





Evaluating the Significance of Coagulation Tests for the Prevention and Treatment of Disseminated Intravascular Coagulation: A Meta-Analysis

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Abstract

Background: We aimed to assess the clinical significance of obstetric coagulation tests in the prevention and treatment of disseminated intravascular coagulation (DIC) and to analyze the characteristics of changes in key coagulation indicators during pregnancy and delivery.

Methods: The system searched PubMed, Embase, Scopus, Web of science, Wanfang Data knowledge service platform, VIP and China Knowledge Network databases for relevant literature from inception to Aug 2024. Two researchers independently screened the literature, extracted the information and evaluated the risk of bias of the included studies. Statistical analysis was performed using Stata/SE 16.0 software.

Results: Twelve studies involving 2531 cases were included. Key findings versus non-pregnant women showed: significantly higher maternal D-dimer (Mean Difference (MD)=1.08, 95% Confidence Interval (CI): 0.61, 1.56) and fibrinogen (MD=1.57, 95%CI: 1.04, 2.10); and lower prothrombin time (PT) (MD=1.13, 95%CI: 0.43, 1.83) and activated partial thromboplastin time (APTT) (MD=0.73, 95%CI: 0.31, 1.16). Longitudinal trends across pregnancy trimesters were also significant: D-dimer increased from 0.24 mg/L to 0.46 mg/L and 0.72 mg/L (*P*=0.02); fibrinogen rose from 3.94 g/L to 4.38 g/L and 5.05 g/L (*P*<0.001); and PT demonstrated statistically significant changes (*P*=0.00).

Conclusion: Obstetric coagulation tests effectively reflect changing coagulation status during pregnancy, providing great value for early DIC prevention and intervention. Regular monitoring of key indices can help optimize clinical DIC management and offer more comprehensive strategies for obstetric patients.

Keywords: Obstetrics; Disseminated intravascular coagulation; Coagulation test

Introduction

The process of pregnancy and delivery is a specific physiological state for women, during which the activity of both the coagulation and fibrinolytic systems is significantly increased and maintained at high levels to adapt to the physiological changes and reduce the risk of postpartum hemorrhage (1). Among them, D-dimer and fibrino-

gen (FIB), significantly elevated during pregnancy to keep the blood in a hypercoagulable state, contribute to postpartum hemostasis (2). D-dimer is the solubilization product of fibrinolytic crosslinked fibrin, which mainly reflects the fibrinolytic function (2). Fibrinogen is a macromolecular protein synthesized by the liver and directly in-



volved in coagulation after conversion to fibrin, so it is also known as coagulation factor I. After conversion to fibrin, it is directly involved in the formation of blood clots, and its level increases significantly during pregnancy, which helps to maintain hypercoagulability during pregnancy (3). Obstetric disseminated intravascular coagulation (DIC) is an acute microvascular intracoagulation syndrome, which usually occurs on top of a severe primary disease and is characterized by hemorrhage, microcirculatory disorders, microvascular endovascular embolism, accompanied by secondary hyperfibrinolysis (4). DIC can lead to systemic multiorgan failure, which may be lifethreatening if not treated in a timely manner (5). Due to the rapid onset of DIC and the more complex condition of patients, the prognosis is often poor (5). Therefore, early detection and intervention treatment can effectively improve patient prognosis and reduce mortality.

Currently, several studies have reported reference standards for relevant coagulation indices during pregnancy and delivery for the prevention, diagnosis and treatment of obstetric DIC (1, 2, 6-9). Obstetric DIC poses a major threat to the health of mothers and infants due to its high incidence and severe prognosis. However, there is a lack of systematic evaluation of the specific value of indicators such as D-dimer and fibrinogen in the diagnosis and prevention of obstetric DIC. In addition, significant changes in blood coagulation status during pregnancy and the lack of standardized reference intervals pose a challenge to clinical diagnosis.

In this study, we evaluated the changes in indicators such as D-dimer and fibrinogen levels in obstetric coagulation tests through Meta-analysis of the existing literature, aiming to provide an evidence-based basis for clinical diagnosis and treatment.

Methods

Literature search strategy

This meta-analysis was performed in strict accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) regulations (10). Literature search covered English and Chinese literature published from Ian 1995 to Aug 2024 in PubMed, Embase, Scopus, Web of science, Wanfang Data, Wipro (VIP) and National Knowledge Infrastructure (CNKI) databases. The literature was searched using a combination of subject headings and unqualified search terms including "pregnancy" (OR "gestation" OR "postpartum" OR "partus"), "D-dimer" (OR "DD" OR "fibrinogen" OR "FG" OR "FIB" OR "blood coagulation") and "DIC" (OR "Disseminated Intravascular Coagulation"). In addition, this study examined citation indexes and reference lists for relevant studies not identified in the original databases.

Inclusion and exclusion criteria Inclusion criteria

- 1) Type of study design: case-control studies, cohort studies, RCTs, cross-sectional, etc. were used, and the full text is available.
- 2) Subjects: Participants were all healthy pregnant women over 18 yr of age, including pregnant women (early, mid and late pregnancy) and non-pregnant women.
- 3) Comparison: "Normal maternal" was defined as women without any complications or underlying diseases, diagnosed as pregnant with a single live foetus in a regular medical institution; "Nonpregnant women" was defined as healthy pregnant women of childbearing age who were not pregnant and did not have any underlying diseases.
- 4) Outcome: Reporting of D-dimer and/or FIB blood test data with no missing data.

Exclusion criteria

- 1) Duplicate articles or no full text;
- 2) Studies that lacked key outcome indicators needed for this study (e.g., D-dimer or fibrinogen, etc.), or had missing or incorrect data that could not be made up or corrected;
- 3) Include studies of women with co-morbidities (e.g., diabetes, deep vein thrombosis, hypertension, placenta praevia, etc.) or who are not in their childbearing years. This criterion was intended to ensure homogeneity of the study popu-

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lation and to exclude confounding factors that might affect coagulation parameters;

- 4) Studies with a sample size of less than 40 participants;
- 5) Animal studies.

Data extraction of information

We collected the following data: title of the article, first author, year of publication, Country/region, type of study design, study subgroups and sample sizes, mean age of the participants and its standard deviation (if any), and the results of the reported blood tests for D-dimer and/or fibrinogen content.

Quality evaluation

The quality of the literature was independently evaluated by 2 researchers based on the NOS scale (Newcastle-Ottawa Scale) (11), and when there was a difference of opinion, it was discussed with a third party to reach agreement. The NOS scale consists of 3 dimensions with a total of 8 entries: i.e., 4 entries on selection of study subjects, 1 entry on between-group comparability, and 3 entries on outcome measures; except for the entry on between-group comparability scored with a maximum score of 2 points, all other entries can be scored with a maximum of 1 point, and the score ranges from 0 to 9 points. The higher the total score, the higher the quality of the study. Studies with a score of 6-9 were considered to be of high quality, and those with a score of 0-5 were considered to be of low quality.

Statistical Methods

Data from D-dimer and/or FIB blood tests in non-pregnant healthy pregnant women and healthy pregnant women were analyzed in this study using Stata/SE 16.0 software. The outcome indicators were continuous variables, so they were expressed as Mean Difference (MD) and their 95% Confidence Interval (CI). Q-test was used to assess inter-study heterogeneity; if $I^2 < 50\%$ and P > 0.1, it indicated less heterogeneity and a fixed-effects model was used; otherwise, a random-effects model was used to calculate the combined effect value. Forest plots were drawn to describe the statistical results of meta-analysis. Considering the changes in coagulation function during pregnancy, this meta-analysis analyzed subgroups of data at three stages of pregnancy: early (0-12+6 wk), middle (13-27+6 wk) and late (28-41+6 wk). Funnel plots were used to assess publication bias, further assessed by Egger's test. Differences were statistically significant at P<0.05.

Ethics approval and consent to participate

As this study involved the summary and analysis of other studies, it did not involve medical ethics approval or patient-informed consent.

Results

Results of Literature Search Screening

Overall, 342 articles were retrieved from seven databases. After eliminating duplicates, the remaining 65 articles were screened by browsing titles, keywords, and abstracts, and 32 full-text articles were obtained and then read in full according to the inclusion and exclusion criteria. Eventually, 12 studies (12-23) were included in this meta-analysis. The literature screening process is shown in Fig. 1.

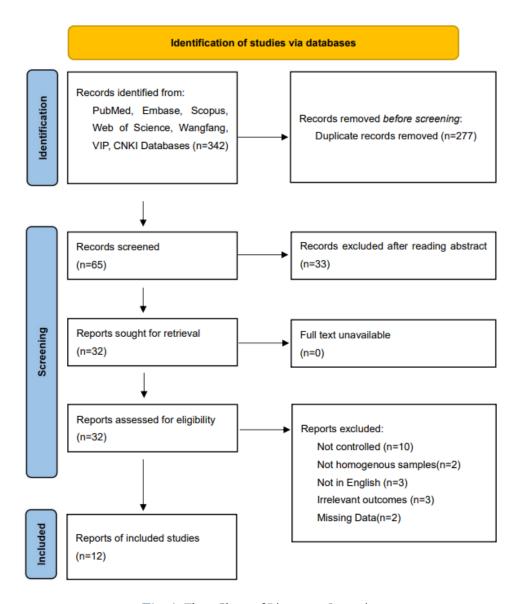


Fig. 1: Flow Chart of Literature Screening

Basic characteristics of the included studies

The 12 included papers were all original studies covering samples from China, France, Italy, Japan, Hungary, the United States, the United Kingdom, and Siberia, with the total sample comprising 2,531 non-pregnant healthy pregnant women and healthy pregnant women, with the mean age mainly centered on the age range of 20 to 44 yr. Study types included retrospective non-randomized subgroup studies and prospective longitudinal studies. The study population was

mainly healthy pregnant women versus non-pregnant women, with some studies subdivided into comparisons of early, middle, and late pregnancy. The outcome indicators were D-dimer, FIB, prothrombin time (PT) and activated partial thromboplastin time (APTT). Testing platforms/methods involved fully automated coagulation analyzers, ELISA assays, among others. The basic characteristics of the included studies are shown in Table 1.

Table 1: Basic characteristics of included studies

Included studies	Coun- try	Mean age (years)	Subgroups	Reported outcomes	Test Platforms/Methods			
Du Y (23)	China	29.63±5.24	Healthy pregnant women vs. non-pregnant women	D-dimer, FIB, PT,APTT	Fully Automated Coagulometer			
Joly B et al.(15)	French	30±5	First, second and third tri- mesters	D-dimer, FIB	Measured by CAT and Fluoroscan Ascent ELISA method			
Hui C et al.(13)	China	29.3±3.75	Non-pregnant women vs. pre-, mid- and post-pregnant women	FIB, PT,APTT	Fully Automated Coagulometer ELISA method			
Cerneca F et al.(14)	Italy	28.9±4.16	Non-pregnant women vs. pre-, mid- and post-pregnant women	FIB,APTT	ELISA method			
Kovac MK et al.(22)	Siberia	30±4.5	First, second and third tri- mesters	D-dimer	BCS XP coagulation			
Liu XH et al.(21)	China	29.50±3.3	Non-pregnant women vs. pre-, mid- and post-pregnant women	FIB,APTT	Fully Automated Coagulometer ELISA method			
Liu J et al.(20)	China	32±6	Non-pregnant women vs. pre-, mid- and post-pregnant women	FIB, PT,APTT	Fully Automated Coagulometer			
Onishi H et al.(19)	Japa- nese	31.4±0.15	First, second and third tri- mesters	D- dimer,FIB PT,APTT	Auto LIA FM kit			
Francalanci et al.(16)	Italy	20±2	Non-pregnant women vs. pre-, mid- and post-pregnant women	D-dimer, FIB	PT-Thromboplastin ELISA method			
Réger B et al.(12)	Hun- gary	28.85±4.3	First, second and third tri- mesters	D-dimer, FIB	ACL 9000			
Kline JA et al.(17)	USA	31	Non-pregnant women vs. pre-, mid- and post-pregnant women	D-dimer	MDA immunoturbidimetric Assay			
Morse M et al.(18)	UK	26.5±4.75	Non-pregnant women vs. pre-, mid- and post-pregnant women	D- dimer,FIB, PT,APTT	IL TestTM PT-Fibrinogen Recombinant IL TestTM APTT- SP			

Quality evaluation of the included literature

Evaluating the quality of the literature based on the NOS scale (11). The quality of the 12 included studies was evaluated using the NOS score, which ranges from 5 to 9, reflecting the differences in quality among the studies. Most of the studies were more explicit about the representation and definition of the experimental (maternal) and control (nonmaternal) groups, and some studies scored lower for the representation of the control group. Studies generally scored high on measures of outcome indicators, indicating more objective and accurate assessment of outcomes. Most studies had more complete follow-up data, but some studies (19,21) had lower follow-up

completeness and incomplete follow-up data. The results of quality evaluation of the included literature are shown in Table 2.

Table 2: Quality evaluation of 12 studies included

Author (year)	Quali-		Selection o	f subjects	Compa-	Measurement of outcome			
(Ref No.)	ty as- sess- ment score (NOS)	Representative of experimental group	Representative of control group	Definition of experi- mental group	Definition of control group	rability between groups	Meas- urement of out- come indica- tors	Duration of follow-up	Follow- up com- plete- ness
Du Y 2019(23)	8	0	1	1	1	2	1	1	1
Joly B et al. 2013(15)	6	1	0	1	0	0	1	1	1
Hui C et al. 2012(13)	9	1	1	1	1	1	1	1	1
Cerneca F et al. 1997(14)	8	1	1	1	1	0	1	1	1
Kovac MK et al. 2015(22)	5	1	0	1	0	0	1	1	0
Liu XH et al. 2009(21)	7	0	1	1	1	0	1	1	1
Liu J et al. 2012(20)	7	1	0	1	1	1	1	1	0
Onishi H et al. 2007(19)	5	1	0	1	0	0	1	1	1
Francalanci et al.1995 (16)	8	1	1	1	1	0	1	1	1
Reger B et al.2013 (12)	6	1	0	1	0	0	1	1	1
Kline JA et al. 2005(17)	7	1	1	1	1	0	0	1	1
Morse M et al. 2004(18)	8	1	1	1	1	1	0	1	1

Meta-analysis results

Differences in D-dimer concentrations between healthy pregnant women and non-pregnant women.

Overall, 12 studies were included in this metaanalysis, of which 4 studies examined the changes in D-dimer concentration at different stages of pregnancy (early, mid and late pregnancy). The results of heterogeneity test showed that I²>50%, *P*<0.001, so the random effect model was used for meta-analysis. The results of the forest plot showed that healthy maternal blood D-dimer concentration was significantly higher than that of healthy non-pregnant women, and the difference was statistically significant (MD=1.08, 95%CI: 0.61, 1.56) (Fig. 2).

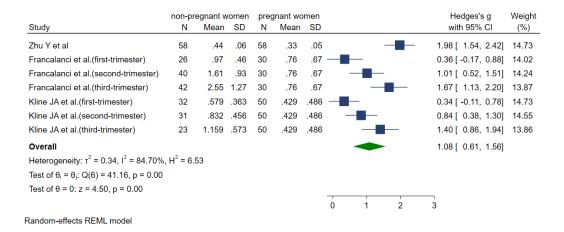


Fig. 2: The forest plot of the impact of pregnancy on blood D-dimer concentration

Differences in fibrinogen concentration between healthy pregnant women and non-pregnant women

The results of the heterogeneity test for the included studies were $I^2 = 95.56\%$, P < 0.001, so meta-analysis was performed using the random

effects model. Healthy maternal blood fibrinogen levels were significantly higher than those of healthy non-pregnant women, and the results were statistically significant (MD=1.57, 95%CI: 1.04, 2.10) (Fig. 3).

	non-pregnant women			pregnant women						Hedges's g	Weight
Study	N	Mean	SD	N	Mean	SD				with 95% CI	(%)
Zhu Y et al	58	3.02	.69	58	4.11	1.28	-			-1.05 [-1.44, -0.67	7.79
Hui.C et al.(first-trimester)	58	4	1.01	50	2.52	.7		+	-	1.67 [1.23, 2.11	7.70
Hui.C et al.(second-trimester)	58	4.13	1.12	50	2.52	.7		-	-	1.68 [1.25, 2.12	7.69
Hui.C et al.(third-trimester)	58	4.47	.99	50	2.52	.7			-	2.23 [1.75, 2.71	7.62
Cerneca F et al.(first-trimester)	117	4.12	.69	45	3.68	.83				0.60 [0.25, 0.95	7.85
Cerneca F et al.(second-trimester)	117	4.63	.83	45	3.68	.83		-	-	1.14 [0.78, 1.50	7.82
Cerneca F et al.(third-trimester)	117	5.38	1.07	45	3.68	.83		-	-	1.68 [1.29, 2.06	7.78
Liu XH et al.(first-trimester)	120	3.72	.71	120	2.38	.62				2.00 [1.69, 2.31	7.90
Liu XH et al.(second-trimester)	120	3.78	.71	120	2.38	.62				2.09 [1.78, 2.41	7.90
Liu XH et al.(third-trimester)	120	4.27	.88	120	2.38	.62			-	2.48 [2.14, 2.81	7.86
Francalanci et al.(first-trimester)	26	4.22	.88	30	3.34	.54		-	\vdash	1.21 [0.64, 1.77	7.44
Francalanci et al.(second-trimester)	40	4.79	.59	30	3.34	.54			_	2.52 [1.89, 3.15	7.29
Francalanci et al.(third-trimester)	42	5.22	.97	30	3.34	.54			-	2.27 [1.68, 2.86	7.37
Overall								•	•	1.57 [1.04, 2.10	l
Heterogeneity: $\tau^2 = 0.90$, $I^2 = 95.569$	$6, H^2 = 2$	22.50									
Test of $\theta_i = \theta_j$: Q(12) = 282.02, p = 0	.00										
Test of $\theta = 0$: $z = 5.81$, $p = 0.00$											
						-;	2	0	2	4	
Random-effects REML model											

Fig. 3: The forest plot the impact of pregnancy on blood FIB concentration (g/L)

Differences in prothrombin time between healthy pregnant women and non-pregnant women

The results of the heterogeneity test for the included studies were $I^2=98.33\%$, P=0.00, so meta-analysis was performed using random effects

model. Healthy maternal prothrombin time was significantly shorter than that of healthy non-pregnant women and the results were statistically significant (MD=1.13, 95% CI: 0.43, 1.83) (Fig. 4).

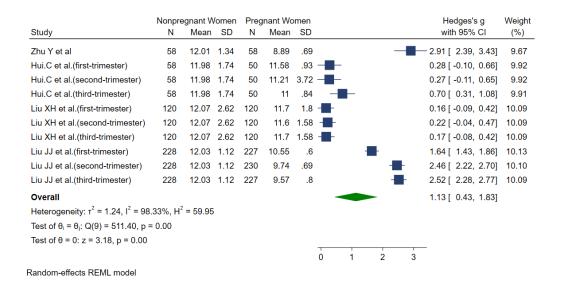


Fig. 4: Forest plot of the effect of pregnancy on prothrombin time

Differences in activated partial thromboplastin time between healthy pregnant women and nonpregnant women

The results of the heterogeneity test for the included studies were $I^2=94.20\%$, P=0.00, so meta-analysis was performed using random effects

model. Activated partial thromboplastin time was significantly shorter in healthy pregnant women than in healthy non-pregnant women and the results were statistically significant (MD=0.73, 95% CI: 0.31, 1.16), (Fig. 5).

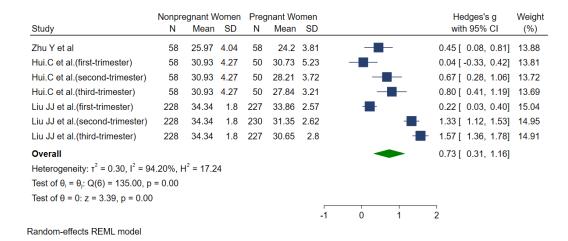


Fig. 5: Forest plot of the effect of pregnancy on activated partial thromboplastin time

Subgroup analysis Changes in D-dimer concentration at different stages of pregnancy

In meta-analysis, the results of subgroup analyses at different stages of pregnancy showed that maternal blood D-dimer concentration gradually increased as the expected date of delivery approached. Four studies were included in early pregnancy, and the maternal blood D-dimer concentration in early pregnancy was 0.24 (95% CI: 0.11, 0.38); five studies were included in midpregnancy, and the maternal blood D-dimer con-

centration in mid-pregnancy was 0.46 (95% CI: 0.24, 0.68); and in late pregnancy: six studies were included, and the maternal blood D-dimer concentration in late pregnancy reached 0.72 (95% CI: 0.36, 1.07). The concentration of D-dimer

increased significantly with the progression of pregnancy, especially reaching its highest in late pregnancy, and was statistically different between the stages (P=0.02) (Fig. 6).

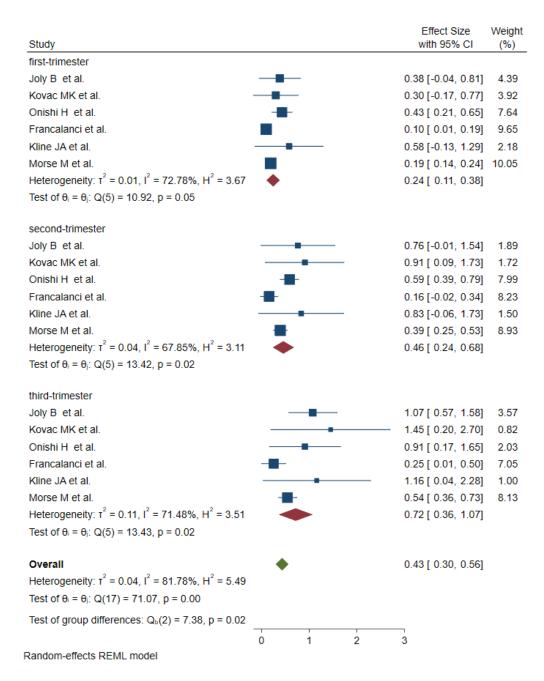


Fig. 6: Subgroup analysis of the effect of pregnancy on blood D-dimer concentration

Changes in maternal blood fibrinogen concentration at different stages of delivery and delivery

Maternal blood fibrinogen concentration gradually increased as the expected date of delivery approached. The blood fibrinogen concentrations in early, middle and late pregnancy were 3.94

(95% CI: 3.69, 4.18), 4.38 (95% CI: 4.1, 4.67), and 5.05 (95% CI: 4.71, 5.40), respectively. There was a statistically significant difference in blood fibrinogen concentration between early, middle and late pregnancy (P<0.001). The results of subgroup analysis are shown in Fig. 7.

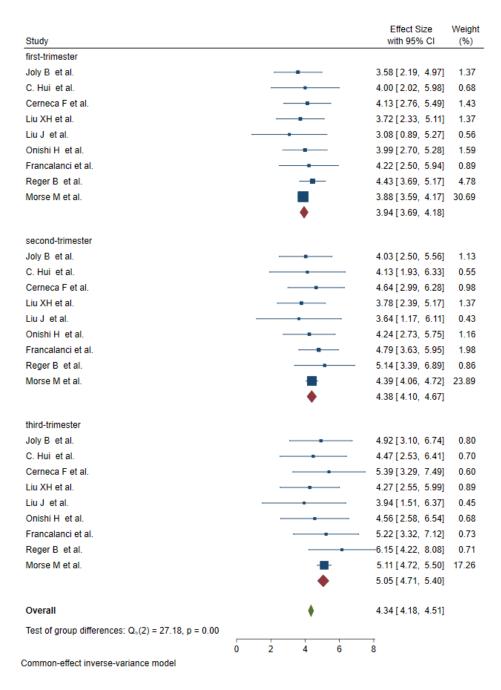


Fig. 7: Subgroup analysis forest plot of the impact of pregnancy on blood fibringen concentration

Changes in prothrombin time at different stages of healthy pregnant women

The prothrombin time in early, middle and late pregnancy was 0.38 (95% CI: -0.22, 0.98), 0.96 (95% CI: -0.67, 2.59) and 0.41 (95% CI: -0.12,

0.95), respectively. There was a statistically significant difference in prothrombin time between early, mid and late pregnancy (P=0.00). The results of the subgroup analysis are shown in Fig. 8.

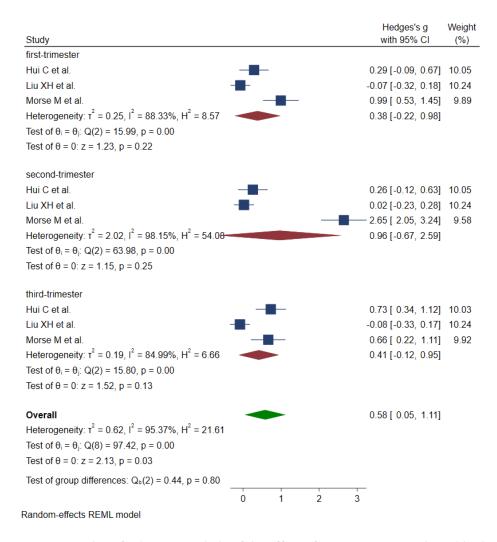


Fig. 8: Forest plot of subgroup analysis of the effect of pregnancy on prothrombin time

Publication bias

Egger's method is a statistical method used to detect publication bias in meta-analyses by assessing the relationship between effect estimates and their standard errors through regression analysis. If publication bias is present, small samples or non-significant results may tend to be unpublished, leading to systematic bias in the re-

sults. The funnel plot showed a slight asymmetry (Figs. S1-S2) We further quantified this using Egger's method, and statistical tests suggested that there was no publication bias in the results of fibrinogen: P=0.9864. The P-value of D-dimer was <0.05, suggesting that there may be publication bias regarding D-dimer.

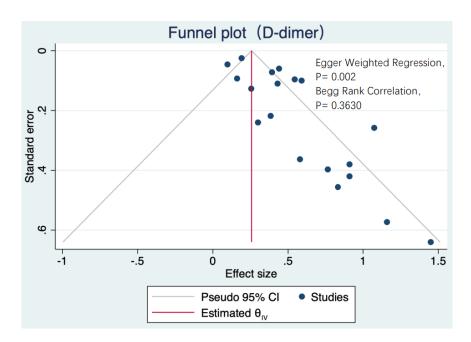


Fig. S1: The funnel plot (D-dimer)

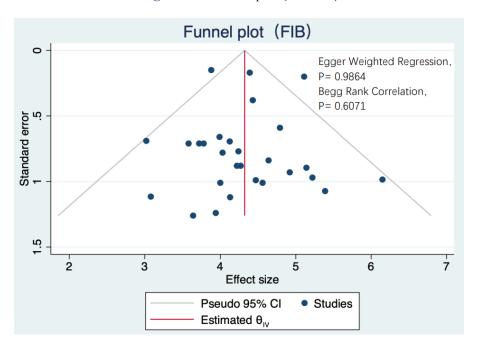


Fig. S2: The funnel plot (FIB)

Sensitivity Analysis

Sensitivity analyses were performed using Stata to assess the robustness of the results as shown in Figs. 9 and 10. The analyses presented pooled meta-analysis estimates and confidence intervals

by sequentially excluding individual studies. Studies were categorized according to pregnancy trimesters, with effect estimates and their intervals visualized using circles and vertical lines in the forest plot.

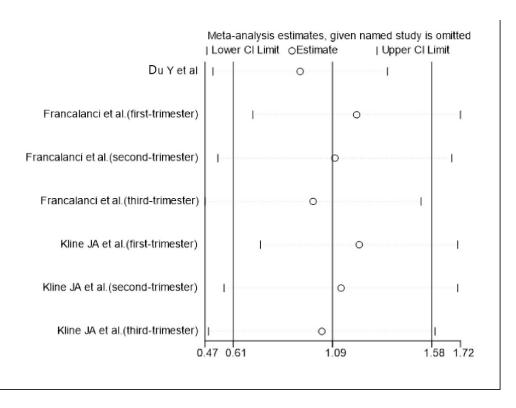


Fig. 9: Sensitivity analysis (D-dimer)

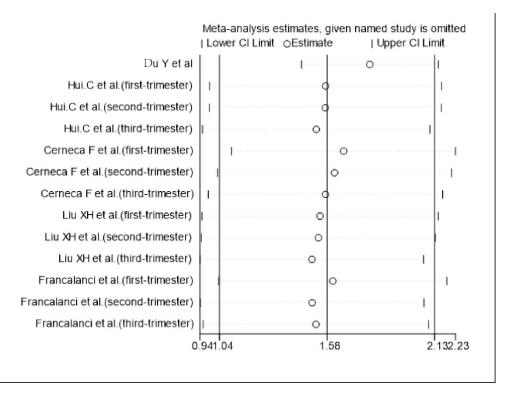


Fig. 10: Sensitivity analysis (fibrinogen)

Discussion

During pregnancy, the level of oestrogen in pregnant women is significantly elevated, which can stimulate the increased secretion of platelets, coagulation factors, and inhibitors of FIB activator in the blood, which leads to a hypercoagulable state of the blood (24). This particular normal physiological state is mainly a response of the body to cope with postpartum haemorrhage (25). DIC can be secondary to many clinical conditions (e.g., multi-organ trauma, sepsis, infectious shock) and obstetric conditions (in utero foetal death, amniotic fluid embolism, placental abruption, eclampsia, etc.) (5). The examination of patients with DIC is based on tests such as haematology, coagulation routine indexes, plasma ichthyoglobulin paracoagulation test (3 P test), and thrombus tetramer (26).

However, existing studies lack an authoritative standard reference range for the assessment of maternal coagulation. Although there is some scattered literature on the parameters of the body's coagulation indices during pregnancy and delivery, the results are mixed and even partially contradictory (2,6,7,13,24,25,26-28), and the inconsistency may be due to the limited number of samples included in the studies and the lack of consistency of blood samples collected during pregnancy. However, acute DIC occurring in obstetrics progresses very rapidly and is associated with haemorrhage (from postoperative wounds, reproductive tract, etc.) as well as multiorgan ischaemia, which leads to impaired function of vital organs and is extremely difficult to treat, thus leading to a very high maternal and foetal mortality rate (26).

The aim of this study was to evaluate the changes of key coagulation indexes in healthy pregnant women at different gestational periods by meta-analysis, and to explore their application value in the early detection and prevention of DIC. This study delineates the temporal characteristics of coagulation parameters in healthy pregnant women, establishing essential baseline references for

high-risk population research. In this study, significant heterogeneity was observed across multiple outcomes (I²>90%). We conducted trimesterspecific subgroup analyses to minimize variations attributable to differences in gestational periods. Additionally, disparities in detection methodologies across studies—including fully automated coagulation analyzers, ELISA, and immunoturbidimetry—as well as regional and ethnic variations in study populations, may substantially influence coagulation parameter measurements and serve as critical sources of heterogeneity. Although a random-effects model was employed to mitigate these effects, future investigations should incorporate sensitivity analyses and meta-regression to systematically explore heterogeneity origins. Standardized testing protocols and more homogeneous population selection during study design phases are essential to enhance the stability and reliability of analytical outcomes. A systematic search of Chinese and English databases resulted in the inclusion of 12 studies with a total of 2531 samples.

Based on the aggregated data from this study, the pooled results demonstrated that a significant upregulation of coagulation activity in healthy pregnant women compared to their non-pregnant counterparts. Meta-analysis revealed that healthy pregnant women had significantly higher Ddimer levels (MD=1.08, 95% CI: 0.61-1.56) and fibrinogen concentrations (MD=1.57, 95% CI: 1.04–2.10) compared to non-pregnant women. This phenomenon may be attributed to pregnancy-associated hormonal stimulation and subsequent platelet/leukocyte aggregation, leading to elevated D-dimer levels in maternal circulation (7). Furthermore, shortened PT (MD = 1.13, 95% CI: 0.43-1.83) and APTT (MD=0.73, 95% CI: 0.31–1.16) were observed in pregnant women relative to non-pregnant controls, indicating a heightened propensity for hypercoagulability and an elevated risk of developing DIC. These findings underscore the critical importance of routine coagulation profiling and dynamic monitoring in DIC prevention and management. Collectively,

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the observed alterations in the coagulation system during pregnancy likely represent physiological adaptations to meet the hemostatic demands of childbirth.

In the present meta-analysis, we systematically evaluated four key coagulation parameters: Ddimer, fibrinogen, PT, and APTT. The elevated D-dimer and fibrinogen levels, along with shortened PT and APTT, observed in healthy pregnant women reflect a physiologic hypercoagulable state that supports postpartum hemostasis (29). D-dimer, a specific degradation product of cross-linked fibrin, serves as a critical biomarker reflecting the activation of both coagulation and fibrinolysis (30). In DIC, excessive thrombin generation triggers widespread microthrombosis, while compensatory hyperfibrinolysis leads to markedly elevated D-dimer levels (30). Fibrinogen, a pivotal coagulation factor, is consumed during this process, and its dynamic level is a marker of DIC severity (31). Therefore, the physiologic elevation of these parameters during pregnancy establishes a higher baseline. Our meta-analysis quantified that the mean D-dimer level in healthy pregnant women was significantly elevated compared to non-pregnant women. This finding is consistent with longitudinal studies which demonstrate that D-dimer levels increase progressively and significantly throughout gestation, peaking in the third trimester (32). Notably, one such study established trimester-specific reference intervals and reported that in the third trimester, 99% of healthy pregnant women exhibited D-dimer levels above the conventional cut-off point of 500 µg/L (32). The reported reference intervals (e.g., 551-3333 µg/L for the third trimester (32)) underscore that the 'normal' range in pregnancy is substantially shifted. Consequently, the pooled mean concentration in the third trimester in our study (0.72 mg/L, equivalent to 720 µg/L) approaches or exceeds the conventional diagnostic threshold used in non-pregnant populations. This systematic increase highlights that any clinical application of D-dimer for ruling out pathology, such as DIC, must account for this pregnancy-induced physiologic shift. Sustained levels significantly above the expected gestational mean should raise suspicion for an underlying coagulopathy.

This study synthesizes the results of several studies through systematic evaluation and Metaanalysis, which enhances the statistical validity of the findings and has a high value in evidencebased medicine. However, the study has several limitations. 1) The included studies exhibited heterogeneous methodological quality and were restricted by relatively small sample sizes, which limited the capacity to adequately control for confounding variables such as age and ethnicity. Physiological profiles (e.g., hormonal fluctuations) and coagulation mechanisms may systematically differ across age strata and racial/ethnic groups due to variations in genetic predispositions. These methodological constraints, compounded by potential systematic differences in study inclusion criteria, may introduce publication bias into the pooled estimates. 2) This study primarily enrolled healthy women as subjects, failing to cover the high incidence of DIC in parturients with severe underlying diseases, thus unable to fully elucidate the impact of different pathological conditions on DIC risk. 3) The high heterogeneity in the study results may be attributed to significant variations in sample sizes, substantial statistical errors, as well as differences in underlying maternal conditions, age, gestational stage, and delivery methods, all of which could influence coagulation parameters.

Future studies will include more women with different underlying diseases and incorporate other coagulation indices that may affect DIC, such as platelet count and fibrin degradation products, in order to more comprehensively assess the risk of obstetric DIC. In addition, the reference ranges and clinical thresholds for each coagulation indicator need to be clarified to guide clinical decision-making for early recognition and prevention of DIC.

Conclusion

The physiological changes in maternal D-dimer and fibrinogen levels should be interpreted with

caution and in context, as they do not necessarily predispose pregnant women to DIC.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Availability of data and materials

The datasets used in the analysis was collected by online search, and the datasets analyzed in the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest

There are no financial or non-financial competing interests.

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