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D-Dimer Reference Range in Each Trimester of Pregnancy-Need to Detect Venous Thromboembolism of Pregnancy

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Abstract

Venous thromboembolism [VTE] is common in pregnant females but limitations for timely diagnosis using non-invasive techniques delays the diagnosis and cause increased morbidity. Inability to use radiological methods and physiological increase of D-dimer values in pregnancy inhibits the use of non-pregnant reference ranges of D-dimer. The Present study aims to develop a reference range for healthy pregnant women and compare the D-dimer values of known cases of DVT in pregnancy. Using the strict exclusion criteria in 100 pregnant females only 17 were included finally in study group. Four samples from each participant were drawn during each trimester including 4 weeks post-partum. A progressive increase in D-dimer was found as the period of gestation increased followed by a fall at 4 weeks post-partum. The D-dimer values were statistically different from each other in all trimesters and post-partum. The 75th percentile of D dimer levels in all the three trimesters and at 4 weeks post-partum exceeded 255ng/ml [reference value in reagent kit insert]. When these values were compared with the values from pregnant females with DVT in each trimester [24] it showed statistically significant difference with a pattern as D-dimer values were 5 times,4 times and 3 times higher in pregnant women with DVT as compared to normal pregnancy in our study. The normal D-dimer reference range of pregnancy if known can help to diagnose VTE. Larger studies which include clinical assessment tools along with D-dimer evaluation in pregnant (normal and VTE) are required to further strengthen D-dimer as non-invasive method to diagnose VTE in pregnancy.

Keywords: D-dimer; Venous thromboembolism; Pregnancy; Deep vein thrombosis; Reference range

Introduction

Normal pregnancy is often referred to as a physiological hypercoagulability state. The changes include increased thrombotic activity, which is due to increase in the plasma coagulation factor activity of Factor I, VII, VIII, IX, X and XII along with decrease in the concentration of the natural clotting inhibitor as protein S. Additional, there is intensified process of platelet adhesion and platelet aggregation [1,2]. The high procoagulation activity during normal pregnancy [from conception until delivery], results in increased fibrin turnover [increased concentrations of D-dimer, a recognized marker of activation of fibrinolysis] [3] and thus increased D-dimer does not necessarily mean any existence of hyper fibrinolysis [as in non-pregnant state] [4,5,6].

Pregnancy puts women in a high-risk group for developing VTE especially in the puerperium with an estimated 20 times increase in relative risk [7,8]. VTE diagnosis in pregnancy/ puerperium is a great challenge for clinicians [6]. The most popular pre-test probability criteria [Wells Pre-test probability criteria] [9] for DVT does not include pregnancy as a risk factor. Radiological imaging modalities like Computed tomography pulmonary angiogram [CTPA] and lung ventilation/perfusion scans [V/Q] which can be well used in non-pregnant state for diagnosis of VTE, cannot be used in pregnancy due to increased risk of developmental damage to the fetus [10].

Therefore, the question arises that can a non-invasive, easily available D-dimer test can be used to rule out presence of VTE in Pregnancy and post-partum? Since the D-dimer values in pregnant females have higher values than non - pregnant state, the normal reference range of D-dimer in pregnancy in each

trimester is required, so that pregnant, suspected VTE cases can be differentiated from the normal pregnant state. This study carries significance as there is a paucity in the medical literature for published reference ranges of maternal plasma D-dimer during all the trimesters of a normal pregnancy, including the postpartum period in Southeast Asian pregnant female population.

Method

Pregnant females aged between 20-35 years from 11 weeks-13 weeks period of gestation were included in the study at the start after strictly implementing the exclusion criteria (Table 1). Out of 100 screened, samples were collected from 39 booked pregnant women who did not develop any complications during pregnancy or postpartum period. All were screened during each trimester for exclusion criteria so that cases which during any time in the entire pregnancy came under it, can be excluded. About 5 ml of whole blood was collected in 3.2% sodium citrate during first antenatal visit [first trimester] 11-13 weeks. The second sample [Second trimester] was drawn between 24-26 weeks. The third sample [Third trimester] was drawn between 34-36 weeks. The last, fourth sample was drawn four weeks postpartum.

Table 1: Exclusion criteria for pregnant females to be included in final study group.

Exclusion Criteria at the Time of Registration	Exclusion Criteria During Present Pregnancy
Age < 20 years and > 35 years	Gestational diabetes
Family or personal history of thromboembolic disorder	Preeclampsia/ Eclampsia
Morbid obesity (BMI >40 Kg/m^2)	Abruption placenta
Family or personal history of bleeding disorder	. Cholestasis of pregnancy
Infection with fever (>38 C)	Acute fatty liver of pregnancy
History of Autoimmune disorders	Intrauterine growth restriction
History of liver or kidney disease	Still birth
If taking any anticoagulant (oral or parenteral)	Inability to return to the hospital due to geographical inaccessibility
History of any recent surgery	
History of diabetes mellitus/ hypertension	
Previous obstetric complications (still birth/ Intrauterine growth restriction/ spontaneous abortion/ abruption placenta/ gestational diabetes/ pre-eclampsia/ eclampsia).	

The plasma samples stored at -70 ºC were thawed at 37 ºC in water bath. D dimer was then assayed on ACL Elite pro Automated analyser which works on the principle of Latex enhanced turbidimetric immunoassay. The test was carried out as per the operating protocol by the manufacturer. The statistical analysis was done on SPSS version 21 software. Machine was subjected to regular Quality controls and were within limits.

Result

A total of 39 subject's blood samples were collected in 3.2 % sodium citrate vial for D- dimer in this study. Unfortunately, 14 patients were lost to follow up as did not return to hospital and hence were excluded from the study. Samples from 25 patients (4 samples each) were tested for D dimer. Of these, samples from 8 pregnant women could not be included due to technical issues. Thus 4 samples obtained at appropriate times collected from 17 pregnant women were finally available for the study.

The present study showed that among the pregnant between the age group 0f 20-35 years, there was no statistically significant variation in D dimer levels (Table 2). Parity [11 Nulliparous v/s 6 Multiparous] did not affect the D-dimer values statistically (Table3). Mean value of D-dimer in each trimester of pregnancy and 4 weeks post- partum [n=17] were 314.76ng/ml, 370.29ng/ml, 418.59ng/ml and 272.18 ng /ml in 1st, 2nd, 3rd trimester and 4 weeks post-partum respectively (Table 4). The difference of D - dimer values were statistically significant between the three trimesters and post-delivery 4 weeks. The 75th percentile of D dimer levels in all the three trimesters and at 4 weeks post- partum exceeded 255ng/ml. The maximum level of D dimer in 17 patients assayed 4 times was found to be 929ng/mL in the 3rd trimester. Since the sample size was less than 20 in our study, confidence interval could not be calculated. How ever the Median and Inter-Quartiles ranges [IQR] of D-dimer for 1st trimester Median 302 ng/ml [IQR 261-338 ng/ml], 2nd trimester with Median value 321ng/ml [IQR 268-396ng/ml],3rd trimester Median value 344 [IQR 216-285 ng/ml].

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Table 2: Distribution of D-dimer according to age of the patients (N=17).

	Age category	N	Mean	Std. Deviation	Minimum	Maximum	P value
1st trimester	20-25	5	257.6	74.718	135	319	0.093
	26-30	7	293.43	61.161	188	368	
	31-35	5	401.8	155.938	255	577	
	Total	17	314.76	111.648	135	577	
2nd trimester	20-25	5	393.8	136.959	272	625	0.284
	26-30	7	303.29	59.601	238	402	
	30-35	5	440.6	224.85	227	757	
	Total	17	370.29	149.474	227	757	
3rd trimester	20-25	5	524.8	204.39	194	733	0.295
	26-30	7	332.57	96.005	205	520	
30-35		5	432.8	295.913	204	929	
	Total	17	418.59	206.438	194	929	
4week post partum	20-25	5	301.4	128.436	187	520	0.323
	26-30	7	231	43.882	183	293	
	30-35	5	300.6	96.996	231	470	
	Total	17	272.18	91.974	183	520	

Table 3: Distribution of D- dimer according to Parity.

Parity			1st Trimester	2nd Trimester	3rd Trimester	4 Weeks Post-partum	P Value
Nulliparous	N		11	11	11	11	0.016
	Mean		315	401.9	451.27	273.27	
	Std. Deviation		95.052	176.156	236.028	90.653	
	Minimum		188	227	194	183	
	Maximum		565	757	929	520	
	Percentiles	25th	267	272	283	219	
		50th (Median)	310	324	349	262	
		75th	319	594	637	293	
Multi-Parous	N		6	6	6	6	0.281
	Mean		314.33	312.33	358.66	270.16	
	Std. Deviation		147.71	56.627	135.262	103.0833	
	Minimum		135	238	205	183	
	Maximum		577	390	559	470	
	Percentiles	25th	225	257.5	234.25	206.25	
		50th (Median)	280.5	312.5	335	236.5	
		75th	412.75	365.25	495.25	328.25	
Test Applied - Friedman test							

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Table 4: Mean value of D-dimer in each trimester of pregnancy and 4 weeks post -partum (n=17).

		1st Trimester	2nd Trimester	3rd Trimester	4 Week Post Partum	P Value
Mean (ng/ml)		314.76	370.29	418.59	272.18	0.005
Std. Deviation (ng/ml)		111.648	149.474	206.438	91.974	
Minimum (ng/ml)		135	227	194	183	
Maximum(ng/ml)		577	757	929	520	
Percentiles	25th	261	268	263.5	216.5	
	50th (Median)	302	321	344	245	
	75th	338.5	396	539.5	287.5	

Discussion

A normal pregnancy is characterized by changes in hemostasis towards hypercoagulation due to altered levels of coagulation factors, venous stasis, some vascular damage. Abnormal hemostasis leads to more venous thromboembolism in pregnant females as compared to nonpregnant women. The three important limitations for early diagnosis of VTE in a pregnant women are firstly the signs and symptoms of DVT and PE overlap with physiological changes of pregnancy [especially dyspnea and leg swelling] complicatingthe early clinical assessment. Secondly, D dimer levels increase with gestational age, its conventional cut off 500 ng/ml to diagnose VTE has limited value in pregnant women. Lastly, pregnant women cannot be investigated with imaging modalities due to risk of exposure of the fetusto radiations, [risk of teratogenesis and carcinogenesis] [10]. D-dimer as a non-invasive test can help to rule out VTE in pregnant women once the reference range is known. The sample size was small in our study like of the study which had normal pregnant subjects as 18 [11].

Another study was done that included not only pregnant [24 in number] but also [non pregnant 10 in number] and 33 women with complicated pregnancies (hypertension, diabetes Mellitus) [12]. However few studies with larger sample size were also conducted [13-17]. This age group was taken for two reasons, firstly, this is the most common age of pregnancy in southeast Asian population [18]. and secondly the increase of D-dimer values with age was seen in 100% of the women >40 years with higher D dimer levels as compared to 44% and 43% women aged 20 years and 30 years respectively [12].

According to British Committee of Standards in Hematology guidelines [19,20] the cut-off value to exclude VTE needs to be confirmed locally in minimum of 200 subjects in laboratory. However, this approach is not possible inall laboratories and thus the manufacturer cut off may be used. In present study, the kit insert shows that cut off of D-dimer values as a reference was 255ng/ml, but it was not specified that out of 300 cases taken to develop this cut off, how many were pregnant females. Hence kit insert reference range cannot be used for pregnant females.

Table 5: Comparison of Mean and Reference ranges in current study and previous publications on D-dimer levels in Pregnancy. D-Dimer (ng/ml).

Sno	Author	Study population	instrument	Journal / year	Age group	1st trimester/ Range	2st trimester/ Range	3st trimester/ Range	6-8 weeks post partum
1	Mirjana et al	89	Instrumentation laboratory (IL)	2009	18-40	222 (121-474)	326 (171-733)	475(206-890)	223(110-390)
2	Aldona et al (64)	37	Enzyme linked fluorescence assay	2020	25-44	376 (247-505)	688(252-1124)	1082(646-1168)	Not done
3	Nornattasa (69)	101	Instrumentation laboratory (IL)	2019	18-48	481(<1070)	1073 (357-1748)	1533(771-2410)	Not included
4	Tang et al	Metanalysis (30 Studies,15514)	variable	2018	18-44	570ng/ml (430-710)	980ng/ml (750-1210)	1480ng/ml (1810-1770)	790ng/ml (430-1160)
5	Our study	18	ACL Elite pro	2023	20-35	314 ng/ml (261-338)	370 ng/ml (268-396)	418 ng/ml (263-539)	223 ng/ml(216-287)

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In the present study, the reference range values derived, when compared with those obtained from few other studies, some interesting observation were seen as shown in Table 5. Firstly, all the studies, showed the D-dimer levels increased as the duration of pregnancy increased until it falls to lower levels post-partum. The wide discrepancy between D-dimer values in different studies may be likely due to different assays and analyzers used, rather than geographic or ethnic differences.

In the present study, reagent manufacturer abnormal cut off values for VTE >255ng/ml was exceeded in 76.5% of the patients in 1st trimester, 88.2% of the patients in 2nd trimester,76.5% of the patients in 3rd trimester and 53% [6-8 weeks post-partum].If, the cut off is raised to >500ng/ml [as in non-pregnant], it showed that 12% in first trimester,18 % in second trimester, 35% in third trimester and 5% in post-partum have values >500ng/ml as in graphical presentation Figure 1.

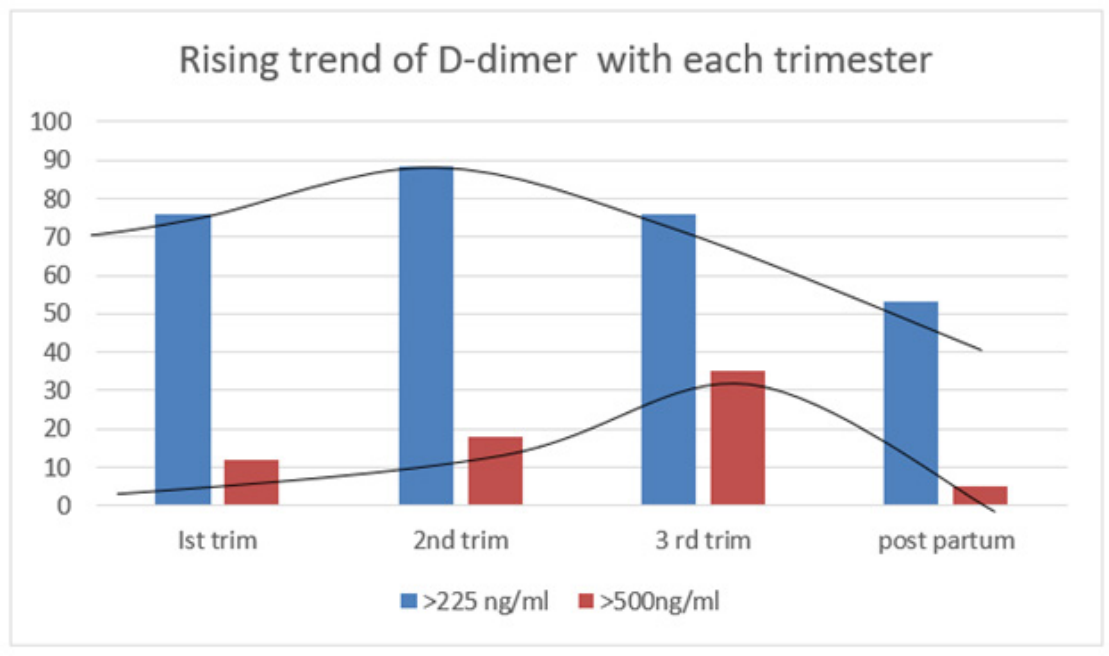

Figure 1: Pattern of D-dimer values when cut off is kept at >500 ng/ml instead of 255 ng/ml as given in kit insert of reagent.

Two recent prospective studies [21,22] correlated that when the cut off values of D-dimer were taken as < 500ng/ml, along with Wells Pretest Probability [9] of low, intermediate grade in pregnant, the safety of D-dimer use to exclude VTE in pregnant patients holds great promises. According to these studies, at 3 months follow up for thromboembolic risk in pregnant in categories of low and intermediate risk (Wells Pretest Probability criteria) and D-dimer values were < 500ng/ml, was just 2/981 and 1/312.

These observations were perfectly in line with the recent recommendations from the International Society of Thrombosis & Hemostasis, suggesting that the upper bound of the 3-month VTE risk should be below 2% in diagnostic strategies for VTE [23]. In our study, although we did not clinically categorize (Wells Pretest Probability criteria) still the exclusion criteria and follow up at 4 weeks, showed that all the 17 patients did not develop VTE.

Study done by Mirjana et al. [24] showed that the pregnant females with DVT in first trimester had 7-7.6 times higher values of D-dimer than the mean D-dimer value in the first trimester normal pregnant females. When compared with the D-dimer values in second trimester in pregnant with DVT, it was 1.6-5.4 times higher than the values in second trimester normal pregnant females. Lastly, in third trimester the D-dimer values in the pregnant with DVT was 2-3.8 times higher than the normal pregnant females.

When we compared the D-dimer values obtained in our study with the values from pregnant females with DVT in different trimesters from the study [24] and analyzed [unpaired t test] the values were statistically significant (Table 6&7). Thus, a trend of 5,4,3 times respectively for 1st,2nd &3rd trimester was seen when compared with D-dimer values in DVT [24].

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Table 7: Comparison between D-dimer values in 17 subjects with normal pregnancy with pregnant cases with DVT.

Group	Group I (OUR VALUES ng/ml)	Group II (Confirmed cases of DVT in pregnancy ng/ml) [24]	T	DF	95% Confidence Interval	P value
1st Trimester						
N	17	10	30.36	25	-1369 to -1195.28	<.0001
Mean ± SD	313.76 ± 111.64	1596 ± 95				
SEM	27.07	30				
2nd Trimester						
N	17	10	5.52	25	-1318.42 to -601.57	<.0001
Mean ± SD	370 ± 149.47	1330±700				
SEM	36.25	221.36				
3rd Trimester						
N	17	10	6.64	25	-966.09 to -508.72	<.0001
Mean ± SD	418.6±206.43	1156 ±374				
SEM	50	118.27				

N. Total number of cases studied, SD. Standard deviation, SEM. Standard Error of Mean

Conclusion

Pregnant population has not been studied extensively to develop the D- dimer as non- invasive method to detect or rule out VTE. Although cancer has been as one of the elements in Wells Pre-test probability criteria, pregnancy has not been included in the clinical assessment /predictive scales. Larger studies which include clinical assessment tools along with d-dimer evaluation in pregnant women [normal and with VTE] are required. Till then, the values of 5 times, 4 times and 3 times the reference range in 1st,2nd and 3rd trimester of pregnancy can be considered to indicate DVT in pregnant females.

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