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Original Research Article

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

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Abstract:

Introduction: Venous thromboembolism (VTE) is common in pregnant females but limitations of 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.

Material and Method: Firstly, the normal non-pregnant reference range of D-dimer was established in laboratory. Using the strict exclusion criteria on 100 pregnant females, only 17 were included finally in study group. The preanalytical variables which can affect the D-dimer values were taken care. Four samples from each participant were drawn during each trimester, including 4 weeks post-partum.

Results: A progressive increase in D-dimer was noted 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 255 ng/ml (the reference value given in kit insert). When these values were compared with the values from pregnant females with DVT in each trimester, it showed statistically significant difference with a pattern as D-dimer values were 5 times, 4 times and 3 times higher respectively in 1st, 2nd and 3rd trimester in pregnant women with DVT as compared to normal pregnancy values in our study.

Conclusion: The normal D-dimer reference range of pregnancy if known can help to diagnose VTE.

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 anticoagulants 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 is 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].

The use of D-dimer to rule out PE in pregnancy is recommended in only two of the available guidelines (European Society of Cardiology (ESC)and Working Group in Women's Health of the Society of Thrombosis and Haemostasis) [11,12],whereas the remaining five guidelines (Australasian Society of Thrombosis and Haemostasias-Society of Obstetric Medicine of Australia and New Zealand, American Thoracic Society-Society of Thoracic Radiology, EANM,

Royal College of Obstetricians and Gynaecologists, and Society of Obstetricians and Gynaecologists of Canada) recommend against the use of D-dimer in this setting [13-17]. Limitation to use D-dimer mostly is due to availability of limited and inconsistent data on sensitivity and NPV of D-dimer for suspected VTE in pregnancy, lack of Clinical Decision Rule specific for pregnancy to stratify patient according to Pre -Test Probability and lastly unclear appropriate cutoff of D-dimer test because of D-dimer physiological increase during pregnancy.

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 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

Subjects: The was a cohort study conducted at the tertiary care hospital. The study was conducted for a period of 6 months. The study was done on pregnant females aged between 20-35 years from 11 weeks- 13 weeks period of gestation. The participants went through strict exclusion criteria (Table 1). Ethical Approval from institute and Informed Consent from each participant was taken.

Method: To study reference range for an analyte certain common rules should be followed such as the study population should be selected after predefined inclusion and exclusion criteria. Included individuals should reflect the population that will be primary group. All considerations of pre analytical and analytical variables to be considered. Same consideration for sample collection, processing, reagent lot and storage must be employed. Calculated reference limits should be compared with other laboratories using the same method, reagent, instruments.

First, D-dimer reference range in normal healthy population at our laboratory was studied. Out of healthy 22 participants (both male and female), the mean value was 192.27 ng/ml. The standard deviation was 23.9 and the reference range (mean ± 2SD) was 184.5-240ng/ml.

The Preanalytical and Analytical variables were taken care of by using good quality vacutainers, sample adequacy was checked. Platelet poor plasma prepared, QC checked. Machine was calibrated, and QC was within limits. The study samples were run as batch. Out of 100 pregnant females who were 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 the exclusion criteria were 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.

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 analyzer, Instrumentation Laboratory, USA) which works on the principle of Latex enhanced turbidometric immunoassay. Test was carried out as per the operating protocol by the manufacturer. Machines were subjected to regular Quality controls and were within limits. The statistical analysis was done on SPSS version 21 software.

Results

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 analysis.

The results showed that among the pregnant, between the age group of 20-35 years, there was no statistically significant difference 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 pregnant females (n=17) were 314.76 ng /ml, 370.29 ng /ml, 418.59 ng/ml and 272.18 ng /ml in 1st, 2nd, 3rd trimester and 4 weeks post-partum respectively. (Table 4)

The maximum level of D dimer in 17 patients assayed 4 times was found to be 929 ng/mL in the 3rd trimester. Since the sample size was less than 20 in our study, confidence interval could not be calculated. However 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 216-385 ng/ml).

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 duration
Age < 20 years and > 35 years	Gestational diabetes
Family or personal history of thromboembolic disorder	Preeclampsia/ Eclampsia
Morbid obesity (BMI >40 Kg/m2)	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	Previous obstetric complications (still birth/ Intrauterine growth restriction/ spontaneous abortion/ abruption placenta/ gestational diabetes/ preeclampsia/ eclampsia).
History of diabetes mellitus/ hypertension	
Previous obstetric complications (still birth/Intrauterine growth restriction/ spontaneous abortion/ abruption placenta/ gestational diabetes/ preeclampsia/ eclampsia).	

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

	Age category	N	Mean	Std. Deviation	Minimum	Maximum	P value
1st trimester	20-25	5	257.60	74.718	135	319	
	26-30	7	293.43	61.161	188	368	
	31-35	5	401.80	155.938	255	577	0.093
	Total	17	314.76	111.648	135	577	
2nd trimester	20-25	5	393.80	136.959	272	625	
	26-30	7	303.29	59.601	238	402	
	30-35	5	440.60	224.850	227	757	0.284
	Total	17	370.29	149.474	227	757	
3rd trimester	20-25	5	524.80	204.390	194	733	
	26-30	7	332.57	96.005	205	520	
	30-35	5	432.80	295.913	204	929	0.295
	Total	17	418.59	206.438	194	929	
4week postpartum	20-25	5	301.40	128.436	187	520	
	26-30	7	231.00	43.882	183	293	
	30-35	5	300.60	96.996	231	470	0.323
	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 postpartum	P value
Nulliparous	N		11	11	11	11	
	Mean		315.00	401.90	451.27	273.27	
	Std. Deviation		95.052	176.156	236.028	90.653	
	Minimum		188.00	227.00	194.00	183.00	
	Maximum		565.00	757.00	929.00	520.00	
	Percentiles	25th	267.00	272.00	283.00	219.00	0.016
		50^{th} (Median)	310.00	324.00	349.00	262.00	
			319.00	594.00	637.00	293.00	
MultiParous	N		6	6	6	6	
	Mean		314.33	312.33	358.66	270.16	
	Std. Deviation		147.710	56.627	135.262	103.0833	
	Minimum		135.00	238.00	205.00	183.00	
	Maximum		577.00	390.00	559.00	470.00	
	Percentiles	25th	225.00	257.50	234.25	206.25	
		50^{th} (Median)	280.5000	312.5000	335.0000	236.5000	0.281
		75th	412.75	365.25	495.25	328.25	
Test Applied - Friedman test							

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	261.00	268.00	263.50	216.50	
	50th (Median)	302.00	321.00	344.00	245.00	
	75th	338.50	396.00	539.50	287.50	

Table 5: Comparison of Mean and Reference ranges in current study and previous publications

Sno	Author	Study population	instrument	Journal /year	Age group	1st trimester/ Range ng/ml	2nd trimester/ Range ng/ml	3rd trimester/ Range ng/ml	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	37	Enzyme linked fluorescence assay	2020	25-44	376 (247-505)	688 (252-1124)	1082 (646-1168)	Not included
3	Nornattasa et al	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	570 (430-710)	980 (750-1210)	1480 (1810-1770)	790 (430-1160)
5	Our study	18	Instrumentation laboratory (IL)	2023	20-35	314 (261-338)	370 (268-396)	418(263-539)	223(216-287)

Table 6: 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) (kovac M et al)	t	df	95% Confidence Interval	P value
1st Trimester						
Total number of cases	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

Discussion

A normal pregnancy is characterized by changes in hemostasis towards hypercoagulation due to altered levels of coagulation factors, venous stasis, 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 (specially dyspnea and leg swelling) complicating the early clinical assessment. Secondly, D- dimer levels increase with gestational age, so the conventional cut off of < 500 ng/ml to rule out VTE has limited value in pregnant women. Lastly, pregnant women cannot be investigated with imaging modalities due to risk of exposure of the fetus to radiations, (risk of teratogenesis and carcinogenesis) [10].

In the present study, the sample size was small, like the study which had normal pregnant subjects as 18. [19] Another study was done that included not only pregnant (24 in number) but also (nonpregnant 10 in number) and 33 women with complicated pregnancies (hypertension, diabetes Mellitus) (20). However few studies with larger sample size were also conducted [21,22,23,24,25].

We took the age group (25-35 years) for three reasons, firstly, this is the most common age of pregnancy in southeast Asian population (26) and secondly studies show a physiological increase of D-dimer values with age 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 (20).Thus in order to prevent any bias we limited the age group to 25-35 years (most common age of pregnancy).

According to British Committee of Standards in Hematology guidelines [27,28] the cut-off value to exclude VTE needs to be confirmed locally in minimum of 200 subjects in a laboratory. However, this approach is not possible in all laboratories and thus the manufacturer's cut off may be used. In present study, the kit insert showed that cut off 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. Moreover, in the present study group all 17 cases had mean value higher than 255ng/ml. Hence kit insert reference range cannot be used for pregnant females.

In the present study, some interesting observations were seen when the normal reference range in each trimester were compared with those obtained from few other studies, as shown in (Table 5). Firstly, in all studies, the D-dimer levels increased as the duration of pregnancy increased until they falls to lower levels, post-partum. The wide discrepancy between D-dimer values in different studies seen. This might be due to different assays and analyzers used and age group taken, rather than geographic or ethnic differences.

In the present study, reagent manufacturer abnormal cut off values for VTE >255 ng/ml was exceeded in 76.5% of the patients in 1st trimester, 88.2% of the patients in 2ndtrimester,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.

Two recent prospective studies [29,30] correlated that when the cut off values of D-dimer were taken as < 500 ng/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 < 500 ng/ml, was just 2/981 and 2/478 respectively. 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 [31].

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 [32] 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 were 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 [32] and analyzed [unpaired t test] the values were statistically significant. (Table 6). Thus, a trend of 5,4,3 times respectively for 1st,2nd &3rd trimester was seen when compared with D-dimer values in DVT [32].

Limitations of study: Present study included small sample size; further studies which include larger group along with clinical pretest should be done.

Conclusion

The kit insert cut off values of D-dimer cannot be used in pregnant. Normal pregnant population has not been studied extensively for validating the normal D- dimer values. Larger studies which

include clinical assessment tools along with D-dimer evaluation in pregnant women [normal and with VTE] are required. Our observations of D-dimer as reference range in 1st,2nd and 3rd trimester of pregnancy needs validation in normal and pregnant with VTE in further studies.

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