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Trimester-specific coagulation and anticoagulation reference intervals for healthy pregnancy

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ABSTRACT

Background: Due to the normal physiological need of pregnancy and childbirth, the haemostatic system of pregnant women is different from that of healthy non-pregnant women. The aim of this study was to establish trimester-specific reference intervals of coagulation screening tests and thrombophilia markers in pregnancies without complications of females with Han ethnicity from North China.

Methods: In total 744 Han healthy pregnant women (first trimester 207 cases, second trimester 222 cases and third trimester 315 cases) and 121 healthy non-pregnant women were recruited in North China. Eight tests—activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (Fib), D-Dimer, antithrombin (AT), protein C (PC) and free protein S (fPS)—were processed on ACL TOP automated coagulation analyzer. The non-parametric 2.5th–97.5th percentiles reference intervals were calculated to establish trimester-specific reference intervals.

Results: The reference intervals for APTT, PT, TT, Fib, D-Dimer, AT, PC, and fPS at first trimester were 26.4–41.9 s, 9.7–12.5 s, 11.7–17.0 s, 2.38–4.44 g/L, 0.01–0.31 μg/mL, 72–120%, 29–150%, 21–143%, respectively. At second trimester, the reference intervals were 24.4–35.8 s, 8.5–13.2 s, 10.0–16.0 s, 2.40–5.97 g/L, 0.05–0.73 μg/mL, 68–125%, 20–138%, 24–155%, respectively. At third trimester, the reference intervals were 25.6–34.9 s, 8.6–12.4 s, 11.1–15.5 s, 2.79–5.91 g/L, 0.14–2.82 μg/mL, 56–119%, 20–134%, 17–140%, respectively. From the first trimester to the third trimester, APTT, PT and TT presented shortened trends, Fib and D-Dimer presented increasing trends, AT, PC and fPS activity presented decreasing trends, respectively.

Conclusions: The trimester-specific reference intervals of coagulation screening tests and thrombophilia markers in pregnancies without complications of females with Han ethnicity from North China are presented in this study, which may provide effective evidence for doctors to accurately diagnose and treat the disease during pregnancy.
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1. Introduction

The determination of reference intervals is the key step of laboratory testing, which is important for clinicians to make an accurate evaluation and decide whether patients need further examinations or treatments [1,2]. Pregnancy is a special physiological process of women. Due to the normal physiological need of pregnancy and childbirth, the haemostatic system creates a physiological hypercoagulable state [3,4] – the relative increase in blood coagulation function, but the relative decrease in blood anticoagulation function. These changes of pregnant women are different from those of non-pregnant women. So, the reference intervals of coagulation screening tests and thrombophilia markers based on non-pregnant healthy women are inappropriate for pregnant women, which even may interfere with the accurate diagnosis or effective treatment of disease during pregnancy. Therefore, it is important to establish the specific reference intervals of coagulation screening tests and thrombophilia markers for healthy pregnant women.

There have been some studies about coagulation function of normal pregnant women, but most of these studies are only for certain stages of pregnancy, most of these just include fewer coagulation tests, and most of these are mainly about white people [4,5,6]. However, there are some differences in different trimesters of pregnancy. So, trimester-specific reference intervals are essential for the accurate diagnosis of haemostatic status during pregnancy [7,8]. Currently, there have been few comprehensive large studies on trimester-specific reference intervals of coagulation and anticoagulation tests in Han pregnant women of the North China.

Therefore, in this study, we report trimester-specific reference intervals of coagulation screening tests and thrombophilia markers by Han healthy pregnant women in the north of China.

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2. Materials and methods

2.1. Subjects and samples

744 pregnant women aged 21–47 years were enrolled from outpatients and inpatients of Peking University Third Hospital, from 2014 to 2016. Overall pregnant women are Han ethnicity in North China (including of Shandong province, Beijing Municipality, Tianjin Municipality, Hebei province, Shanxi province, Jilin province, and Inner Mongolia Autonomous Region). Exclusion criteria consisted of the following: history of recurrent abortion (≥3 times), preeclampsia and placental abruption, history of venous thrombosis or pathological bleeding, hereditary or acquired thrombophilia, autoimmune disorder, tumors, diabetes, cardiopathy, acute or chronic infection, chronic nephropathy. All 744 pregnant women were assigned to 3 groups by the number of gestational weeks: First trimester = 1–12 weeks, Second trimester = 13–27 weeks, Third trimester = 28–40 weeks. A total of 121 healthy non-pregnant women aged 20–49 years were also recruited in this study. The exclusion criteria of non-pregnant women were the same as that of pregnant women. This study conformed to the CLSI (Clinical Laboratory Standards Institute) document CA28-A3c [11], and the tests included prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), fibrinogen (Fib), D-Dimer, and the activity of free protein S (fPS), protein C (PC) and antithrombin (AT). This study was approved by the Hospital Research and Ethical committee. Every participant provided informed consent before any study procedures were undertaken.

Blood samples were collected by venipuncture of an antecubital vein into vacuum tubes (Becton Dickinson Medical Devices Co Ltd., Franklin Lakes, New Jersey) containing 1:9 volume of 0.109 mol/L sodium citrate.

2.2. Laboratory instruments

All assays were performed on an automated coagulation analyzer (ACL TOP®, Instrumentation Laboratory, Spain). These tests were detected according to standard operating procedures (SOP) of the instrument.

2.3. Reagents

Test	Method	Reagent
APTT	Clotting time method (by turbidimetry)	SynthASil kit (Instrumentation Laboratory, Spain).
PT	Clotting time method (by turbidimetry)	RecombiPlasTin 2G kit (Instrumentation Laboratory, Spain).
TT	Clotting time method (by turbidimetry)	Thrombin Time kit (Instrumentation Laboratory, Spain).
Fibrinogen level	Clauss method	Fibrinogen-C XL kit (Instrumentation Laboratory, Spain).
D-Dimer level	Latex enhanced immunoassay	D-Dimer HS kit (Instrumentation Laboratory, Spain).
PC	Chromogenic assay	Protein C (Instrumentation Laboratory, Spain).
fPS	Clotting time method (by turbidimetry)	ProS Kit (Instrumentation Laboratory, Spain).
AT	Chromogenic assay	Liquid Antithrombin kit (Instrumentation Laboratory, Spain).

2.4. Statistical analysis

Statistical analyses were performed using SPSS Version 16.0 software. The ages of subjects and the gestational weeks of pregnancy were presented as the mean ± SD. The 2.5th–97.5th percentile reference intervals [12] were defined for all parameters. The D/R ratio by Dixon [11] was used to exclude outliers, but it didn't detect any data unless biological reasons or clear analytical could be demonstrated. Statistical comparisons were tested with Mann-Whitney U and Kruskal-Wallis tests. A two-tailed P-value <0.05 was considered significant.

Table 1
Characteristics of the pregnant and non-pregnant women.

	Number	Age (years)	Gestational age (weeks)
Non-pregnancy	121	32 ± 7	–
Pregnancy			
First trimester	207	31 ± 4	8.00 ± 2.50
Second trimester	222	32 ± 4	21.00 ± 4.25
Third trimester	315	30 ± 3	33.00 ± 3.50

3. Results

Nonparametric trimester-specific reference intervals were established by the data of 744 healthy pregnant women. The ages of subjects and the gestational weeks were described in Table 1. There were no significant difference of ages between non-pregnant women and pregnant women. There were also no difference among maternal ages at first trimester, second trimester and third trimester. The median and 2.5th–97.5th percentile reference intervals of coagulation screening tests and thrombophilia markers at first trimester, second trimester, third trimester and non-pregnant women are listed in Table 2.

From the group of the first trimester to the third trimester, The comparison of APTT, PT, TT, D-Dimer, Fib, AT, PC, fPS were showed in Figs. 1–3, respectively.

4. Discussion

Laboratory detection results are usually compared with their reference intervals before clinicians make medical diagnoses or management decisions [13]. During pregnancy, because of the physiological need of pregnant women and fetuses, there are some differences in haemostatic system [3,4,14]. Thus, providing reliable and accurate reference intervals of healthy pregnant women is very important. This study set out to establish trimester-specific reference intervals for PT, TT, APTT, Fib, D-dimer, PC, fPS and AT in the healthy pregnant women. We selected every sample carefully and did our best to ensure each trimester was represented by a certain number samples. Finally, 744 samples were obtained—first trimester 207 cases, second trimester 222 cases, third trimester 315 cases, moreover, there were no differences in the age of each trimester pregnant women.

The medians and 95% reference intervals for coagulation screening tests and thrombophilia markers of trimester special pregnant women were showed in Table 2. From Figs. 1–3, APTT, PT and TT showed a shortened trend from the group of the first trimester to the third trimester; the level of Fib and D-Dimer showed an increasing trend in these three groups; the activity of AT, PC and fPS presented a decreasing trend in these three groups. These results indicated that with the increasing gestational age from the first trimester to the third trimester, the coagulation function is gradually strengthened, and the anticoagulation function is relatively weak. The results of APTT, PT, TT and Fib were similar to that of Liu et al. [4]. In the study of Liu et al., they also found that coagulation tests of APTT, PT and TT showed a shortened trend with the increasing of the gestational weeks, and the level of Fib and D-dimer showed an increasing trend, respectively. In the study of Barbara R et al. [15], they also found that compared with non-pregnant women, higher reference ranges of the level of D-dimer and Fib were showed for all gestational age. D-Dimer, which is a blood coagulation and fibrinolysis test, is widely used to rule out thromboembolism because of its high negative predictive value in clinical [16]. Fib,

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