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A retrospective cohort analysis of plasma TAT level trends and adverse pregnancy outcomes in early pregnancy patients with newly diagnosed VTE

Rong Zhang[1†], Xiao Mei Wang[1†], Chao Yun Jiang[1], Tian Hong Cai[1], Jian Feng He[1], Kai Chen[1], Dian Xi Chen[1] and Teng Hui Zhan[1*]

Abstract

Objective Venous thromboembolism (VTE) is a leading cause of maternal mortality, yet effective biomarkers for early prediction of adverse pregnancy outcomes remain limited. We aimed to investigate the association between changes in thrombin-antithrombin complex (TAT) levels and adverse pregnancy outcomes in early-pregnancy patients with VTE.

Methods In this retrospective cohort study, we enrolled 89 pregnant women diagnosed with VTE during early pregnancy (< 14 weeks) who received care at Fujian Maternity and Child Health Hospital between June 2021 and May 2024. Plasma TAT levels measured in early and mid-pregnancy were collected as exposure variables, while adverse pregnancy outcomes (including miscarriage, preterm birth, and fetal growth restriction) served as outcome variables. Multivariate regression analysis was performed to evaluate the association between TAT level changes and adverse pregnancy outcomes, adjusting for potential confounding factors including age, BMI, and obstetric history. Additionally, threshold effect analysis was conducted.

Results After adjusting for potential confounding factors including age, BMI, and underlying conditions, changes in TAT levels were significantly associated with a reduced risk of adverse pregnancy outcomes (adjusted OR = 0.62, 95% CI: 0.47–0.80). Threshold effect analysis identified a critical turning point of -2.87 in TAT level changes (TATp2-1), below which the risk of adverse outcomes increased significantly (adjusted OR = 0.37, 95% CI: 0.22–0.63).

Conclusion The association between TATp2-1 and adverse pregnancy outcomes in early pregnancy VTE patients was non-linear. A threshold effect was observed with an inflection point of -2.87. When the TATp2-1 were below − 2.87, there was a significantly increased risk of adverse pregnancy outcomes.

Keywords Venous thromboembolism, Plasma TAT, Early pregnancy, Adverse pregnancy outcomes, Cohort study

†Rong Zhang and Xiao Mei Wang contributed equally to this work.

*Correspondence:
Teng Hui Zhan
zth182999@fjmu.edu.cn
[1]Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, 18 Daoshan Road, Gulou District, Fuzhou City, Fujian Province, China

Introduction

Pregnancy-associated venous thromboembolism (PA-VTE) remains a leading cause of maternal mortality. Studies indicate that the incidence of PA-VTE is approximately 1 per 1,000 pregnancies [1]. In China, the reported incidence of PA-VTE in pregnant and postpartum women ranges from 0.4 to 1.3 per 1,000, with deep vein thrombosis (DVT) accounting for 83.3% and pulmonary embolism (PE) for 16.7% of cases [2, 3]. Recent years have witnessed an increasing trend in PA-VTE incidence in China, particularly associated with rising cesarean section rates, advanced maternal age, and other risk factors such as gestational diabetes [3].

Pregnancy induces a hypercoagulable state characterized by elevated coagulation factors, decreased anticoagulant protein activity, and suppressed fibrinolysis. Additionally, factors such as uterine enlargement-induced venous stasis, reduced physical activity during pregnancy, and vascular injury during delivery contribute to increased VTE risk [4]. Patients with VTE demonstrate significantly higher rates of pregnancy complications, including preterm birth, fetal growth restriction, and gestational hypertension [5]. Therefore, early identification of high-risk populations [6], timely diagnosis, and appropriate treatment are crucial for improving maternal and fetal outcomes.

While D-dimer is the most commonly used screening marker for VTE, its performance characteristics during pregnancy are suboptimal, with reported sensitivity and specificity of 73% and 15%, respectively [7]. This limitation underscores the urgent need for alternative screening markers. Thrombin-antithrombin complex (TAT), a marker of coagulation activation, serves as a sensitive indicator of coagulation system activation [8]. Elevated TAT levels suggest hypercoagulability and may predict increased thrombotic risk [9]. In non-pregnant populations, elevated TAT levels have shown strong correlations with disease occurrence and prognosis, and their predictive value is widely recognized [10–12].

Current research on TAT during pregnancy has primarily focused on establishing reference ranges. A Chinese study suggested that the normal TAT range for healthy pregnant women in early pregnancy is 0.40–3.65 ng/mL [13]. However, since definitive reference ranges for TAT in pregnant women remain undefined, the predictive value of single TAT measurements is limited. To address this limitation, we chose to investigate the dynamic changes in TAT levels. Currently, there is a paucity of research examining the relationship between TAT level trends and pregnancy outcomes in early-pregnancy VTE patients.

This retrospective cohort study aims to investigate the association between plasma TAT level trends and adverse pregnancy outcomes in early-pregnancy VTE patients. The significance of this research is threefold: first, monitoring TAT dynamics may provide a novel marker for early identification of high-risk populations; second, the findings will inform individualized anticoagulation strategies; and finally, our multi-model analysis approach and nonlinear association assessment will provide comprehensive evidence clarifying the relationship between TAT and pregnancy outcomes.

Methods

Ethical approval

This study was approved by the Ethics Committee of Fujian Provincial Maternal and Child Health Hospital (Ethical Guidelines for Research Projects: No. 2024KY167) and conformed to the Declaration of Helsinki. The requirement for informed consent was waived by the Ethics Committee because this retrospective analysis was limited to preexisting data collected as part of the standard care or treatment. Furthermore, data anonymization and privacy were protected.

Study design

Study population

This single-center retrospective cohort study was conducted at Fujian Maternity and Child Health Hospital between June 2021 and May 2024, with follow-up until December 2024. The study population comprised pregnant women with VTE diagnosed during early pregnancy. VTE diagnosis was confirmed by either: (1) Deep vein thrombosis through compression ultrasonography or CT venography, or (2) Pulmonary embolism through CT pulmonary angiography or ventilation-perfusion scanning. Inclusion criteria were: (1) Pregnant women in early pregnancy (<14 weeks); (2) Confirmed diagnosis of deep vein thrombosis of lower extremities or pulmonary embolism; (3) Standardized anticoagulation therapy and follow-up under specialist supervision. Exclusion criteria included: (1) Concurrent serious illnesses requiring additional treatment; (2) Pre-pregnancy diagnosis of deep vein thrombosis of lower extremities or pulmonary embolism, or currently receiving anticoagulation therapy for other conditions; (3) Incomplete clinical data.

Variables

The exposure variable was the trend of plasma thrombin-antithrombin complex (TAT) levels. TAT was measured using ELISA (Siemens Healthcare Diagnostics Products GmbH, Germany), with all samples processed and analyzed within 2 h of collection. Initial measurement (TATp1) was performed after VTE identified in first trimester and anticoagulant therapy was initiated, while the second measurement (TATp2) was conducted during second trimester. TAT change (TATp2-1) was defined as the difference between TATp2 and TATp1.

The outcome variable was abnormal pregnancy, defined as the occurrence of any of the following conditions: preterm birth (< 37 weeks), low or high birth weight (< 2500 g or > 4000 g), 5-minute Apgar score < 7, obstetric complications (including postpartum hemorrhage, placental abruption, premature rupture of membranes), miscarriage or fetal death, or fetal growth restriction. Outcome assessment was performed by obstetricians blinded to TAT results based on medical records. Covariates were selected based on literature review [14–16] and expert consensus, including: age, education level, number of pregnancies and births, BMI (Body Mass Index), delivery methods, abnormal fetal position, gestational diabetes, gestational hypertension, preeclampsia, uterine fibroids, assisted reproduction, thyroid diseases, and thrombophilia. Thyroid diseases were specifically included as covariates due to their relatively high prevalence (12.4%) in our study population and their established association with hypercoagulability and adverse pregnancy outcomes [17]. Our research includes all types of thrombophilia, including hereditary thrombophilia (such as protein C deficiency, protein S deficiency, antithrombin deficiency, and factor V Leiden mutation) and acquired thrombophilia (primarily antiphospholipid syndrome). For the diagnosis of thrombophilia, we follow the American Society of Hematology 2023 guidelines for thrombophilia testing published by ASH in 2023 [18]. Missing data were less than 5% for all variables and were handled using complete case analysis.

Table 1 Baseline characteristics of study participants according to TATp2-1 tertiles

Characteristics	Low	Middle	High	*P*-value
N	30	29	30	
Demographics				
Age (years, mean ± SD)	32.3 ± 4.2	34.9 ± 4.9	33.7 ± 5.4	0.156
BMI (kg/m^2, mean ± SD)	26.8 ± 3.7	26.9 ± 3.1	27.4 ± 4.1	0.715
Education level (n, %)				
University	24 (80.0)	25 (86.2)	23 (76.7)	0.678
High school	5 (16.7)	4 (13.8)	5 (16.7)	0.998
Middle school	1 (3.3)	0 (0.0)	2 (6.7)	0.245
Obstetric history (n, %)				
Primigravida	13 (43.3)	8 (27.6)	10 (33.3)	0.145
Delivery method (n, %)				
Vaginal	16 (53.3)	18 (62.1)	17 (56.7)	0.823
Cesarean	14 (46.7)	11 (37.9)	13 (43.3)	0.754
Pregnancy complications (n, %)				
Gestational diabetes	3 (10.0)	9 (31.0)	7 (23.3)	0.136
Gestational hypertension	2 (6.7)	1 (3.4)	3 (10.0)	0.868
Pre-eclampsia	1 (3.3)	5 (17.2)	0 (0.0)	0.015
Uterine fibroids	6 (20.0)	7 (24.1)	6 (20.0)	0.905
Medical conditions (n, %)				
Thrombophilia	10 (33.3)	8 (27.6)	8 (26.7)	0.828
Thyroid diseases	2 (6.7)	5 (17.2)	3 (10.0)	0.423
Assisted reproduction	1 (3.3)	5 (17.2)	5 (16.7)	0.182
Pregnancy outcome (n, %)				
Abnormal pregnancy	8 (26.7)	13 (44.8)	22 (73.3)	0.001

TATp2-1 = the difference between second trimester TAT level and first trimester TAT level. BMI = Body Mass Index

Definition and treatment protocol

According to the American College of Obstetricians and Gynecologists (ACOG) [19], pregnancy periods were defined as follows: first trimester (≤ 13 + 6 weeks of gestation) and second trimester (14 + 0 to 27 + 6 weeks of gestation). All patients diagnosed with VTE received standardized anticoagulation therapy in accordance with the clinical guidelines [20–25]. The anticoagulation protocol consisted of therapeutic doses of low molecular weight heparin (LMWH), with dosage adjusted based on body weight and renal function. Treatment was initiated immediately upon VTE diagnosis and continued throughout pregnancy and the postpartum period until 42 days after delivery. All patients underwent systematic follow-up by a multidisciplinary team including obstetricians and thrombosis specialists.

Statistical analysis

Continuous variables were presented as mean ± standard deviation for normal distribution or median (minimum, maximum) for skewed distribution. Categorical variables were expressed as frequencies or percentages. Between-group differences were assessed using $\chi 2$ test for categorical variables, Student's t-test for normally distributed continuous variables, or Mann-Whitney U test for skewed distributions.

The association between plasma TAT changes and abnormal pregnancy outcomes was analyzed in three steps. First, we employed hierarchical regression models: Model 1 (unadjusted), Model 2 (adjusted for sociodemographic factors), and Model 3 (fully adjusted for all covariates in Table 1). This stepwise approach assessed the robustness of the association under different adjustment strategies.

Second, we explored potential nonlinear relationships using generalized additive models with penalized spline method. When nonlinearity was detected, we identified the inflection point using a recursive algorithm and constructed a two-piecewise linear regression model. The optimal model was selected based on log-likelihood ratio tests.

Third, we conducted stratified analyses using either linear regression or generalized additive models. Continuous variables were categorized based on clinical cutpoints or tertiles for interaction analyses. Effect modifications were evaluated using likelihood ratio tests. For sensitivity analysis, we treated plasma TAT changes as a categorical variable and calculated P for trend, validating the primary analysis and examining potential nonlinearity.

The statistical software is packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). A two-sided P value < 0.05 was considered statistically significant.

Results

The selection of patients

After screening based on inclusion and exclusion criteria, a total of 203 participants were excluded due to experiencing VTE outside of early pregnancy and non-standard anticoagulant therapy. Among the remaining 121 participants, 3 had other severe comorbidities, 9 had been diagnosed with deep vein thrombosis of the lower limbs or pulmonary embolism prior to pregnancy, 8 were receiving anticoagulant therapy for other conditions, and 12 had incomplete clinical data. Ultimately, 89 patients were included in the data analysis (Fig. 1).

Baseline characteristics of participants

The baseline characteristics of patients were listed in Table 1. The patients were stratified into three groups based on TATp2-1 tertiles (Low: $n = 30$, Middle: $n = 29$, High: $n = 30$).The baseline characteristics, including age (32.3 ± 4.2 vs. 34.9 ± 4.9 vs. 33.7 ± 5.4 years, $P = 0.156$), BMI (26.8 ± 3.7 vs. 26.9 ± 3.1 vs. 27.4 ± 4.1 kg/m², $P = 0.715$), and educational level ($P > 0.05$), were comparable among the three groups. The majority of patients (> 75%) had university education across all groups.

No significant differences were observed in obstetric history parameters ($P = 0.145$), and delivery methods ($P > 0.05$). Common pregnancy complications such as gestational diabetes ($P = 0.136$), gestational hypertension ($P = 0.868$), uterine fibroids ($P = 0.905$), and thrombophilia ($P = 0.828$) showed similar distributions among the groups.

However, significant differences were noted in two critical outcomes. Pre-eclampsia showed a distinctive pattern among groups (Low: 3.3%, Middle: 17.2%, High: 0%, $P = 0.015$). Most notably, the incidence of abnormal pregnancy demonstrated a significant increasing trend across TATp2-1 tertiles (Low: 26.7%, Middle: 44.8%, High: 73.3%, $P = 0.001$), suggesting a potential association between TATp2-1 levels and adverse pregnancy outcomes.

Multivariate analysis

We listed the results of multivariate analyses in Table 2. Multivariate analysis revealed significant associations between TAT levels and the risk of abnormal pregnancy. While the TATp1 showed no significant association (adjusted OR = 0.97, 95%CI: 0.84–1.13, $P = 0.719$), the TATp2 demonstrated a significant protective effect (adjusted OR = 0.66, 95%CI: 0.53–0.83, $P = 0.0003$). Notably, the TATp2-1 exhibited an even stronger protective effect (adjusted OR = 0.62, 95%CI: 0.47–0.80, $P = 0.0004$).

Further stratified analysis revealed a significant dose-response relationship between TATp2-1 and abnormal pregnancy risk (P for trend = 0.0006). Compared to the low-level group, the high-level group showed a significantly reduced risk of abnormal pregnancy (adjusted OR = 0.07, 95%CI: 0.02–0.33, $P = 0.0007$), representing a 93% risk reduction. This association remained robust after controlling for potential confounders including age, education, number of pregnancies, BMI, and other relevant factors.

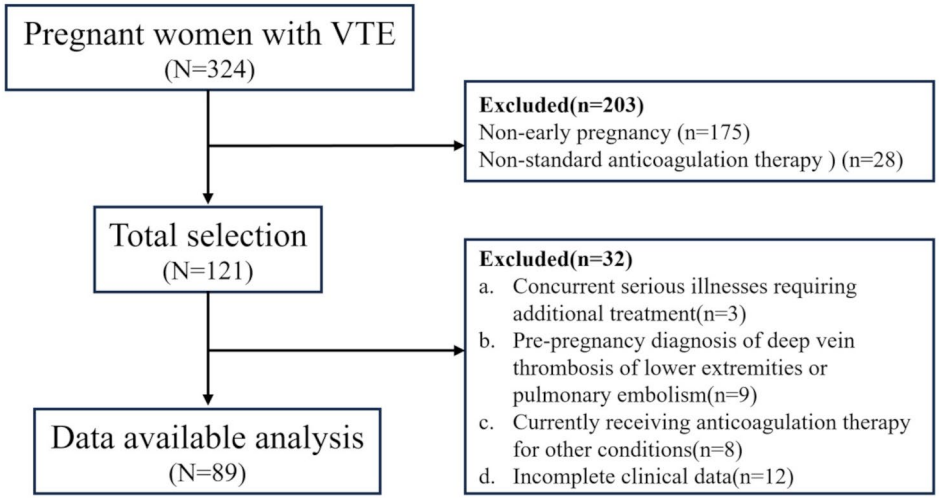

Fig. 1 The flowchart of patients' selection. VTE: Venous thromboembolism

Table 2 Results of multivariate analysis

Variables	Non-adjusted Model (OR,95%CI)	Minimally-adjusted Model (OR,95%CI)	Fully-adjusted Mode (OR,95%CI)
Continuous measures			
TATp1	1.00 (0.89, 1.13)	1.01 (0.89, 1.14)	0.97 (0.84, 1.13)
	P = 0.945	*P* = 0.924	*P* = 0.719
TATp2	0.76 (0.66, 0.88)	0.77 (0.66, 0.89)	0.66 (0.53, 0.83)
	P = 0.0003*	*P* = 0.0007	*P* = 0.0003
TATp2-1	0.73 (0.62, 0.86)	0.73 (0.61, 0.86)	0.62 (0.47, 0.80)
	P = 0.0002	*P* = 0.0003	*P* = 0.0004
TATp2-1 tertiles			
Low	Reference	Reference	Reference
Middle	0.45 (0.15, 1.33)	0.42 (0.13, 1.35)	0.38 (0.08, 1.75)
	P = 0.149	*P* = 0.146	*P* = 0.214
High	0.13 (0.04, 0.42)	0.13 (0.04, 0.42)	0.07 (0.02, 0.33)
	P = 0.0005	*P* = 0.0008	*P* = 0.0007
P for trend	0.0005	0.0007	0.0006

TATp1: Initial measurement was performed after VTE identified in first trimester, TATp2: second measurement was conducted during second trimester. TATp2-1: TAT change between TATp2 and TATp1.Non-adjusted Model: not adjusted for other covariant. Minimally-adjusted model: adjusted for age and education level. Fully-adjusted model: adjusted for age, education level, number of pregnancies, number of births, BMI, delivery methods, abnormal fetal position, gestational diabetes, gestational hypertension, pre-eclampsia, uterine fibroids, assisted reproduction, thyroid diseases, and thrombophilia. OR: odds ratio; CI: confidence interval

The analyses for non-linear relationship and the saturation or threshold effects

Smooth curve fitting analysis revealed complex association patterns between TAT levels and abnormal pregnancy risk (Fig. 2). The initial TAT measurement (TATp1) showed a mild non-linear relationship, though the overall trend was not significant. In contrast, the second TAT measurement (TATp2) demonstrated a marked downward trend, with abnormal pregnancy risk consistently decreasing as TAT levels increased from 4 to 18. Most notably, the change in TAT levels (TAT2-1) exhibited a significant non-linear association with abnormal pregnancy risk: remaining relatively stable when TAT2-1 was below − 2, then showing a sharp decline in risk when TAT2-1 exceeded − 2, before plateauing at values above 2, suggesting an optimal threshold for protective effects.

We analyzed the association between TAT levels and abnormal pregnancy risk using both linear and non-linear models in Table 3. The linear model showed no significant association between TATp1 and abnormal pregnancy risk (OR = 0.97, 95%CI: 0.84–1.13, *P* = 0.719). However, the TATp2 demonstrated a significant protective effect (OR = 0.66, 95%CI: 0.53–0.83, *P* = 0.0003), indicating a 34% risk reduction for each unit increase in TATp2.

Notably, the TATp2-1 not only exhibited a significant protective effect (OR = 0.62, 95%CI: 0.47–0.80, *P* = 0.0004) but also demonstrated a clear non-linear association (likelihood ratio test *P* = 0.004). Further threshold analysis revealed that when TATp2-1 exceeded − 2.87, the risk of abnormal pregnancy decreased significantly (OR = 0.37, 95%CI: 0.22–0.63, *P* = 0.0002), suggesting a stronger protective effect beyond this threshold.

The results of subgroup analyses

Subgroup analyses revealed distinct patterns of association between TAT levels and abnormal pregnancy risk across different populations in Table 4. Overall, both the TATp2 and TATp2-1 demonstrated significant protective effects (OR = 0.69, 95%CI: 0.57–0.85, *P* < 0.001; OR = 0.67, 95%CI: 0.53–0.84, *P* < 0.001, respectively).

In age-stratified analyses, although no significant interaction was observed (P interaction > 0.05), the protective effect was more pronounced in participants aged ≤ 35 years (TATp2: OR = 0.58, 95%CI: 0.41–0.82; TATp2-1: OR = 0.62, 95%CI: 0.45–0.86). Notably, thrombophilia status showed a marginally significant interaction (P interaction = 0.052), with stronger protective effects observed in patients with thrombophilia (TATp2: OR = 0.46, 95%CI: 0.26–0.82). BMI-stratified analyses indicated consistent protective effects across BMI levels (P interaction > 0.05), with slightly stronger effects in the lower BMI group (≤ 26 kg/m²).

Discussion

This retrospective cohort study investigated the association between plasma TAT level trends and adverse pregnancy outcomes in early pregnancy VTE patients. The study included 89 consecutive cases, implemented standardized follow-up protocols, and employed comprehensive analytical approaches including multi-model analysis and nonlinear association assessment. The results demonstrated that decreasing TAT was associated with adverse pregnancy outcomes, with this association becoming more pronounced when TAT changes exceeded − 2.87 (OR = 0.37, 95%CI: 0.22–0.63, *P* = 0.0002).

Our findings align with and extend previous research on TAT as a prognostic biomarker. Recent studies have demonstrated the value of dynamic TAT monitoring in various clinical settings. Huang et al. reported that TAT dynamics significantly predicted outcomes in VTE patients [9], while elevated TAT levels in both plasma and hematoma fluid strongly correlated with intracerebral hemorrhage severity [26]. A recent meta-analysis further established that elevated TAT levels were independently associated with poor outcomes in ischemic stroke patients [27]. Additionally, TAT level fluctuations have shown predictive value for acute kidney injury following pediatric cardiopulmonary bypass surgery [28], supporting the universal significance of TAT dynamics in disease prognosis. However, our study presents several unique contributions. Whereas previous research has primarily concentrated on establishing TAT reference ranges [29,

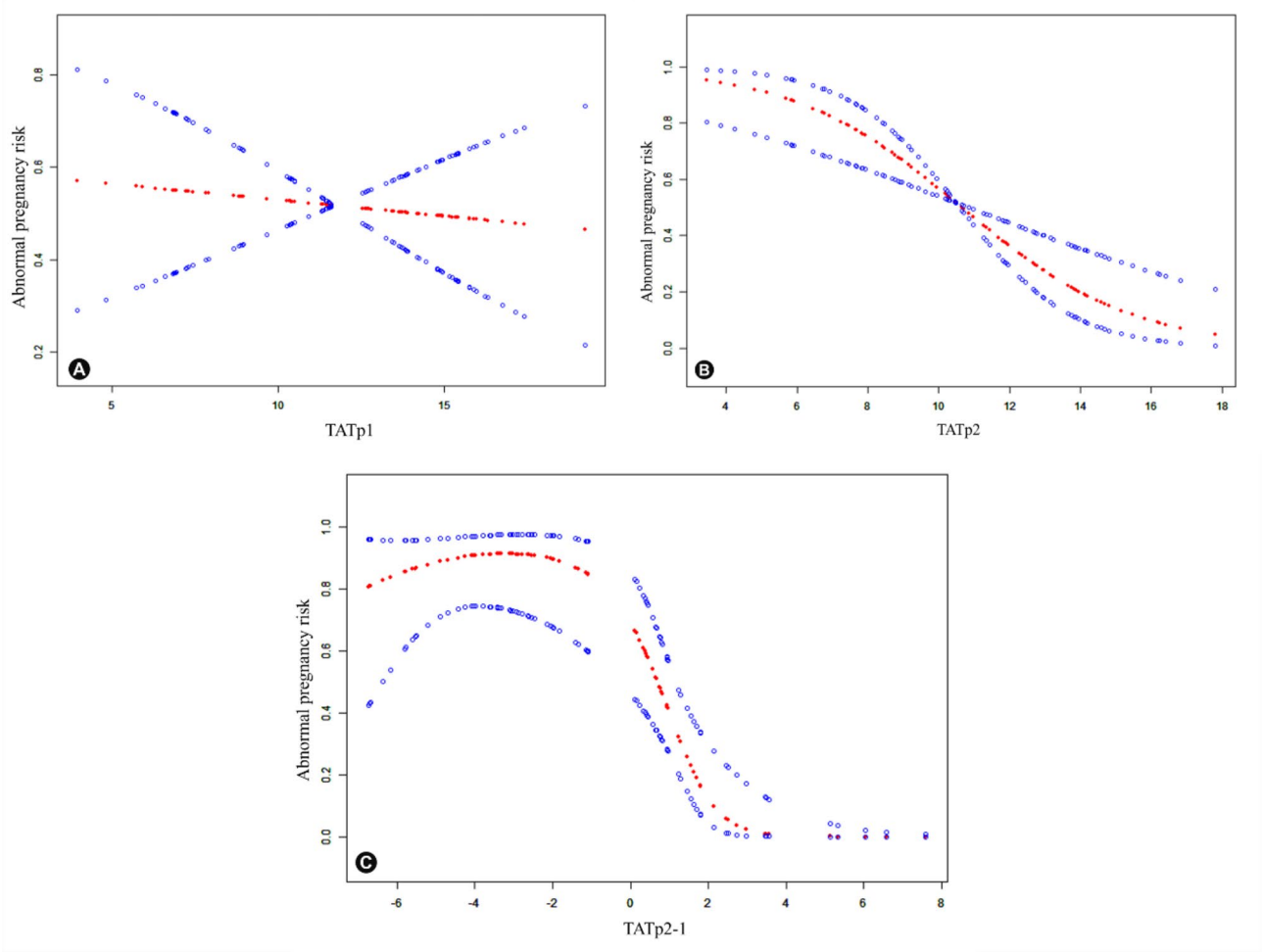

Fig. 2 Non-linear associations between TAT measurements and abnormal pregnancy risk. Smooth curve fitting analysis showing the relationship between abnormal pregnancy risk (y-axis) and TAT measurements (x-axis). Panel **A** shows the association with TATp1, Panel **B** with TATp2, and Panel **C** with TATp2-1. Red dashed lines represent the fitted curves, and blue dotted lines indicate 95% confidence intervals

30], our study was the first to identify a specific threshold value (-2.87) for TAT changes associated with adverse pregnancy outcomes. This novel finding, derived through comprehensive analytical approaches including nonlinear association assessment and threshold effect analysis, provides a concrete clinical reference point. Mechanistically, as Akiko et al. [31]. recently demonstrated, pregnancy-induced changes in coagulation represent a dynamic process, with TAT variations directly reflecting coagulation system activation status.

Our findings provide novel insights into the clinical management of VTE during early pregnancy. The newly established threshold value (-2.87) for TAT level changes represents not only an objective and possible predictor but also a significant step toward precision medicine. The physiological significance of this threshold warrants careful consideration. A marked reduction in TAT levels (below − 2.87) may reflect excessive anticoagulation that disrupts the delicate hemostatic balance required for optimal placental development and function. During normal pregnancy, controlled activation of coagulation is essential for proper placentation, with localized thrombin generation facilitating trophoblast invasion and vascular remodeling. Excessive suppression of this process, as indicated by substantial TAT reduction, may impair placental development and subsequently lead to adverse pregnancy outcomes.Furthermore, this threshold may represent a critical point at which the coagulation-anticoagulation balance shifts excessively toward anticoagulation, potentially compromising microvascular placental perfusion. Studies have demonstrated that both hypercoagulability and excessive anticoagulation can negatively impact pregnancy outcomes, suggesting an optimal range for hemostatic markers during pregnancy. Additionally, since TAT also interacts with inflammatory pathways, pronounced TAT reductions may reflect alterations in inflammatory responses that further contribute to placental dysfunction. The above mechanism is merely a

Table 3 Linear and non-linear associations between TAT levels and risk of abnormal pregnancy

Models and Parameters	TATp1	TATp2	TATp2-1
Linear Model			
OR (95% CI)	0.97 (0.84, 1.13)	0.66 (0.53, 0.83)	0.62 (0.47, 0.80)
P-value	0.719	0.0003	0.0004
Non-linear Model			
Threshold point (K)	8.94	15.82	-2.87
Below threshold			
OR (95% CI)	0.59 (0.29, 1.19)	0.68 (0.54, 0.86)	1.74 (0.82, 3.71)
P-value	0.141	0.001	0.149
Above threshold			
OR (95% CI)	1.11 (0.88, 1.41)	NA	0.37 (0.22, 0.63)
P-value	0.375	0.995	0.0002
LR test P-value	0.131	0.358	0.004

TATp1: Initial measurement was performed after VTE identified in first trimester, TATp2: second measurement was conducted during second trimester. TATp2-1: TAT change between TATp2 and TATp1.OR: Odds ratio; CI: Confidence interval; NA: Not applicable; LR: Likelihood ratio

All models were adjusted for age, education, number of pregnancies, number of births, BMI, delivery methods, abnormal fetal position, gestational diabetes, gestational hypertension, pre-eclampsia, uterine fibroids, assisted reproduction, thyroid diseases, and thrombophilia

hypothesis proposed by researchers and has not yet been further verified.

The clinical implications of this discovery are threefold: first, it provides quantifiable criteria for clinical decision-making, enabling more objective risk assessment; second, it facilitates timely identification of patients requiring treatment modifications; and third, it offers a reliable monitoring indicator for prognostic evaluation. Based on these findings, we propose several improvements to current clinical practice: First, for patients with TATp2-1 below the critical threshold of -2.87, we recommend considering adjusting the low molecular weight heparin (LMWH) dosage (typically reducing by 10-20%) to prevent excessive anticoagulation while maintaining therapeutic efficacy. Meanwhile, correlation studies with anti-Xa activity monitoring can be conducted to explore the lower therapeutic range for these patients. Second, we recommend implementing a more stringent monitoring protocol for high-risk patients (TATp2-1 below −2.87), measuring TAT levels every 4–6 weeks (rather than the usual quarterly monitoring) to promptly identify adverse trends and implement interventions quickly. Third, we propose a TAT-stratified management framework that categorizes patients into three risk levels: low risk (TATp2-1 > 0), continuing standard anticoagulation protocol with routine monitoring; moderate risk (-2.87 ≤ TATp2-1 ≤ 0), maintaining current dosage but increasing monitoring frequency; high risk (TATp2-1 < -2.87), implementing the aforementioned dose adjustments with enhanced monitoring. Fourth, given the association between TAT dynamic changes and adverse pregnancy outcomes, increased fetal monitoring should be considered for patients with unfavorable TAT trends. Finally, we advocate for a multidisciplinary approach, involving thrombosis specialists, obstetricians, and maternal-fetal medicine experts, to develop personalized management plans for patients with TAT levels below the critical threshold, ensuring optimal balance between anticoagulation efficacy and safety. However, implementation of these recommendations requires further evidence-based validation. Additionally, we recognize that implementing TAT testing in routine obstetric care requires careful consideration of several practical issues. Currently, TAT measurement through ELISA has become relatively mature. Sample collection requires specific handling procedures: blood must be

Table 4 Results of subgroup analysis and interaction analysis

Subgroups	*N*	TATp1 (OR,95%CI)	TATp2 (OR,95%CI)	TATp2-1 (OR,95%CI)
Age groups		P(interaction) = 0.902	P(interaction) = 0.196	P(interaction) = 0.203
≤ 35 years	60	0.97 (0.80, 1.18)	0.58 (0.41, 0.82)**	0.62 (0.45, 0.86)**
> 35 years	29	0.89 (0.33, 2.44)	0.80 (0.58, 1.10)	0.83 (0.58, 1.18)
Thrombophilia status		P(interaction) = 0.220	P(interaction) = 0.052	P(interaction) = 0.392
No	63	0.95 (0.79, 1.15)	0.75 (0.61, 0.93)**	0.70 (0.54, 0.91)**
Yes	26	0.83 (0.62, 1.11)	0.46 (0.26, 0.82)**	0.56 (0.33, 0.93)*
BMI categories		P(interaction) = 0.640	P(interaction) = 0.360	P(interaction) = 0.712
≤ 26 kg/m^2	38	0.90 (0.69, 1.19)	0.62 (0.44, 0.86)**	0.64 (0.46, 0.89)**
> 26 kg/m^2	51	1.01 (0.81, 1.27)	0.74 (0.58, 0.94)*	0.69 (0.51, 0.94)*
Overall effect	89	0.96 (0.83, 1.11)	0.69 (0.57, 0.85)***	0.67 (0.53, 0.84)***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

TATp1: Initial measurement was performed after VTE identified in first trimester, TATp2: second measurement was conducted during second trimester. TATp2-1: TAT change between TATp2 and TATp1

All models were adjusted for age, education, number of pregnancies, number of births, BMI, delivery methods, abnormal fetal position, gestational diabetes, gestational hypertension, pre-eclampsia, uterine fibroids, assisted reproduction, thyroid diseases, and thrombophilia (except when used as stratification variable)

collected in citrate tubes and processed within 2 h, with testing typically taking 3 to 4 h to complete, at a cost of approximately 70 RMB per test. However, consistency between laboratories remains a challenge as different commercial ELISA kits may produce varying reference ranges. Future research priorities should focus on: conducting large-scale multicenter prospective studies to validate our findings; exploring the combined utility of TAT with other biomarkers; develop instant TAT tests with faster turnaround times, validate simplified sample processing workflows, and establish a unified standardized system; and evaluating the long-term effectiveness of TAT-guided individualized treatment protocols. These efforts will further elucidate the clinical value of TAT in managing pregnancy-associated VTE.

Our study exhibits three principal methodological strengths. First, we implemented a rigorous standardized follow-up protocol with TAT measurements conducted at predetermined timepoints (early and mid-pregnancy), enhancing the reliability of our findings through systematic data collection. Second, we employed a comprehensive analytical strategy. Beyond conventional multivariate regression analysis, we innovatively incorporated nonlinear association assessments and threshold effect analyses, which not only elucidated the complex relationship between TAT level changes and pregnancy outcomes but also established, for the first time, a clinically applicable threshold. Notably, our subgroup analyses identified specific populations (patients under 35 years of age, those with thrombophilia tendencies, and those with BMI ≤ 26 kg/m^2) for whom TAT monitoring demonstrated superior predictive value, thereby providing more targeted clinical guidance. Furthermore, our detailed documentation of clinical characteristics and treatment processes, including anticoagulation protocols and dose adjustments, offered valuable insights into the relationship between TAT level changes and treatment responses.

Several important limitations of our study warrant careful consideration. First, the selective nature of our study population limits the generalizability of our findings. According to our inclusion/exclusion criteria, we excluded patients with autoimmune diseases, malignancies, and severe hepatic or renal dysfunction. These comorbidities might influence TAT level dynamics, and therefore, the applicability of our findings to these specific populations requires further validation. Second, as an inherent limitation of single-center studies, although we implemented standardized follow-up protocols and strict quality control measures, our results need verification through large-scale multicenter studies. Third, our study population consisted exclusively of Chinese Han participants, which significantly limits the applicability of our findings to other ethnic and racial groups. Therefore, extreme caution must be exercised when attempting to extrapolate these findings to non-Chinese or non-Han populations, and validation studies in multi-ethnic populations are necessary before clinical application in other populations. Furthermore, the observational nature of our study design only allows us to establish associations between TAT level changes and pregnancy outcomes, rather than determine causality. In addition, regarding the specific subtypes of thrombophilia, due to sample size limitations, we did not conduct stratified analysis or sensitivity analysis for these subtypes. However, in our preliminary stratified analysis, we observed a marginally significant interaction between the presence or absence of thrombophilia tendency and pregnancy outcomes. Therefore, we believe it is necessary to conduct more in-depth research for verification. Finally, while we adjusted for known confounding factors such as age, BMI, and underlying conditions in our statistical analyses, there might be unidentified confounders influencing our results, which warrants further investigation in future prospective studies.

Conclusions

The association between TATp2-1 and adverse pregnancy outcomes in early pregnancy VTE patients was non-linear. A threshold effect was observed with an inflection point of -2.87. When the TATp2-1 were below − 2.87, there was a significantly increased risk of adverse pregnancy outcomes.

Author contributions

Concept and design: TH Z, XM W and R Z; data collection and analysis: CY J, DX C, JF H, K C and TH C; drafting of the article: TH Z, XM W and R Z; critical revision of the article for important intellectual content: TH Z; study supervision: TH Z.All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study was approved by the Ethics Committee of Fujian Provincial Maternal and Child Health Hospital and strictly adhered to the tenets of the Declaration of Helsinki (IRB: No. 2024KY167).

Competing interests

The authors declare no competing interests.

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