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Original Article

Physiological D-Dimer Concentration in Pregnancy

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ABSTRACT

Objective: To determine the mean D-Dimer concentration in third trimester of normal pregnancy so new thresholds can be determined and applied in this population for ruling out venous thromboembolism.

Methodology: A cross sectional study conducted at the Department of Pathology, PAEC General Hospital, Islamabad. Sample size of 127 was calculated by using WHO sample size calculator at 95% confidence interval. Normal healthy pregnant females of third trimester attending the OPD of Gynecology and Obstetrics in PAEC were inducted in study through non-probability convenient sampling.

Results: Among 127 normal healthy pregnant females in third trimester enrolled>90% had D-Dimer concentration of more than 0.5µg/ml. (Mean value being1.0 $\pm$ 0.55 µg/mL).The range of D-Dimer was 0.05 to 5.0µg/ml.

Conclusion: Mean D-Dimer concentration was found to be higher in majority of cases in our study than conventional cutoff value of 0.5 µg/ml used in general population for diagnostic workup of venous thromboembolism. D-dimer test can still prove to be useful for the exclusion of thromboembolic state in pregnant women, if new cutoff baseline is defined in this special population.

Keywords: D-Dimer concentration, pregnancy, Venous Thrombo-embolism

Introduction

Pregnancy is a prothrombotic state in which risk of venous thromboembolism (VTE) increases to about 5to 10 folds compared to age matched non pregnant females[1].This risk diminishes drastically after delivery except mild risk which persists for 12 weeks postpartum[2,3]. In pregnancy associated VTE most (approximately 80%) episodes are isolated deep vein thrombosis (DVT) mostly in left leg, and 20% of the episodes are associated with pulmonary embolism(PE).[4]So VTE is an important cause of maternal morbidity and mortality specially in the Western world.

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Moreover, physiological changes occurring during pregnancy can mimic symptoms of VTE i.e. pain or swelling in legs and shortness of breath due to weight gain or anemia. Objective testing to determine the presence or absence of VTE is very important. The diagnosis of VTE is based upon clinical probability scoring system(e.g. Wells scoring system), D-dimer estimation (a prognostic biomarker for VTE) and imaging tests[5-7]. D-Dimer is a specific cross linked Fibrin degradation product[8] which is raised in thrombosis but is also raised in trauma, inflammation, sepsis, malignancy, following surgery, cardiac disease and in normal pregnancy.[5,6,7,9]In pregnant females, D-dimer testing is either underutilized or if tested and conventional cutoff value of 0.5mg/L[10] is applied, can lead to misdiagnosis of VTE. Some studies recommend gestational age specific reference interval[11] while other recommend imaging test as cornerstone for diagnosis of VTE[3].D-dimer can still be used in pregnant females as a biomarker for VTE, if mean plasma concentration of D-Dimer in this population is revaluated. In this way, pregnant female will not have to undergo exposure to ionizing radiation in form of spiral CT and lung ventilation/perfusion scans which can increase

the risk of developmental damage to fetus[12] or expensive test like venous ultrasonography as a diagnostic process of VTE .Moreover, in many clinics and smaller hospitals venous ultrasonography is not always available whereas a quantitative D-Dimer test which is rapid and reliable may be more easily available.

The current study was undertaken to determine the mean value of D-Dimer in healthy pregnant females of third trimester so the magnitude of increase in D-Dimer concentration could be evaluated and new thresholds could be determined and applied in this special population while testing for possible venous thromboembolism. Moreover, no local data of its value in third trimester of normal pregnancy was available.

Methodology

A cross sectional study was conducted at the Department of Pathology, PAEC General Hospital Islamabad from January 2013 to January 2014.Sample size of 127 was calculated by using WHO sample size calculator at 95% confidence interval.Healthy pregnant females of third trimester attending the OPD of Gynecology and Obstetrics, PAEC were included in the study.Sample was selected by non-probability consecutive sampling. After informed consent, history data Performa was filled in isolation. A venous blood sample of 3 ml was collected from everyone in a standard citrated tube properly labeled with name, date and patient control number.Inside laboratory the samples were centrifuged at 3000 g for 15 minutes to separate plasma for D-Dimer levels evaluation by fully automated particle enhanced Immunoturbimetricassay(for the quantitative determination of D-Dimer antigen by monoclonal antibody (8D3) covalently coupled to polystyrene particles).

The normal D-Dimer concentration using automated Immunoturbimetric method was taken as <0.5µg/ml[10].All collected data was entered in SPSS version 20. Descriptive statistics was used to calculate the mean and standard deviation for continuous data that is D-Dimer values in third trimesters of pregnancy. Gender and parity being qualitative (ordinal) variables were expressed in terms of frequency and percentages. Effect of age, gestational week and gravidity on D-Dimer levels was checked by Univariate linear regression analysis.

Results

The mean age of 127 enrolled pregnant females was 28.6 ± 4.2 years (range 18-40yrs.), patient were categorized according to age and gravidity(Table1-2).Our study showed that >90% females had D-Dimer concentration of more than 0.5µg/ml.

Table 1: Age of study patients

Age (years)	No of patients	%age
Up to 20	3	2.3%
21 to 25	26	20.4%
26 to 30	62	48.8%
31 to 40	36	28.3%
Mean ± SD	28.6 ± 4.2	

(Mean value being1.0 ± 0.55 µg/mL). 90.7 %(115)of our patient had elevated D-dimer of >0.5µg/ml. Gestational week has a significant positive correlation of D-Dimer concentration with p-value of 0.027 (F 13, 1.99). Our study showed no significant correlation of age and gravidity on D-Dimer levels.

Table 2: Gravidity in the study (n=127)

Gravidity	No of patients	%age
Primigravida	34	26.7%
Multigravida	90	70.8%
Grand multigravida	3	2.3%

Conclusion

The mean D-Dimer concentration in our selected study population group was found to be higher than the conventional cutoff value of 0.5µg/ml used in general population. This shows that normal pregnancy causes a positive D-Dimer test by third trimester if this conventional value is used to define abnormal results.

Discussion

The findings of our study re-emphasized the fact that conventional D-dimer threshold of 0.5ug/L has little value in excluding VTE in pregnancy. This is because even normal pregnancy is associated with physiological increase in D-dimer levels. So new thresholds of D-dimer should be defined before utilizing this test for ruling out VTE in pregnancy. Our study showed that >90% females had D-Dimer concentration of more than 0.5µg/ml which was taken as normal cutoff for diagnosis of VTE. Mean value in our study is 1.0 ± 0.55 µg/mL which is comparable and in continuation with many previous studies done on the topic.

A study by Cuis et al[13]on trimester-specific reference intervals of coagulation screening tests and thrombophilia markers in pregnancies without

complications of females with Han ethnicity from North China showed that from the first trimester to the third trimester, APTT, PT and TT presented shortened trends, Fibrinogen and D-Dimer presented increasing trends, AT, PC and fPS activity presented decreasing trends, respectively.

Many studies like ours using D-Dimer in pregnancy with 0.5µg/ml cut off value for diagnosis of VTE showed higher value except that we focused on 3rd trimester and did not include 1stand 2ndtrimesters and perpurem phase. A study by Ercan et al[15] showed that if the threshold of 0.50 mg/L for diagnosis of VTE is used, 4.8% of pregnant women in the second trimester and 23.8% of pregnant women in the third trimester would have D-dimer levels exceeding this cut-off value. Reference intervals of D-dimer were determined as 0.11–0.40 mg/L; 0.14–0.75 mg/L and 0.16–1.3 mg/L in first, second and third trimester, respectively.A study by Ierene et alwas done on 102 healthy pregnant women.[10]Plasma D-dimer levels were measured during the three trimesters of pregnancy, using a latex-based immunoturbidimetric assay. D-dimer levels increased progressively and significantly through pregnancy and peaked in the third trimester, in which D-dimer levels were above the conventional cut-off point (500 µg/L) in 99% of pregnant women. The following reference intervals were defined: first trimester: 169–1202 µg/L, second trimester: 393–3258 µg/L and third trimester: 551–3333 µg/L.Katrine K. Hedengran[16] suggests D-dimer progressively increased throughout the pregnancy. As early as weeks 13–20, more than 25% of the pregnant women had D-dimer levels at or above 0.5 mg/L, and by weeks 36–42, practically all of the pregnant women had values above this conventional threshold.They suggested that a threshold of 1.0 mg/L could offer clinical value until gestational week 30, but approaching full term most healthy women have D-dimer values above this limit. Similarly, other studies suggest the threshold during pregnancy should be increased to 1.0 or 2.0 mg/L [17]

In 2 studies the threshold of normal D-Dimer was below the one we used as normal cut-off yet the findings showed D-Dimer well above the cut offs.Murphy et al [8]found that pregnancy increased the D-Dimer concentration in a stepwise fashion from conception till birth across all gestational ages. Seven hundred and sixty healthy pregnant women were investigated between gestational age week 5 and 48 hours postpartum. There was a clear steady increase in median D-dimer concentrations over the complete gestational period. Additionally, the 95th centile estimates for all gestational time-points were above the accepted non-pregnancy normal cut-off concentration (224 ng/ml)which is equal to 0.22µg/ml.They found that there was a continuous increase in D-dimer concentrations across all gestations.A study by Kovac et al [14] showed a linear relationship between gestation and D-dimer concentration.It concluded that 84% of women had a normal D-dimer in first trimester,33% had a normal concentration in second trimester, and1% had a normal concentration by the third trimesterif the threshold of 230 ng/mL (0.23µg/ml) was used. They found out that the D-Dimer level elevated with the progress of pregnancy from first trimester to third and reached the highest level in the latter.They also established clear correlation between raised D-Dimer,USG and development of VTE in pregnant females .They noted that D-Dimer was6.7 to 7.6 times higher in first while 2.0 to 3.8 times higher in 3rd trimester when it was associated with thrombosis and positive ultrasound findings($p<0.0001$).For 3rd trimester we have noted value of D-Dimer>5 times from normal cut off(maximum value being 5µg/ml) when not even associated with thrombotic episode.

In line with previous studies, this study also suggests that if a D-dimer threshold during pregnancy is warranted, then it should be gestational age-specific and should be interpreted with great precaution.Pregnancy has strong association with VTE and at the same time D-dimer levels are also physiologically raised in pregnancy.Although the use of D-Dimeras a predictor of VTE is highly beneficial, specially, in resource constraint settings due to its quick and non-invasive features but a consensus has been reached by many investigators that the level of cut off should be set high to screen out the true positive casesonly. This study has many advantages which includes a reasonable sample of pregnant women observed for D-Dimer levels. Very few studies are conducted to determine the mean D-Dimer concentrations in our local populations and the information generated will show us the way to set the cut point for D-Dimer according to the population mean.

Recommendations

1-We submit our findings as first step in redefining the cut off or threshold values of D-Dimer in pregnant females so this test is avidly used to rule out thromboembolism but further studies are still required.

2-These cut off values are meant for hypothetical purpose only and are not recommended to be used clinically before further research is done.
3-We recommend evaluation of D-Dimer values preconception, in each trimester, and post-partum in each pregnant female so that level and pattern of raise in D-Dimer can be more precisely evaluated.
4-We also recommend co-relation of D-Dimer values with that of plasma Fibrinogen levels which is also elevated in pregnant females.

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