Assessment of Hypercoagulability state during multiple Pregnancies in Sudanese women in Kassala state

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Abstract:

This distributive cross sectional was done to evaluate hemostatic mechanism by measuring PT, APTT, Fibrinogen and D.dimer among Sudanese multi pregnant.

In this study the determination of some coagulation test in multiple pregnant women as well as the control non pregnant women can give idea about the risk factor for thrombosis. The study was carried out at Kassala state, east Sudan. Blood samples were collected from 75 participants 50 of them were multi pregnant women, were as twenty five were healthy non pregnant women selected as control group. Five and half ml of venous blood was drown from each patient and placed in tri sodium citrate container, then centrifuged for platelet poor plasma {PPP}, prothrombin time (PT), activated partial thromboplastin time {APTT} ,Fibrinogen level and D.dimer were assessed by automated devises.

Key words: hypercoagulability state, multiple pregnancies, Sudanese women, Kassala State, Sudan

INTRODUCTION

Coagulation in the physiology, the process by which a blood. [1] {Editors of Encyclopedia Britannica}. Clot is formed. (also known as clotting) is the process by which blood changes from a liquid to a gel. It potentially results in homeostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion, and aggregation of platelets along with deposition and maturation of fibrin. Disorders of coagulation are disease states which can result in bleeding (hemorrhage or bruising) or obstructive clotting (thrombosis). [2] David Lillicrap et al 2009. The concept of coagulation as cascade of proteolytic reactions evolved extrinsic and intrinsic path ways meeting in a common path way. [3] {Curr Hematol 2005}.

Extrinsic is The main role of the tissue factor pathway is to generate a "thrombin burst", a process by which thrombin, the most important constituent of the coagulation cascade in terms of its feedback activation roles, is released very rapidly. FVIIa circulates in a higher amount than any other activated coagulation factor. Intrinsic begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation. Common pathway is a division of coagulation in two pathways is mainly artificial; it originates from laboratory tests in which clotting times were

measured after the clotting was initiated by glass (intrinsic pathway) or by thromboplastin (a mix of tissue factor and phospholipids). In fact thrombin is present from the very beginning, already when platelets are making the plug. Thrombin has a large array of functions, not only the conversion of fibrinogen to fibrin, the building block of a hemostatic plug. In addition, it is the most important platelet activator and on top of that it activates Factors VIII and V and their inhibitor protein C (in the presence of thrombomodulin), and it activates Factor XIII, which forms covalent bonds that crosslink the fibrin polymers that form from activated monomers.[4](Pallister CJ and Watson MS.2010).

Pregnancy is range from 37 to 42 weeks and divided to three trimesters each trimester lasts between 12 and 14 weeks {first, second and third trimester} [5] {Tracy sticker 2014}.while there are no hand and fast rules, these distinctions are useful in describing the change that take place over time .pregnancy causes physiologic changes in all maternal organ system .most return to normal after delivery   [6] {Duva, et al 2010}.

Is the propensity of pregnant women to develop thrombosis {blood clots} .pregnancy itself is a factor of hypercoagulability as a physiology adaptive mechanism to prevent post partum bleeding [7] {clinical hand book page 264} However, when combined with an additional underlying hyper coagulability states, the risk of thrombosis or embolism may become substantial. The observations of study that identify the activation of blood coagulation and fibrinolysis to diagnose hyper coagulablility state such as   thrombophilia   during pregnancy that lead to risk of venous thromboembolism   in pregnant women at two to six times that of non pregnant women [8] {Greer ,1999}.

This study is aimed to Assess women [PT, PTT, Fibrinogen level and D.dimer]   among multiple Pregnancies in

Sudanese then correlate the results to the age of each woman and the times of child peering.

MATERIALS AND METHODS

Across sectional descriptive study was conducted in kassla state in Sudan to evaluate the coagulation tests PT/APTT/Fibrinogen /D.dimer among multi pregnancies women during the period September 2015 to April 2016.

Blood samples were collected from fifty women with [six or more pregnancies times] in their third trimester and twenty five control samples were collected as control non pregnant healthy women.

This project was approved by the ethical committee of the medical laboratory sciences Alneelain University, consents was also taken from participants.

Select individuals were informed with details objectives of the study and its importance in the future. Data were collected using self administered pre coded questionnaire which was specifically designed to the study information.

Participants' data were analyzed by SPSS computer program version 21.Any disorder that affected in the coagulation parameter as drugs, or disorders excluded from the study. Venous blood 4.5 ml was collected in containers containing 0.5 ml tri sodium citrate as anti coagulant, then blood samples were centrifuged after thoroughly mixing for 15 minutes at 3000 rpm to obtain plate let poor plasma.

Prothrombin Time

PT was measured the amount of time it take for your blood plasma to clot [9] {Heather Ross 2015|}.   by adding 0.1 ml of plasma in glass tube +0.2 from mixture reagent the test performed in a water path and then the end point recorded by stop watch. Normal range 12-16 seconds.

Activated Partial Thromboplastin Time

APTT to measure the clotting time of plasma after activation of contact factors indicate of efficiency of the intrinsic path way, the test depend on the contact factors and on factor VIII and XI, but also with the reaction with factors X ,V, prothrombin and fibrinogen .[10]{Lewis SM ,et al 2006} . NR 26- 40 sec.

Fibrinogen level

A fibrinogen activity test also known as a factor 1assay .it used to determine the level of fibrinogen in your blood .fibrinogen, or factor 1, is a blood plasma protein that is made in liver. [11]{ Corinna Underwood 2016}

Measured by added 0.2ml fibrinogen reagent to the 0.2ml of plasma, after incubated of the plasma at 37C for 1-3 minutes. NR 200- 400mg/l

D.dimer

Principle of the test depend on the sandwich immune detection method, D.dimer is the degradation product 0f cross linked (by factor X111) fibrin. [12] {Reka Szigeti 2014} the test is processed by I CHROMA reader to show D.dimer concentration in the specimens, NR UP to 300ng /ml.

RESULTS

In this across sectional descriptive study a total of 75 Sudanese women were enrolled. 50 (67 %)   cases samples of them were collected from women with six or more recurrent pregnancies and 25 (33%) controls samples collected from healthy non pregnant women as control grope. Age ranged from 25 to 45 years (32.3 ± 6.1)

In the present study the biochemical parameters like Activated partial thromboplastin time, Prothrombin time,

Fibrinogen levels and D.dimer were estimated in 25 controls and 50 cases, descriptive data showed in Table I, II.

The mean and standard deviation of Activated partial thromboplastin time (seconds) in control group was 31.3 ± 2.2 were as the cases result 37.5 ± 5.5, the difference is statistically significant between the case and control groups with P.value (0.00) as shown in Table 3. The correlation between the results to the age of the women and the number of pregnancies was statistically insignificant (The data is not should).   (0.645) (0.835) respectively as shown in Table 3.

The mean and standard deviation of Prothrombin time in control group is 12.8 ± 0.6 as compared to 14.9± 1.9 in test group. The difference is statistically significant between case and control P.value (0.00), the correlation was statistically insignificant   with age and number of pregnancies   P.value (0.955), (0.248) (The data is not should)   , shown in table {1} {2} The mean and standard deviation of Fibrinogen levels (mg/dl) i n controls is 250± 50 as compared to 572 ± 194 in test group. The difference is statistically significant between case and control P. value (0.00), and statistically insignificant with age number of pregnancies P.value (0.212), (0.124) (The data is not should), as shown in Table {3}.

The mean and standard deviation of D.dimer in controls is 217 ± 59 compared to 1171 ± 345 in test group. The difference is statistically significant between case and control P. value (0.00), and statistically insignificant with age number of pregnancy P.value (0.611), (0.436) (The data is not should), as shown in Table {3}.

**Table {1}: Descriptive data for all Coagulation parameters in multi pregnant women**

Parameters	NO	Minimum	Maximum	Mean	SD
PT	50	12.1	20.0	14.1	1.9
APTT	50	30.0	57.1	37.5	5.5
Fibrinogen	50	335	1045	572	194
D.dimer	50	551	2404	1171	345

Table {2}: Descriptive data for all Coagulation parameters in control group

Parameters	No	Minimum	Maximum	Mean	SD
PTT	25	11.9	14.2	12.8	0.6
APTT	25	28.3	36.0	31.3	2.2
Fibrinogen	25	201	395	250	50
D.dimer	25	137	320	217	59

Table {3}: Correlation of coagulation parameters between case and control

| NO	Sample		NO	Mean ± SD	P.value
I	PT	Case	50	14.9 ± 1.9	0.00
		Control	25	12.8 ± 0.6	
II	APTT	Case	50	37.5 ± 5.5	
		Control	25	31.3 ± 2.2	0.00
III	Fibrinogen	Case	50	572 ± 194	0.00
		Control	25	250 ± 50	
IV	D.dimer	Case	50	1171 ± 345	
		Control	25	217 ± 59	0.00
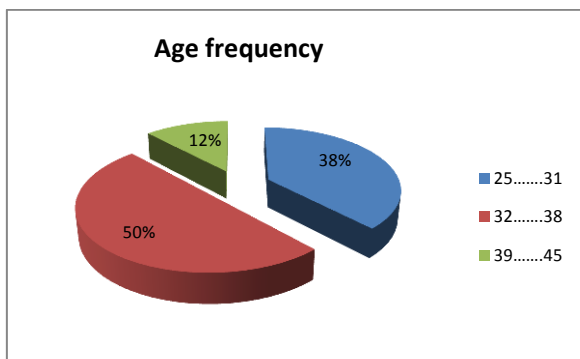
Figure: Coagulation parameters Mean's comparison between samples and controls
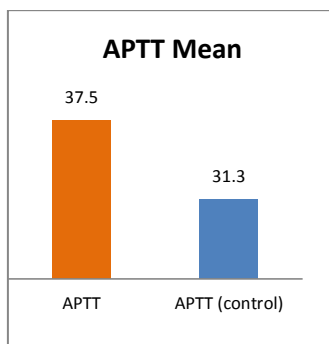
Figure {1}: Pregnancy Frequency
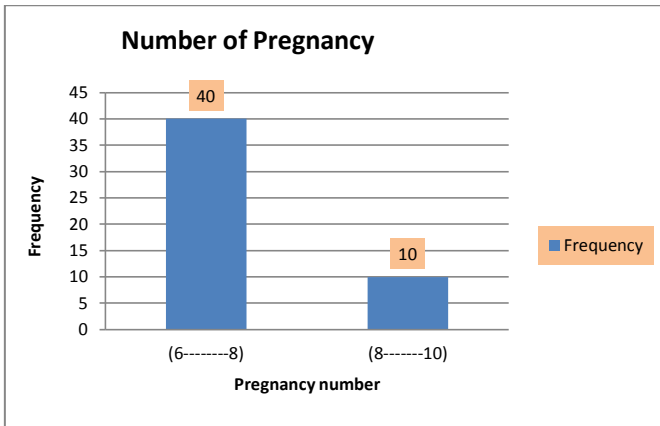
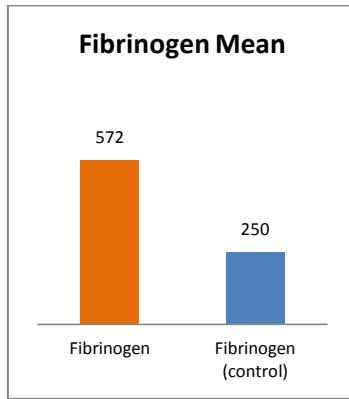**Figure {2}: PT Mean's comparison between sample and control**
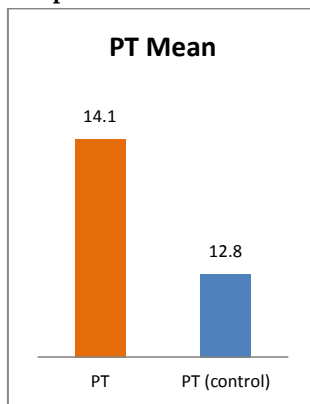
Figure {3}: APTT Mean's comparison between sample and control
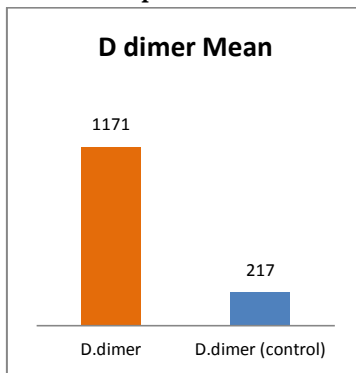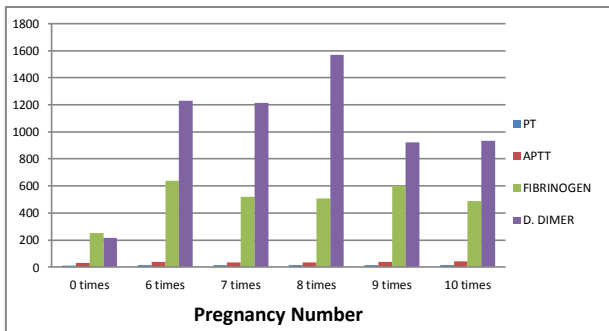
Figure {4}: Fibrinogen Mean's comparison between sample and control

Fibrinogen Mean

Figure {5}: D dimer Mean's comparison between sample and control

D dimer Mean

Figurers {6} : Coagulation parameters comparison between samples and controls

DISCUSSION

Pregnancy is a state of hyper coagulation, which is likely an adaptive mechanism to reduce the risk of hemorrhage during and after the delivery process. Unfortunately as a result of the hypercoagulable state, thromboembolism is one of the leading causes of death associated with pregnancy, particularly in developed nations, with clinically significant venous thromboembolism occurring in 1 of every 1000 to 2000 pregnancies [13] [14] . Although many of the coagulation factors are increased during pregnancy, none are quite to the extent of factor VII and fibrinogen.

In the present study the biochemical parameters like Activated Partial Thromboplastin time, Prothrombin time, Fibrinogen Levels And D.dimer were studied in multiple pregnancies women and control non pregnant women include Frequency of age groups 25-31 years 19 (38%), 32-38 years 25 (50%) and 39-45 years 6 (12%) .Frequency of number of pregnancy 5-7 40 (80%) and 8-10 10 (20%). Results of the present study has been discussed in two groups: Control subjects (non pregnant women), Sample (multiple pregnant women)

Control group
A total number of 25 non pregnant women were studied. The age group of these subjects ranges from 25 To 45 years. The results of estimation of Activated Partial Thromboplastin time, Prothrombin time Fibrinogen level and D.dimer level were within normal limits.

Case group
A total number of 50 cases of multiple pregnant women have been studied. The age group of these subjects ranges from 25 To 45 Years .All subjects showed an increase in plasma APTT

levels when compared with non pregnant women and the difference was statistically significant .All subjects also showed an increase in plasma Prothrombin Time when compared with non pregnant women the levels as well as the difference was statistically significant .There is significant increase in plasma fibrinogen levels in cases when compared with non pregnant women, as well as the D-dimer level. The study showed an increased in the mean of the D.dimer due to increase degradation of fibrin by the action of coagulation factor and increase in fibrinolytic activity which reflect in the prolongation of thrombin Changes in coagulation profile that occur in normal pregnancy includes the biochemical adaptation especially the haematological changes that occur in response to pregnancy are profound. Also the statistical analysis show that no significant relation between the plasma APTT, Prothrombin Time, plasma fibrinogen levels , D.dimer levels and the age or the number of pregnancies.

Plovdiv Bul .Konstantin**,** *et al.,* in Bulgaria reported that the pregnant women had statistically significantly higher values for: prothrombin time (PT) (P < 0.0001), thrombin time (TT) (P < 0.0001), fibrinogen (P < 0.0001), activity of factor VII (P < 0.0001), factor X (P < 0.0001) and alpha2-antiplasmin (P < 0.002), plasma concentration of D.dimer (plsDD) (P < 0.0001) and activity of heparin cofactor II (HCII) (P < 0.002). They had statistically significantly lower activity of protein C (PrC) (P < 0.0001) and of total protein S (TPrS) (P < 0.0001).

Similar as [15] Andrea H. James study Venous Thromboembolism in Pregnancy.   (NC. 2009), the purpose of this review is to summarize that show significant increase of DVT 6 times compare with non pregnant women

The incidence of pregnancy-related venous thromboembolic events was 13 per 10,000 deliveries. Cesarean delivery was associated with a fivefold increased risk of venous thromboembolic events is agreement.

A Korean study similarly found that increased age was not associated with VTE in pregnancy [16] .in addition advanced age was not a significant associated with an age found in Department of Obstetrics and Gynecology, and Coagulation Research, University of Lundin [17].

CONCLUSION

The levels of several blood coagulation factors are increased during pregnancy. Estimation of these biochemical parameters plays an important role in the diagnosis of hypercoaguability and the evaluation of risk factors, early detection and effective antenatal services, proper management will decrease the maternofoetal mortality, morbidity and also prenatal mortality.

RECOMMENDATION

Multi pregnant women should be routinely screened for coagulation tests. In order to get more informative data should used further investigations in multi pregnant women include (Anti phospholipids APAs ,factor V Leiden ,protein C ,protein S and anti thrombin generation tests). Future studies should be conducted using a higher sample size to end up with more accurate results. Multiple pregnancies should be advised to seek for delivery services in advanced health facilities to avoid maternal and prenatal morbidities and mortalities to deliver in well equipped health facilities since here there is possibility of having resources for complications intervention.

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