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Trimester-specific reference intervals for kaolin-activated thromboelastography (TEG®) in healthy Chinese pregnant women

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ABSTRACT

Objective: There has been little published work about the reference intervals of thromboelastography (TEG®) tests in pregnancy. Our aim was to establish the trimester-specific reference intervals of TEG tests for healthy pregnant women.

Methods: After excluding outliers, a total of 753 apparently healthy pregnant women aged from 19 to 44 years including 252 first trimester women, 340 second trimester women and 161 third trimester women were enrolled in our study. Non-fasting venous blood samples were collected. TEG tests were done on kaolin activated samples and processed on TEG 5000 Hemostasis Analyzer. Nonparametric 2.5th–97.5th percentile intervals were used to define the reference intervals.

Results: There were significant differences for TEG tests in pregnant women compared with non-pregnant women. The reference intervals for R, K, Angle, MA, Ly30 and CI were 4.1–10.4 min, 0.9–3.1 min, 53.6–75.9°, 46.1–69.8 mm, 0–10.7% and −5.5–2.5 respectively at first trimester; 3.9–9.7 min, 0.8–2.4 min, 56.7–78.0°, 49.8–72.1 mm, 0–9.7% and −3.7–2.9 at second trimester; 3.8–9.0 min, 0.8–2.5 min, 57.6–79.3°, 49.4–75.9 mm, 0–8.8% and −3.0–2.6 at third trimester.

Conclusions: We established trimester-specific reference intervals of TEG® tests for healthy pregnant women. It's critical to accurate assessment of global haemostatic status during pregnancy and in pregnancy complications.

1. Introduction

Pregnancy is a special physiological process for women. During pregnancy, the coagulation function is enhanced and the anticoagulation function is weakened. The haemostatic system creates a physiological hypercoagulable state, to meet the normal physiological need of pregnancy and protect the mother against peripartum haemorrhage [1–4]. The monitoring of coagulation and anticoagulation function during pregnancy is of great significance for the prevention, diagnosis and intervention of some obstetric complications such as obstetric haemorrhage and venous thromboembolism [5–7].

Common coagulation assays such as prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen (FIB) fail to give comprehensive information about the kinetics of clot formation, clot strength, the interactions among the clotting factors, platelet function and fibrinolysis. Thromboelastography (TEG®) offers an approach to assess the dynamic interaction of plasma clotting factors and platelets, from clot formation through its lysis [8]. The TEG analyzer using a small blood sample of whole blood, measures the interaction of platelets with protein coagulation cascade from the time of placing the blood in the TEG analyzer until initial fibrin formation, clot rate, strengthening, and fibrin-platelet bonding, to eventual clot lysis. Time, rate, strength, and stability of clot indicate whether the patient has normal, hypo-, or hypercoagulable state [9–12].

The physiological changes in haemostatic system during pregnancy may affect the biochemical parameters [13,14]. The laboratory reference intervals for the TEG tests based on non-pregnant healthy subjects are inappropriate for pregnant women, which may hinder the

Abbreviations: TEG, thromboelastography; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen

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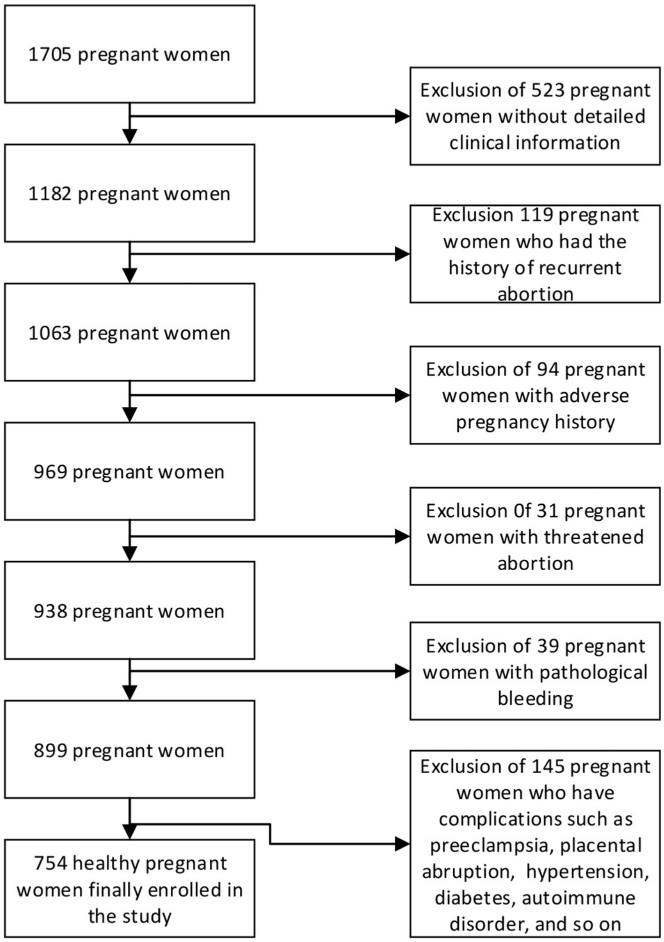

Fig. 1. The procedure for selection of the healthy pregnant women.

accurate diagnosis and treatment of haemostatic disorders during pregnancy. Consequently, it is significant to establish the specific reference interval of TEG tests for pregnant women [15,16].

There are some published data on the reference intervals of TEG tests [5,17–20]. The current studies on pregnant women only assess a certain period (early pregnant, late pregnant or peripartum), and also use ROTEM not TEG [21–23]. In this study, our main aim was to establish the trimester-specific reference intervals in healthy pregnant women for TEG tests.

2. Materials and methods

2.1. Subjects

This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University.

A total of 1705 pregnant women were enrolled from outpatients of the First Affiliated Hospital of Zhengzhou University for prenatal care between June 2017 and January 2019. To select apparently healthy pregnant women, a majority of pregnant women no detailed clinical information were excluded first. Then we adopt the following exclusion criteria: acute or chronic infections, tumor, cardiovascular, renal, hepatic or respiratory disease, autoimmune disorder, a history of thromboembolic or clotting disorders, pathological bleeding, recurrent abortion (≥ three times), preeclampsia, placental abruption, threatened abortion, hypertension, or diabetes [13–16,24]. 951 pregnant women were excluded and finally 754 apparently healthy pregnant women (aged 19–44 years) were included in our study. The stepwise exclusion was depicted in the Fig. 1. Enrolled pregnant women were divided according to their gestational weeks into three groups: first (1–12 weeks), second (13–27 weeks) and third trimester (28–40 weeks). A total of 145 healthy non-pregnant women, aged 18–45 were recruited as control. The exclusion criteria of non-pregnant women were the same as that of pregnant women. All the recruited people in this study are Chinese Han.

3. Methods

Non-fasting venous blood samples were collected in 0.109 mol/L trisodium citrate tubes (Becton Dickinson, Plymouth, UK) containing one part trisodium citrate with nine parts venous blood for TEG tests. All analyses were performed immediately with fresh samples. Samples were transported from the site of blood withdraw to the laboratory every hour by trained workers, and analyzed within 1 h after blood collection by two defined skilled operators to reduce the possibility variability.

For each TEG test, pipette 1 mL citrated whole blood sample into a kaolin tube (Haemonetics Corporation, Braintree, USA) and make it flow down the wall. Cap and mix blood with the kaolin by gentle inversion five times. 340 μL kaolin-activated blood was pipetted into a plain cup in which 20 μL 0.2 mol/L $CaCl_2$ was pre-pipetted, and analyzed using the TEG 5000 Hemostasis Analyzer System (Haemoscope Corporation, Niles, USA). In TEG system, a cylindrical plain cup that holds the blood is oscillated through an angle of 4°45′. A pin is suspended in the blood by a torsion wire and is monitored for motion. The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal leading to a graphical output (Fig. 2).

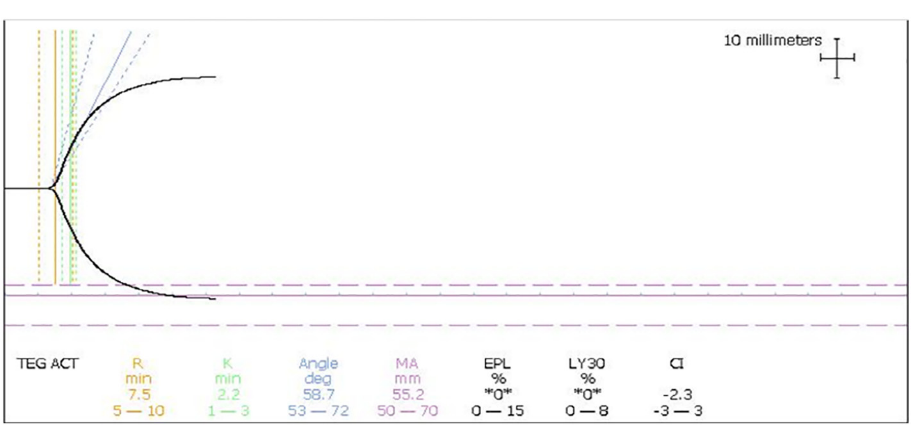

Fig. 2. An example thromboelastography trace of healthy pregnant woman in the first trimester. Reaction time (R; R is the period of time of latency from the time that the blood was placed in the TEG analyzer until the initial fibrin formation. This represents the enzymatic portion of coagulation.), clot formation time (K; K is a measure of the speed to reach a certain level of clot strength. This represents clot kinetics.), alpha angle (Angle; Angle measures the rapidity of fibrin build-up and cross-linking. This represents fibrinogen level.), maximum amplitude (MA; MA is a direct function of the maximum dynamic properties of fibrin and platelet. This represents platelet function.), percentage lysis at 30 min (LY30; LY30 measures the rate of amplitude reduction 30 min after MA. This represents clot lysis.), Coagulation Index (CI; CI that is derived from the R, K, MA and Angle describes the overall coagulation.)

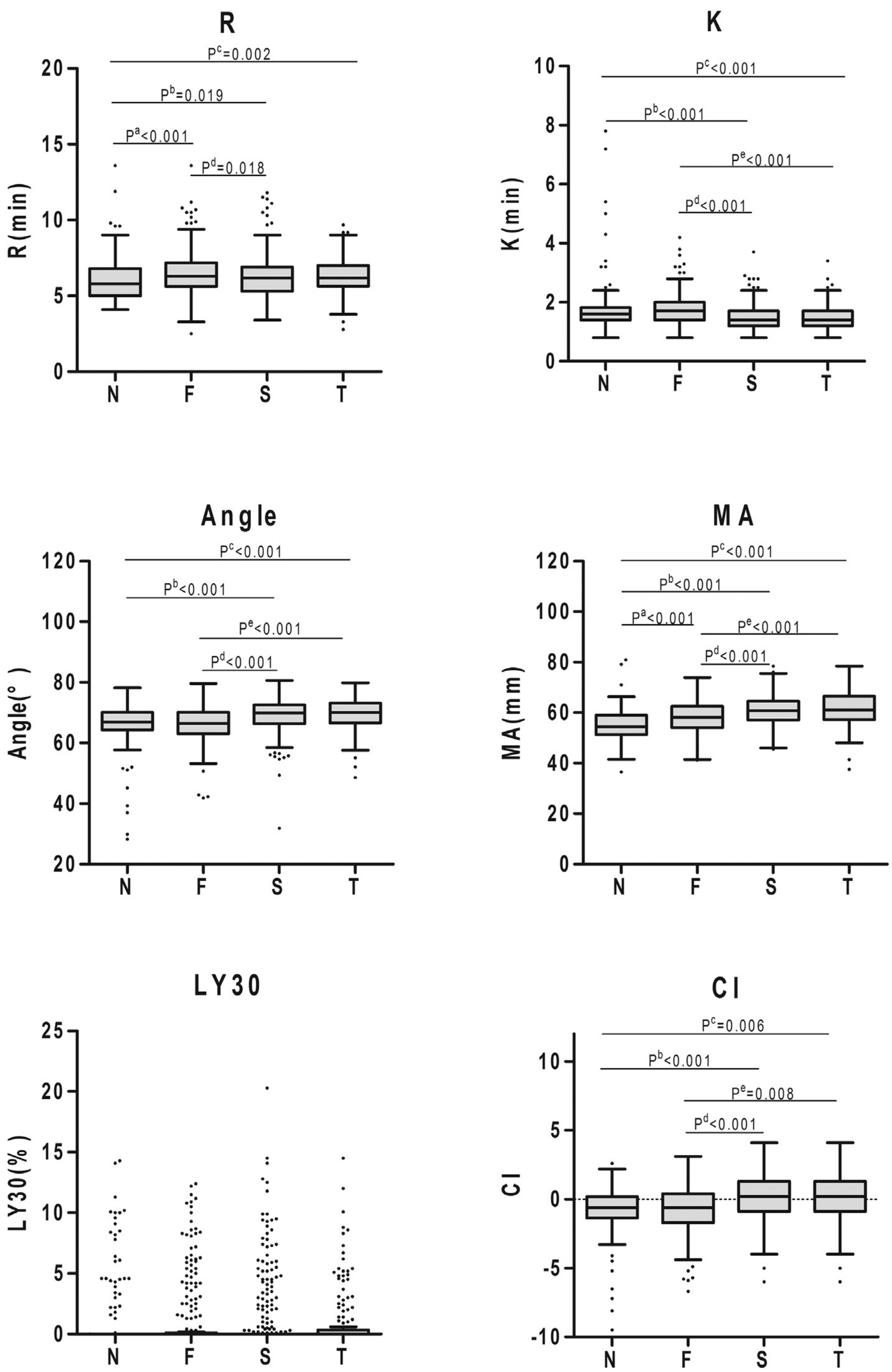

Fig. 3. The comparison of TEG parameters among the first, second, third trimester pregnant women and non-pregnant women. N, non-pregnant women; F, first trimester; S, second trimester; T, third trimester. The upper edge and the lower edge of the box represent the 25th percentile to the 75th percentile respectively. The bar in the middle of box plot represents the median value. The upper horizontal line and the lower horizontal line of the box plot indicate the 75th percentile plus 1.5 times interquartile distance (1.5IQR) and 25th percentile minus 1.5IQR respectively. Circles indicate values that greater than 75th percentile plus 1.5IQR or less than 25th percentile minus 1.5 IQR. P^a: N vs F; P^b: N vs S; P^c: N vs T; P^d: F vs S; P^e: F vs T.

The TEG trace generates a lot of quantitative parameters which include reaction time (R), clot formation time (K), alpha angle (Angle), maximum amplitude (MA), percentage lysis at 30 min (LY30), coagulation Index (CI), estimated Percent Lysis (EPL), projection of MA (PMA), time to MA (TMA), amplitude or clot strength at a specific time (A), shear elastic modulus strength (G and E), thrombodynamic index (TPI). R, K, Angle, MA, LY30 and CI are widely accepted. While EPL, PMA, TMA, A, G, E and TPI are only proposed by the manufacturer. Therefore, we analyze these widely used parameters (R, K, Angle, MA, LY30 and CI) in this study.

3.1. Statistical analysis

All data were analyzed with IBM SPSS statistics 19.0 software (IBM, NY, USA). The normality of the data was tested using the Kolmogorov–Smirnov test. Outliers were removed using Dixon test as follows: D is the absolute difference between an extreme observation (large or small) and the next largest (or smallest) observation, and R is the range of all observations, including extremes. If the value of D is equal to or greater than one-third of the range R, the extreme observation is deleted. According to the recommendation by Clinical Laboratory and Standards Institute (CLSI) C28-A3, the reference intervals were defined by nonparametric 95th percentile intervals (2.5th and 97.5th percentiles) [25,26].The 90% confidence intervals for reference

Table 1
The reference intervals (2.5th & 97.5th percentiles) with 90% confidence intervals (in brackets below) for TEG of trimester-specific pregnant women and non-pregnant women.

	First trimester	Second trimester	Third trimester	Non-pregnant
R (min)	4.1–10.4 (3.6–4.2) (9.4–10.8)	3.9–9.7 (3.8–4.2) (8.8–10.8)	3.8–9.0 (3.3–4.4) (8.4–9.2)	4.1–10.6 (4.1–4.2) (9.1–13.6)
K (min)	0.9–3.1 (0.8–1.1) (2.8–3.5)	0.8–2.4 (0.8–0.8) (2.3–2.8)	0.8–2.5 (0.8–0.8) (2.3–2.8)	1.1–5.2 (0.9–1.2) (3.3–7.2)
Angle (°)	53.6–75.9 (45.4–55.4) (74.9–77.0)	56.7–78.0 (55.5–59.8) (77.7–79.6)	57.6–79.3 (52.3–59.5) (77.4–79.6)	38.4–76.4 (29.9–51.6) (72.7–76.7)
MA (mm)	46.1–69.8 (44.6–47.8) (68.6–70.9)	49.8–72.1 (48.5–51.5) (70.7–73.4)	49.4–75.9 (41.4–50.7) (74.3–76.9)	46.3–65.2 (41.5–47.0) (64.4–79.2)
LY30 (%)	0–10.7 (0–0) (8.5–11.4)	0–9.7 (0–0)(8.3–12.5)	0–8.8 (0–0) (6.7–12)	0–10.6 (0–0) (8.6–14.3)
CI	−5.5–2.5 (−5.9 to −3.9) (2.2–2.6)	−3.7–2.9 (−3.9 to −2.9) (2.6–3.4)	−3.0–2.6 (−5.4 to −2.4) (2.2–2.7)	−7.5–1.9 (−9.5 to −4.8) (1.6–2.6)

R, reaction time; K, clot formation time; Angle, alpha angle; MA, maximum amplitude; LY30, percentage lysis at 30 min; CI, coagulation index.

limits were calculated. Nonparametric tests Mann-Whitney U and Kruskal-Wallis H were used to compare the difference among groups. $P < 0.05$ was considered statistically significant.

4. Results

After excluding outliers, a total of 753 apparently healthy pregnant women including 252 first trimester women (aged 19–42 years), 340 second trimester (aged 19-43 years) women and 161 third trimester women (aged 19–44 years) were enrolled in our study.

The Kolmogorov–Smirnov test indicated that the distribution of R, K, Angle, MA, LY30 and CI were not in normally distributed. Therefore, we used nonparametric tests to compare the difference among groups. The values of R, K, Angle, MA and CI showed significantly differences between the pregnant women and non-pregnant women ($P < 0.001$, $P < 0.001$, $P = 0.001$, $P < 0.001$ and $P = 0.001$). We observed a significant decrease in the value of R and K ($P = 0.058$, $P < 0.001$) and a significant increase in Angle, MA and CI values (all the three $P < 0.001$) from the first trimester to the third trimester. The values of K, Angle, MA and CI showed significantly differences between the pregnant women in the first and second trimester (For K, Angle, and MA $P < 0.001$; for CI, $P = 0.008$). While no significant differences were observed in the value of LY30 among the three groups ($P = 0.523$). The comparisons of the R, K, Angle, MA, LY30 and CI were showed in Fig. 3.

The reference intervals and 90% confidence intervals of TEG assay for pregnant women at first, second and third trimester and non-pregnant women were list in Table 1.

5. Discussion

TEG was invented by Harter in 1948 and applied to clinical practice in the 1980s. It was widely used to monitor coagulopathy and anticoagulant therapy in liver transplantation and cardiac surgery and guide intraoperative transfusion. TEG was used to assess the haemostatic disorders in obstetric complication until the early 1990s [27]. It is a point-of-care test and easy to perform. Although widely using TEG in obstetrics remains a need for further large, multicenter, and more high-powered studies to generate evidence regarding clinical outcomes [28]. Literatures have reported several potential areas for using TEG in obstetrics, such as guiding transfusion therapy in postpartum haemorrhage, assessing the anticoagulant effect of low molecular weight heparin during pregnancy, guiding the treatment of disseminated intravascular coagulation, assessing the effect of amniotic fluid on coagulation function in pregnant women, monitoring coagulation in pre-eclampsia, and predicting severe pre-eclampsia during pregnancy [28–36]. Pregnancy reference intervals should always be used when assessing results of TEG in pregnancy.

In this study, we studied the differences of TEG parameters in different pregnancy periods, and established the trimester-specific reference intervals for TEG assay. The values of R, K, Angle, MA and CI showed significant differences between pregnant women and non-pregnant women. There were significant differences for R, K, Angle, MA and CI among the pregnant women in the first, second and third trimester. Compared with pregnant women in the first trimester, we observed a lower K value and higher Angle, MA and CI value both in the second and third trimester. The r value showed difference only between the first and second trimester. While no differences of TEG parameters were observed between the second and the third trimester.

Della Rocca et al. [37] and Antony et al. [38] reported the TEG results in normal pregnancy both gestational age > 37 weeks. The values of R, K and Angle in both studies were similar with the third trimester pregnant women in our study, while the MA value were higher and LY30 were lower than our study. Different of gestational ages and activators (28–40 weeks, kaolin-activated blood in our study; > 38 weeks, without activators in Della Rocca's study; and > 37 weeks and celite-activated in Antony study) may be the main cause of the differences. The third trimester pregnant women in our study showed a higher R value and a lower MA value compared with Davies's study [5] and Polak's study [39]. While the value of K and Angle was similar. In Davies's study, the pregnancy women were present for induction of labor or elective caesarean delivery, and TEG tests were carried out on TEG 3000 analyzer with celite-activated blood. These differences may contribute to the differences in results between us. According to CLSI C28-A3 guideline, a minimum of 120 healthy subjects are required to establish 95% reference intervals for each subgroup. In the laboratory statistics, greater statistical power can be obtained with results from larger population. In Polark's study, the reference intervals were established with 60 third trimester women. The reference intervals in our study were established with 161 third trimester women. Therefore, the results of our study were more representative. The race difference and regional disparity in the two studies may also contribute to the difference in results. The values of R, K, MA, LY30 and CI in Macafee's study were higher than the third trimester pregnant women in our study, while the Angle was lower compared with our study [24]. The reference populations in Macafee's study were pregnant women undergoing caesarean section under spinal anaesthesia, which may be the main reason for the difference between the results of Macafee's study and our study. The results of R, K and CI in our study showed a decreasing trend than the normal reference intervals provided by the manufacturer. While the Angle, MA and LY30 showed an increasing trend. Using the normal reference intervals based on normal non-pregnant people to assess pregnant women haemostatic status may lead to misjudgment. A single pregnant reference interval will be too simplified to prevent the interpretation of the TEG results in different conditions. Therefore, each laboratory should establish a reference interval suitable for the characteristics of the population in the region. It is significant to establish the trimester specific reference intervals for pregnant women. The limitation of our study was that we didn't have access to the healthy postpartum women. Therefore, we were unable to compare the values during pregnancy with the postpartum women. Further studies on the reference intervals of TEG tests for different population are needed.

In conclusion, there were significant differences for R, K, Angle, MA and CI between pregnant women and non-pregnant women. We established trimester-specific reference intervals of TEG ® tests for healthy pregnant women. It's critical to accurate assessment of global haemostatic status during pregnancy using TEG®. The trimester-specific reference intervals will be useful for physicians to make exact medical decision and appropriate medical intervention, as the reference intervals are significantly different between the pregnant and non-pregnant population.

Declaration of competing interest

All authors declare no potential conflicts of interest.

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