Original Article

A cross-sectional study of coagulation parameters in normal and high risk pregnancy

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To asses coagulation parameters Prothrombin time, Activated Partial Thromboplastin Time, Thrombin Time, D-dimer in pregnant women. A cross sectional study of 282 patients attending antenatal outpatient department at AIIMS, New Delhi were recruited. Among the 282 subjects, 251 were pregnant and 31 were controls. Plasma was tested for coagulation parameters Prothrombin time (PT), Activated Partial Thromboplastin Time (aPTT), Thrombin Time (TT), D-dimer using Sysmex CA-1500 automated coagulation analyser. The study included 282 women of which 31 were non pregnant while 251 were pregnant. The value of PT was within the normal range (10-12 seconds) during all the three trimesters, while it was on the lower side of normal in the third trimester. The value of APTT was within the normal range (24-40 seconds) during all the three trimesters, however the value was highest during the second trimester. The value of TT was within the normal range (15-23 seconds) during first and third trimester while the second trimester showed marginal rise in the value. D-dimer was normal (<0.5microg/ml) in the second trimester while the first and third trimester showed increased value. Normal pregnancy causes an alteration in coagulation with prothrombin time, activated partial thromboplastin time, Thrombin time which asses the extrinsic, intrinsic and common coagulation pathway respectively were within the normal limits throughout pregnancy while D-dimer an assay of fibrin degradation products showed higher values during the first and the third trimester.

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Key words **: Coagulation, prothrombin time, activated partial thromboplastin time, thrombin time, D-dimer, pregnancy.**

Pregnancy is a normal physiological change and is associated with changes in coagulation system. This change contributes in maintaining a state of haemostasis. This haemostasis plays a major role in continuing normal pregnancy and also preventing excessive bleeding during delivery and puerperium[1,2]. While these physiological changes may be important for minimizing intrapartum-blood loss, they entail an increased risk of thromboembolism during pregnancy and the post-partum period.

There is activation of blood coagulation and a simultaneous increase in fibrinolysis without signs of organ dysfunction during normal pregnancy. These changes increase as pregnancy progresses. There are gestational age specific reference ranges for routine haemostatic assays like prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and fibrinogen (Fib) during pregnancy which may have a bearing on clinical decisions during various pregnancy complications[3]. During delivery, there is consumption of platelets and blood coagulation factors, including fibrinogen. Fibrinolysis improves and increases fast following childbirth and expulsion of the placenta, resulting in increased D-dimer levels. These changes are self-limiting at normal delivery. The hemostatic changes, noted during pregnancy, normalize after delivery within 4 to 6 weeks[4,5].

The coagulation system undergoes significant change during pregnancy. The clinician caring for the parturient must understand these changes, particularly when the parturient has a pre-existing haematological condition. Because many haematological conditions are rare, there often is limited information to guide the obstetric and anaesthetic management of these parturients.

Thus we conducted a cross sectional study on various coagulation markers like prothrombin Time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), D-dimer during pregnancy in both normal and abnormal pregnancies.

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Materials and Methods

The study is a prospective cross-sectional study conducted on 282 pregnant ladies visiting the obstetric outpatient department (OPD) for antenatal checkup in AII India Institute of Medical Sciences, New Delhi between 1st November 2012 to 31st March 2013. Criteria for inclusion was all pregnant ladies visiting the antenatal OPD. Exclusion criteria included pregnant ladies with sepsis and malignancy. Patients with co-morbid conditions like hypertension, gestational diabetes, hypothyroidism, hyperthyroidism, intrahepatic cholestasis, heart disease, anemia, coagulation disorder were included in the high risk group. The control group included 31 non pregnant healthy ladies. The study included 251 patients in the test group while 31 patients in the control group after giving participant information and taking consent. Ethical clearance was obtained from our institutional Ethics committee.

Measurement

In the morning as fasting state a total of 5ml of blood sample for the study was obtained by peripheral vein sampling. A total of 1.8 ml of peripheral venous blood was collected in sodium citrate containing vacutainer. The sample was centrifuged and the plasma thus obtained for coagulation study ie, Prothrombin Time (PT), Activated partial thromboplastin time (APTT), Thrombin time (TT) and D-Dimer assay. The coagulation markers were tested within 60 minutes of blood collection.The assay was performed on CA-1500 automated coagulation analyser (Sysmex CA-1500 YZB Japan 1419) which measures the test value using scattered light detection method.

Due to non availability of test reagents during the study period some tests could not be done in all cases.

Statistical Analysis

Descriptive measures such as mean, standard deviation, median and inter quartile range values were calculated. Since numbers of observations in each category were not adequate to apply parametric rest, non parametric Mann-Whitney "U" test was carried out. ANOVA was used to test the significance of differences between pregnant group and non pregnant women and among different trimesters of pregnancy. Further to see linear associations between two study variables bi variate correlation coefficient were computed. For all statistical rests a probability value of $p<0.05$ was considered statistically significant.

Results

The characteristic of women are shown in Table 1.

The study included 282 women of which 31 were non pregnant while 251 were pregnant.

The youngest participant was 20 years old while eldest was 40 years with the median age being 27 years.

Among the pregnant women 66(26.3%) were aged 20-24 years, 105(41.8%) 25-29 years, 65 (25.9%) 30-34 years and 15(6.0%) were more than 35 years of age.

A total of 88(35.1%) women were primigravida while 163(64.9%) women were multigravida.

A total of 71(28.3%) women were in first trimester of gestation, 76(30.3%) women were in second trimester and 104(41.4%) women were in third trimester of gestation.

Table 1— *Characteristics of patients*

No of patients :	
Total number	282
Non-pregnant women	31
Pregnant women	251
Age :	
Age range	20-40 years
Median age	27 years
Parity :	
Primigravida	88(35.1%)
Multigravida	163(64.9%)
Trimester :	
First	71(28.3%)
Second	76(30.3%)
Third	104(41.4%)

The median value of various coagulation markers in the three trimesters are shown in Table 2.

Table 2 — *Median values of various tests according to trimester in pregnant ladies*

Tests	PT (seconds)	APTT (seconds)	TT (seconds)	D-dimer (mcg/ml)
Non pregnant state	11	30	16	<0.1
First trimester	10.5	27.10	18.3	0.7750
Second trimester	10	28.45	24.8	0.5000
Third trimester	9.95	25.8	23.7	0.7500
Overall in pregnant state	10.15	27.1	22.2	0.675

The value of PT was within the normal range (10-12 seconds) during all the three trimesters, while it was on the lower side of normal in the third trimester.

The value of APTT was within the normal range (24-40 seconds) during all the three trimesters; however the value was highest during the second trimester.

The value of TT was within the normal range (15-23 seconds) during first and third trimester while the second trimester showed marginal rise in the value.

D-dimer was normal (<0.5microg/ml) in the second trimester while the first and third trimester showed increased value.

The values of D-dimer in various trimesters are shown in Table 1 and Fig 1.

In the present study 77(30.7%) pregnant ladies had high risk factor. Of the high risk group ladies 9(3.6%) had hypertension associated with pregnancy, 20(26.0%) had gestational diabetes, 9(3.6%) had hyperthyroidism, 3(3.9%) had epilepsy, 2(2.3%) had hypothyroidism, 13(16.9%) had intrahepatic cholestasis of pregnancy. 16(20.8%) had heart disease, while 9(3.6%) had coagulation disorder. The medial values of various coagulation markers in various disease conditions are shown in Table 2.

According to bivariate analysis the Pearson correlation was significant between age and PT(207). And between TT and APTT (250).

Discussion

Normal pregnancy involves many changes in maternal physiology including alterations in hematologic param-

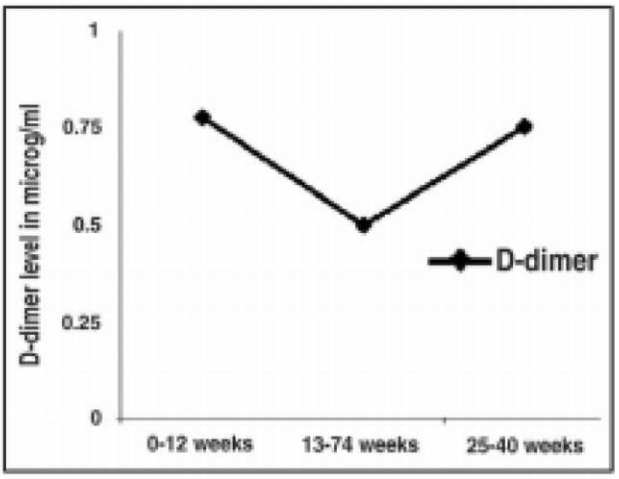

Fig 1 — The values of D-dimer in various trimesters

Table 3 — *Median values of various tests parameters along with p value in various disease conditions*

Disease condition number (%)	PT (seconds)	APTT (seconds)	TT (seconds)	D-dimer (mcg/ml)
Hypertension 9(3.6)	10.1 (p=0.527)	26.9 (p=0.991)	21.8 (p=1.000)	0.75 (p=0.847)
GDM 20(20.6)	10.1 (p=0.899)	26.9 (p=0.760)	21.7 (p=1.000)	0.75 (p=0.387)
Hyper-thyroidism 1(3.9)	10.1 (p=0.531)	26.9 (p=0.482)	21.7 (p=0.473)	0.75 (p=0.847)
Epilepsy 3(3.9)	10.1 (p=0.531)	26.9 (p=0.482)	21.8 (p=1.000)	0.75 (p=unable to compute)
Hypo-thyroidism 2(2.3)	10.1 (p=0.889)	26.9 (p=0.603)	22.4 (p=0.473)	0.75 (p=0.648)
Intrahepatic cholestasis 13(16.9)	10.1 (p=0.853)	26.9 (p=0.731)	22.4 (p=0.606)	0.74 (p=0.354)
Heart disease 16(20.8)	10.1 (p=0.597)	26.9 (p=0.727)	22.4 (p=0.605)	0.75 (p=0.735)
Coagulation disorder 9(3.6)	10.1 (p=0.346)	27.05 (p=0.450)	21.7 (p=1.000)	0.75 (p=0.123)

eters[1-3]. These changes include expansion in maternal blood and plasma volume. as well as an increase in the levels of some plasma proteins that alters the balance of coagulation and fibrinolysis[5]. During pregnancy the concentrations of coagulation factors VII, VIII, IX, X, XII and von Willebrand factor rise significantly thus making pregnancy a hypercoagulable state to prevent hemorrhage at time of childbirth. This is reflecting in various laboratory tests done to asses' coagulation[1]. Prothrombin time (PT) reflects the function of exogenous coagulative pathway while aPTT reflects the function of endogenous coagulative pathway. Thrombin time (TT) can reflect the content and structure of plasma fibrinogen to some extent[4].

In the present study the value of PT was within the normal range during all three trimesters. These results are similar to the studies of Han *et al*[4], Millar *et al*[6], Babiker *et al*[7], and found PT to be significantly prolonged during pregnancy. However, Hui *et al*[8] observed prothrombin time to be decreased in mid and late pregnancy. Srimala *et al*[9] also found decreased prothrombin time during normal pregnancy when compared with age matched control groups of non pregnancies and attributed it to changes in hemostatic balance in the direction of hypercoagulability with increased concentration of all clotting factors except factor XI and XIII.

Liu *et al*[3] found highest reference range for PT in first trimester, lowest in second and intermediate in third trimester.

The value of aPTT was within the normal range during all the three trimesters in present study. However Han *et al*[4] and Hui *et al*[8] found aPTT to be shortened in mid and late pregnancy while Babiker *et al*[7] found aPTT to be significantly prolonged during pregnancy in their study .

Liu *et al*[3] found aPTT to be highest in first trimester, lowest in second and lowest in third trimester of pregnancy.

The value of TT was within the normal range in the present study. However Han *et al*[4] found significantly higher thrombin time in pregnant subjects as compared to control subjects. This was also observed in the works of other authors. Study by Amilo *et al*[10] suggested that the increase in coagulation factors observed during pregnancy are due to increased thrombin generation.

D-dimer is a specific degradative product resulting from the hydrolysis of fibrin monomer[4]. It is considered as an indirect marker of thrombosis and fibrinolytic activity[4]. Maternal D-dimer concentrations rise progressively during pregnancy from conception to delivery with rise being more in pre-eclamptic pregnancies[4]. Murphy *et al*[11] observed a continuous increase in median D-dimer concentration over the complete gestational period while which were well above the cut off concentration in non-pregnant stage.

Despite the decrease in fibrinolytic activity, levels of fibrin degradation products including D-dimers have been shown to rise with advancing gestational age.The increase in coagulation activity may manifest as increased D-dimer, and this change takes 6-8 weeks to return to normal after delivery[6]. In the present study levels of D-dimer showed increased values in first and third trimester but were within normal levels (<0.5mcg/ml) in second trimester. Kline *et al*[16] found that pregnancy increased the D-dimer concentration in a stepwise fashion from preconception to the third trimester. Liu *et al*[3] observed lowest TT in third trimester, intermediate in first trimester and highest in second trimester or pregnancy. Previous research has shown higher D-dimer concentration in pregnant women with pre-eclampsia as compared to normotensive women[12,19]. However in the present study although D-dimer levels increased during pregnancy, there was no significant change in hypertensive disorders. It could be due to less patients (only

9 cases) and only mild hypertension in the present study.

Increased fibrinogen has been observed in disseminated intramuscular coagulation (DIC) in which there is thrombocytopenia, prolonged coagulation times, reduced coagulation, inhibitors and high levels of fibrin …. products and D-dimers[13-15].

Erez *et al*[16] studied blood coagulation tests on all women during pregnancy and observed increased maternal plasma fibrinogen concentrations during pregnancy, gradual decrease of maternal platelets during pregnancy with no change in prothrombin time and aPTT with advance gestation. They established normographs for pregnancy and constructed DIC score based on ROC curve analysis. Even in animal studies on mares who have peripartum haemorrhage as a recurring hazardous… showed a positive correlation between fibrinogen levels and late pregnancy and a negative correlation between fibrinogen levels and early postpartum. The shortening of PT recorded near parturition along with increase in platelets and fibrinogen at foaling may reflect a physiological hyper-coagulation state to constrain heavy bleeding enhancing mares chance of survival[18].

Conclusion

In conclusion, our results indicate normal prothrombin time, activated partial thromboplastin time, thrombin time assesing the extrinsic, intrinsic and common coagulation pathways respectively throughout pregnancy. However D-dimer an assay of fibrin degradation products showed higher values during the first and the third trimester of pregnancy. Larger studies are needed to confirm the findings of present study.

Compliance with Ethical Requirements and Conflict of Interest : All procedures followed were in accordance with the Ethical Standard of the Responsible Committee on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from the patient. The study was conducted in department of Obstetrics and Gynaecology in collaboration with department of Lab Medicine. The work is designed and was performed after taking ethical clearance from the Institutional ethical committee. All the authors declare no conflict of interest with any pharmaceutical company or hospital. The authors have no financial disclosures to make.

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