International Journal of Women's Health

Dovepress

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ORIGINAL RESEARCH

Prediction of Unexplained Recurrent Miscarriages Using Thromboelastography

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Objective: This study investigates the thromboelastography (TEG) changes in patients with unexplained recurrent spontaneous abortion (URSA) to identify effective diagnostic markers for URSA.

Methods: We retrospectively analyzed 160 URSA patients from the Gynecology Department of the First People's Hospital of Lianyungang (June 2017 - June 2020) and compared them with 190 healthy, fertile women without adverse pregnancy histories (control group). TEG parameters were assessed using logistic regression, applying stepwise selection for model optimization. Model performance was evaluated using Receiver Operating Characteristic (ROC) curves, determining sensitivity and specificity. The Youden index identified optimal cut points for predictive probabilities.

Results: Significant differences were observed between the URSA and control groups in coagulation reaction time (R), clot formation time (K), clot formation rate (Angle-α), and maximum clot strength (MA) ($P<0.05$). Multivariable logistic regression identified R, Angle-α, and MA as independent URSA risk factors. The model demonstrated excellent discrimination (AUC: 0.940; 95% CI: 0.918–0.962). The optimal cut point of predictive probability (Youden index) was $P=0.355$, yielding a sensitivity of 0.925 and specificity of 0.795.

Conclusion: URSA patients exhibit a hypercoagulable state even when not pregnant. More research is needed to validate our findings and explore the potential clinical implications of anticoagulants in treating URSA.

Keywords: unexplained recurrent spontaneous abortion, thromboelastography, prothrombotic state, coagulation function

Introduction

The Practice Committee of the American Society for Reproductive Medicine (ASRM) characterizes recurrent spontaneous abortion (RSA) as the loss of two or more pregnancies.[1] Globally, the criteria for RSA diverge, primarily depending on the count of miscarriages, yet there is a universal emphasis on the urgency of advancing research for RSA prevention. Recurrent miscarriages not only jeopardize the health of expecting mothers but also place a substantial emotional and financial strain on their families.[2] For approximately 40–50% of RSA patients, the precise cause and disease mechanism remain elusive, leading to a categorization of these cases as unexplained recurrent spontaneous abortion (URSA).[3] As the number of miscarriages escalates, the recurrence rate of URSA correspondingly rises, reaching

Received: 21 April 2024
Accepted: 25 September 2024
Published: 27 September 2024

an alarming risk level of 40% following three successive miscarriages. The prognosis deteriorates with advancing maternal age.[4] The multifaceted pathogenesis of URSA and the diverse clinical presentations significantly stymie research progress in its prediction and prevention. Consequently, it is of critical importance to identify clinically significant URSA predictive indicators, enabling the implementation of early, targeted preventive strategies, and thereby ameliorating the prognosis for pregnant women.

The prethrombotic state (PTS) denotes a condition characterized by heightened blood coagulation, leading to systemic hemodynamic changes and a propensity for thrombus formation. During pregnancy, pathological hypercoagulability can result in local microthrombi within the placenta, fostering the formation of fibrotic deposits and infarctions. Such phenomena can induce fetal ischemia and hypoxia, precipitating adverse pregnancy outcomes. This is identified as a principal cause of RSA.[5] Studies have indicated that abnormalities in coagulation and blood rheology are present before pregnancy in patients with URSA.[6] In early pregnancy, when there is an inclination towards thrombus formation, proactive anticoagulant therapy is recommended, which can enhance the pregnancy outcomes for women experiencing recurrent miscarriages.[7] Traditional coagulation routines and D-dimer tests may not fully reveal a patient's coagulation status and lack the timeliness required to detect initial coagulation abnormalities, thereby displaying latency. Thromboelastography (TEG), however, can dynamically monitor and extensively evaluate a patient's coagulation cascade response, platelet functionality, and fibrinolysis, exhibiting higher sensitivity and accuracy.[8] TEG has demonstrated promising results in dynamic coagulation monitoring in the context of interventional surgery and tissue transplantation patients,[9,10] yet its use in obstetrics and gynecology research remains limited. This study aims to juxtapose the elastographic parameters between URSA patients and healthy women of reproductive age, assess the clinical value of thromboelastography in forecasting URSA, and explore appropriate clinical PTS detection strategies. Prompt detection of PTS in URSA is crucial for understanding its etiology and facilitating early preventative treatments.

Methods

Study Participants

We recruited 160 patients diagnosed with URSA from the Department of Gynecology at the First People's Hospital of Lianyungang, spanning the period from June 2017 to June 2020, to form the research group (URSA group). To be eligible for the study, the following criteria were applied: 1) the patient fulfilled the diagnostic criteria outlined in the "Expert Consensus on the Diagnosis and Treatment of Recurrent Miscarriage"[11] 2) more than 3 months had elapsed since the patient's last miscarriage; and 3) the patient was not pregnant at the time of the visit. Patients were excluded from the study if they: 1) were aged under 18 or over 40; 2) had major organ diseases or autoimmune conditions; 3) were diagnosed with endocrine disorders, such as diabetes or thyroid irregularities; 4) suffered from obesity, hyperlipidemia, or cardiovascular diseases; or 5) had taken hormonal drugs, anticoagulants, antiplatelet, or fibrinolytic medications within the last three months.

From June 2017 to June 2020, a total of 526 URSA patients were treated at the Department of Gynecology at the First People's Hospital of Lianyungang City. According to the inclusion and exclusion criteria, 366 patients were excluded: 63 had miscarriage within the prior 3 months, 72 did not meet the age requirements, 65 were pregnant at the time of consultation, 58 had significant organ or autoimmune diseases, 66 had endocrine disorders, and 42 had been treated with hormone drugs, anticoagulants, antiplatelet, or fibrinolytic medications within the last three months. As a result, 160 eligible URSA patients were included in the study. Additionally, 190 healthy, non-pregnant women of childbearing age with no adverse obstetric history were randomly selected as the control group during the same period (Figure 1). The exclusion criteria for the control group mirrored those of the URSA group.

Laboratory Test Procedure

Venous blood of 2 mL was collected from a patient's elbow after a 10-hour overnight fast. The sample was then injected into an anticoagulant tube containing a 3.2% concentration of sodium citrate to inhibit clotting. The blood sample was incubated with a Kaolin reagent for a minimum of 10 minutes. Following this, 1000-ul whole blood was extracted from the anticoagulant tube using a pipette and transferred into a tube containing a Kaolin activator. The tube was then securely capped and inverted five times to ensure the blood mixed completely with the reagent and flowed appropriately.

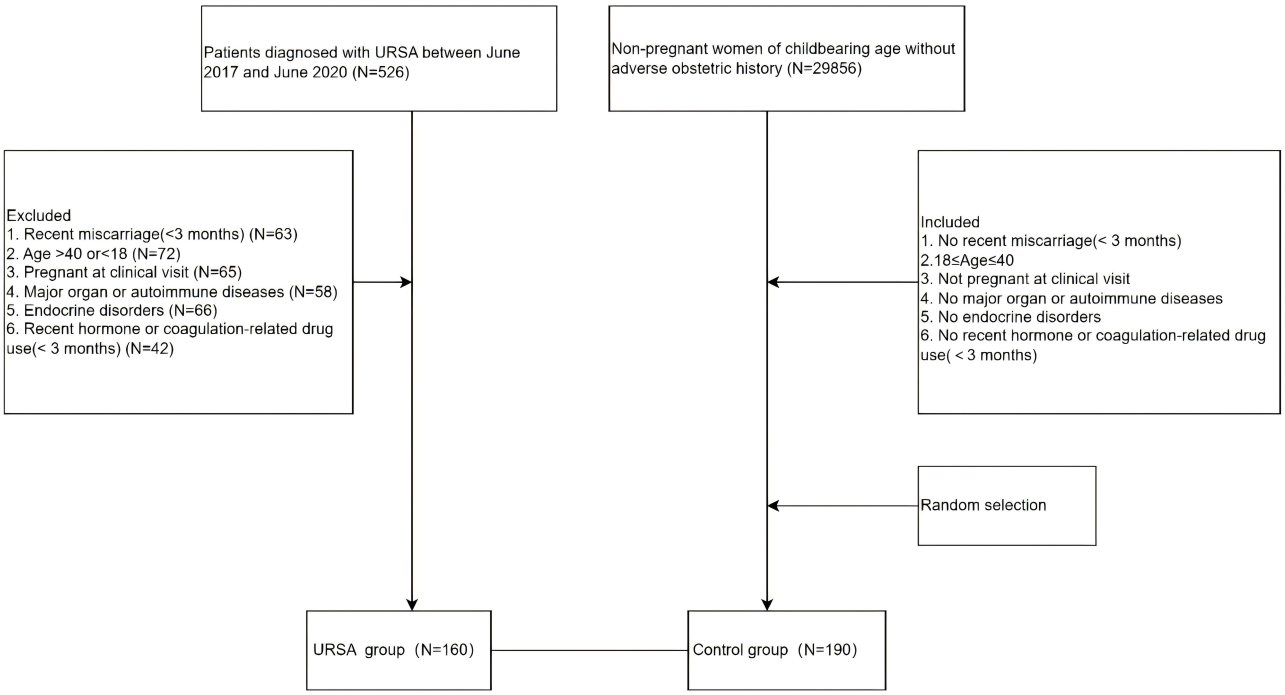

Figure 1 Flowchart of selection of the study participants.
Abbreviation: URSA, unexplained recurrent spontaneous abortion.

The mixture was subsequently left undisturbed for 3 to 5 minutes to allow the Kaolin to fully activate the blood sample. A cup was prepared, and 20-ul calcium chloride was added to the bottom, followed by an additional mixing. Thereafter, a 340-ul Kaolin-activated blood sample was slowly drawn and gently injected along the cup's inner wall. The cup was then raised, and the test was completed using a TEG analyzer to obtain all the key TEG parameters. The TEG analysis was conducted using a TEG5000 coagulation analyzer from the Haemoscope Corporation in conjunction with its compatible reagents and software systems. Briefly, the TEG5000 utilizes an electromechanical transducer connected to a pin, suspended by a torsion wire, to measure whole blood viscoelasticity. This pin, inserted into a cuvette or cup, rotates at an angle of 4° to 45°. As fibrin strands form within the cup, the resulting impeded movement is transmitted through the pin and torsion wire to a tracking device. The pin's movement, influenced by the clot's shear force, is recorded on thermosensitive paper, displaying clot formation time, clot strength, and fibrinolysis time. All procedures were strictly adhered to as per the provided instructions. The test was conducted by the Laboratory Department of the First People's Hospital of Lianyungang City, Jiangsu Province.

In this study, we focused on four coagulation factors in their association with URSA. 1) coagulation reaction time (R): This term refers to the duration (in minutes) from the onset of coagulation to the creation of the first fibrin clot, as indicated when the plotted graph reaches 2 mm. This measure demonstrates the cumulative effect of all clotting factors participating in the coagulation process, inclusive of intrinsic, extrinsic, and common pathways; 2) clot formation time (K): This is the time span (in minutes) needed from the conclusion of the R time until the plotted graph reaches 20 mm. It embodies the combined contribution of fibrin and platelets at the commencement of clot formation, effectively signifying the rate of clot formation; 3) clot formation rate (Angle-α): This is the angle formed by a tangent line drawn from the clot formation point to the peak arc of the plotted graph with the horizontal line. It represents the cooperative interaction of fibrin and platelets at the onset of clot formation, ie, the rate of clot formation. In instances of severe hypocoagulability where the clot amplitude does not reach 20 mm, the K value cannot be determined. Under such circumstances, the Angle-α measurement proves to be more significant; and 4) maximum clot strength (MA): This denotes the peak amplitude and maximum shear stress coefficient (in millimeters) represented on the TEG graph. It characterizes the highest strength of the clot being formed and the stability of clot formation.

Statistical Analysis

The collected data were expressed as mean ± standard deviation, and the differences between the URSA group and the control group were analyzed using the *t*-test. Factors identified with statistically significant differences in univariable logistic regression served as the candidate variables in a multivariate stepwise regression analysis, with important predictors selected by employing the stepwise method. The receiver operating characteristic (ROC) curve was subsequently plotted and the area under the curve (AUC) was computed. The AUC acted as the principal criterion for assessing clinical diagnostic value: an AUC above 0.5 suggested some predictive value, above 0.7 signified moderate predictive value, and above 0.9 implied high predictive value. The optimal cut-off value was determined using the Youden index, with the corresponding sensitivity (SE) and specificity (SP) calculated.[12] All data processing and statistical analyses were performed using SPSS 22.0 (IBM Corp, Armonk, NY, USA) and R version 4.3.1 (https://www.r-project.org/), with a P-value below 0.05 denoting statistical significance.

Results

Comparison between the URSA group and the control group revealed several differences: URSA patients exhibited a lower R-value (5.37±0.50 vs 6.41±0.70) and K-value (1.55±0.94 vs 1.99±0.35) but a higher Angle-α (71.36±1.42 vs 68.98±3.11) and MA (62.24±4.22 vs 59.74±3.46) than the control group (all Ps<0.05). However, there was no significant difference in age between the two groups (P>0.05; Table 1).

Univariable logistic regression revealed that all four factors are associated with the risk of URSA. Specifically, R-value (OR: 0.033, 95% confidence interval [CI]: 0.016–0.066, P<0.001) and K-value (OR: 0.021, 95% CI: 0.008–0.054, P<0.001) were associated with a decreased risk of URSA, while Angle-α (OR: 1.662, 95% CI: 1.448–1.908, P<0.001) and MA (OR: 1.183, 95% CI: 1.115–1.255, P<0.001) were associated with an increased risk of URSA (Table 2). Although K-value did not show a significant association (OR: 0.600, 95% CI: 0.199–0.910, P=0.114), all four factors were also selected as important predictors of URSA by the stepwise variable selection using AIC (Table 2).

Table 1 Characteristics of the Study Participants

Variables	URSA Group (N=160)	Control Group (N=190)	t	P
Age (years)	30.16±3.71	30.36±4.75	0.457	0.648
R (min)	5.37±0.50	6.41±0.70	16.301	<0.001*
K (min)	1.55±0.94	1.99±0.35	5.939	<0.001*
Angle-α (deg)	71.36±1.42	68.98±3.11	9.405	<0.001*
MA (mm)	62.24±4.22	59.74±3.46	5.983	<0.001*

Notes: Data were presented as mean±standard deviation. *Indicate significant difference (P<0.05).
Abbreviations: URSA, unexplained recurrent spontaneous abortion; R, reaction time; K, clot kinetics; Angle-α, alpha angle; MA, maximum amplitude.

Table 2 Logistic Regression Analysis of URSA-Related Factors

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P	OR (95% CI)	P
R (min)	0.033 (0.016–0.066)	0.001*	0.021 (0.008–0.048)	0.001*
K (min)	0.021 (0.008–0.054)	0.001*	0.600 (0.199–0.91)	0.114
Angle-α (deg) (deg)	1.662 (1.448–1.908)	0.001*	1.264 (1.051–1.531)	0.013*
MA (mm)	1.183 (1.115–1.255)	0.001*	1.248 (1.132–1.386)	0.001*

Note: *Indicate significant difference (P<0.05).
Abbreviations: URSA, unexplained recurrent spontaneous abortion; OR, odds ratio; CI, confidence interval; R, reaction time; K, clot kinetics; Angle-α, alpha angle; MA, maximum amplitude.

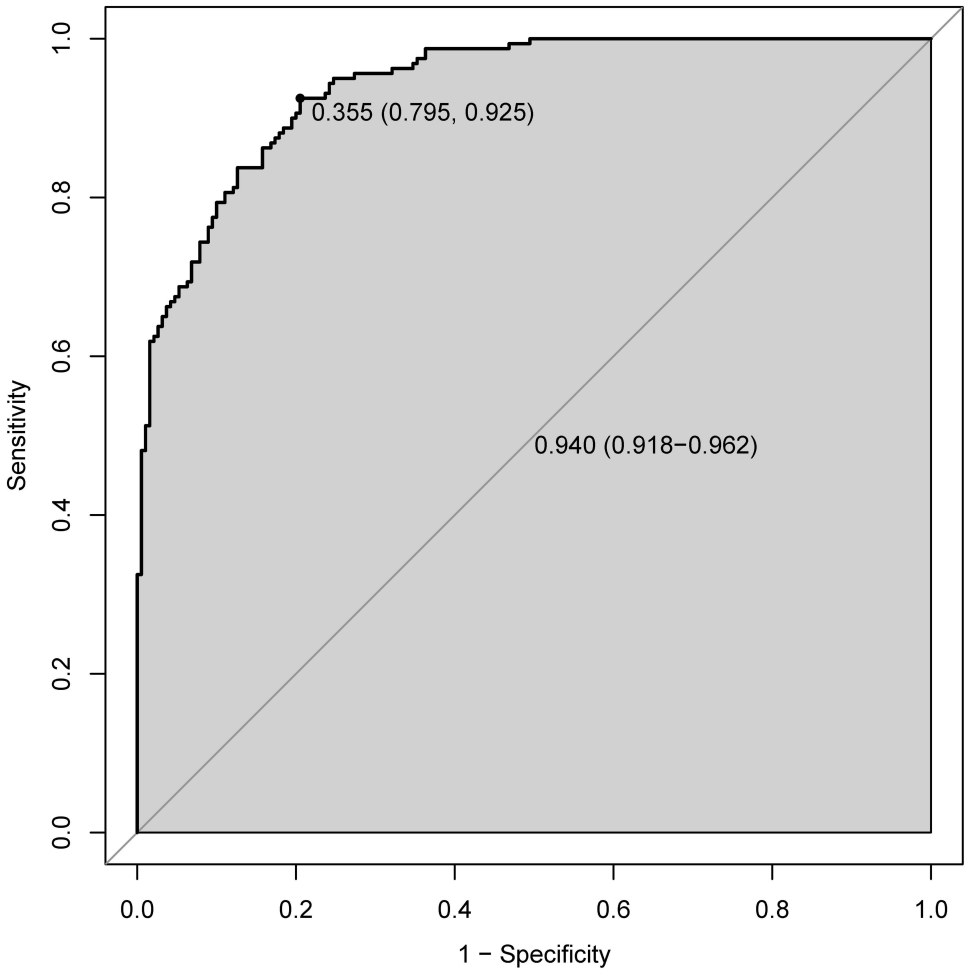

Figure 2 Receiver operating characteristic curves of TEG parameters for predicting URSA. The corresponding area under the ROC curve (AUC) is 0.940, and the optimal cut point of the predicted probabilities, as determined by the Youden index, was 0.355, which led to a sensitivity of 0.795 and a specificity of 0.925.
Abbreviations: ROC, receiver operating characteristic; AUC, under the ROC curve; URSA, unexplained recurrent spontaneous abortion.

The multivariate logistic regression showed an AUC of 0.940 (95% CI: 0.918–0.962), indicating that the built regression model has a good discrimination ability. The optimal cut point of the predicted probabilities as determined by the Youden index was P=0.355, which led to a sensitivity of 0.925 and a specificity of 0.795 (Figure 2). The model also demonstrated good calibration: the calibration intercept was 0 (95% CI: −0.34 to 0.34), and the calibration slope was 1.00 (95% CI: 0.78 to 1.22; Figure 3).

Discussion

In this study, we examined TEG parameters in URSA patients and compared them to those of healthy non-pregnant women of childbearing age without any history of adverse pregnancies, delving into their clinical implications. Our findings revealed that URSA patients exhibited lower R and K values than their healthy counterparts, whereas their Angle-α and MA values were notably higher. This suggests that even when not pregnant, URSA patients exhibit a hypercoagulable state, potentially accompanied by abnormalities in clotting factors, fibrinogen, and platelet function. Through multivariable logistic regression analysis, both Angle-α and MA emerged as independent risk factors for URSA. The developed model demonstrated robust discriminatory power. Consequently, our data underscores the potential of early TEG evaluation for URSA patients, enabling timely interventions to mitigate adverse pregnancy outcomes.

In our study, we observed that R levels in the URSA group were notably lower than in the control group, with a discernible negative correlation between R and URSA risk. The R-value symbolizes the duration needed for clotting

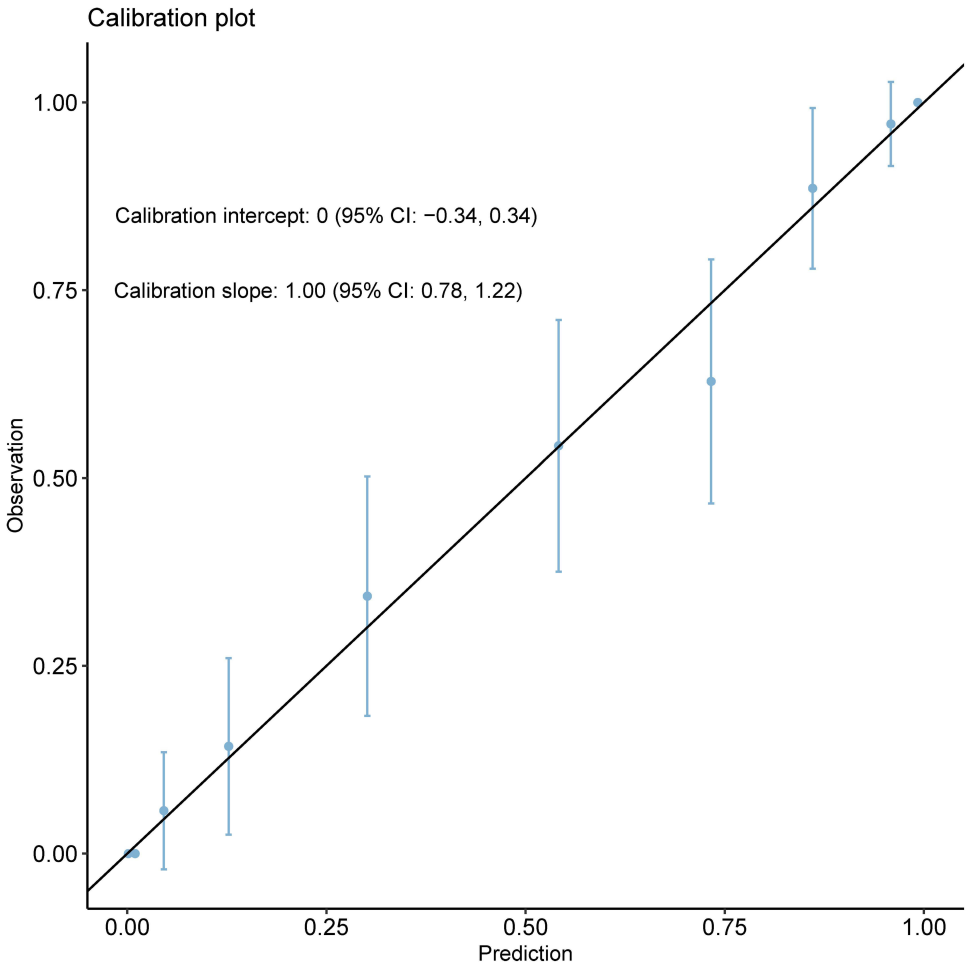

Figure 3 Calibration plot of the prediction model. The solid diagonal line represents the line of perfect calibration. The x-axis represents the predicted probabilities, and the y-axis represents the observed proportions. The subjects were divided into 10 groups by using deciles of the predicted probability. The dots represent the observed proportion of URSA, and the vertical lines represent the 95% confidence interval for the proportion of URSA within the deciles.
Abbreviation: URSA, unexplained recurrent spontaneous abortion.

factors to activate and subsequently form fibrin, serving as an indicator of clotting factor activity. An attenuated R-value is suggestive of a hypercoagulable state.[13] Consistent with our findings, prior research has established that individuals with recurrent miscarriage histories exhibit diminished thromboelastogram R-values when juxtaposed against pregnant women with uneventful pregnancies or those devoid of successive miscarriage histories.[14] Thromboelastography has proven instrumental in forecasting the propensity for recurrent miscarriages and assessing fetal prognosis in such populations.[15] The aberrant activity of clotting factors has a pivotal role in the genesis of PTS. Earlier investigations identified clotting factor V anomaly as the predominant genetic predisposition towards thrombus formation.[16] Both Protein C and Protein S are contingent upon vitamin K. Their synergistic interaction aids in activating clotting factors while concurrently curtailing blood coagulation. Notably, deficiencies in Protein S and Protein C frequently underpin the emergence of PTS in RSA sufferers.[17] Intriguingly, the odds of experiencing RSA are magnified by approximately 3.45 times in individuals deficient in Protein S relative to the wider population.[18] Given the R-value's acute sensitivity in mirroring clotting factor activity, leveraging it for a timely appraisal of URSA patients' coagulation profile is of paramount clinical pertinence.

Our study indicates that the URSA group exhibited elevated levels of Angle-α and MA in comparison to the control group. Angle-α serves as an indicator of blood clot formation speed, with a greater angle denoting quicker clot formation.[19] MA, on the other hand, measures platelet aggregation functionality: an increased MA suggests an elevated risk of microvascular thrombus development.[20] An abnormal elevation in MA signals the need to enhance the potency of antithrombotic medications, prompting adjustments in dosage and drug type based on MA values.[21] It is noteworthy that patients with URSA

exhibit increased platelet aggregation even before pregnancy. Studies have confirmed the presence of thrombosis in the decidual vessels and procoagulant microparticles in women with recurrent miscarriage.[22] Thrombosis may still occur during pregnancy in patients without obvious triggers, and routine thrombophilia screening is often insufficiently sensitive. Therefore, additional diagnostic tests are required to comprehensively assess the thrombosis risk in these patients.[23,24] TEG stands out as a singular methodology that encapsulates the interplay between clotting factors, platelets, and fibrinogen, offering a visual depiction of clotting kinetics. It furnishes a more immediate and thorough assessment of a patient's coagulative state than conventional markers. As a complementary tool to traditional coagulation assessments, TEG's precision and lucidity are commendable.[25] Existing research corroborates its pivotal clinical role in steering anticoagulant regimens, moderating heparin dosages,[26] gauging the suppressive action of aspirin on platelets, and bolstering pharmaceutical safety.[27] In the context of diagnosing and treating URSA patients, the potential of TEG appears to be promising.

Our research has certain limitations. Primarily, it is a single-center study with a constrained sample size. Future investigations could greatly benefit from multi-center collaborations, which would allow for the standardization of criteria and the inclusion of a more diverse subject pool, along with extensive clinical data. Our study is retrospective. Our findings need to be validated by prospective research with larger sample sizes. Additionally, randomized controlled trials (RCTs) are essential to explore the clinical effects of anticoagulants in treating URSA. Future studies should consider incorporating a broader range of factors and systematically screening for thrombophilia to potentially improve the accuracy of predictive models. Moreover, this study predominantly concentrates on female participants. To gain a more holistic understanding, future research should include male participants, focusing on both partners for a comprehensive analysis. A significant limitation of our current approach is the lack of long-term follow-up on patients' clinical outcomes. Longitudinal studies would be particularly valuable in offering deeper insights into the enduring risks of thrombosis, the trajectory of pregnancy outcomes, and fetal health.

In summary, this study contrasted the TEG parameter differences between URSA patients and healthy, non-pregnant women of childbearing age with no adverse pregnancy history. Our findings suggest that URSA patients may exhibit abnormalities in coagulation factors, fibrinogen, and platelet function even when not pregnant. More research is needed to validate our findings and explore the potential clinical implications of anticoagulants in treating URSA.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The First People's Hospital of Lianyungang (No. KY-20221216001-01).

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Author Contributions

Jinjin Xu, Yang Yan and Guixue Guan contributed equally to this paper and share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Key Talents in Maternal and Child Health Care in Lianyungang City (No. FRC202003), Special Project on Promoting Scientific and Technological Innovation in Xuzhou City in 2022 (Key Research and Development Program (Social Development) - Standardized Treatment of Key Diseases) (No. KC22096), Youth Talent Training Fund Project of the First People's Hospital of Lianyungang (No. QN2219) and Youth Talent Training Fund Project of the First People's Hospital of Lianyungang (No. QN202120). Dr. Yang's research was supported by National Institute of Health/National Institute on Aging grants P30AG10161, R01AG15819, R01AG17917, R01AG033678, R01AG36042, U01AG61356, and 1RF1AG064312– 01.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

References

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2020;113(3):533–535. doi:10.1016/j.fertnstert.2012.09.023
2. Quenby S, Gallos ID, Dhillon-Smith RK, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet*. 2021;397(10285):1658–1667. doi:10.1016/S0140-6736
3. Gu H, Li L, Du M, et al. Key gene and functional pathways identified in unexplained recurrent spontaneous abortion using targeted RNA sequencing and clinical analysis. *Front Immunol*. 2021;12:717832. doi:10.3389/fimmu.2021.717832
4. Hennessy M, Dennehy R, Meaney S, et al. Clinical practice guidelines for recurrent miscarriage in high-income countries: a systematic review. *Reprod Biomed Online*. 2021;42(6):1146–1171. doi:10.1016/j.rbmo.2021.02.014
5. Wu Y, Xin M, Han Q, et al. Extensive serum biomarker analysis in the prethrombotic state of recurrent spontaneous abortion. *J Cell Mol Med*. 2021;25(14):6679–6694. doi:10.1111/jcmm.16671
6. Awolumate OJ, Kang A, Khokale R, et al. Role of low molecular weight heparin in the management of unexplained recurrent pregnancy loss: a review of literature. *Cureus*. 2020;12(10):e10956. doi:10.7759/cureus.10956
7. Hamulyak EN, Scheres LJ, Marijnen MC, et al. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. *Cochrane Database Syst Rev*. 2020;5(5):D12852. doi:10.1002/14651858.CD012852.pub2
8. Fan D, Ouyang Z, Ying Y, et al. Thromboelastography for the prevention of perioperative venous thromboembolism in orthopedics. *Clin Appl Thromb Hemost*. 2022;28:1309707817. doi:10.1177/10760296221077975
9. Willis J, Carroll C, Planz V, et al. Thromboelastography: a review for radiologists and implications on periprocedural bleeding risk. *Abdom Radiol (NY)*. 2022;47(8):2697–2703. doi:10.1007/s00261-022-03539-9
10. Thakkar M, Rose A, Bednarz B. Thromboelastography in microsurgical reconstruction: a systematic review. *JPRAS Open*. 2022;32:24–33. doi:10.1016/j.jpra.2021.12.005
11. Obstetrics Subgroup, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association. [Chinese expert consensus on the diagnosis and treatment of recurrent spontaneous abortion]. *Chin J Obstet Gynecol*. 2022;57(09):653–667. doi:10.3760/cma.j.cn112141-20220421-00259
12. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3(1):32–35. doi:10.1002/1097-0142
13. Diebel LN, Liberati DM, Karadjoff A, et al. Detection of glycocalyx degradation in real time: a conceptual model of thromboelastography. *Surgery*. 2023. doi:10.1016/j.surg.2023.08.045
14. Yao H, Ji Y, Zhou Y. Analysis of blood coagulation indexes, thromboelastogram and autoantibodies in patients with recurrent pregnancy loss. *Pak J Med Sci*. 2022;38(7):2005–2010. doi:10.12669/pjms.38.7.6284
15. Zhang GM, Zhuang ZH. The maximum amplitude of thromboelastography can be used for predicting recurrent spontaneous abortion. *Am J Reprod Immunol*. 2022;87(5):e13538. doi:10.1111/aji.13538
16. Eslami MM, Khalili M, Soufizomorrod M, et al. Factor V Leiden 1691G > A mutation and the risk of recurrent pregnancy loss (RPL): systematic review and meta-analysis. *Thromb J*. 2020;18:11. doi:10.1186/s12959-020-00224-z
17. Akdemir Y, Ayvaci H, Uludogan M. Effect of multiple thrombophilic gene mutations on uterine artery blood flow in nonpregnant recurrent pregnancy loss patients: are we searching enough? *J Matern Fetal Neonatal Med*. 2020;33(14):2466–2472. doi:10.1080/14767058.2019.1569618
18. Liu X, Chen Y, Ye C, et al. Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. *Hum Reprod*. 2021;36(5):1213–1229. doi:10.1093/humrep/deab010
19. Shastry S, Mohan G, Pa P, et al. Role of Thromboelastogram in monitoring the activation of the coagulation pathway and assessing the associated risk factors for hypercoagulable state in transfusion dependent thalassemia patients. *Transfus Apher Sci*. 2023;62(2):103583. doi:10.1016/j.transci.2022.103583
20. Jian F, Lu C, Jia H, et al. Characteristics of blood clotting on thromboelastography in patients with early burns. *Transfus Apher Sci*. 2023;62:103824. doi:10.1016/j.transci.2023.103824
21. Harada M, Sajima T, Onimaru T, et al. Changes in platelet function and coagulation after transcatheter aortic valve implantation evaluated with thromboelastography. *Open Heart*. 2022;9(2):e002132. doi:10.1136/openhrt-2022-002132
22. Lu X, Liu Z, Zhang X, et al. Prothrombotic state of patients with unexplained recurrent spontaneous abortion. *Int J Gynaecol Obstet*. 2015;131(2):161–165. doi:10.1016/j.ijgo.2015.04.049
23. O'Donnell J, Riddell A, Owens D, et al. Role of the Thrombelastograph as an adjunctive test in thrombophilia screening. *Blood Coagul Fibrinolysis*. 2004;15(3):207–211. doi:10.1097/00001721-200404000-00002
24. Akinshina S, Makatsariya A, Bitsadze V, et al. Thromboprophylaxis in pregnant women with thrombophilia and a history of thrombosis. *J Perinat Med*. 2018;46(8):893–899. doi:10.1515/jpm-2017-0329
25. Kataria S, Juneja D, Singh O. Approach to thromboelastography-based transfusion in cirrhosis: an alternative perspective on coagulation disorders. *World J Gastroenterol*. 2023;29(9):1460–1474. doi:10.3748/wjg.v29.i9.1460
26. Panigada M, G EI, Brioni M, et al. Thromboelastography-based anticoagulation management during extracorporeal membrane oxygenation: a safety and feasibility pilot study. *Ann Intensive Care*. 2018;8(1):7. doi:10.1186/s13613-017-0352-8
27. Shen W, Zhou JY, Gu Y, et al. Establishing a reference range for thromboelastography maximum amplitude in patients administrating with antiplatelet drugs. *J Clin Lab Anal*. 2020;34(4):e23144. doi:10.1002/jcla.23144