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Coagulation Parameters in Singleton and Twin Pregnancies

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ABSTRACT

Background: Coagulation and fibrinolytic systems affect maternal and fetal health in both singleton and twin pregnancies. Any abnormal deviation can have fatal implications like pre-eclampsia, venous thromboembolism, anemia, fetal asphyxia and haemorrhage.

Objective: We aimed to assess changes in coagulation and fibrinolytic systems throughout pregnancy (singleton and twin) through comparing the parameters for coagulation: Fibrinogen (Fib), activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT) and D-dimer (DD).

Subjects and methods: An interventional study was conducted on 300 pregnant women (194 singleton and 106 twin pregnancies), who were randomly recruited from 2019 to 2024 from the Outpatient Clinic of the General Military Hospital in Alexandria, Egypt. During routine antenatal care, coagulation parameters (Fib, APTT, PT, TT and DD) were analyzed during all trimesters of pregnancy.

Results: The mean maternal age showed no significant difference, whereas a twin pregnancy was significantly higher (P=0.000*) in primigravida (65.1%) than in multipara (34.9%). All coagulation parameters (TT, Fib, APTT and PT) showed significantly higher trends with increasing gestation in both singleton and twin pregnancy except for TT, which was the only coagulation parameter that did not show any significant difference **(**P=0.856).

All parameters of coagulation (TT, Fib, APTT and PT) showed significantly higher trends in twin pregnancies compared to singleton pregnancies in the first and final trimesters of pregnancy. In the second trimester of pregnancy Fib and TT showed significantly higher trends (P= 0.000*) in twin pregnancies than singleton pregnancies, whereas APTT and PT showed no significant differences (P= 0.017 and P= 0.699 respectively). D-dimer revealed significantly higher (P= 0.001*) trends in twin pregnancies compared to singleton pregnancies in the final trimester of pregnancy.

Conclusion: With increasing gestation, almost all coagulation parameters showed significantly higher trends in singleton and twin pregnancies. Individual trends in twin pregnancies were significantly higher in almost all coagulation parameters compared to singleton pregnancies.

Keywords: Parameters of coagulation, Twin pregnancies, Fibrinogen (Fib), Activated partial thromboplastin time (APTT), Prothrombin time (PT), Thrombin time (TT) and D-dimer (DD).

INTRODUCTION

Pregnancy is a physiological dynamic process caused by placental hormones leading to changes affecting all organ systems. These physiological changes ensure optimal nutrition and oxygen supply to the mother as well as the fetus, but induce changes in most biochemical test results [(1)]. Proper understanding of these changes allows accurate assessment of test results, identification of abnormalities and therefore appropriate management implementation [(2)].

Regarding the hematological system, pregnancy creates state of secondary hypercoagulability, manifested by an increase of physiological coagulation factors I, VII, VIII, IX, X, and XII [(3)]. Platelet production as well as aggregation increases, as do the levels of endogenous anti-coagulants like for example protein S. Thus developing a resistance to activated protein C. Moreover, an overall state of hypercoagulability is caused by impaired fibrinolysis due to plasminogen activator inhibitor (PAI), which is secreted by the placenta [(4)]. On the one hand, this hyper-coagulable state prevents bleeding at delivery, but on the other hand it increases the danger of thrombotic diseases mostly venous thromboembolism (VTE), which causes pregnancy-related morbidity and mortality [(5,6)]. The hyper-coagulable state also increases the risk for recurrent pregnancy loss, placental vascular problems (such as fetal demise) and pre-eclampsia [(7)].

Twin pregnancies put a heavier physical burden on pregnant women than singleton pregnancies and show profound physiological differences. Nevertheless, coagulation parameters lack thorough assessment and coagulation parameters of twin pregnancies still refer to the standards of singleton pregnancies and lack precise variation intervals [(8)].

SUBJECTS AND METHODS

In this experimental study, 194 pregnant women with a singleton pregnancy and 106 women with twin pregnancies were randomly recruited from routine antenatal care visits at the Outpatient Clinic of the General Military Hospital in Alexandria, Egypt over a period of 5 years (2019-2024). Coagulation parameters included fibrinogen (Fib), activated partial thromboplastin time

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(APTT), prothrombin time (PT), thrombin time (TT) and D-dimer (DD) were assessed in all trimesters of pregnancy.

Inclusion criteria: Any pregnant woman with a singleton or twin pregnancy and willing to participate. Normal BMI.

Exclusion criteria: (Aiming to recruit apparently healthy pregnant women): History of habitual abortion. History of smoking. History of any type of assisted reproductive technology like ICSI or IVF. History of thrombosis. History of chronic diseases (e.g. diabetes mellitus, heart, liver, kidney, thyroid, etc.). History of a recent infection. History of surgery or trauma within the previous 30 days. History of blood transfusions within the previous 6 months. History of anticoagulant drug use (e.g. aspirin or heparin). History of obstetric complications (e.g. pregnancy-induced hypertension syndrome, gestational diabetes mellitus, placenta abnormalities, etc.).

Blood samples were collected by venipuncture of an antecubital vein and stored in vacuum tubes containing 3.8% sodium citrate.

Ethical approval: All pregnant women were subjected to an informed written consent before participating in the study and this study was approved by the Ethics Committee of the General Military Hospital and it has been performed according to the World Medical Association's 2013 revision of the Declaration of Helsinki for human experimentation.

Statistical analysis

The statistical software SPSS version 25 (Armonk, NY: IBM Corp) was used to manage and analyze data. Mean ± SD was used to present the ages of the pregnant women and the paired student`s t-test was used for statistical comparisons of the changes in coagulation parameters over the three gestational trimesters in singleton and twin pregnancies. The independent student`s t test was used for statistical comparisons of coagulation parameters between singleton and twin pregnancies at the same gestational trimester. To show and analyze differences between data, the Chi-square test was applied and in all cases. $P \leq 0.05$ indicated statistical significance.

RESULTS

Mean maternal age showed no significant difference between pregnant women, whereas twin pregnancies were significantly higher (P=0.000*) in primigravida (65.1%) than in multipara (34.9%) (Table1).

Table (1): Maternal age and gravity in singleton and twin pregnancy

Variable	Singleton Pregnancy (n=194)	Twin Pregnancy (n=106)	P-Value
Age in years (Mean ± SD)	26 ± 5.9	27 ± 6.1	P=0.682
Gravity			
• Primigravida	120 (61.9%)	69 (65.1%)	**P=0.000***
• Multipara	74 (38.1%)	37 (34.9%)	**P=0.000***

In the second trimester of singleton pregnancy, all coagulation parameters (Fib, APTT, PT and TT) showed significantly higher (P=0.000*) trends than in the first trimester (Table 2).

Table (2): Coagulation parameters in the first and second trimesters of singleton pregnancy

	First trimester	Second trimester	p-value
Fib	3.25 ± 0.34 g/L	4.05 ± 0.37 g/L	**P=0.000***
APTT	29.13 ± 1.40 s	27.45 ± 1.32 s	**P=0.000***
PT	11.01 ± 0.41 s	10.19 ± 0.35 s	**P=0.000***
TT	13.70 ± 0.75 s	13.14 ± 0.62 s	**P=0.000***

In singleton pregnancy`s third trimester, the coagulation parameters Fib, APTT and PT showed significantly higher (P=0.000*) trends than in the second trimester. TT was the only coagulation parameter that did not show any significant difference (P=0.856) between the second and third trimesters of singleton pregnancy (Table 3).

Table (3): Coagulation parameters in the second and third trimesters of singleton pregnancy

	Second trimester	Third trimester	p-value
Fib	4.05 ± 0.37 g/L	4.31 ± 0.39 g/L	**P=0.000***
APTT	27.45 ± 1.32 s	26.33 ± 1.23 s	**P=0.000***
PT	10.19 ± 0.35 s	9.91 ± 0.36 s	**P=0.000***
TT	13.14 ± 0.62 s	13.13 ± 0.56 s	**P=0.856**

In the second trimester of twin pregnancy, all coagulation parameters (Fib, APTT, PT and TT) showed significantly higher (P=0.000*) trends than in the first trimester (Table 4).

Table (4): Coagulation parameters in the first and second trimesters of twin pregnancy

	First trimester	Second trimester	p-value
Fib	3.58 ± 0.41 g/L	4.27 ± 0.39 g/L	**P=0.000***
APTT	30.13 ± 1.61 s	27.04 ± 1.55 s	**P=0.000***
PT	10.68 ± 0.27 s	10.18 ± 0.14 s	**P=0.000***
TT	13.18 ± 0.70 s	12.85 ± 0.45 s	**P=0.000***

In the third trimester of twin pregnancy, all coagulation parameters (Fib, APTT, PT and TT) showed significantly higher (P=0.000*) trends than in the second trimester (Table 5).

Table (5): Coagulation parameters in the second and third trimesters of twin pregnancy

	Second trimester	Third trimester	p-value
Fib	4.27 ± 0.39 g/L	4.54 ± 0.44 g/L	**P=0.000***
APTT	27.04 ± 1.55 s	28.40 ± 1.30 s	**P=0.000***
PT	10.18 ± 0.14 s	9.64 ± 0.20 s	**P=0.000***
TT	12.85 ± 0.45 s	12.88 ± 0.44 s	**P=0.000***

All coagulation parameters (APTT, Fib, PT and TT) showed significantly higher (P=0.000*) trends in twin pregnancies than in singleton pregnancies in the first and third trimester of pregnancy. In the second trimester fibrinogen and TT showed significantly higher trends (P=0.000*) in twin pregnancies than in singleton pregnancies, whereas APTT and PT showed no significant differences (P= 0.017 and P= 0.699 respectively). In the third trimester D-Dimer showed significantly higher (P=0.001*) trends in twin pregnancies compared to singleton pregnancies (Table 6).

Table (6): Coagulation parameters in singleton and twin pregnancy

	Singleton pregnancy	Twin pregnancy	P-Value
First trimester			
• Fib	3.25 ± 0.34 g/L	3.58 ± 0.41 g/L	**P=0.000***
• APTT	29.13 ± 1.40 s	30.13 ± 1.61 s	**P=0.000***
• PT	11.01 ± 0.41 s	10.68 ± 0.27 s	**P=0.000***
• TT	13.70 ± 0.75 s	13.18 ± 0.70 s	**P=0.000***
Second trimester			
• Fib	4.05 ± 0.37 g/L	4.27 ± 0.39 g/L	**P=0.000***
• APTT	27.45 ± 1.32 s	27.04 ± 1.55 s	**P=0.017**
• PT	10.19 ± 0.35 s	10.18 ± 0.14 s	**P=0.699**
• TT	13.14 ± 0.62 s	12.85 ± 0.45 s	**P=0.000***
Third trimester			
• Fib	4.31 ± 0.39 g/L	4.54 ± 0.44 g/L	**P=0.000***
• APTT	26.33 ± 1.23 s	28.40 ± 1.30 s	**P=0.000***
• PT	9.91 ± 0.36 s	9.64 ± 0.20 s	**P=0.000***
• TT	13.13 ± 0.56 s	12.88 ± 0.44 s	**P=0.000***
• DD	0.68 ± 0.43 µg/mL	1.38 ± 0.95 µg/mL	**P=0.001***

DISCUSSION

Pregnancy is a state of hypercoagulability increasing the danger of developing VTE and preeclampsia [9]. We aimed to compare all coagulation parameters (APTT, Fib, PT, TT and DD) in singleton and twin pregnancies over the gestational trimesters.

The current study showed that all coagulation parameters (APTT, Fib, PT and TT) showed significantly higher trends with increasing gestation in both singleton and twin pregnancy except for TT, which did not show any significant difference (P=0.856) between the second and third trimesters of singleton pregnancy. A case control study performed on singleton pregnancies showed that increased thrombin activity has been suggested in the physiology of preeclampsia. The study showed that patients with early and late-onset preeclampsia had elevated levels of TT at 8-16 weeks of gestation. The study recommends that selective patients could benefit from LMWH to prevent preeclampsia and fetal growth restriction [10]. Similar results were reported by a prospective cohort study and a cross sectional study. Both studies reported that Fib increased significantly from the no gravid period to the third trimester and all coagulation parameters increased by the third trimester except for PT and APTT, which showed decreasing levels in the third trimester [11,12].

The current study showed that all coagulation parameters (APTT, Fib, PT and TT) showed significantly higher (P=0.000*) trends in twin pregnancies than in singleton pregnancies throughout gestation. Similar results were reported by a prospective cohort study performed on 300 pregnant women. The study reported that in the middle and late pregnancy, the coagulation and fibrinolytic systems underwent a series of changes in order to meet the needs of pregnancy. Levels of coagulation parameters in twin pregnancies gradually increased and exceeded levels of coagulation parameters in singleton pregnancies [13]. Another study performed on a total of 40 746 cases (38 320 singleton and 2426 twin pregnancy cases) assessed indicators related to coagulation function in twin and singleton pregnancies throughout gestation. The study stressed that specific reference intervals for coagulation parameters for singleton as well as twin pregnancies were crucially needed [8].

The current study showed that D-Dimer showed significantly higher (P=0.001*) trends in twin pregnancies than in singleton pregnancies particularly in the third trimester of pregnancy. Similar results were reported by **Bellesini *et al.*** [14] who suggested that D-dimer was not only safe but also useful in predicting, diagnosing and managing suspected VTE in pregnancy. However, the available data were insufficient and further trials were necessary to identify and validate a D-dimer cutoff level during singleton and twin pregnancies. The need for valid cutoff values for all coagulation parameters was stressed by multiple studies that showed a significant correlation of coagulation parameters and the prediction, occurrence, progression, and degree of negative outcomes like hypertensive disorders, fetal asphyxia, anemia, postpartum hemorrhage and chiefly VTE [15,16].

LIMITATIONS

Our study had several limitations. Firstly, it might have been constrained by the sample size and selection of the study population, resulting in a lack of generalizability. Secondly, a single study cannot precisely express the dynamic alterations in coagulation parameters throughout gestation, and longitudinal follow-up studies are required for a more profound understanding and for the identification and validation cut off levels.

CONCLUSIONS

All coagulation parameters (APTT, Fib, PT and TT) showed significantly higher trends with increasing gestation in both singleton and twin pregnancy. Compared to singleton pregnancies, twin pregnancies showed significantly higher trends in all coagulation parameters with increasing gestation, except for the second trimester APTT and PT trends that showed no significant differences. Third trimester DD also showed significantly higher trends in twin pregnancies than in singleton pregnancies.

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