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RESEARCH ARTICLE

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Application of thromboelastography in diagnosing normal pregnancies and pregnancies with complications

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Abstract

Background: This observational study aimed to compare the potential application of thromboelastography (TEG) in diagnosing women with normal pregnancy (NP) and women with threatened abortion (TA), missed abortion (MA), embryo arrest (EA), fetal death (FD), history of abnormal pregnancy (HAP), and antiphospholipid antibody syndrome (AA).

Methods: According to the relevant clinical criteria, patients were divided into groups, and their blood samples were subjected to TEG. Next, the parameters R, K, α-angle, MA, LY-30, G, and coagulation index (CI) were analyzed. Partial correlation analysis was used to analyze correlation between groups of data. LSD-t test and Dunnett's T3 test were used to analyze continuous variables. Ordinal categorical variables were compared using ordinal logistic regression analysis and estimate odds ratio of risk factors. A receiver operating characteristic (ROC) curve was constructed to detect the ability of TEG to recognize various parameters, and areas under the curve were compared using Delong's test for diagnosing pregnancy-related diseases.

Results: MA had a negative effect on the MA parameter in TEG; EA had a negative effect on the MA and G parameters; HAP had a negative effect on the CI parameter and a positive effect on the R parameter; AA had a negative effect on the CI parameter. Compared with that of the NP group, the G of the EA ($p = 0.014$) group and the CI of the TA ($p = 0.036$) MA ($p = 0.08$) EA ($p = 0.026$) HAP ($p = 0.000004$) and AA ($p = 0.002$) groups were reduced. In the ordinal logistic regression analysis, compared with that of the NP group, the high R value of the HAP group accounted for more than that of the NP group (OR = 48.76, $p = 0.001$); the high K value of the AA group accounted for more than that of the NP group (OR = 17.00, $p = 0.023$); the angle value distributions of the TA and AA groups were different from that of the NP group (OR = 3.30, $p = 0.039$; OR = 0.14, $p = 0.029$); the low MA value of the MA, EA, and HAP groups accounted for more than that of the NP group (OR = 0.16, $p = 0.03$; OR = 0.26, $p = 0.005$; OR = 0.11, $p = 0.008$); and the low CI value of the HAP group accounted for more than that of the NP group (OR = 0.09, $p = 0.005$). In the ROC analysis, there were no significant differences in the TEG parameters of pregnant women belonging

to the NP and TA, NP and MA, NP and EA, NP and FD, NP and HAP, and NP and AA groups ($p > 0.05$).

KEYWORDS
pregnancy, thromboelastography

1 | INTRODUCTION

During pregnancy, the coagulation system in women undergoes considerable changes to prevent bleeding.[1,2] If the coagulation system in pregnant women is not functioning optimally, incidents such as bleeding and miscarriage are prone to occur[3]; if the coagulation system in pregnant women is hyperfunctional, the risk of venous thrombosis is high.[4] It has been reported that in the presence of pregnancy complications such as fetal death (FD) and missed abortion (MA), the maternal blood coagulation function is impaired, posing a threat to the health of pregnant women.[5] Therefore, it is critical to perform coagulation-related laboratory tests on women during pregnancy.

At present, many indicators such as activated partial prothrombin time and prothrombin time are used to detect blood coagulation function in the body. However, these indicators can only detect changes in part of the blood coagulation function in the body and cannot completely assess coagulation function.[6] Thromboelastography (TEG), as a currently accessible laboratory test, can reflect the dynamic changes in the coagulation process and has high application value in evaluating platelet function.[7] Common TEG parameters are R, K, α-Angle, MA, LY-30, G, and coagulation index (CI). Such parameters influence the activity and function of coagulation factors and fibrinogen, and the function of platelet aggregation and the fibrinolytic system in the body. Evaluations to determine whether the patient's current coagulation status is normal.[8,9] The global TEG standard is applicable to the Asian population. At present, the reference ranges for normal values of each TEG parameter are as follows: R (5–10 min in the non-pregnancy period and 2–8 min in the pregnancy period), K (1–3 min in the non-pregnancy period and gestational period), α-angle (53°–72° in the non-pregnancy period and 60°–77° during pregnancy), MA (50–70 mm in the non-pregnancy period and 64–76 mm during pregnancy), LY-30 (0–7.5 in the non-pregnancy period and 0–3 during pregnancy), CI (−3–3 in the non–pregnancy period and 0–5 during pregnancy), and G (pregnancy and non-pregnancy values are 4.50–11.00d/sc).

TEG has been used extensively to monitor the coagulation function of patients after the administration of anticoagulant drugs and after percutaneous coronary artery therapy to evaluate the coagulation status of patients with postpartum hemorrhage and vaginal bleeding in late pregnancy.[10,11] The potential application of TEG in the diagnosis of pregnancy complications such as pre-eclampsia has been confirmed by previous studies.[12] However, no studies have confirmed the significance of each parameter in TEG in the clinical diagnosis of pregnant women with threatened abortion (TA), MA, embryo arrest (EA), fetal death (FD), history of abnormal pregnancy (HAP), and antiphospholipid antibody syndrome (AA). Therefore, this study evaluated the diagnostic value of changes in TEG parameters for the above-mentioned diseases.

2 | MATERIALS AND METHODS

2.1 | Subjects

Pregnant women who underwent routine prenatal check-ups at Huangshi Central Hospital during pregnancy were selected as the research subjects. The selection criteria for women with healthy pregnancy are as follows: 1. aged between 18 and 45 years; 2. no HAP; and 3. no history of abnormal blood coagulation. TA diagnosis criteria: 1. early or middle pregnancy; 2. a small amount of vaginal bleeding accompanied by lower abdominal pain; and 3. closed uterine orifice, intact fetal membranes, no pregnancy is excluded, and the size of the uterus is consistent with the gestational age. MA diagnosis criteria: the embryo has not been excreted after 2 months of stopping development. EA diagnostic criteria: when the gestational age is ≥6 weeks, as confirmed via B-ultrasound, either there is no gestational sac or the gestational sac is deformed or shrunken; the gestational sac is ≥4 cm but no fetal buds can be seen, and the fetal buds (head arm length) ≥4~5 mm with vaginal ultrasound revealing no fetal heartbeat. FD diagnostic criteria: 1. gestational age ≥20 weeks and 2. after ultrasound diagnosis, the fetal heart rate and fetal movement disappeared, and the skull collapsed. Diagnostic criteria for HAP: a history of abnormalities during pregnancy such as gestational diabetes and abnormal fetal growth and development in the uterus. AA diagnostic criteria: (1) thrombosis confirmed by ultrasound diagnosis, and vascular inflammation or a history of pregnancy events caused by placental insufficiency ruled out by histopathology; (2) after two or more laboratory examinations at an interval of more than 12 weeks, the standard enzyme-linked immunosorbent assay method confirmed either the presence of antiphospholipid or β2 glycoprotein I antibodies in blood samples or the presence of phospholipid anticoagulants in plasma, as listed in the International Thrombosis and Hemostasis Association lupus anticoagulant or phospholipid-dependent antibody standards. This study was approved by the hospital ethics committee, and all patients had signed an informed consent form.

2.2 | Methods

TEG was performed using a thromboelastometer BVCA-I (Bring Biology, China). A vacuum blood collection tube containing 3.2%

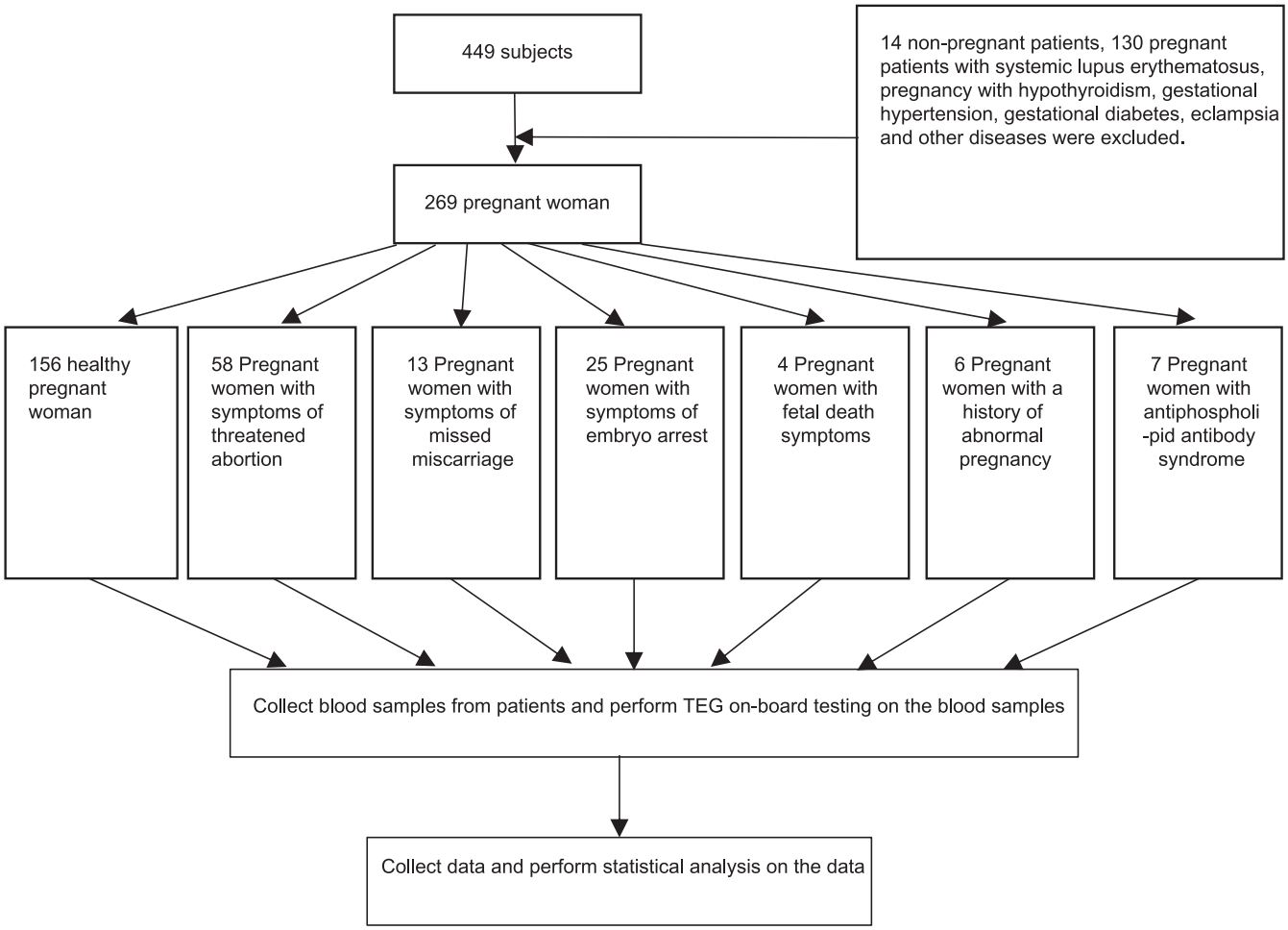


FIGURE 1 Research flow chart

TABLE 1 Patient characteristics

	NP ($n = 156$)	TA ($n = 58$)	EA ($n = 13$)	MA ($n = 25$)	FD ($n = 4$)	HAP ($n = 6$)	AA ($n = 7$)
Age,years	30 (20–41)	29 (21–43)	28 (20–37)	29 (24–43)	28.5 (28–34)	28.5 (25–37)	29 (26–33)

Note: Data are presented as *n* or median.

sodium citrate anticoagulant was used to collect 2 ml of whole blood from the participants; the blood was mixed with the anticoagulant by turning the tube upside down, and 0.34 ml blood sample was added to the reaction cup. Next, 20 μl of 0.2 mmol/L $CaCl_2$ solution was added to the reaction cup, and the resultant mixture was immediately tested on the machine. Sample-related parameters were determined after the experiment.

2.3 | Data analysis

Levene's test was used to determine the homogeneity of variance for different groups of continuous variables. Thereafter, the LSD-t test and Dunnett's T3 test were performed for continuous variables with homogeneous and uneven variance. Next, the test values of the samples were divided into three categories: low, normal, and high, according to the international standard reference range, and ordinal logistic regression was used to test the ordinal categorical variables. The receiver operating characteristic (ROC) curve analysis was used to preliminarily evaluate the significance of each experimental parameter in the thromboelastic diagram for clinical diagnosis by calculating the area under the curve (AUC) using Delong's test to further compare the differences between the ROC curves of each parameter. IBM SPSS Statistics 26 (IBM Corp, Armonk, NY, USA) was used to analyze and calculate all data and plot the ROC curve, and GraphPad Prism 5 was used to draw various graphs. The MedCalc software was used to analyze and compare the ROC curves of each TEG parameter under the same disease. The sample screening, data collection, and data analysis processes are shown in Figure 1.

TABLE 2 Correlation of the TEG parameters of each experimental group after excluding the effect of age

Analysis	TA	MA	EA	FD	HAP	AA
R	0.120	0.054	−0.013	−0.013	0.282④	0.110
K	0.062	0.126	0.079	−0.095	0.144	0.148
α-Angle	−0.073	−0.123	−0.093	0.108	−0.153	−0.143
MA	−0.088	−0.173①	−0.209②	0.058	−0.145	−0.154
LY-30	0.096	0.089	0.048	0.012	−0.063	−0.055
G	−0.072	−0.136	−0.183③	0.038	−0.133	−0.030
CI	−0.125	−0.150	−0.117	0.075	−0.267⑤	−0.179⑥

①P=0.025;
②P=0.005;
③P=0.014;
④P=0.000296;
⑤P=0.001;
⑥P=0.023.

3 | RESULTS

3.1 | Overall condition of patients

Samples and data were collected from pregnant women who came to Huangshi Central Hospital for prenatal check-ups from August 24, 2020, to November 05, 2021; the samples were screened and classified according to the aforementioned grouping method. Finally, the categorization of patients was as follows: 156 cases in the NP group, 58 cases in the TA group, 13 cases in the MA group, 24 cases in the EA group, four cases in the FD group, six cases in the HAP group, and seven cases in the AA group. The age data of the patients in each group are shown in Table 1.

3.2 | Data correlation analysis between groups

Partial correlation analysis was used to exclude the effect of maternal age on the analysis results, and then the correlation between the data of the NP group and those of other experimental groups was analyzed. The results are shown in Table 2. There was no correlation between the data of NP and TA, and NP and FD groups; MA had a negative effect on the MA parameter in TEG; EA had a negative effect on the MA and G parameters; HAP had a negative effect on the CI parameter and a positive effect on the R parameter; AA had a negative effect on the CI parameter.

3.3 | Comparison of TEG parameters of different groups

As shown in Figure 2F,G, compared with that of the NP group, the G of the EA ($p = 0.014$) group and the CI of the TA ($p = 0.036$), MA ($p = 0.08$), EA ($p = 0.026$), HAP ($p = 0.000004$), and AA ($p = 0.002$) groups were reduced.

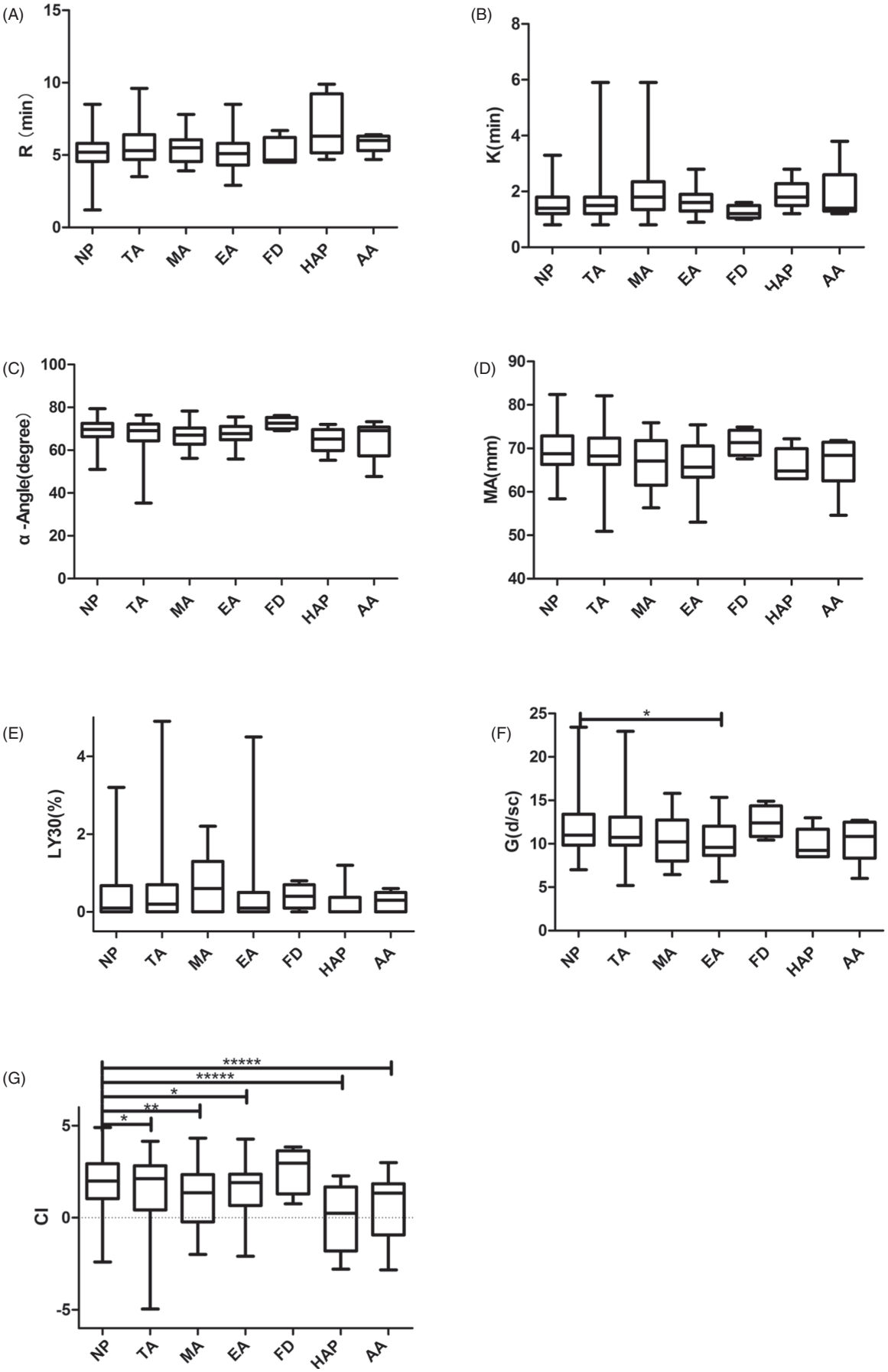
3.4 | Correlation analysis of TEG parameters as ordered categorical variables

According to the international reference value range, the TEG parameters are divided into three ordinal categorical variables: low, normal, and high (LY-30 is divided into two categories: normal and high). As shown in Figure 3A,B,C, D, G, the high *R* value of the HAP group accounted for more than that of the NP group (OR = 48.76, $p = 0.001$); the high *K* value of the AA group accounted for more than that of the NP group (OR = 17.00, $p = 0.023$); the angle value distribution of the TA, AA group is different from that of the NP group (OR = 3.30, $p = 0.039$; OR = 0.14, $p = 0.029$); the low MA value of the MA, EA, and HAP groups accounted for more than that of the NP group (OR = 0.16, $p = 0.03$; OR = 0.26, $p = 0.005$; OR = 0.11, $p = 0.008$); and the low CI value of the HAP group accounted for more than that of the NP group (OR = 0.09, $p = 0.005$).

3.5 | ROC analysis

To determine the application value of each TEG parameter in the diagnosis of pregnancy-related complications (including TA, MA, EA, FD, AP, and AA), we used ROC preliminary analysis and compared the AUC of each parameter. Subsequently, we used Delong's test to further compare differences between the ROC curves of each parameter. There were no significant differences in TEG parameters of pregnant women between the NP and TA, NP and MA, NP and EA, NP and FD, NP and HAP, and NP and AA groups ($p > 0.05$, see Figure 4).

FIGURE 2 TEG in each group of normal pregnancy (NP), threatened abortion (TA), missed abortion (MA), fetal arrest (EA), fetal death (FD), abnormal pregnancy history (HAP), and antiphospholipid antibody syndrome (AA). Box diagram of each parameter: *R* (1A), *K* (1B), angle (1C), MA (1D), LY-30 (1E), G (1F), and CI (1G). Figure citation: The author is based on the TEG test data from the Clinical Blood Transfusion Department of Huangshi Central Hospital from 2020.8 to 2021.11


(A)
R（min）
15
10
5
0
NP TA MA EA FD HAP AA
(B)
K(min)
8
6
4
2
0
NP TA MA EA FD HAP AA
(C)
α -Angle(degree)
100
80
60
40
20
0
NP TA MA EA FD HAP AA
(D)
MA(mm)
90
80
70
60
50
40
NP TA MA EA FD HAP AA
(E)
LY30(%)
4
2
0
NP TA MA EA FD HAP AA
(F)
G(d/sc)
25
20
15
10
5
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*
NP TA MA EA FD HAP AA
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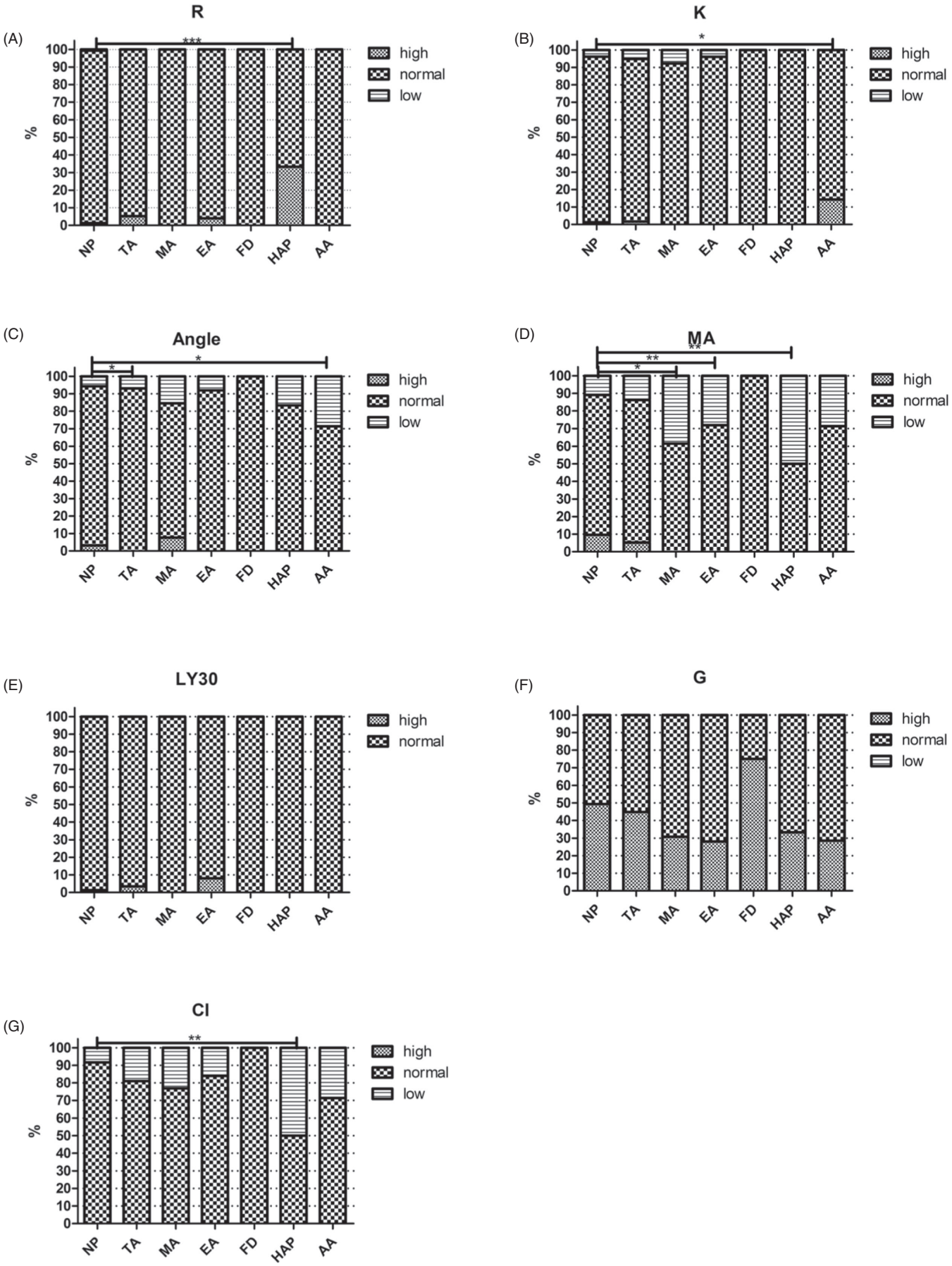

FIGURE 3 Normal pregnancy (NP), threatened abortion (TA), missed abortion (MA), fetal arrest (EA), fetal death (FD), abnormal pregnancy history (HAP), and antiphospholipid antibody syndrome (AA) in each group. TEG parameters R (3A), K (3B), angle (3C), MA (3D), LY-30 (3E), G (3F), and CI (3G) are used as stacked graphs for the analysis of ordered categorical variables

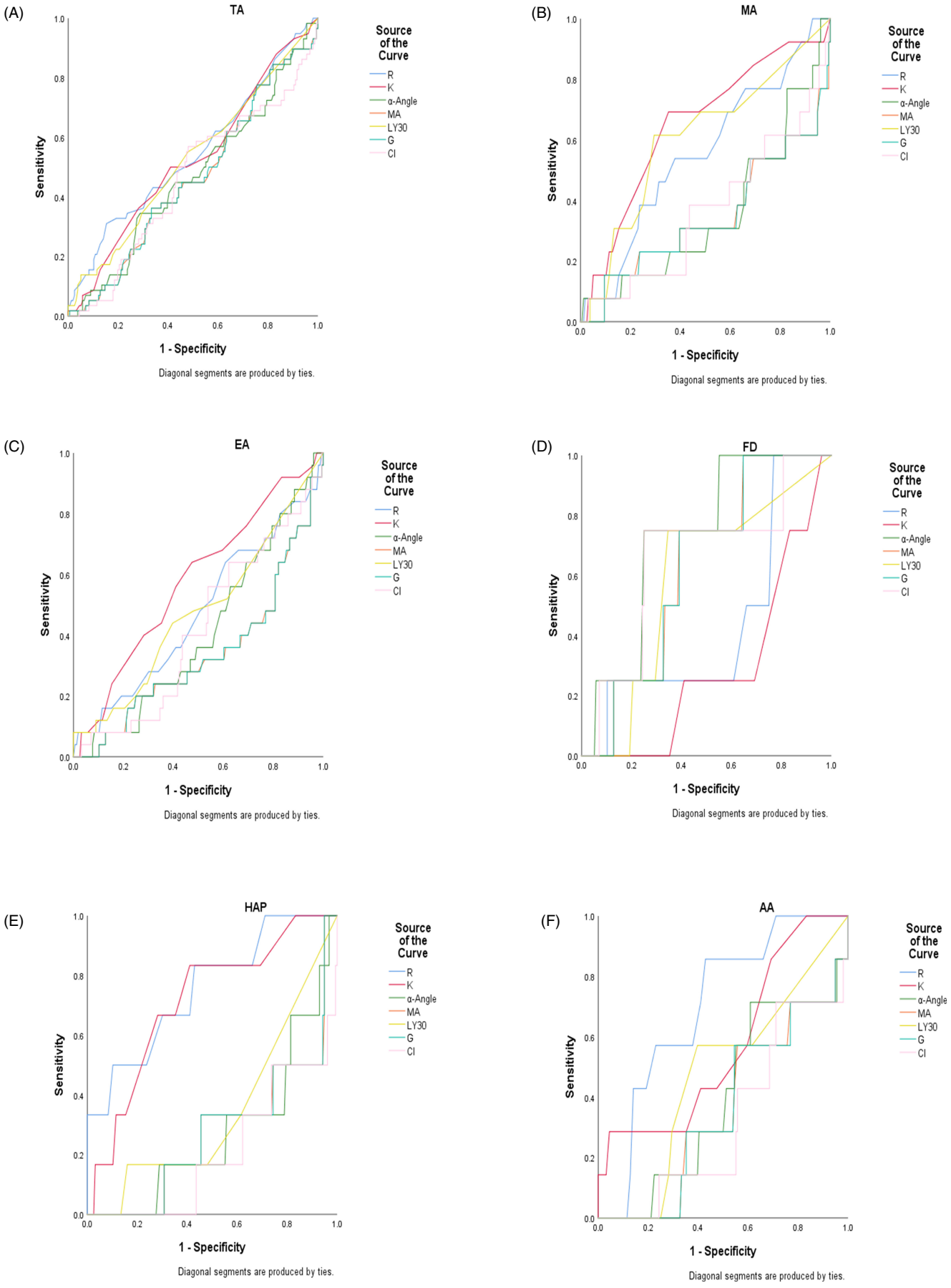

FIGURE 4 ROC analysis of the TEG parameters (R, K, Angle, MA, LY-30, G, and CI). Figure citation: The author is based on the TEG test data from the Clinical Blood Transfusion Department of Huangshi Central Hospital from 2020.8 to 2021.11

4 | DISCUSSION

Obstetric-related diseases, especially FD, may damage the coagulation function of the mother and cause bleeding.[13,14] Coagulation-related tests such as TEG can evaluate the coagulation function to predict the possibility of bleeding.[15,16] Previous studies have pointed out that changes in parameters such as R, K, and α-angle in TEG can reflect shifts in coagulation status during pregnancy and are related to pregnancy progression.[17,18] Therefore, it is of great importance to evaluate whether TEG can better distinguish NP from TA, MA, and FD.

In this study, we found that TEG parameters are different between some experimental groups and control groups. For example, the CI value of the TA group was decreased, and the ratio of the angle value lower than the upper limit of the normal reference value was higher than that of the NP group, indicating that the coagulation function is low, and there could be a problem of inadequate fibrin levels or function. Studies have shown a negative correlation between serum progesterone concentrations and early pregnancy outcomes,[19] and progesterone can promote thrombosis,[20] so that low progesterone concentrations may be the cause of reduced blood coagulation levels in TA patients. The CI value of the MA group was decreased, and the proportion of the MA value lower than the upper limit of the normal reference value was higher than that of the NP group, indicating that the patients may have low coagulation function due to low platelet count or function. As early as 1955, researchers pointed out that a dead fetus would adversely affect the coagulation function of pregnant women,[21] which is consistent with our findings. In the EA group, the G and CI values decreased, and the MA ratio was lower than the normal reference interval in the EA group, the MA value decreased, and the proportion was lower than the normal value reference interval. Yang et al. analyzed the villi of NP and EA patients and found that the gene expression levels of the coagulation cascade pathway were different.[22] In the MA group, the proportion of the MA value decreased, and values lower than the normal reference interval were greater, implying that either the function of platelets (or fibrinogen) was low or the platelet count (PC and fibrinogen) had decreased. Interestingly, Dankova et al. found that the number of platelets in normal pregnant women was lower than that in patients who underwent abortion; however, the average fibrinogen content was higher than that in patients who underwent abortion.[23] We found that compared with the participants in the NP group, the HAP group had more people with a slightly higher R value and higher than the upper limit of the reference value, a minor decrease in CI value, and a higher percentage of people with an MA value lower than the lower limit of the reference value. This was statistically significant, which indicates that either the activity of the coagulation factor was decreased or the coagulation factor was insufficient for HAP patients, and the platelet function was decreased. Many studies have reported that abnormal coagulation may be one of the important pathophysiological factors leading to abnormal pregnancy, including the consumption of coagulation factors,[24] which is consistent with our research results. In addition, the CI value of the AA group was low, which may be related to the patients receiving low-dose aspirin or low-molecular-weight heparin in advance of undergoing TEG testing. Regarding stillbirths, Muin et al. conducted a retrospective study on patients with in utero fetal death after a single birth and observed no significant difference in PC, PT, and other parameters,[25] which is consistent with our results. Unlike our non-significant TEG results, Ikeuchi observed that patients with TA suffered abortion caused by decreased plasma plasminogen concentrations and increased C1 inactivator levels, and finally speculated that the decrease in urokinase inhibitory activity that leads to an increase in villous tissue fibrin activity is the potential reason for the miscarriage.[26]

This study had a few limitations. First, the population size of the subjects in each group, especially the number of patients with FD, was relatively small; this needs to be further studied in the future. Second, due to certain conditions, no further follow-up of patients was conducted to understand the subsequent changes in their condition, which needs to be further improved. To conclude, this study confirmed that TEG has evident merit in the clinical diagnosis of TA, MA, EA, AA, and HAP and provides a reference for subsequent diagnosis of related diseases.

5 | CONCLUSION

TEG has a good clinical significance in the diagnosis of TA, MA, EA, AA, and HAP.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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