

COAGULATION PROFILE IN DIFFERENT TRIMESTERS OF PREGNANCY TO IDENTIFY HIGH RISK PREGNANCY

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Abstract

Background: The physiological changes in pregnancy may serve to protect the mother from the hazard of bleeding imposed by placental and delivery, but they also carry the risk of an exaggerated response, localized or generalized, to coagulant stimuli. After correlating the trends of coagulation profile in all three trimesters of pregnancy with parameters [Body Mass Index (BMI), Glycemic status, Blood Pressure Status]; We can find out high risk pregnancies so that special attention can be given during pregnancy, labour and postpartum period.

Material & Methods: A observational prospective analytic study done on 100 Pregnant ladies who were visited to routine antenatal clinic in the department of Obstetrics & Gynecological SMS Medical College and attached group of hospitals, on outdoor basis were selected in their first trimester (after 8 week gestation) in SMS medical college & attached group of hospitals during April 2017 to March 2018. The study protocol was approved by the Institutional Ethics Committee. All participants submitted informed consent before enrolment. After taking proper history, all the subjects underwent clinical examination comprising of general physical examination, assessment of vital parameters and systemic examination.

Results: Our study that the mean age of study subjects was 26.46 ± 3.34 years. There was significant but weak positive correlation of D Dimer with BMI and Blood sugar in all trimesters of pregnancy. Significant correlation was found between APLA with DBP and MAP in 1st trimester of pregnancy. No correlation was found between APLA and other parameters in any trimester of pregnancy.

Conclusion: We concluded that there were increased in FDP, D-Dimer, INR, APLA while platelets count, PT and aPTT were decreased. Further prospective study will be required to measure the outcome of pregnancy so we can define a high-risk pregnancy and those will get special attention in peripartum period.

Keywords: Trimester, Pregnancy, D Dimer, BMI, Blood pressure, Correlation

Introduction

Pregnancy is associated with various physiological changes, which tend to affect most of the body system and some of these begin immediately after conception continuing through delivery to the postpartum period in order to accommodate both the maternal and fetal needs.

There are so many factors which directly or indirectly affects the coagulation system just like co-morbid condition (hypertension, diabetes mellitus, thyroid disorders), Infections, Disseminated Intravascular Coagulation (DIC), obesity, dietary habits etc. which produces morbidity and mortality in antepartum as well as postpartum periods.

Hyperglycemia in pregnancy either on going diabetes or gestational diabetes itself presents symptoms of hypercoagulability and hypo fibrinolysis. Hyperglycemia have abnormalities of endothelium, platelets, clotting factors, natural anticoagulants and fibrinolytic system (by stimulating PAI-1 production). All these changes are

directly or indirectly caused by hyperglycemia. Most of studies indicate that coagulation processes predominate over fibrinolytic activity in hyperglycemia cases.¹

Pregnancy induced hypertension (PIH) is defined as hypertension that develops as the direct result of gravid state. It includes gestational hypertension, Preeclampsia and Eclampsia. Chaware SA et al (2017)² studied and found that severe Preeclampsia and eclampsia were characterized by thrombocytopenia and coagulation abnormalities indicating intravascular coagulation. Platelet count and aPTT had predictive value in screening for consumptive coagulopathy in the severe cases of Preeclampsia and eclampsia. Sharma UK et al (2016)³ conducted a study and concluded that the abnormalities pertaining to coagulation parameters in PIH indicate the impending intravascular coagulation.

Some researcher showed that increased incidence of pre-eclampsia, premature rupture of membrane in those patients

who had coagulation dysregulation in their gestational periods. Sarika Singh *et al*⁴ studies on the coagulation profile also showed that there is increase chance of PROM, pre-eclampsia and other uneventful condition more with coagulation dysregulation.

Keren *et al*⁵ studies that Shortened PT and aPTT, reflecting increased thrombotic activity in maternal plasma, could serve as a marker of real preterm labor in women with premature uterine contractions.

Madan R *et al*⁶ showed that hypercoagulable state as indicated by decreased fibrinolysis and increased coagulability is responsible as one of the factors for the development of microvascular complications of diabetes mellitus.

The incidence of thromboembolic disease is probably increased during pregnancy^{7,8}, venous thromboembolism events were higher in patient with deranged coagulation profile, so many studies also proved same. Swarropa *et al*⁹ studies on effectiveness of D-dimer in venous thromboembolism and found that d-dimer level was higher in VTE.

Thus, it is important to know variations in hemostatic profiles during pregnancy so that adequate measures can be taken well in time to minimize pregnancy related morbidity and mortality.

As Indian data in this context are lacking so this study was planned to assess incidence of coagulation abnormalities (FDP, D-dimer, aPTT, PT-INR, Platelet count, APLA) in pregnancy and to correlate these coagulation abnormalities with risk factors (body mass index, blood pressure and glycemic status).

Material & Methods:

A observational prospective analytic study done on 100 Pregnant ladies who were visited to routine antenatal clinic in the department of Obstetrics & Gynecological SMS Medical College and attached group of hospitals, on outdoor basis were selected in their first trimester (after 8 week gestation) in SMS medical college & attached group of hospitals during April 2017 to March 2018. The study protocol was approved by the Institutional Ethics Committee. All participants submitted informed consent before enrolment.

Inclusion Criteria

- Pregnant women willing to give consent to participate in the study.

Exclusion Criteria

- Previous Thromboembolic episode
- H/o Oral contraceptive pill
- H/O Acquired Thrombophilia or Family History

- H/O Previous Complicated Pregnancy
- H/O Smoking
- H/O Malignancy

Clinical Examination

After taking proper history, all the subjects underwent clinical examination comprising of general physical examination, assessment of vital parameters and systemic examination.

BLOOD PRESSURE MEASUREMENT

Blood pressure was measured in the arm manually by following the guidelines given by the British and Irish Hypertension Society 2017¹⁰ Blood pressure was measured twice for each subject.

Specimen collection and hematological analysis:

Blood sample were collected from 100 pregnant women in all three trimesters. About 6 ml venous blood samples were drawn by the lab technician from pregnant women. Each blood sample was divided into EDTA tube (2ml), 3.2% Tri-Sodium Citrate tube (2ml) and plain tube (2ml). EDTA tube was used for complete blood count, then added blood sample to citrated tube for ESR analysis. Tri sodium citrate tube was used for PT, INR, APTT and fibrinogen analysis. Plasma samples were obtained by centrifugation at room temperature at 4000 rpm for 10 minutes to analyzed samples during 3 hours after blood collection. Plain tubes were left for short time to allow blood to clot. Then, serum samples were obtained by centrifugation at room temperature at 4000rpm for 5 minutes to measure serum related investigations.

Statistical Analysis

Nominal / categorical variables were summarized as frequency and percentage Continuous variables were summarized as mean and standard deviation and were analyzed using repeated measure ANOVA test for intra group comparison at different trimester and one way ANOVA test for inter group comparison.

Results:

Our study that the mean age of study subjects was 26.46 ± 3.34 years with most of the subjects (49) being in the age of 25 – 29 years (table 1). There was significant but weak positive correlation of D Dimer with BMI and Blood sugar in all trimesters of pregnancy. No correlation was found between D Dimer and Blood pressure in any trimester of pregnancy (table 2).

Our study shows that there was weak positive correlation of FDP with BMI in 1st and 2nd trimester of pregnancy. Moderate correlation was found between FDP and Blood sugar in 3rd trimester of pregnancy (table 3). In present, the weak positive correlation of PT with BMI in 1st trimester of pregnancy (graph 1).

The present study shows that there was weak negative correlation of platelet count with Blood sugar in 1st trimester of pregnancy (table 4) and there was moderate correlation of APLA with Blood sugar in all trimester of pregnancy. Significant correlation was found between APLA with DBP and MAP in 1st trimester of pregnancy. No correlation was found between APLA and other parameters in any trimester of pregnancy.

Discussion:

The age range of the subjects included in our study was 19-35 years. Majority of the subjects (49 %, 49/100) were in the 25-29 years group. Only 1 % (1/100) subject was in <20 years age group. The mean ages of pregnant women were 26.4 years. **Federico et al**¹¹ studies on coagulation profile in pregnant women with mean age 28.9±4.16 years (age range 22-41 years). **Zaccheus et al**¹² conducted study in pregnant ladies with mean age 28.4±4.2 years (age range 16-41 years). **D.G. Woodfield et al**¹³ (1968) studied FDP in pregnant women with mean age 24±5 years (age range 18-24 years). So the mean age and age range in our study is in echo with other studies with same purpose.

D-Dimer was increase from first to third trimester of pregnancy in patients with all BMI groups, however this increase was significant only in BMI 18.5-24.9 Kg/m² and BMI ≥24.9 Kg/m² group (P<0.001). While comparing in same trimester there was no significant difference was found in D Dimer level across all BMI groups. The reason behind this because in obese patients there is increased concentration and enhanced activity of plasma coagulation factor as well as impaired fibrinolysis, systemic inflammation, endothelial dysfunction, disturbance of lipid and glucose metabolism and insulin resistance and also pleiotropically acting genes may contribute to the clustering of procoagulant and metabolic risk factor in obese patients. There was weak but significant correlation found between BMI and d-dimer level in our study. **Franco CK et al**¹⁴ conducted a study on BMI and fibrinolytic activity and found that D-dimers were positively correlated with BMI (r=0.003, p<0.001). This results match with our study.

There was significant but weak positive correlation of D Dimer with Blood sugar in all trimesters of pregnancy (r<0.03, p<0.01). **El Asrar MA**¹⁵ et al showed that there was significant increase in d-dimer level both in type 1 (p<0.05) as well as type 2 (p<0.05) diabetes patient as compared with non-diabetic patients. There was increase in D Dimer from first to third trimester of pregnancy in patients with all hypertensive as well as normotensive, however this increase was significant only in patients who were normotensive and pregnancy induced hypertension (PIH) (P<0.05) but no correlation was found with between D Dimer and Blood pressure in any trimester of pregnancy. (P>0.05). But those ladies who had controlled blood pressure on antihypertensive drugs didn't had significant correlation (p=0.315). In our study no correlation was found between D Dimer and Blood pressure in any trimester of pregnancy.

FDP was increased from first to third trimester of pregnancy in patients with all BMI groups. This increase was statistically significant across all BMI groups (P<0.05). On comparison in the same trimester, FDP was found to be high in higher BMI group in all trimesters of pregnancy, but it was statistically significant in first and second trimester only. There was weak positive correlation of FDP with BMI in 1st (r=0.298, p=0.02) and 2nd (r=0.249, p=0.012) trimester of pregnancy. **Michel T**¹⁶ conducted a study on FDP in obese patient and showed that there was increase statistically significant in FDP level in obesity (P=0.03) as compare to non-obese patient. FDP level increase in obese patient because recent experimental studies demonstrated a pro-inflammatory role for FDP at the molecular level. It has been suggested that fibrin and its degradation products play an important role in the inflammatory process, namely through stimulation of interleukin (IL)-124 and IL-8,25 and expression of intracellular adhesion molecule-1 (ICAM-1) in obese people.

FDP was increase from first to third trimester of pregnancy in patients with any glycemic status, and this increase was significant in both normoglycemic and hyperglycemic groups (P<0.001). On comparison in the same trimester, no significant difference was found in FDP level across both glycemic groups in first and second trimester of pregnancy. However, in third trimester, the FDP was significantly higher in patients with BS≥126mg/dl (P=0.006). Moderate correlation was found between FDP and Blood sugar in 3rd trimester (r=0.347, p=0.001) of pregnancy. **Agata et al**¹⁷ conducted a study and showed that statistically significant increase in FDP level (3.5±0.2 vs 2.9±0.2) p value <0.05 in diabetic patient as compared to non-diabetic patients.

There was increase in FDP from first to third trimester of pregnancy in patients with normotensive, chronic hypertensive, and pregnancy induced hypertension and this increase was significant in all patients (P<0.001). On comparison in the same trimester, however no significant difference was found in FDP level across all Blood Pressure status. There was positive correlation of FDP with DBP (r=0.290, p<0.001) and MAP (r=0.236, p=0.012) in our study. **Asiya et al**¹⁸ observed higher mean FDP level in hypertensive patients (346±64.16) compared to control (276.75±37.31) and this difference was statistically significant (p=0.002). This finding also matches with our study results.

Prothrombin time was decline from first to third trimester of pregnancy in patients with BMI 18.5-24.9 Kg/m² and BMI ≥24.9 Kg/m² (P=0.001). On comparison in the same trimester, no significant difference was found in Prothrombin time across all body mass index (BMI) groups in second and third trimester of pregnancy. There was positive correlation of PT with BMI in 1st trimester (r=0.215, p=0.031) of pregnancy. There was significant decline in prothrombin time from first to third trimester of pregnancy in patients with normoglycemic status, but not in hyperglycemic patients (P<0.001). In our study no

correlation was found between PT and glycemic status in any trimester of pregnancy. A small study done by **Obeagu et al**¹⁹ on coagulation profile in diabetic patients and showed that no significant change in level of prothrombin time in DM (17.2 ± 3.2) as compared to Non-diabetic patient (16.5 ± 2.8) ($p > 0.05$).

There was decline in prothrombin time from first to third trimester of pregnancy in patients with all blood pressure status, however this decline was significant only in normotensive patients ($P < 0.001$). On comparison in the same trimester, however no significant difference was found in prothrombin time across all blood pressure status. No correlation was found between PT and blood pressure status in any trimester of pregnancy. **Naaz MD et al**¹⁸ showed in their study that the mean and standard deviation of prothrombin time (sec) in controls is 12.49 ± 1.45 as compared to 16.7 ± 1.83 in test group. ($p < 0.001$). This was suggestive of impact of blood pressure on prothrombin time as occurs in our study.

In our study there was decline in platelet count from first to third trimester of pregnancy in patients with all BMI groups, however this decline was significant only in BMI $18.5-24.9 \text{ Kg/m}^2$ and BMI $\geq 24.9 \text{ Kg/m}^2$ group ($P < 0.05$). On comparison in the same trimester, no significant difference was found in platelet count across all BMI groups in any trimester of pregnancy.

There was decline in platelet count from first to third trimester of pregnancy in patients with any glycemic status, however this decline was significant only in patients with BS $< 126 \text{ mg/dl}$ ($P < 0.001$). On comparison in the same trimester, no significant difference was found in platelet count across both glycemic groups in any trimester of pregnancy. There was weak negative correlation of platelet count with Blood sugar in 1st trimester of pregnancy. **Bronisz et al**²⁰ showed in their study that there was significant negative correlation between glycemic status with pregnancy and platelets count. They found that platelets count ($\times 10^3$) in first, second and third trimesters were 200 ± 9.8 , 201.9 ± 10.1 and 172.0 ± 9.0 respectively. (1 vs 3; 2 vs 3 $p < 0.05$). These findings are similar to our study. The thrombocyte survival time to be reduced in diabetes which may be associated with greater thrombocyte use during pregnancy due to hyperglycemia and increased blood sugar level also impeded prostacyclin synthesis by endothelial cells and glycosylated collagen stimulates platelet adhesion, degranulation and aggregation more intensely.

There was decline in platelet count from first to third trimester of pregnancy in patients with all Blood pressure status, however this decline was significant only in normotensive and chronic HTN patients ($P < 0.05$). On comparison in the same trimester, however no significant difference was found in platelet count across all BP status. **Sameer et al**²¹ April 2014 indicated the mean platelet count in normal pregnancy was 2.39 lakhs/cubic mm and severe PIH was 1.6 lakhs/cubic mm with significant P-value < 0.001 . **Asiya et al**¹⁸ conducted a study and found that

mean and standard deviation of platelets count (lakhs/cu mm) in controls is 2.76 ± 0.42 as compared to 1.86 ± 0.29 in test group. ($p < 0.001$)

In our study there was increase in APLA IgM from first to third trimester of pregnancy in patients with all BMI groups, however this increase was significant only in BMI $18.5-24.9 \text{ Kg/m}^2$ ($P < 0.001$). On comparison in the same trimester, no significant difference was found in APLA IgM level across all BMI groups in any trimester of pregnancy. No correlation was found between APLA and BMI in any trimester of pregnancy.

There was increase in APLA IgM from first to third trimester of pregnancy in patients with any glycemic status, however this increase was significant only in patients with BS $< 126 \text{ mg/dl}$ ($P < 0.001$). On comparison in the same trimester, significant difference was found in APLA IgM level across both glycemic groups in any trimester of pregnancy. There was positive correlation of APLA with Blood sugar in first trimester ($r = 0.365$, $p = < 0.001$), second trimester ($r = 0.401$, $p < 0.001$) and third trimester ($r = 0.416$, $p < 0.001$) of pregnancy.

There was increase in APLA IgM from first to third trimester of pregnancy in patients with all Blood pressure status, however this increase was significant only in normotensive patients ($P < 0.001$). On comparison in the same trimester, however no significant difference was found in APLA IgM across all BP status. Significant correlation was found between APLA with DBP ($r = 0.075$, $p = 0.457$) and MAP ($r = 0.237$, $p = 0.017$) in 1st trimester of pregnancy.

The results of this study showed that coagulation trends in all three trimesters of pregnancy and also correlate them with blood pressure status (normotensive, chronic hypertensive and pregnancy induced hypertension) and blood sugar status. FDP, D-Dimer, APLA and INR are increased while platelets counts, PT and aPTT were declined.

Conclusion:

On the basis of such studies, we can predict the outcome of pregnancy and can identify those high-risk pregnancies in which we have to give special attention during antenatal as well as postnatal periods so as to minimize the morbidity and mortality maternal as well as fetal.

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