Received: 26 November 2020 | Revised: 18 January 2021 | Accepted: 20 January 2021

DOI: 10.1002/jcla.23724

RESEARCH ARTICLE

WILEY

Changes in levels of coagulation parameters in different trimesters among Chinese pregnant women

Wengong Wang[1] | Kai Long[2] | Fenglin Deng[3] | Wei Ye[1] | Pingwei Zhang[1] | Xi Chen[1] | Weiguo Dong[1] | Ping Zheng[1] | Xinxin Zhang[1] | Tianyu Yang[1] | Weihong Chen[1] | Kai Yang[1]

[1]Department of Laboratory Medicine, Hubei Provincial Hospital of Integrated Chinese and Western Medicine, Wuhan, China

[2]Shenzhen Mindray Bio-Medical Electronic Co, Ltd, Shenzhen, China

[3]Department of laboratory medicine, Wuhan Petrochemical Hospital, Wuhan, China

Correspondence
Kai Yang, Department of laboratory medicine, Hubei Provincial Hospital of Integrated Chinese and Western Medicine, No.11, Lingjiao Lake Road, Wuhan 430015, China.
Email: yangkdct@163.com

Abstract

Background: This article is to explore changes in levels of coagulation parameters in different trimesters among healthy pregnant women in China.

Methods: A total of 760 eligible women were enrolled (first-trimester group: *n* = 183, second-trimester group: *n* = 183, third-trimester group: *n* = 263, non-pregnant group: *n* = 131). Seven parameters including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), D-dimer (DD), fibrinogen degradation products (FDP), and antithrombin III (ATIII), of all participants were collected. The non-parametric 2.5th–97.5th percentiles reference intervals were calculated for each parameter.

Results: The reference intervals for FIB, PT, APTT, TT, FDP, DD, and ATIII at first trimester were 2.11–4.32 g/L, 10.90–13.85 s, 24.60–39.28 s, 12.95–15.88 s, 0.04–2.55 μg/mL, 0.03–1.15 μg/mL, and 75.57%-125.31%, respectively. The reference intervals at second trimester were 2.31–4.77 g/L, 9.70–12.64 s, 24.16–35.43 s, 12.95–15.88 s, 0.15–7.40 μg/mL, 0.08–2.13 μg/mL, and 74.35%-119.28%, respectively. For the third-trimester, the intervals were 2.39–4.96 g/L, 9.20–11.95 s, 23.90–35.51 s, 13.41–18.00 s, 0.55–13.43 μg/mL, 0.15–3.60 μg/mL, and 71.61%-118.29%, respectively. The third-trimester group showed decreased PT, APTT, and ATIII and increased FIB, TT, DD and FDP as compared with the other groups.

Conclusion: In this study, level changes of coagulation parameters in different trimesters were observed. And the ranges for coagulation parameters were presented, which may provide some reference for clinicians to more accurately monitor the coagulation and fibrinolytic system in pregnant women.

KEYWORDS
Chinese pregnant women, coagulation parameters, reference intervals

Wengong Wang and Kai Long are first co-authors and contributed equally to this work.

1 | INTRODUCTION

Pregnancy is a special physiological process, which can affect the coagulation and fibrinolytic system of pregnant women. During pregnancy, changes of hormone levels in vivo are observed, especially in the third trimester of pregnancy when estrogen and progesterone reaches the peak value, resulting in hypercoagulable state in pregnant women.[1,2] Abnormal hypercoagulable state during pregnancy are prone to thrombotic and bleeding disorders,[3] which can threaten the health and even life of pregnant women and fetuses. Therefore, routine coagulation tests are extremely important for pregnant women to monitor the coagulation and fibrinolytic system.

Parameters, such as prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), D-dimer (DD), fibrinogen degradation products (FDP), and antithrombin III (ATIII), are commonly included in coagulation tests for evaluating the prenatal coagulation and fibrinolytic system.[4,5] Most reference samples were based on samples obtained from healthy non-pregnant women.[5] However, these biochemical parameters during pregnancy are different from those under non-pregnant conditions for physiological changes in different trimesters.[6] It indicates that routinely used reference intervals cannot be applied for pregnant women; otherwise, it may affect the clinical diagnosis and treatment. In addition, there have been several studies on the coagulation function of healthy pregnant women, but most of them are based on Western population.[5,7-11] For healthy Chinese pregnant women, few studies have reported the trimester-specific changes of coagulation function.[12-14] In order to explore the coagulation parameter changes in different trimesters among healthy Chinese pregnant population, we analyzed coagulation parameters in a number of Chinese healthy pregnant women and tried to present the reference interval of blood parameters in difference trimesters.

2 | MATERIAL AND METHODS

2.1 | Study population

Totally, 760 healthy pregnant women who underwent prenatal tests and women without pregnancy who underwent normal physical examination in Hubei Provincial Hospital of Integrated Chinese and Western Medicine from June 2018 to August 2019 were selected. Data on the seven parameters of coagulation tests, including FIB, PT, APTT, TT, FDP, DD, and ATIII, of the participants in different trimesters of pregnancy and those without pregnancy were collected.

The study was approved by the Ethics Committee of Hubei Provincial Hospital of Integrated Chinese and Western Medicine with the approval number of 2020011. All participants have signed the informed consent forms.

2.2 | Eligibility criteria

The participants who met the following criteria were included the following: (a) participants with no history of thrombotic and bleeding disorders, or liver and kidney diseases; (b) participants with normal results of liver and kidney function tests; (c) participants with no use of aspirin, contraceptives, or other drugs that affect coagulation and fibrinolytic system a month before enrollment.

2.3 | Measurement of coagulation tests

A total of 4.5 mL of fasting blood samples was collected and placed in 0.5 mL vacuum tubes containing 109 mmol/L sodium citrate. After mixing, the tubes were centrifuged immediately at 3,000 r/min for 10 min. All tests were completed within 2 h. ExC810 fully auto coagulation analyzer (Mindray Bio-Medical Electronics Co., Ltd.) was used for measurement. All reagents and calibrators were purchased from Changdao Biotechnology Co., Ltd. and were operated in strict accordance with standard procedures. All standard internal quality control was performed daily.

2.4 | Statistical analysis

The mean ±standard deviation ($\bar{x} \pm s$) was used for describing a normally distributed set of measurement data; the one-way analysis of variance was used for comparison between groups, and Bonferroni's method was applied for pairwise comparison of factors with statistical differences. The median and interquartile range [M (Q1, Q3)] was used for non-normally distributed data; the Kruskal-Wallis H test was used for comparison between groups, and the Dwass-Steel-Critchlow-Fligner test procedure was used for pairwise comparison of factors with statistical difference. The non-parametric 2.5^{th}-97.5^{th} percentiles reference intervals were calculated for each parameter. All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc.). $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline clinical characteristics

In this study, a total of 760 eligible women were enrolled and divided into four groups: the first-trimester group (Gestational age: 0–13 weeks, n = 183), second-trimester group (Gestational age: 14–27 weeks, n = 183), third-trimester group (Gestational age: ≥28 weeks, n = 263), and the non-pregnant group (n = 131). The mean age was 28.42 ± 4.90 years, and the mean gestational age was 23.72 ± 12.19 weeks. Figure 1 shows the flow chart of the study.

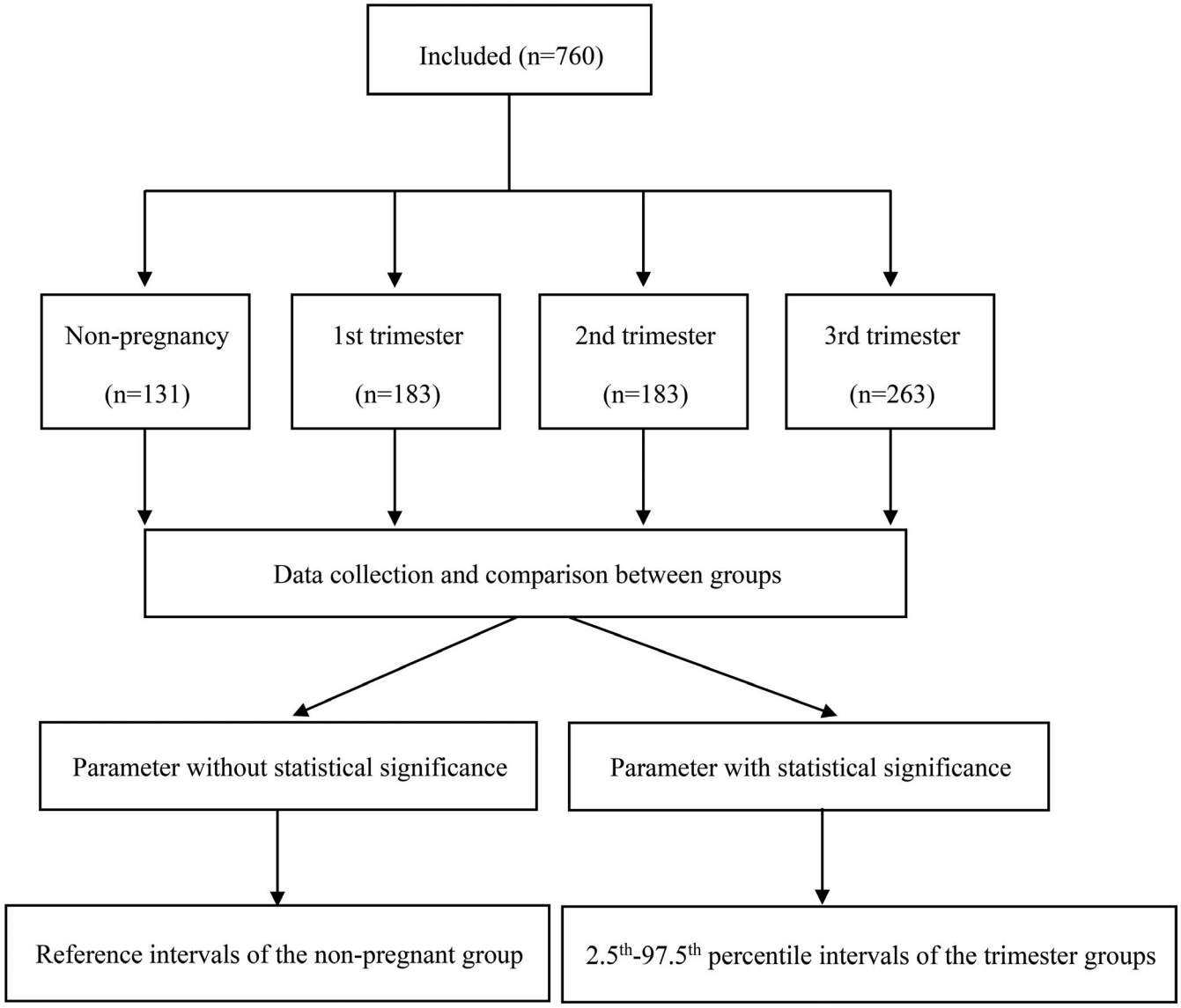

FIGURE 1 Flowchart of the study

3.2 | Differences in coagulation parameters among groups

The differences in FIB (F = 113.730, p < 0.001), PT (F = 194.380, p < 0.001), APTT (F = 30.590, p < 0.001), TT (F = 10.930, p < 0.001), FDP (χ^2 = 259.659, p < 0.001), DD (χ^2 = 312.191, p < 0.001), and ATIII (F = 93.770, p < 0.001) were all statistically significant among groups (Table 1).

After multiple comparisons, the FIB and DD levels progressively increased throughout the pregnancy, and significant differences were found in all groups (all p < 0.05). There were no significant differences in the levels of PT and FDP between the first-trimester group and the non-pregnant group (all $p \geq 0.05$). However, the PT levels significantly decreased and FDP levels increased in the second- and third-trimester groups as compared with the other two groups, respectively (all p < 0.05). In addition, the APTT and ATIII levels in all trimester groups were all significantly lower than those in non-pregnant group (all p < 0.05). Meanwhile, significant difference in APTT was observed in the third-trimester group compared to the non-pregnant group (p < 0.05), and the ATIII levels both in the second- and third-trimester groups were significantly lower than that in the first-trimester group (p < 0.05). Besides, the third-trimester group showed significantly higher TT level as compared with the other three groups (all p < 0.05) (Table 1).

3.3 | Reference intervals of coagulation parameters among groups

3.3.1 | FIB

The reference intervals of FIB were 1.81–3.29 g/L, 2.11–4.32 g/L, 2.31–4.77 g/L, and 2.39–4.96 g/L in the non-pregnant, first-trimester, second-trimester, and third-trimester groups,

TABLE 1 Differences in seven coagulation parameters among groups

	Groups						
Parameters	**Non-pregnancy**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Total**	**Statistics**	***p***
FIB, g/L	2.39 ± 0.38	2.95 ± 0.62[a]	3.27 ± 0.65[a]	3.56 ± 0.69[a]	3.14 ± 0.74	F = 113.730	<0.001
PT, s	12.31 ± 1.26	12.11 ± 1.00	11.06 ± 0.84[a]	10.35 ± 0.72[a]	11.28 ± 1.23	F = 194.380	<0.001
APTT, s	32.13 ± 2.92	30.02 ± 3.75[a]	29.18 ± 3.03[a]	29.03 ± 3.05[a]	29.84 ± 3.39	F = 30.590	<0.001
TT, s	14.57 ± 0.96	14.92 ± 1.48	14.92 ± 1.50	15.35 ± 1.26[a]	15.01 ± 1.36	F = 10.930	<0.001
FDP, μg/ml	1.13(0.65, 1.53)	1.23(0.61, 2.04)	2.23(1.15, 3.35)[a]	3.64(2.50, 5.28)[a]	2.01(1.01, 3.61)	χ^2 = 259.659	<0.001
DD, μg/ml	0.21(0.14, 0.31)	0.25(0.17, 0.36)[a]	0.45(0.28, 0.75)[a]	0.84(0.54, 1.43)[a]	0.40(0.23, 0.82)	χ2 = 312.191	<0.001
ATIII, %	114.74 ± 10.31	99.61 ± 13.40[a]	95.64 ± 11.86[a]	93.80 ± 12.34[a]	99.25 ± 14.22	F = 93.770	<0.001

[a]Represents $p < 0.05$ as compared with the non-pregnant group.
[b]Represents $p < 0.05$ as compared with the 1st-trimester group.
[c]Represents $p < 0.05$ as compared with the 2nd-trimester group.

respectively. The lower and upper reference limits in different trimester groups were all significantly higher than those in the non-pregnant group (all $p < 0.001$). FIB gradually increased throughout the pregnancy, with the highest level in the third trimester (Figure 2, Table 2).

3.3.2 | PT

The reference intervals of PT were 10.90–13.85 s, 10.41–14.04 s, 9.70–12.64 s, and 9.20–11.95 s in the non-pregnant, first-trimester, second-trimester, and third-trimester groups, respectively. The reference intervals in the second- and third-trimester groups all significantly decreased (all $p < 0.001$). PT progressively decreased with the increase of the gestational age, with the lowest level in the third trimester (Figure 2, Table 2).

3.3.3 | APTT

The reference intervals of APTT in the non-pregnant, first-trimester, second-trimester, and third-trimester groups were 27.10–37.70 s, 24.60–39.28 s, 24.16–35.43 s, and 23.90–35.51 s, respectively. Significant differences in APTT reference intervals were observed in different trimester groups compared to the non-pregnant group (all $p < 0.001$). APTT slightly decreased with the increase of gestational age (Figure 2, Table 2).

3.3.4 | TT

The reference interval of TT in the non-pregnant, first-trimester, second-trimester, and third-trimester groups were 12.95–15.88 s, 12.40–17.48 s, 12.26–18.32 s, and 13.41–18.00 s, respectively. Significant difference was only observed in the third-trimester group as compared with the non-pregnant group ($p < 0.001$). TT slightly increased throughout the pregnancy (Figure 2, Table 2).

3.3.5 | FDP

The reference intervals of FDP were 0.04–2.55 μg/mL, 0.01–4.82 μg/mL, 0.15–7.40 μg/mL, and 0.55–13.43 μg/mL in the non-pregnant, first-trimester, second-trimester, and third-trimester groups, respectively. The second- and third-trimester groups had significant higher reference intervals of FDP as compared with the non-pregnant group (all $p < 0.001$). FDP elevated progressively throughout the pregnancy, with the highest level in the third trimester (Figure 2, Table 2).

3.3.6 | DD

The reference intervals of DD were 0.06–0.46 μg/mL, 0.03–1.15 μg/mL, 0.08–2.13 μg/mL, and 0.15–3.60 μg/mL in the non-pregnant, first-trimester, second-trimester, and third-trimester groups, respectively. Significant differences in DD reference intervals were found in the first-trimester ($p = 0.019$), second-trimester ($p < 0.001$) and third-trimester ($p < 0.001$) groups as compared with the non-pregnant group. DD increased gradually with the pregnancy, with the highest level in the third trimester (Figure 2, Table 2).

3.3.7 | ATIII

The reference intervals of ATIII in the non-pregnant, first-trimester, second-trimester, and third-trimester groups were 99.38%-125.31%, 75.57%-125.31%, 74.35%-119.28%, and 71.61%-118.29%, respectively. The reference intervals in different trimesters were all significantly lower than that in the non-pregnant

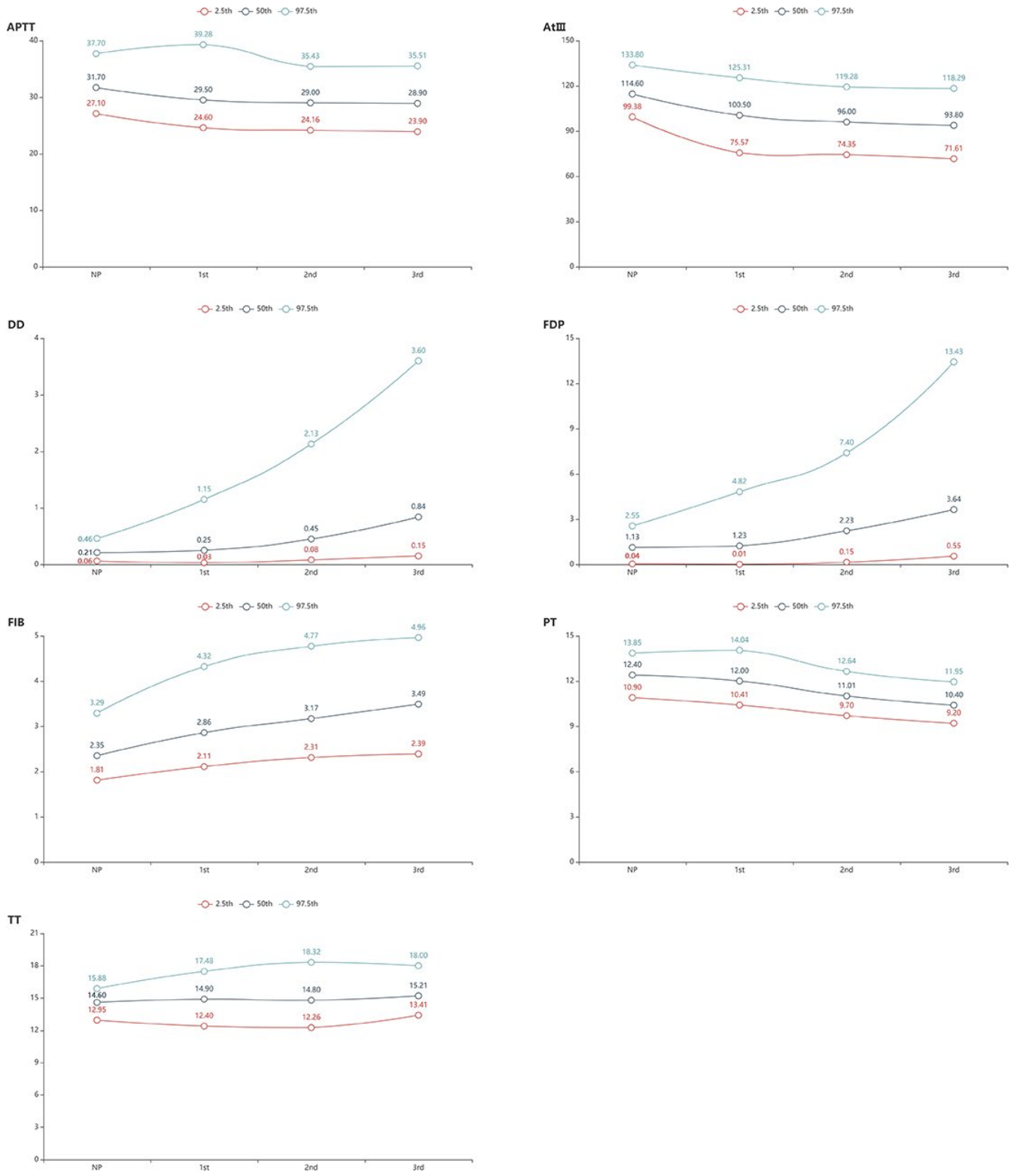

FIGURE 2 Percentile curves of parameters in different trimesters

group (all $p < 0.001$). ATIII gradually decreased throughout the pregnancy, with the lowest level in the third trimester (Figure 2, Table 2).

For parameters in the trimester groups with no significant differences from the non-pregnant group, we obtained the non-pregnant reference intervals. For parameters in different trimesters with significant difference from the non-pregnancy, the 2.5^{th}-97.5^{th} percentile intervals of the trimester groups were used as the corresponding reference interval. See Table 3 for the reference interval of each parameter.

TABLE 2 Comparisons of reference intervals for seven coagulation parameters among groups

Parameters	*N*	Percentiles			Reference intervals	*p* (Compared with non-pregnancy)
		2.5th	50th	97.5th		
FIB, g/L						
Non-pregnancy	131	1.81	2.35	3.29	1.81–3.29	—
1st trimester	183	2.11	2.86	4.32	2.11–4.32	<0.001
2nd trimester	183	2.31	3.17	4.77	2.31–4.77	<0.001
3rd trimester	263	2.39	3.49	4.96	2.39–4.96	<0.001
PT, s						
Non-pregnancy	131	10.90	12.40	13.85	10.90–13.85	—
1st trimester	183	10.41	12.00	14.04	10.41–14.04	0.352
2nd trimester	183	9.70	11.01	12.64	9.70–12.64	<0.001
3rd trimester	263	9.20	10.40	11.95	9.20–11.95	<0.001
APTT, s						
Non-pregnancy	131	27.10	31.70	37.70	27.10–37.70	—
1st trimester	183	24.60	29.50	39.28	24.60–39.28	<0.001
2nd trimester	183	24.16	29.00	35.43	24.16–35.43	<0.001
3rd trimester	263	23.90	28.90	35.51	23.90–35.51	<0.001
TT, s						
Non-pregnancy	131	12.95	14.60	15.88	12.95–15.88	—
1st trimester	183	12.40	14.90	17.48	12.40–17.48	0.133
2nd trimester	183	12.26	14.80	18.32	12.26–18.32	0.122
3rd trimester	263	13.41	15.21	18.00	13.41–18.00	<0.001
FDP, μg/ml						
Non-pregnancy	131	0.04	1.13	2.55	0.04–2.55	—
1st trimester	183	0.01	1.23	4.82	0.01–4.82	0.206
2nd trimester	183	0.15	2.23	7.40	0.15–7.40	<0.001
3rd trimester	263	0.55	3.64	13.43	0.55–13.43	<0.001
DD, μg/ml						
Non-pregnancy	131	0.06	0.21	0.46	0.06–0.46	—
1st trimester	183	0.03	0.25	1.15	0.03–1.15	0.019
2nd trimester	183	0.08	0.45	2.13	0.08–2.13	<0.001
3rd trimester	263	0.15	0.84	3.60	0.15–3.60	<0.001
ATIII, %						
Non-pregnancy	131	99.38	114.60	133.80	99.38–133.80	—
1st trimester	183	75.57	100.50	125.31	75.57–125.31	<0.001
2nd trimester	183	74.35	96.00	119.28	74.35–119.28	<0.001
3rd trimester	263	71.61	93.80	118.29	71.61–118.29	<0.001

4 | DISCUSSION

In the present study, we tried to explore the trimester-specific changes in coagulation parameters, including FIB, PT, APTT, TT, FDP, DD, and ATIII, in healthy Chinese pregnant women. A total of 629 healthy pregnant women were enrolled with 131 non-pregnant cases included as controls.

In this study, the third-trimester group showed decreased PT, APTT, and ATIII and increased FIB, TT, DD, and FDP as compared with the other groups. The results may indicate that the coagulation function was progressively increased and the anticoagulation function was declined with the increasing gestational age. Similar results of declining markers of APTT, PT, and ATIII were observed in the study of Cui et al.[4] APTT mainly reflects intrinsic coagulation pathway. Due to the hypercoagulable state during pregnancy, platelets and coagulation factors are consumed in large amounts, which may lead to the decreasing trend of APTT with the gestational age. In addition, PT reflects extrinsic coagulation pathway. Due to physiological changes during pregnancy, coagulation factors fail to timely synthesize, which may lead to a decrease in

TABLE 3 Reference intervals of parameters during non-pregnancy and at different trimesters

Parameters	Reference intervals			
	Non-pregnancy	1st trimester	2nd trimester	3rd trimester
FIB, g/L	1.81–3.29	2.11–4.32	2.31–4.77	2.39–4.96
PT, s	10.90–13.85	—	9.70–12.64	9.20–11.95
APTT, s	27.10–37.70	24.60–39.28	24.16–35.43	23.90–35.51
TT, s	12.95–15.88	—	—	13.41–18.00
FDP, μg/ml	0.04–2.55	—	0.15–7.40	0.55–13.43
DD, μg/ml	0.06–0.46	0.03–1.15	0.08–2.13	0.15–3.60
ATIII, %	99.38–133.80	75.57–125.31	74.35–119.28	71.61–118.29

Note: "—" represents no significant difference as compared with the non-pregnant group.

PT.[13] Many studies have reported that PT and APTT were significantly shorter in pregnant women.[9,15] ATIII plays a key role in inhibiting the blood coagulation, and the lower levels of ATIII during pregnancy could have been caused by increased clotting-enzymes production.[8] This could explain our finding that ATIII gradually decreased with the increase of gestational age, with the lowest level in the third trimester.

In addition, the rising markers of FIB, DD, and FDP have also been demonstrated in the study of Cui et al.[4] FIB, a blood coagulation test, is widely used in the diagnosis of disseminated intravascular coagulation or hyperfibrinolysis.[4] According to our results, FIB gradually elevated with pregnancy, with the highest level occurring in the third trimester, which may suggest a hypercoagulable state *in vivo*. DD, the smallest fragment of FDPs, is widely used to rule out thromboembolism for its high negative predictive value in clinical.[16,17] Our results suggested that DD and FDP increased with the gestational age, with the highest levels in the third trimester. The increase in DD has been considered as a sensitive marker of fibrinolytic activity. It has been speculated that increased fibrinolytic activity primarily occurred on the placental uterine interface, while the elevated levels are probably due to localized increase in fibrin formation.[18-20] For TT, many studies have reported its shortened trend during pregnancy.[4,9,15,21] Kong et al. reported no significant decline in TT during different trimesters.[14] However, our results suggested that the TT levels in different trimesters were all slightly higher than that in non-pregnant women, and significant increase in the level of TT was observed in the third trimester. The difference here is probably due to different reagents, instruments, or preanalytical conditions. During pregnancy, the blood volume of pregnant women increases and peaks in the third trimester. The cardiovascular hyperdynamic circulation is maintained, which may lead to fibrinogen abnormalities.[13]

To our knowledge, there are currently many similar studies on Western pregnant women. [5,7,8,10,11] Sekiya et al. reported that the APTT, PT, and ATIII levels remained unchanged during pregnancy and were within the non-pregnant ranges, while the levels of FIB and DD increased markedly. [5] In another study, PT and APTT were found significantly shorter, and plasma concentrations of FIB and DD were significantly higher, especially in the third trimester. And no remarkable difference was found in ATIII activity. [8] In the study of Uchikova et al., the pregnant women in the third trimester showed remarkably higher values for PT, TT, FIB, and DD. [10] Similar results on the FIB and DD levels were demonstrated in another two studies, which demonstrated a progressive increase in FIB and DD throughout pregnancy [7,11] Herein, we could find some differences in the changes of coagulation parameters during pregnancy in Chinese and Western population, especially the changes in APTT, PT and ATIII. We speculated that the difference here may be attributed to different study populations and experimental designs such as the use of reagents and instruments and grouping settings.

According to our results, the changes of coagulation parameters were observed in healthy pregnancy women, which suggested that the normal ranges of coagulation parameters may not be suitable for pregnant women. In view of this, the ranges for these parameters based on healthy Chinese pregnant women were presented, which may provide some inspirations for clinicians to establish reference intervals for healthy pregnant women, thereby better monitoring the coagulation and fibrinolysis system of pregnant women. However, there were some limitations in our study. Firstly, the sample size in our study is not large enough, which requires a larger sample size for more objective results. Secondly, we adopted a retrospective study where data from different pregnant and non-pregnant women in different trimesters were collected. The individual difference may affect the objectivity of results. Thirdly, different reagents, instruments, or testing conditions may play a part on clinical laboratory results, which indicated that our results should be interpreted with caution and need to be further verified in other laboratories. In addition, it's worth mentioning that although our statistical results suggested no significant differences between the second- and third-trimester groups for APTT and ATIII, decreasing trends were observed in their percentile curves. Due to the small sample size of our study, it cannot be concluded that ATIII levels in the second and third trimesters were not evident. In addition, similar declining trends were also reported in other Chinese studies. [4,9] Herein, we considered that the reference intervals in the second and third trimester may be retained and set separately. In the future, a longitudinal study with a larger sample size observing the same population in different trimesters is required for more persuasive results.

5 | CONCLUSION

In this study, changes in levels of coagulation parameters in different trimesters were observed. And the ranges for coagulation parameters were presented, which may provide some reference for clinicians to more accurately monitor the coagulation and fibrinolytic system in pregnant women.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study was performed in line with the principles of the 1964 Helsinki Declaration and was approved by the Ethics Committee of Hubei Integrated Traditional Chinese and Western Medicine Hospital on February 2nd, 2020, with registration number 2020011. Also, an informed consent was obtained from all subjects included in the study.

CONSENT FOR PUBLICATION

All the contributing authors agreed for the publication in this journal.

CONFLICT OF INTEREST

There is no conflict of interest in this work.

AUTHORS CONTRIBUTIONS

WG Wang and K Long designed the study and wrote the manuscript. FL Deng, W Ye, PW Zhang, and X Chen collected the data. WG Dong, P Zhang, XX Zhang, TY Yang, and WH Chen analyzed the data. K Yang reviewed and improved the manuscript. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All the data released to this work are available at the corresponding author.

ORCID

Kai Yang https://orcid.org/0000-0002-4723-4491

REFERENCES

1. Zheng X, Xiao W. Detection of four parameters of coagulation assay and D-dimer in late-term pregnant women (in Chinese). *Chin J Microcirc*. 2012;22(02):77.
2. Hansen AT, Andreasen BH, Salvig JD, Hvas AM. Changes in fibrin D-dimer, fibrinogen, and protein S during pregnancy. *Scand J Clin Lab Invest*. 2011;71(2):173-176.
3. Fan F. *Establishment of reference interval of D-Dimer during pregnancy and application in venous thromboembolism and postpartum hemorrhage (in Chinese)*. Guangzhou, China: Sourthern Medical University; 2018.
4. Cui C, Yang S, Zhang J, et al. Trimester-specific coagulation and anticoagulation reference intervals for healthy pregnancy. *Thromb Res*. 2017;156:82-86.
5. Szecsi PB, Jorgensen M, Klajnbard A, Andersen MR, Colov NP, Stender S. Haemostatic reference intervals in pregnancy. *Thromb Haemost*. 2010;103(4):718-727.
6. Sekiya A, Hayashi T, Kadohira Y, et al. Thrombosis prediction based on reference ranges of coagulation-related markers in different stages of pregnancy. *Clin Appl Thromb Hemost*. 2017;23(7):844-850.
7. Gutierrez GI, Perez CP, Martinez UJ, Garcia IO, Angeles JP, Garcia GR. D-dimer during pregnancy: establishing trimester-specific reference intervals. *Scand J Clin Lab Invest*. 2018;78(6):439-442.
8. Hammerova L, Chabada J, Drobny J, Batorova A. Longitudinal evaluation of markers of hemostasis in pregnancy. *Bratisl Lek Listy*. 2014;115(3):140-144.
9. Liu J, Yuan E, Lee L. Gestational age-specific reference intervals for routine haemostatic assays during normal pregnancy. *Clin Chim Acta*. 2012;413(1–2):258-261.
10. Uchikova EH, Ledjev II. Changes in haemostasis during normal pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2005;119(2):185-188.
11. Reger B, Peterfalvi A, Litter I, et al. Challenges in the evaluation of D-dimer and fibrinogen levels in pregnant women. *Thromb Res*. 2013;131(4):e183-187.
12. Guo Q, Lai X, He S, et al. Interval study of D-dimer and Coagulation Index in healthy pregnant women of appropriate age (in Chinese). *China Continuing Med Educ*. 2020;12(19):96-98.
13. Zuo G. Characteristics and clinical analysis of coagulation function and D-dimer in pregnant women during different pregnancy periods (in Chinese). *PSY*. 2020;15(06):57-59.
14. Kong Q, Yuan C, Li L, Deng K, Peng J. Investigation on the changes of blood coagulation index in normal pregnant women during different periods of gestation (in Chinese). *Chinese Journal of Health Laboratory Technology*. 2016;26:3267-3268+3271.
15. Han L, Liu X, Li H, et al. Blood coagulation parameters and platelet indices: changes in normal and preeclamptic pregnancies and predictive values for preeclampsia. *PLoS One*. 2014;9(12):e114488.
16. Nijkeuter M. Lack of evidence to support use of D-dimer in pregnant women with a suspicion of pulmonary embolism. *Emerg Med J*. 2015;32(6):501.
17. Hedengran KK, Andersen MR, Stender S, Szecsi PB. Large D-dimer fluctuation in normal pregnancy: a longitudinal cohort study of 4,117 samples from 714 healthy Danish Women. *Obstet Gynecol Int*. 2016;2016:3561675.
18. Dempfle CE. What role does the measurement of fibrinogen and its derivatives have in the diagnosis of disseminated intravascular coagulation? *Blood Rev*. 2002;16(Suppl 1);S23-28.
19. Dempfle CE, Wurst M, Smolinski M, et al. Use of soluble fibrin antigen instead of D-dimer as fibrin-related marker may enhance the prognostic power of the ISTH overt DIC score. *Thromb Haemost*. 2004;91(4):812-818.
20. Dempfle CE. Validation, calibration, and specificity of quantitative D-dimer assays. *Semin Vasc Med*. 2005;5(4):315-320.
21. Gong JM, Shen Y, He YX. Reference intervals of routine coagulation assays during the pregnancy and puerperium period. *J Clin Lab Anal*. 2016;30(6):912-917.

How to cite this article: Wang W, Long K, Deng F, et al. Changes in levels of coagulation parameters in different trimesters among Chinese pregnant women. *J Clin Lab Anal*. 2021;35:e23724. https://doi.org/10.1002/jcla.23724