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D-dimer and fibrinogen levels in normal pregnant women in Sudan

Abstract

During normal pregnancy a number of changes in blood clotting and fibrinolysis proteins have been reported so indicating the existence of a state of Hypercoagulability. In addition to fibrinogen and D dimer is frequently checked during pregnancy, in particular during at risk pregnancy, but the exact pattern of D-dimer modifications during uncomplicated pregnancy is not definitively described. The aim of this study is to establish the levels of fibrinogen and D-dimer levels in 40 (66,7%) normal pregnant Sudanese females age 32.6±3.67 compared with 20 (33.3%) normal non pregnant women as control categorized in to three different age groups (A: 20-28year; B: 29- 39year; C: above 40year). D-dimer and fibrinogen levels have been measured in 40 consecutive normal pregnant women. The range of D-dimer values for all test groups was 0.232±0.231(0.08-1.7mg/L) (reference range is <0.2mg/L), 83% of group A were <0.2mg/L not different from controls, while about 38 % of group B and C were >0.2mg/L. Mean D-dimer levels were significantly higher in patients groups (0.24mg/L) ($p<0.01$) vs. control group (0.13mg/L) On other hand, mean fibrinogen levels were found not significantly different in test and control groups (3.66g/L) vs. control group (3.67g/L) ($p\geq0.05$, Sig t Test =0.58).

Keywords: pregnancy, D-dimer, fibrinogen, hypercoagulable state, Sudanese

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Introduction

In pregnant women various differences in blood clotting and fibrinolysis have been demonstrated in comparison to non-pregnant women.[1] Pregnancy is characterized by a hypercoagulable state due to a number of alterations of both blood coagulation and fibrinolysis[1,2] may be, this state protects from fatal hemorrhage during delivery,[3] but it can also favor thromboembolic events.[4,5] This phenomenon, apparently caused by hormonal changes,[6] creates continuous changes of the levels of clotting and fibrinolytic factors during the whole period.[7] A progressive increase in plasma D-dimer, considered as an index of the entity of the changes in fibrin deposition and consequent lysis, has been demonstrated in normal pregnancy.[8] the evaluation of D-dimer was poorly investigated and only a few clinical studies were performed to clarify the usefulness of this test,[9] However D-dimer increase does not necessarily mean the existence of a condition of hyper fibrinolysis but simply a physiological response of fibrinolytic system to increased fibrin deposition consecutive to enhanced thrombin generation.[10,11] Because hypo fibrinolysis can be one important factor predisposing to a number of complications such as thromboembolism, the evaluation of fibrinolytic system in pregnancy could be of importance. This, however, is very complex and the determination of a reference range of different hemostatic parameters can require an accurate investigation due to the contemporary activation of blood coagulation.[12] In pregnancy, the D-dimer test could be useful to obtain a simple and rapid assessment of the fibrinolytic activity.

Due to their relative simplicity, assays of fibrin degradation products have become a well-established diagnostic tool for detecting states of hypercoagulability. Fibrinogen, fibrin and D-dimer, are widely employed. An increase in plasma D-dimer levels has been demonstrated in the third trimester of normal and complicated pregnancies by some authors (8-11) but not by others.[13] And a predictive role of D-dimer levels for the development of preeclampsia was suggested.[13] Fibrinogen, also called serum fibrinogen, plasma fibrinogen and factor I, is a protein produced by the liver. Fibrinogen helps stop bleeding by helping formation of blood clots. During normal blood clotting, fibrinogen is broken down by an enzyme called thrombin into short fragments of fibrin. Thrombin also activates a substance called Factor XIII. Factor XIII helps weave the fibrin fragments into a complex lattice, closing off injured blood-vessel walls. Blood platelets attach to the fibrin fragments, clumping together to form blood clots and stop bleeding.[14] Fibrinogen is a sticky, fibrous coagulant in the blood that appears to significantly Increase the risk of experiencing one of the leading causes of death and disability stroke.[15] Fibrinogen is a vital component of coagulation; cleavage of fibrinogen yields fibrin monomers that polymerize to form a network of fibers, constituting the blood clot. Human fibrinogen is secreted from hepatocytes in its phosphorylated form, with 20-25% of circulating fibrinogen phosphorylated exclusively at α-chain Ser3 and Ser345. Phosphorylation of fibrinogen is elevated in acute phase conditions, venous thrombosis and ovarian cancer, but little is known about the regulation and effects of this modification.[16] Fibrinogen first-derivative concentration was mildly elevated during pregnancy. These results demonstrate that intravascular fibrin deposition, presumably involving the uteroplacental circulation, is the earliest and most persistent alteration in blood coagulation function noted during pregnancy. Further, the fivefold increase in fibrin deposition during pregnancy over the physiologic, non-pregnant state is accompanied by a significant increase in compensatory fibrinolysis.[17]

Objectives

I. To determine the D-dimer and fibrinogen levels in pregnant women in Khartoum State, Sudan

II. To compare D-dimer and fibrinogen in pregnant and in control

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women in Khartoum State, Sudan

III. To verify if D-dimer and fibrinogen tests may be used in pregnancy as a screening test for a rapid evaluation of thrombosis in pregnant women

Materials and methods

Participants

The participants of this study is 40 (66.7%) normal pregnant Sudanese females from age 32.6±3.67 compared with 20 (33.3%) normal non pregnant women as control group attended Khartoum Teaching Hospital, and Omdurman maternity Hospital in Khartoum state. categorized in to three different age groups (A: 20-28year; B: 29-39year ; C: above 40year).

Samples

1.8ml of Veinus blood was taken from all participants in citrated vacuum containers (1volume of 3.8% Trisodium citrate: 9 volume of blood), then PPP (platelets poor plasma) obtained by centrifugation of samples in 4000rpm for 15 minutes then the supernatant was immediately separated which is PPP plasma, stability of the sample: +15 to +25c for 8 hours or saved in -8°C for longer processing. SPSS ver. 22 program was used for analysis of data.

Procedures

Fibrinogen

Multifibren* U kit from Dade Behring Company was used for Quantitative determination of fibrinogen in plasma by using BFT II semi-automated analyzer from Siemens company.

Principle: The Multifibren* U test is sensitive to a deficiency of fibrinogen or inhibition of thrombin. It measures the formation of a fibrin clot by the action of thrombin on fibrinogen Thrombin is added to citrated plasma at 37°C. The time taken for the mixture to clot is measured and the appearance of the clot noted.

Method: Bring Multifibren* U reagent and all samples to +37°C before using, into a test tube pre warmed to +37°C pipette, Sample-100µL, Incubate for 60 seconds at +37°C, Multifibren* U (+37°C)-200µL and determine coagulation time.

Normal range of fibrinogen: (1.8–3.5g/l)

D dimer

Principle: The latex agglutination method used to detect crosslinked fibrin D-dimers is identical to the test for FDP, the latex beads are coated with a monoclonal antibody directed specifically against fibrin D-dimer in human plasma or serum. Because there is no reaction with fibrinogen, the need for serum is eliminated and measurements can be performed on plasma samples.

Reagents: Reagents from Siemens manufacturer kits for the measurement of D-dimers. These usually contain the latex suspension, dilution buffer, and positive and negative controls.

Method: The manufacturer's protocol should be followed. Undiluted plasma is mixed with one drop of latex suspension on a glass slide and the slide is gently rocked for the length of time recommended in the kit. If macroscopic agglutination is observed, dilutions of the plasma are made until agglutination can no longer be seen.

Interpretation: Agglutination with the undiluted plasma indicates a concentration of D-dimers in excess of <0.2mg/l. The D-dimer level can be quantified by multiplying the reciprocal of the highest dilution showing a positive result by 0.2 to give a value in mg/l.

Normal range: Plasma levels in normal subjects are <0.2mg/l. There has been much study of D-dimer assays as a useful way of excluding thrombosis, but there is naturally a compromise between sensitivity and specificity, especially when a rapid turnaround time is required. The lack of an international standard and the poor correlation between kits mean that the use of kits for this purpose should be validated individually. Latex test using automated analyzers may provide an acceptable compromise.[18] These tests have now been incorporated into clinical guidelines according to their sensitivity.[19,20]

Results

Regarding age groups as appears in Table1 about 60% of participants were from the first group (20–28y). D-dimer was performed for 41 pregnant women and 19 normal healthy non pregnant women as control sample. The data analyzed by using Independent Samples Test (2 tailed) shows significant increase levels of D-dimer in test group (mean 0.23±0.036) compared with control (mean-0.136±0.007) Table 2, P<0.013 Table 3 (Figure 1).

Table1 Age groups frequency

Age	Frequency	Percentage
20-28	35	59.50%
29-39	19.4	32.40%
Above 40	5.6	8.10%
Total	60	100%

Table 2 Group Statistics (D-dimer)

	codes	N	Mean	Std. deviation	Std. error mean
D-dimer	test	41	0.232	0.23087	0.03606
	cont	19	0.1363	0.03095	0.0071

Table 3 Independent Samples Test (D-dimer)

Levene's test for equality of variances		t-test for Equality of means						
F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. Error difference	95% Confidence interval of the difference	
							Lower	Upper
6.555	0.013	1.79	58	0.079	0.09564	0.05342	-0.01131	0.20258
		2.602	43.019	0.013	0.09564	0.03675	0.02153	0.16974

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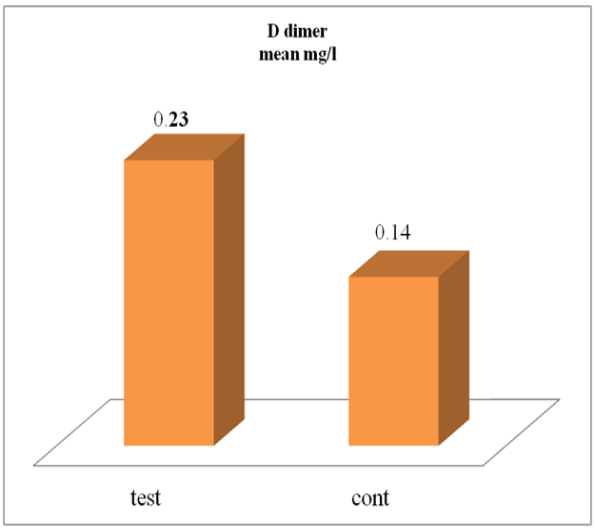

Figure 1 D-dimer compares means.

Fibrinogen also performed for same groups, but no significant differences found between the two groups by using Independent Samples Test in SPSS program ver. 22 Figure 2 (mean 3.66±0.94 for test and 3.78±0.72g/l for control) Table 4 P<0.58 Table 5

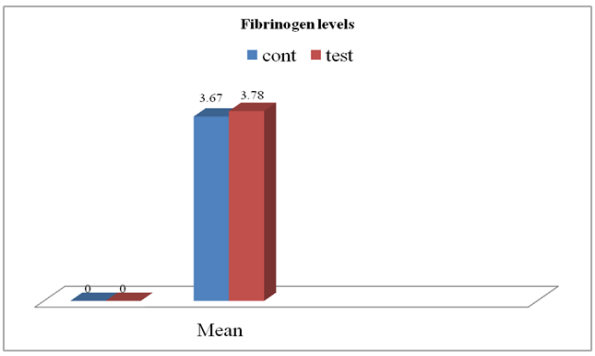

Figure 2 Fibrinogens compare means.

Table 4 Group Statistics

	codes	N	Mean	Std. deviation	Std. error mean
Fibrinogen	test	40	3.6565	0.94716	0.14976
	cont	20	3.7785	0.7172	0.16037

Table 5 Fibrinogen Independent Samples Test

t-test for Equality of means				
t	df	Sig. (2-tailed)	Mean difference	Std. Error difference
-0.507	58	0.614	-0.122	0.24058
-0.556	48.586	0.581	-0.122	0.21942

Discussion

Pregnancy is characterized by a hypercoagulable state due to a number of alterations of both blood coagulation and fibrinolysis, Francalanci et al.[21] Suggests that levels of D-dimer up to 685µg/L (increase levels) may be reached at the end of physiological pregnancy. The thing which we found in our study about levels of D-dimer in pregnant women with is significantly levels of D-dimer in test group compared with control P<0.013 Table 2. On other hand regarding Fibrinogen levels we found no significant differences found between the test (mean-3.66±0.94 for test and 3.78±0.72g/l for control) P<0.58. Also Roger et al.,[22] determined that an emerging need to reconsider fibrinogen and D-dimer values from a different aspect in pregnancy compared to non-pregnant reference intervals. New reference ranges are suggested to be established in pregnancy.[22] No previous study in Sudan had taken this relationship between fibrinogen and D-dimer levels in normal pregnant Sudanese women, although Fatima et al.[23] Suggests that the level of fibrinogen and D-dimer is significantly increased in preeclampsia pregnant women when compared with normal pregnant women.[23]

Conclusion

From this study, it is concluded that the level of D-dimer is significantly increased in pregnant women when compared with normal non pregnant women, While No significant differences founded in fibrinogen level between the two groups.

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None.

Conflict of interest

The author declares that there is no conflict of interest.

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