (weight ≤ 500 g) 2 or more times consecutively before 20 weeks of pregnancy with the same sex partner. It is a common disease in women of childbearing age [1]. According to patient data from the various regions of China and from different classes and different age groups, the spontaneous abortion related incidence is up to 15%~40% [2]. The incidence of continuous spontaneous abortion 2 or more times is higher than 5%. The incidence of continuous spontaneous abortion 3 or more times is approximately 0.5~3% [3]. Early abortion is usually defined as an abortion before 12 weeks of pregnancy. Late abortion usually means an abortion from 12 weeks to less than 28 weeks of pregnancy [4]. Primary recurrent abortion means that there is no history of full-term live birth prior to the recurrent abortion. Secondary
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recurrent abortion means that there is a labor history of full-term live birth prior to recurrent abortion [5].

The time of pregnancy loss is very important in inferring the cause of the disease. Studies have shown that patients with pregnancy loss in the early stage account for more than 90% of randomly selected patients with recurrent abortion [6]. The pathogenesis of recurrent spontaneous abortion (RSA) is very complex. The defined causes in studies include endocrine disorder, chromosome aberration, infection, genitalia deformity, and dysimmunity. However, the causes are still unable to be determined in nearly half of the RSA patients.

Research scholars have found that RSA is closely related to prethrombotic state. Therefore, by strengthening the testing of the prethrombotic state, RSA can be screened. Meanwhile, interventional therapy can be performed in advance. Thus, the morbidity of abortion is reduced [7]. At present, the medical profession has not defined the prethrombotic state related test measures of RSA. However, the relevant hematology indexes, such as D-dimer, antithrombase-III, tissue plasminogen activator, plasminogen activator inhibitor-1, etc., can reflect the relevant changes in the coagulation and fibrinolysis dynamics. Therefore, the changes in above-mentioned measures in patients with RSA were analyzed in this paper. The relationship between the level of the hematology index and the occurrence of recurrent spontaneous abortion was compared.

PRISMA guidelines were strictly followed in this study.

Materials and methods

Search strategy

The recurrent abortion and prethrombotic state keywords were searched with MeSH, including “pregnancy”, “hemodynamics”, “D-Dimer”, “antithrombin”, “tissue plasminogen activator”, “plasminogen activator inhibitor-1”, “hematology index”, and “fibrinolysis dynamic”. The search criteria were suitable for PubMed, CNKI, Wanfang Data Journal Resources, and the Springer databases. The preliminary retrieval was redone before the final analysis in order to include the most recent studies. All the subjects in the included literature were human beings.

Inclusion criteria

(1) Study type: Retrospective cohort study; (2) Experimental group (EG): The number of abortions in patients with recurrent spontaneous abortion ≥ 2; (3) Control group (CG): Had no history of adverse pregnancy and at least one history of a normal pregnancy; (4) Results: The levels of D-dimer, AT-III, t-PA, PAI-1, F1+2, TAT, and LA were analyzed in EG and CG.

Exclusion criteria

(1) Non-RCT research. (2) Patients with genetic, endocrine, infection, and reproductive anatomical abnormalities. (3) Patients with non-recurrent abortions.

Data extraction and result measurement

The following information was extracted from the included retrospective cohort studies: the first author, publication year, sample size, patient baseline characteristics, control, number of abortions, hemodynamics, and the hematology index. The author was contacted to obtain data if necessary.

The general data in the study were recorded using a composite table. Author, publication year, country, multicenter or single-center, journal publications, number of patients in each group, study time, and study design were included in the table.

Statistical indexes: D-Dimer, AT-III, t-PA, PAI-1, F1+2, TAT, LA.

Results: The levels of D-dimer, AT-III, t-PA, PAI-1, F1+2, TAT, and LA were analyzed in EG and CG.

Quality assessment

Review manual 5.1.0 was selected, including RCT deviation risk assessment, to assess the specific quality of the ultimately included studies. Specifically, the 7 assessment criteria below were included: (1) Generation of a random sequence; (2) Allocation concealment; (3) Double blinding between implementer and participant; (4) Use of the blind result assessment method; (5) Integrity of result data; (6) Select report; (7) Other sources of bias. The overall potential bias level was summarized with the SIGN method (http://www.sign.ac.uk/methodology/checklists.html) in each study: The bias
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judgment was expressed as “Low risk”, “High risk”, or “Unclear risk”. All differences were resolved by consensus. (1) “A” implied that all or most of the quality criteria were met. Implementation (allowing the assessment of all sources of potential bias); (2) “B” indicated that certain criteria were met; (3) “C” represented little or no sense of satisfaction. In this article, “A” implied that the article was evaluated as a “High-quality study”. “B” indicated that the article was evaluated as a “Medium-quality study”.

Statistical analysis

All the data were analyzed with Review Manager 5.1.0. P < 0.05 implied a significant difference. The summarized effect was estimated by the standard mean deviation (SMD) of the continuous outcomes and 95% confidence interval (95% CI). Ratio and 95% CI were used for the analysis of dichotomous variables. Heterogeneity was evaluated with χ² and I². The fixed effect model was used to calculate the non-significant heterogeneity related data (I² > 50%, P < 0.1). The random effect model (SMD/RR) was adopted to calculate the heterogeneous data (I² < 50%, P < 0.1). Funnel plot was introduced to intuitively assess the publication bias.

Results

Inclusion study

A total of 271 articles were obtained after a comprehensive search of the database. This was reduced to 133 articles after eliminating the duplicate items using EndNote software. After reading the title of each article, the retrieval was narrowed to 26 articles. After carefully studying the full text of each of the 26 articles, 13 eligible studies were ultimately included. The characteristics of the 13 studies are summarized in Table 1, and together they involved a total of 4,714 patients.

Quality assessment

According to the Cochrane manual 5.1, the risks of bias in the study are shown in Table 2. These risks were determined using the 7 criteria. The results showed that the study design method was reported in most of the studies. However, the allocation concealment regimens were rarely reported. Detailed blind designs were reported in some studies. According to the quality assessment, the quality of 4 articles was assessed as A, and 9 articles were assessed as B (Table 2).

Sensitivity analysis

The funnel plots with standard error and accuracy are symmetrical (Figures 2B, 3B, 4B, 5B, 6B, 7B, 8B).

13 clinical retrospective studies were ultimately included. The analysis showed that the prethrombotic state can predict the occurrence of recurrent abortion. The comparison of D-dimer, AT-III, t-PA, PAI-1, F1+2, TAT, and LA between RAG and the normal pregnancy group (NPG) showed that P was less than 15%. The results indicated that the heterogeneity of the index was not significant between the two groups.

The META analysis of the corresponding results were as follows

Comparison of D-dimer values between the recurrent abortion group and the non-abortion pregnancy group: 13 articles describe a comparison of the D-Dimer values between recurrent abortion and non-abortion pregnancies. The D-dimer values were elevated between the
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Table 1. Data summary

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</table>
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Comparison of t-PA values between the recurrent abortion group and the non-abortion pregnancy group: 10 articles describe comparisons of the t-PA values between recurrent abortion and non-abortion pregnancies. The t-PA value was increased between the recurrent abortion group and the non-abortion pregnancy group. The heterogeneity test results were (chi-squared = 8.84, P < 0.00001, I^2 = 3%), so the 95% CI was used. The results showed that the t-PA value of the recurrent spontaneous abortion group was higher than the value of the non-abortion pregnancy group (Z = 15.01, 95% CI = 0.04-0.06), as shown in (Figure 3A, 3B).

Comparison of the AT-III values between the recurrent abortion group and the non-abortion pregnancy group: 13 articles describe comparisons of the AT-III values between recurrent abortion and non-abortion pregnancies. The AT-III value was increased between the recurrent abortion group and the non-abortion pregnancy group. The heterogeneity test results were (chi-squared = 20.44, P < 0.00001, I^2 = 6%), so the 95% CI was used. The results showed that the AT-III value of the recurrent spontaneous abortion group was higher than the value of the non-abortion pregnancy group (Z = 12.36, 95% CI = 0.04-0.06), as shown in (Figure 4A, 4B).

Comparison of the PAI-1 values between the recurrent abortion group and the non-abortion pregnancy group: 13 articles describe comparisons of the PAI-1 values between recurrent abortion group and the non-abortion pregnancy group. The PAI-1 value was increased between the recurrent abortion group and the non-abortion pregnancy group. The heterogeneity test results were (chi-squared = 1765.24, P < 0.00001, I^2 = 2%), so the 95% CI was used. The results showed that the PAI-1 value in the recurrent spontaneous abortion group was higher than it was in the non-abortion pregnancy group (Z = 53.07, 95% CI = 26.65-28.69), as shown in (Figure 5A, 5B).

Comparison of the F1+2 values between the recurrent abortion group and the non-abortion pregnancy group: 13 articles describe comparisons of the F1+2 values between the recurrent abortion group and the non-abortion pregnancy group. The F1+2 value was increased between the recurrent abortion group and the non-abortion pregnancy group. The heterogeneity test results were (chi-squared = 578.67, P < 0.00001, I^2 = 8%), so the 95% CI was used. The results showed that the F1+2 value of the recurrent abortion group was higher than the value of the non-abortion pregnancy group (Z = 10.30, 95% CI = 26.71-39.28), as shown in (Figure 6A, 6B).

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Table 2. Quality evaluation of the 13 studies and evaluations

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Comparison of TAT between the recurrent abortion group and the non-abortion pregnancy group: 13 articles describe comparisons of the TAT values between the recurrent abortion group and the non-abortion pregnancy group. The TAT value increased between the recurrent abortion group and the non-abortion pregnancy group. The heterogeneity test results were (chi-squared = 406.27, \( P < 0.00001 \), \( I^2 = 8\% \)), so the 95% CI was used. The results showed that the TAT value in the recurrent spontaneous abortion group was higher than it was in the non-abortion pregnancy group (\( Z = 136.65 \), 95% CI = 0.15-0.16), as shown in (Figure 7A, 7B).

Comparison of the LA positive rate between the recurrent abortion group and the non-abortion pregnancy group: 3 articles describe comparisons of the LA positive rates between recurrent abortion and non-abortion pregnancy. The positive rate of LA was increased

Figure 2. A. D-Dime between recurrent abortion group and normal pregnancy group (Forest plot); B. D-Dime between recurrent abortion group and normal pregnancy group (Funnel plot).
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between the recurrent abortion group and the non-abortion pregnancy group. The heterogeneity test results were (chi-squared = 0.14, P < 0.00001, I² = 0%), so the 95% CI was used. The results showed that the positive rate of LA in the recurrent abortion group was higher than it was in the non-abortion pregnancy group (Z = 7.47, 95% CI = 12.33-73.54), as shown in (Figure 8A, 8B).

Publication bias

There was no publication bias in any of the randomized controlled studies and the P value was greater than 0.05.

Discussion

At present, relevant studies have found that the prethrombotic state is already present in most abortions [21, 22]. Therefore, a timely intervention for the pre-thrombotic state of pregnant women is particularly important.

D-dimer is a common marker of the blood hypercoagulable state. In a retrospective study, Welles pointed out that D-Dimer showed a sign of an increase in the prethrombotic state in the pregnancy group compared with the non-pregnancy group. It can be used as an indicator for a test of the prethrombotic state [23]. A clinical
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A study by Wolters has shown that the D-Dimer in the normal fertility group was higher than it was in the abortion group [24]. The study result in this paper (Z = 23.18, 95% CI = 24.21-28.68, P < 0.00001) indicated that D-Dimer in RAG increased remarkably compared to the normal fertility group. The result was consistent with that in the study by Welles. The reason is considered to be that the blood system of pregnant women is hypercoagulable during the last weeks of pregnancy. Therefore, it is higher than that in some of the abortion women. As the blood hypercoagulable state in RAG was more serious than it was in NPG, the increase in D-Dimer was more obvious.

AT-III

AT-III is an important physiological substance to maintain a blood coagulation balance and prevent thrombosis in the coagulation system. Recently, the study by Uetstka showed that the thrombophilia caused by AT-III deficiency is related to adverse pregnancy [25]. The study by Tschoepe found that there is no significant change in the activity of AT-III during pregnancy. However, the risk of abortion in some pregnant

![Figure 4](image-url)
women with AT-III deficiency is higher than it is in normal pregnant women. The likelihood of stillbirth has increased fivefold [26]. This meta-analysis showed that the AT-III (Z = 12.36, 95% CI = 0.03-0.05, P < 0.00001) in RAG was lower than it was in NPG. The result is similar to above-mentioned study result. Therefore, the loss of AT-III can lead to the destruction of the blood coagulation balance and hypercoagulability in the body.

**t-PA**

Tissue plasminogen activator (t-PA) is an important regulator of the fibrinolysis system [27]. It can activate the plasminogen and convert it into plasmin. Thus, the thrombus is dissolved [28]. In a relevant study, Song found that the levels of t-PA and PAI-1 in the healthy control group were dramatically lower than the levels in the recurrent spontaneous abortion group [29]. In a report, Podorolskaya pointed out that the higher the number of abortion was, the higher the levels of t-PA and PAI-1 were [30]. Medic-Stojanoska also posited that t-PA can be used as a screening index for patients with recurrent abortion [31]. The meta-analysis showed that t-PA (Z = 15.01, 95% CI = 0.04-0.06, P < 0.00001) in RAG significantly increased com-

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**Figure 5.** A. PAI-1 between recurrent abortion group and normal pregnancy group (Forest plot); B. PAI-1 between recurrent abortion group and normal pregnancy group (Funnel plot).
pared to NPG. The reason may be that recurrent abortion leads to the injury of vascular endothelial cells and an increase in the t-PA release level. Thus, this causes a disorder of the fibrinolytic system.

**PAI-1**

PAI-1 is an important regulator of the fibrinolysis system [32]. After specific binding to t-PA, the activation of fibrinogen is inhibited. Thus, this causes thrombosis [33]. In a relevant study, Sun believed that the PAI-1 gene polymorphism is an important factor in the occurrence of recurrent abortion. Sun also considered that the Mexican ACE I/D gene is a genotype prone to recurrent abortion [34]. In a study, Matuskova suggested that the ACE I/DD genotype is a genotype prone to recurrent abortion. Matuskova also considered that the PAI-14G/4G gene polymorphism may be the cause of thrombophilia [35]. The PAI-1 gene polymorphism varies in different regions. In this study, regarding PAI-1 (Z = 53.07, 95% CI = 26.65-28.69, P < 0.00001), it was not observed that gene polymorphism can increase the incidence of recurrent abortion.

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Figure 6. A. F1+2 between recurrent abortion group and normal pregnancy group (Forest plot); B. F1+2 between recurrent abortion group and normal pregnancy group (Funnel plot).
F1+2

Prothrombin fragment PF1+2 (F1+2) is involved in the production of thromboplastin. It plays an important role in the coagulation system [36]. In a clinical randomized controlled trial, Ignat’ev pointed out that the increase of F1+2 level can provide an early indication of the blood hypercoagulable state in pregnant women [37]. In a clinical study involving 238 subjects, Girolami pointed out that F1+2 is a sensitive early molecular marker in the hypercoagulable state in body. It can be used as a marker of the prethrombotic state [38]. The results in this study indicated that the F1+2 (Z = 10.30, 95% CI = 26.71-39.28, P < 0.00001) in RAG was remarkably increased compared with that in NPG. It can be used as a predictor of recurrent abortion.

TAT

Thrombin-antithrombin complex (TAT) is a sensitive indicator reflecting the formation of
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thrombin [38]. In a clinical study, Girleanu found that the TAT level in recurrent abortion women was higher than it is in normal pregnant women [39]. The meta-analysis indicated that the TAT level in pregnant women with recurrent abortion was higher than the level in normal early pregnant women. The result (Z = 136.65, 95% CI = 0.15-0.16, P < 0.0001) was consistent with the above-mentioned study result. The reason may be that the coagulation system in pregnant women with recurrent abortion is destroyed. The generation of early thrombin is increased. Thus, a hypercoagulable state is caused.

*Lupus anticoagulant (LA)*

Lupus anticoagulant is an autoantibody. At present, a relevant study has found that LA is related to the occurrence of multiple clinical thrombotic diseases [40]. A study by Cui considers that the increase of LA can be an important risk factor of habitual abortion [41]. A study by Nagayoshi of 263 women with recurrent abortion found that the positive rate of LA is up to 17.9% [42]. The meta-analysis showed that there was no significant difference in the LA positive rate (Z = 7.47, 95% CI = 12.33-73.54, P < 0.0001) between RAG and NPG. The reason may be that most of the patients with recurrent abortion suffer from coagulation dysfunction. There is little difference in correlation with the immune system. To further draw a correct conclusion, further, large-sample clinical randomized controlled studies are needed.

In summary, the prethrombotic state can indicate the occurrence of recurrent abortion. It is

**Figure 8.** A. LA between recurrent abortion group and normal pregnancy group (Forest plot); B. LA between recurrent abortion group and normal pregnancy group (Funnel plot).
recommended that obstetricians and gynecologists actively give treatment when they find the existence of recurrent abortion in patients. Thus, abortion is prevented and safe pregnancy is ensured. Due to the limitations of study content in the meta-analysis, it is difficult to perform a clinical randomized controlled study. Therefore, some deviations may exist in the clinical retrospective analysis of the relevant designs in this paper. In addition, a meta-analysis on D-Dimer, AT-III, t-PA and PAI-1 alone is only performed in this paper. The results may be somewhat biased. A combined meta-analysis on multiple indexes can be carried out. Thus, the accuracy of the conclusion is improved.

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Disclosure of conflict of interest

None.

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References


