

Sudan University of Science and Technology
College of Graduate Studies

**Assessment of Plasma D-dimer in Preeclamptic Pregnant Women in
Khartoum State**

تقويم مستوى دايمر (د) في بلازما الدم لدى النساء الحوامل المصابات بارتفاع ضغط الدم في ولاية
الخرطوم

A dissertation submitted in partial fulfillment of M.Sc. Degree in Medical Laboratory
Science_ Clinical Chemistry

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بسم الله الرحمن الرحيم

قال تعالى:

﴿ قل لو كان البحر مدادا لكلمات ربي لنفد البحر قبل أن تنفذ كلمات
ربي ولو جئنا بمثله مددا ﴾

صدق الله العظيم

سورة الكهف آية رقم (١٠٩)

Dedication

I dedication this research to

My father.

My mother.

Who taught me how I could be humanant

My brother and sister.

For their support and kindness

My friends and my colleagues.

The persons whom I love, respect and appreciate...

&

Everyone from whom I learned.

Acknowledgment

Thanks are first and last to Allah who enabled me to conduct this study and give me strength and patience

I would like to acknowledgment and thanks supervisor:

Noon Babiker Mohammed

For her continuous guiding, encouraging words, support and kindness

I would also give my thanks to all person help me in this research from smaller one to largest one in home or university

Grateful to

All pregnant women

For cooperation blood donation

Abstract

Background: Preeclampsia is a multifactorial disease characterized by high blood pressure and proteinuria after the 20th week of pregnancy. Preeclampsia is associated with microvasculature fibrin deposition and maternal organ dysfunction. D-dimer has been used as a marker of production/ degradation of fibrin in vivo.

Objective: To assess plasma D-dimer in preeclamptic pregnant women to find out the effect of hypertension duration and body mass index on the parameter.

Materials and methods: This is case control study. The study was conducted from March to June 2015, and sixty samples from normotensive pregnant women as control chosen randomly from Soba university hospital. All samples were tested for D-dimer. D-dimer was measured by using Nycocard d-dimer, and results were analyzed using statistical of package social science (SPSS), computer program.

Result: The study results showed that the level of D-dimer was significantly increase ($P = 0.017$) in hypertensive preeclamptic pregnant women. Means \pm SD cases versus controls (1.040 ± 0.45 versus 0.31 ± 0.139).

In preeclamptic pregnant women group, the level of D-dimer showed significant strong positive correlation with the duration of hypertension appear ($P = 0.000$).

Also the findings of this study showed that, there was a significant strong positive correlation between level of D-dimer and BMI ($P = 0.003$).

Conclusion: From the result of this study, it is concluded that; the level of D-dimer was significantly increased in preeclamptic pregnant women and correlated with duration and BMI.

مستخلص الدراسة

الخلفية: تسم الحمل هو مرض متعدد العوامل التي تتميز بارتفاع ضغط الدم وزيادة البروتين في البول بعد الأسبوع 20 من الحمل ويرتبط تسم الحمل مع ترسب الأوعية الدموية الدقيقة للفيبرين وضعف أجهزة الأمهات وقد استخدم دايمر (د) كعلامة انتاج او تكسير الفيبرين في الجسم.

الهدف: قياس مستوى دايمر (د) في بلازما الدم لدى النساء الحوامل المصابات بضغط الدم لمعرفة تأثير الزمن ومؤشر كتلة الجسم عليه.

المواد والطرق: أجريت هذه الدراسة لمقارنة مستوى دايمر (د) في النساء الحوامل المصابات بضغط الدم مستون عينه أخذت من هؤلاء في الفترة مابين شهر مارس حتى يونيو تم اختيارهم بطريقة عشوائية من مستشفى سوبا الجامعي، مع ستين عينة من نساء حوامل غير مصابات بضغط الدم كمجموعة تحكم، جميع العينات فحصت دايمر (د). تم قياس مستوى دايمر (د) بواسطة جهاز نيو كارد دايمر (د)، وتم تحليل البيانات بواسطة برنامج الحزمة الإحصائية للعلوم الاجتماعية.

النتيجة: توصلت نتائج هذه الدراسة إلي أن هناك اتفاع ملحوظ في مستوى دايمر (د) وكان الاحتمال الإحصائي للمقارنة (0.017) وكانت النتيجة كالآتي:-

"المتوسط \pm الانحراف المعياري عند مجموعة المصابات مقارنة بمجموعة التحكم"

$$1.040 \pm 0.45 \text{ مقارنة } 0.31 \pm 0.139$$

عند مقارنة مستوى دايمر (د) في مجموعة الدراسة مع مدة ظهور ضغط الدم، كان هناك علاقة قوية ذات دلالة احصائية معنوية (0.000).

أيضا خلصت النتائج إلى انه هناك علاقة ملحوظة بين ارتفاع مؤشر كتلة الجسم وبين التغير في مستوى دايمر (د) وكان الاحتمال الإحصائي (0.003).

الخلاصة: خلصت هذه الدراسة إلي ان مستوى دايمر (د) يحدث له زيادة عند الحوامل المصابات بضغط الدم وله علاقه بالزمن و مؤشر كتلة الجسم.

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List of abbreviations

APC	Activated Protein C
BMI	Body Mass Index
DIC	Disseminated Intravascular Coagulation
FDP	Fibrin Degradation Product
HCP	Hypertension Complicated by Pregnancy
PAI-1	Plasminogen Activator Inhibitor type-1
PAI-2	Plasminogen Activator Inhibitor type-2
PF	Prothrombin Fragment
SD	Standard Deviation
SPSS	Statistical of Package Social Science
TAT	Thrombin Anti-thrombin complex
TF	Tissue Factor
TM	Thrombomodulin
tPA	tissue Plasminogen Activator
vWF	von Willebrand Factor

Chapter one

1. Introduction

1.1 Introduction:-

Hypertension is common medical complication of pregnancy, occurring in about 6-8% of all pregnancies. It is seen in a group of disorders that include preeclampsia-eclampsia, latent or chronic essential hypertension, a variety of renal diseases, and transient hypertension. Preeclampsia and eclampsia, are called toxemias of pregnancy the most dangerous. The early detection of hypertension during pregnancy permits clinical monitoring and prompt therapeutic intervention for severe Preeclampsia and eclampsia. The rate of preeclampsia has increased by nearly one-third. This increase is due in part to rise in the numbers of older mothers and multiple births, where preeclampsia occurs more frequently (Devoe & O'Shaughnessy, 1984).

In literature, D-dimer is found to be a good biochemical marker of thrombosis. Elevation of D-dimer is associated with increased risk of future myocardial infarction, stroke, and peripheral vascular disease (Ernst & Resch, 1993).

1.2Rationale

Preeclampsia become a common condition occurs during pregnancy, it can cause complications for mother, for baby, or for both. It is a great important to identify those high risks of developing eclampsia and other possible complications.

Assay of D-dimer levels may be useful in monitoring disease progression and determining risk of future complications.

Few studies were done to highlight the abnormalities in D-dimer in Preeclampsia; so this study is attempt to study this area.

1.3 Objectives

1.3.1 General Objective:

To assess plasma D-dimer in preeclamptic pregnant women in Khartoum state.

1.3.2 Specific Objectives:

1. To measure D-dimer level in Preeclamptic women.
2. To compare between D-dimer in Preeclamptic women and normal pregnant women.
3. To identify the effect of duration of hypertension on D-dimer levels in preeclamptic women.
4. To correlate between body mass index and D-dimer levels in preeclamptic women.

Chapter two

2. Literature review

2.1. Hypertension:-

Elevated arterial blood pressure is diagnosed when the diastolic is higher than 90 mmHg. Usually, both systolic and diastolic pressure are raised. It is a disease with no known cause in about 90% of cases. These are diagnosed as having essential or benign hypertension, which means we do not know the primary cause. The remaining cases can be secondary to renal disease, hyper secretion of aldosterone (Conn's syndrome), excess glucocorticoids (Cushing's syndrome) or catecholamine secreting tumor of the adrenal medulla. Hypertension is also a symptom of toxemia of pregnancy, which may be due to a presser peptide released by the placenta(Kumar& Clark,. 2005).

Causes:-The majority(80-90%) of patient with hypertentionhave primary elevation of blood pressure, which can be ameliorated only by life-long pharmacological therapy.

1.Essentialhypertension:-

Essential hypertension has a multifactorlala etiology.

A)Genetic factors:

Blood pressure tends to run in families and children of hypertensive parents tend to have higher blood pressure than age-matched children of people with normal blood pressure. This familial concordance of blood pressure may be explained, at least in part by shared environmental influences(Kumar& Clark,. 2005).

B)Fetal factors:

Low birth weight is associated with subsequent high blood pressure. This relationship may be due to fetal adaptation to intrauterine under nutrition with long-term changes in blood vessel structure or in the function of crucial hormonal systems(Kumar& Clark,. 2005).

C)Environmental factors:

Amongst the several environmental factors that have been proposed, the following seem to be the most significant:

- Obesity.
- Alcohol intake.
- Sodium intake.
- Stress.

D)Humeral mechanisms:

The autonomic nervous system, as well as the rennin -angiotensin, natriuretic peptide and kallikrein-kinin system, plays a role in the physiological regulation of short- term changes in blood pressure and have been implicated in pathogenesis of essential hypertension. A low rennin, salt- sensitive, essential hypertension in which patients have renal sodium and water retention has been described. However, there is no convincing evidence that the above systems are directly involved in the maintenance of hypertension (Kumar & Clark; 2005).

2.Secondary hypertension:-

Secondary hypertension is where blood pressure elevation is the result of specific and potentially treatable cause. Secondary forms of hypertension include the following:

A)Renal diseases:

These account for over 80% of the cases of secondary hypertension. The common causes are diabetic nephropathy, chronic glomerulonephritis, adult polycystic disease and renovascular disease. Hypertension can itself cause or worsen renal disease. The mechanism of this blood pressure elevation is primarily due to sodium and water retention, although there can be inappropriate elevation of plasma rennin levels (Kumar & Clark, 2005).

B)Endocrine causes:

- Conn's syndrome.
- Adrenal hyperplasia.
- Cushing's syndrome.
- Acromegaly.

C)Congenital cardiovascular causes:

The major cause is coarctation of the aorta.

D)Drugs:

There are many drugs that have been shown to cause or aggravate hypertension, or interfere with the response to some antihypertensive agents.

E)Pregnancy:

Cardiac output rises in pregnancy but, owing to a relatively greater fall in peripheral resistance, blood pressure in pregnant women is usually lower than in those not pregnant. Hypertension is noted in 8-10% of pregnancies; when detected in the first half of pregnancy or persisting after delivery it is usually due to pre-existing essential hypertension. Hypertension presenting in the second half of pregnancy usually resolves after delivery. When the blood pressure increases to

>160/110 mmHg treatment is warranted for the protection of the mother (Kumar & Clark; 2005).

2.2Pregnancy:-

Normal human pregnancy lasts approximately 40 week as measure from the first day of the last normal menstrual period during pregnancy, women under goes dramaticphysiological and hormonal changes.

Physicians customarily divide pregnancy into three interval call trimester; his are each slightly longer than 13 weak been at the first day of the last menses (Zelzislowa,.1998).

Maternal blood volume increase during pregnancy by an average of 45% plasma volume increase more rapidly than the red blood cell, the concentration of the several blood coagulation factor are increase during pregnancy (Zelzislowa,.1998).

2.2.1Coagulation change during pregnancy:-

Pregnancy is a risk factor for venous thrombosis and the incidence of venous thromboembolism during normal pregnancy is 6-fold higher during pregnancy than in general female population of child-bearing age. This incidence is, however, remarkably low given the increase in markers of haemostatic activation observed during normal pregnancy. During normal healthy pregnancy there are substantial changes in haemostatic system, many of which are procoagulant and supposed to be in preparation for the haemostatic challenge of delivery (Holmes & Wallace,.2005).

Normal haemostatic requires a balance between coagulation and fibrinolysis to maintain the integrity of the vasculature, and complex physiological changes are evident during pregnancies which appear to ensure a constant coagulation/

fibrinolysis balance. This balance is maintained, at least partly, by an increase in fibrinolytic activity, but decrease in other factors such as factor XI and monocyte tissue factor expression may also serve to counterbalance procoagulant changes (Holmes & Wallace, 2005).

Normal pregnancy is often referred to as a hypercoagulable state, with reported changes in the haemostatic system considered to be in preparation for the haemostatic challenge of delivery. Indeed, levels of markers of haemostatic activation such as F1+2 (prothrombin fragment 1+2), TAT (thrombin-antithrombin complex) and D-dimer similar to or higher than those found in patients following a thromboembolic event, have been observed in normal pregnancy (Holmes & Wallace, 2005).

2.2.2 Coagulation factor changes:-

During normal healthy pregnancy there are physiological changes which result in increase in the majority of coagulation factors. Factor XIII, fibrin-stabilizing factor, increase in early stages of pregnancy, returning to non-pregnant values in the third trimester. Levels of factor XII, X and IX increase progressively during pregnancy. In contrast, levels of XI decrease during pregnancy, and it has previously been suggested that this may be a consequence of increased factor XI consumption. However, factor XI activation is a key step in driving thrombin generation, and it is also possible that, in normal pregnancy, levels of factor XI are physiologically lowered to counterbalance the increase in other coagulation factors (Holmes & Wallace, 2005).

Factor VIII levels and coagulation activity (VIIIc) increase progressively during pregnancy. Levels of vWF (von Willebrand factor), which serves as a carrier for factor VIII and plays a role in platelet adhesion, also increase progressively in

pregnancy. Factor VII also increase gradually During normal pregnancy. Increase in factor V concentration in early pregnancy are followed by a decrease and stabilization, whereas factor V coagulation activity (VC) shows a gradual rise throughout gestation (Holmes & Wallace,. 2005).

The blood coagulation cascade is initiated by TF, which forms a proteolytically active complex with factor VII. TF is a transmembrane glycoprotein constitutively expressed by non-vascular cells and aberrantly expressed on monocytes and endothelial cells in the presence of inducers such as the inflammatory cytokines, endotoxin and C-reactive protein, whereas some anti-inflammatory cytokines are known to inhibit monocyte TF expression. Although concentration of soluble TF remain constant during normal pregnancy, monocyte TF activity and expression are lower when compared with non- pregnant subjects. Monocyte TF expression was lower throughout gestation in normal pregnant women, with levels lowest in the second trimester and returning to those of non-pregnant control as soon as 3 days post partum. As TF is the initiator of blood clotting in vivo, lower TF expression and activity on circulation monocytes may play an important role in protecting pregnant women from VTE, despite increase in many of the clotting factors and hypercoagulable state described above (Holmes & Wallace,. 2005).

2.2.3 Inhibitor of blood coagulation:-

Coagulation inhibitor are necessary to ensure that thrombin generation remains limited and localized. Antithrombin III, heparin, heparin cofactor II, a 1 antitrypsin and TF pathway inhibitor are inhibitors of serine proteases of the coagulation cascade such as thrombin, Xa and TF: VIIa. Alteration in the coagulation factors during pregnancy are accompanied by concomitant changes in Coagulation inhibitor. Levels of antithrombin III remain stable during pregnancy, whereas heparin cofactor II and a 1 antitrypsin levels are increase during normal pregnancy.

Little is known about the effect of pregnancy on levels of TF pathway inhibitor, but lower levels during labor have been reported when compared with non-pregnant control (Holmes & Wallace, 2005).

Protein C, TM (thrombomodulin), protein S, C4b binding protein and APC (activated protein C) inhibitor are all components of the protein C system. Activation of this system occurs when TM binds to thrombin, and rapidly degrades factors VIIIa and Va on the phospholipids surface of activated platelets. This reaction increase 10-20 fold when protein C combines with its cofactor protein S. Levels of TM increase throughout pregnancy, whereas levels of total and free protein S gradually decrease. Levels of protein C remain constant during pregnancy, yet acquired APC resistance is reported in up to 50% of normal pregnancies. This increase in APC resistance corresponds with increase in factor VIII and decrease in protein S and APC inhibitor. Overall, pregnancy appears to be associated with a decrease in coagulation inhibitors, although there is also evidence of bi-directional changes in levels or activity of coagulation inhibitors, and it is probable that these complex changes occur to help maintain the coagulation/fibrinolysis balance during normal pregnancy (Holmes & Wallace, 2005).

2.2.4 Fibrinolysis:-

Fibrinolysis controls fibrin deposition, thus maintaining a controlled procoagulant response. tPA (tissue plasminogen activator) converts plasminogen into plasmin, which cleaves fibrin and fibrinogen, yielding fibrin degradation products. A2-antiplasmin, a plasmin inhibitor, and PAI-1 and PAI-2 (plasminogen activator inhibitor type 1 and 2), prevent fibrin degradation by plasmin. Endothelial derived PAI-1 increase during the later stages of pregnancy, whereas placenta derived PAI-2, detectable in the plasma during first trimester, increase substantially throughout pregnancy. Although levels of tPA antigen increase over the course of pregnancy,

tPA activity in early pregnancy is close to the standard range seen in non-pregnant women, and there is a gradual decrease over the course of pregnancy. This decrease in tPA activity is consistent with the increase observed in tPA inhibitor PAI-1 and PAI-2 (Holmes & Wallace, 2005).

Taken together, the changes outlined above suggest that during normal pregnancy the fibrinolytic system is impaired. However, plasminogen levels are increased during pregnancy, whereas levels of the plasmin inhibitor α_2 -antiplasmin are decreased. These changes, together with increase in D-dimer and fibrin degradation products, which are products of fibrin breakdown by plasmin and, thus, markers of fibrinolysis, are indicative of a substantial increase in fibrinolytic system activation, possibly to counterbalance the increase in coagulation factors observed in normal pregnancy and thus leading to the relatively low incidence of VTE in normal pregnancy (Holmes & Wallace, 2005).

2.3D-dimer:-

D-dimer is fibrin degradation product (FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross-linked D fragments of the fibrinogen protein (Dacie J.V., 1991). Since its introduction in the 1990s, it has become an important test performed in patients suspected of thrombotic disorders. In addition, it is used in diagnosis of the blood disorder as disseminated intravascular coagulation (Salvi, 2003).

Coagulation, the formation of a blood clot or thrombus, occurs when the proteins of the coagulation cascade are activated, either by contact with damaged blood vessel wall (intrinsic pathway) or by activation of factor VII by tissue factors. Both pathways lead to the generation of thrombin, an enzyme that turns the soluble blood protein fibrinogen into fibrin, which aggregates into fibrin. Another fragment

site, lead to formation of an insoluble gel which serves as a scaffold for blood clot formation (Dacie& Lewis,.1991).

The circulating enzyme plasmin, the main enzyme of fibrinolysis, cleaves the fibrin gel in a number of places. The resultant fragments, “high molecular weight polymers”, are digested several times more by plasmin to lead to intermediate and then to small polymers (fibrin degradation product). The cross-link between two D fragment remains intact, however, and these are exposed on the surface when the fibrin fragments are sufficiently digested. The typical D-dimer containing fragment contains two D domains and one E domain of the original fibrinogen molecule (Dacie& Lewis,.1991).

D-dimers are not normally present in human blood plasma, except when the coagulation system has activated, for instance because of presence of thrombosis or as disseminated intravascular coagulation. The D-dimer assay depends on the binding of a monoclonal antibody to a particular epitope on the D- dimer fragment. Several detection kits are commercially available: all of them rely on different monoclonal antibody against D- dimer.

D- dimer testing is of clinical use when there is a suspicion of thrombosis and as disseminated intravascular coagulation (DIC) (Dacie& Lewis,.1991).

2.4Preeclampsia:-

Preeclampsia is defined as the occurrence of hypertension during pregnancy (in the absence of other causes of elevated blood pressure) in combination with generalized edema or proteinuria or both. When arterial hypertension due to some other disease such as essential hypertension, renal disease or diabetes mellitus which are already present, additionally elevation of the blood pressure plus edema or proteinuria, justifies the diagnosis of superimposed preeclampsia. In both

instances, the presence of convulsions or coma warrants the diagnosis of eclampsia. The fact that preeclampsia-eclampsia may be superimposed upon an already cardiovascular or renal disease does not justify inclusions of the latter in classification as hypertensive disorder of pregnancy, although all such conditions would appear in any hypertensive disorder pregnancy (Andersen & Harbet, 1977).

Hypertension in pregnant woman may represent either the following:

1. The development of significant of blood pressure during pregnancy in previous normotensive woman. Hypertensive disorder caused by gestation represent combination of gestational edema – proteinuria – hypertension complex.
2. The appearance of pregnancy in patient with essential hypertension, cardiovascular hypertensive disease or renal hypertensive disease, i.e., the hypertensive disease existed prior to pregnancy. This represents hypertension complicated by pregnancy (HCP) (Benedett *et al.*, 1980).

For many decades, these disorder have been called the toxemias of pregnancy. The term gestational hypertension disorder is preferable.

The term eclamptogenic toxemia is sometimes used to denote preeclampsia and eclampsia. Eclampsia actually is the most fulminating degree of preeclampsia, characterized by convulsion in addition to other signs and symptoms of preeclampsia. This spectrum is best referred to as preeclampsia-eclampsia. Although, the two forms of the disorder differ substantially in clinical manifestation and prognosis, the treatment is essentially the same (Benedett *et al.*, 1980).

The principal diagnostic criteria are:

A) Hypertension: average systolic/diastolic blood pressure value (in mm Hg)

for non-pregnant female are:

- 103/70 at age 10.

- 120/80 at age 20.
- 123/82 at age 30.
- 126/84 at age 40.
- 130/86 at age 50.

Adult non-pregnant women are considered to be normotensive with systolic blood pressure less than 140 mmHg or diastolic blood pressure less than 90 mmHg or both. There is some variation with age, race, physiological state, dietary habits and variation with age, race physiological state, dietary habits and heredity (Lothr et al,.1977).

Analysis of serial blood pressure measurement as the bases for diagnosis of hypertension is particularly important in pregnancy. A constant elevation of disorders of diastolic pressure usually warrants a diagnosis of clinical hypertension. Hypertension in pregnant women exists, if one or more of the following is present:

- A systolic pressure of 140 mmHg or more.
- A rise of 30 mmHg or more above the patient's pregnant systolic pressure level.
- A diastolic pressure of 90 mmHg or more.
- A rise of 15 mmHg or more above the pregnant systolic pressure level.

B) Edema:

Edema (excessive accumulation of fluid in tissue) may be either intracellular or only extracellular, i.e.: in the vascular channels or interstitial space. For therapeutic purposes, edema can be viewed primarily as a result of abnormal retention of sodium and water (Benedett.*et al*.,1980).

C) Proteinuria:

a proteinuria is defined as the presence of protein in the urine in concentration of 300 mg/L or more in 24 hours collection or 1 g/L or more in random day time urine specimen (Curent& Olson,.1979).

2.4.1Epidemiology of preeclampsia:-

The incidence of pre-eclampsia varies between 5 and 10 percent depending on the exact definition used and the population studies.

It is more common in primigravid women and at the extremes of reproductive age. The recurrence rate for preeclampsia with the same male partner, is approximately 20 percent, and usually become apparent at a later gestation than in the first pregnancy. A new partner increases individual woman's of recurrence (Whelton.*et al*.,1994)

2.4.2Etiology and risk factors of preeclampsia:

The cause of preeclampsia-eclampsia remains unknown. Important areas of suspicion in the past have been protein and other metabolic disturbances, interferences with hormonal activity or metabolism by the developing placenta, idiosyncratic features of vascular reactivity, nutritional deficiency and smoking. Recent attempts to implicate uteroplacental ischemia have been popular, but this theory is still being examined. Girls delivered of mothers with gestational hypertensive disorder have significantly higher mean blood pressure at age 7 years than girls in the total population (Curent& Olson,.1979).

Preeclampsia is often referred to as the disease of theories, with many mechanisms proposed to account for the clinical picture. Serum from women with preeclampsia is able to activate and damage vascular endothelial cells in vitro, and investigators believe that a poorly perfused trophoblast may release factor X. which enter maternal circulation and damage heart vascular beds (Chesley,.1935).

The nature of this factor has not yet been defined. Other theories include abnormal lipids metabolism, reduce antioxidants status, altered catecholamine homeostasis, abnormal dietary calcium, magnesium and selenium content, reduce production of the nitric oxide and an abnormal immune response to pregnancy (Chesley,.1935).

As changes in many of these pathways are seen in clinically normal pregnancies, the clinical feature of preeclampsia may be observed only when endothelial compensating mechanisms fail.

Whilst vascular dysfunction is important in pathophysiology of preeclampsia, the etiology appears to be due to abnormal trophoblast invasion. Preeclampsia has been described in pregnancies lacking a fetus (molar pregnancies) and in the absence of uterus (abdominal pregnancies), suggesting that the trophoblast is of paramount importance. Approximately 100 – 150 spiral arteries supply the maternal surface of the placenta. Placental bed biopsies have demonstrated that in preeclampsia trophoblast invasion is patchy, and the spiral arteries retain their muscular wall. This is thought to prevent the development of a high-flow, low impedance uteroplacental circulation. The reason why trophoblast invades less effectively in these pregnancies, and why the first pregnancy is subsequently protective, not understood. Extra villous cell trophoblast cell from placental bed biopsies taken from preeclampsia pregnancies do not show the normal adhesion molecules switch characteristic of invasive trophoblast, although the reason for this also remains poorly understood (Chesley,.1935).

2.4.3 Clinical features of preeclampsia:

The sign of preeclampsia insidious in onset. It is of the almost importance that regular visit to a physician for prenatal care start early in pregnancy for the prevention, early detection and treatment of preeclampsia. Achievement of these goals depends on the education of the public as well as profession (Grunfeld.*et al.*,1980).

Symptoms and signs:

Hypertension is the most significant primary sign of preeclampsia. The diastolic blood pressure is more reliable than the systolic because it is less susceptible to extrinsic influences. Any repeated or constant elevation of the diastolic blood pressure of 15 mmHg or more above the normal pregnancy level must be regarded as hypertension. This is also true of elevations of 30 mmHg or more for the systolic pressure. Nevertheless, readings are dependable only when obtained under relatively basal conditions, such elevation of blood pressure, when not accompanied by either of other two cardinal signs of preeclampsia (edema and proteinuria) suggests that the clinical complication is imminent. The diagnosis is confirmed when hypertension is accompanied by edema or proteinuria. The same is true of persistent elevation of diastolic pressure to 90 mmHg or more in patients without prior hypertension (Chesley, 1978).

Diastolic blood pressure of level of 110 mmHg and systolic level of 180 mmHg are frequently encountered in severe preeclampsia, but systolic level over 200 mmHg are rare. These usually reflect the presence of essential hypertension (Lothr *et al.*, 1977).

The cardiovascular component of preeclampsia-eclampsia, specially increased peripheral vascular resistance, may compromise cardiac reserve seriously (Lothr *et al.*, 1977).

Sudden excessive weight gain is a common first sign of impending or actual preeclampsia. It often develops before the hypertension appears. An increase of more than one kg (2.2 lb) week for 3 kg (6.6 lb) in a month is generally regarded as significant. Gradual increases of weight of up to 0.25 – 0.5 kg (0.5 – 1 lb) per week are normal in pregnancy. The weight gain in preeclampsia usually in Sudan because it is due to almost entirely to retention of fluid. The gain may be noted even before generalized edema of preeclampsia. As the actual disease becomes

progresses, gain of as much as 5 kg (11 lb) per week frequently occur. When significant edema or proteinuria exist in the absence of hypertension, subsequent and significant elevation of blood pressure is possible or imminent (Chesley, 1978).

Ordinarily, edema is first noted in the lower legs, and small degree of this is normal in many normal pregnant women as fluid retention progresses to imminent or frank preeclampsia, the patient is likely to note puffiness around the eye and tightness of the finer rings, particularly on arising in the morning. Examination then demonstrates pitting edema, present over the sacrum and deep over the pretibial surfaces (Grunfeld *et al.*, 1980).

Headache either frontal or occipital is the principal symptom of preeclampsia-eclampsia. The frequency and severity of headache is warning of an impending convulsion (Grunfeld *et al.*, 1980).

In the late stage of preeclampsia, the development of epigastric pain may signal the imminence of convulsion. The cause is not clear (Wardle, 1978).

Patients with liver disorders rarely manifest significant hepatic insufficiency because of hepatic reserve and regeneration even during peak of eclampsia. Nevertheless, right upper quadrant pain and intrahepatic hemorrhage may occur with rupture of the capsule, followed by intraperitoneal bleeding in acute surgical emergency (Wardle, 1978).

2.4.4 Laboratory findings of preeclampsia:-

Protein usually appears in urine after the hypertension of preeclampsia becomes apparent. Proteinuria is always an important finding, even in trace amount. The amount varies greatly but when careful determination reveals more than 300mg/L in 24h collection or more than 1g/L in random sample of urine, this is significant proteinuria. Proteinuria is usually the last of the three major signs of preeclampsia to appear (Curent & Olson, 1979).

Oligouria is common and anuria may develop. Hyaline and granular cast may occur but do not commonly appear in urine of patient with eclamptogenic toxemia. Epithelial cast, isolated renal cells, and red blood cells may also be seen (Chesley,.1978).

Chapter three

3. Materials and Methods:

3.1 Material:

3.1.1 Study design:

This is a case control hospital based study.

3.1.2 Study area:

The study was conducted in Soba University Hospital, in Khartoum state.

3.1.3 Study period:

The study was carried during the period from March- June 2015 .

3.1.4 Study population:

The study was conducted on preeclamptic pregnant women as test group and normotensive pregnant as control group.

3.1.5 Inclusion Criteria:

preeclamptic pregnant women as test group.

3.1.6 Exclusion Criteria:

Preeclamptic women with clinical history of renal disease, diabetes mellitus, hypothyroidism and any chronic disease had been excluded.

3.1.7 Sample size:

The study sample size was (120) (60preeclamptic as test group and 60 normotensive pregnant as control) were enrolled in this study.

3.1.8 Blood sampling:

In this study 3 ml of venous blood was collected by standard procedure in trisodium citrate container from each participant in this study. .

3.1.9 Equipments:

Nycocard, syringes, cotton, alcohol, trisodium citrate clean dry containers, ,pipettes(Automatic), stop watch and tips.

3.1.10 Ethical consideration:

Aconsent was taken regarding acceptance to participate in the study and reassurance of confidentiality. Before the specimen was collect, the donor knew that this specimen was collected for research purpose.

3.1.11 Data collection:

The clinical data were obtained from history, clinical examination and hospital follow up records and were recorded on a questionnaire sheet (Appendix (I)).

3.2 Methods:

Nycocard D-dimer single test:

Nycocard D-dimer was used for rapid determination of fibrin degradation product in plasma.

Procedure:

According to manufacture protocol 50µl of washing solution was applied to the test device and allowed to soak into the membrane. 50µl of undiluted platelets-free citrate plasma or control was added to the test device .50µl of conjugate was applied to the test device and 50µl of washing solution was added to the test device (Appendix (II)).

BMI calculation:

From weight and hight BMI calculated by equation :

$$\text{BMI} = \text{Weight (Kg)} / \text{hight (m}^2\text{)}$$

3.3 Quality control:

The precision and accuracy of all methods used in this study were cheeked and was analyzed .

3. 4 Statistical analysis:

Data was analyzed by using the SPSS computer program. Independent T test was applied to compare the mean and SD of D-dimer between test group and control group (P-value ≤ 0.05 is considered significant).

Chapter four

4.Results

Plasma D-dimer level was measured in 60 preeclamptic pregnant women as test group and 60 normotensive pregnant women were enrolled into this study as control group, during the period of March to June 2015.

Plasma D-dimer:

Table (4.1):

Shows a significant difference between the means of D-dimer in test group (hypertensive preeclamptic pregnant) compared to control group (normotensive pregnant).

(mean +SD): (mean 1.040 ± 0.45 versus 0.31 ± 0.139 ; p-value=0.017).

Figure (4.1):

A scatter plot shows a significant moderate positive correlation between the level of D-dimer and the duration of hypertension ($r=0.835$, $p=0.00$).

Figure (4.2):

A scatter plot shows a significant moderate positive correlation between the level of D-dimer and BMI ($r=0.673$, $p=0.003$).

Table (4.1):comparison of the means of D-dimer in hypertensive preeclamptic pregnant group and normotensive pregnant group.

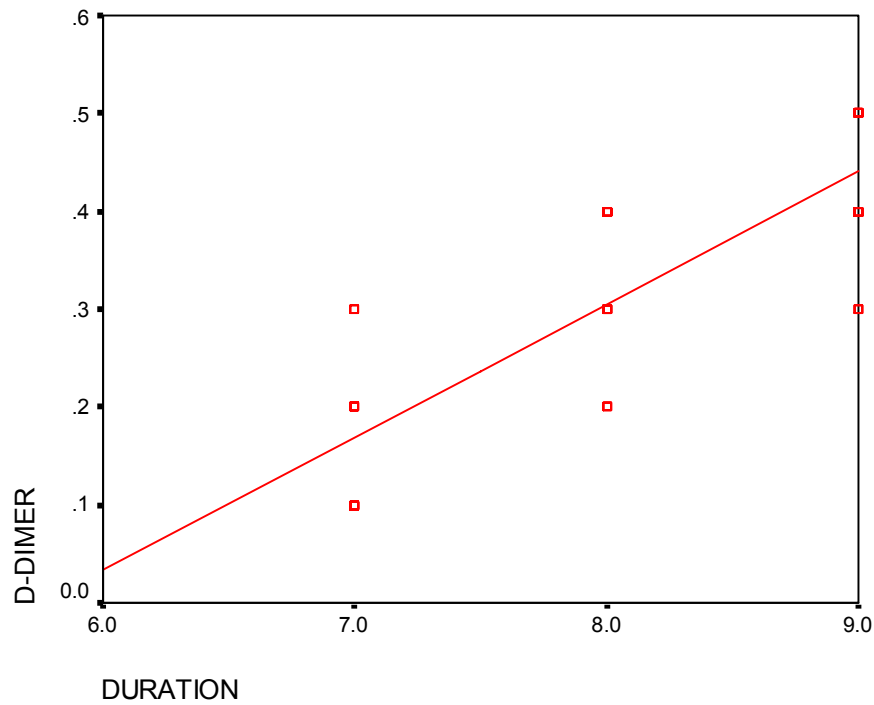
Variable	hypertensive preeclamptic n=60	normotensive pregnant n=60	P vale
D-dimer ng/ml	1.040±0.45	0.31±0.139	0.017

The table shows the mean±SD, and the probability (P).

t-test was used for comparison.

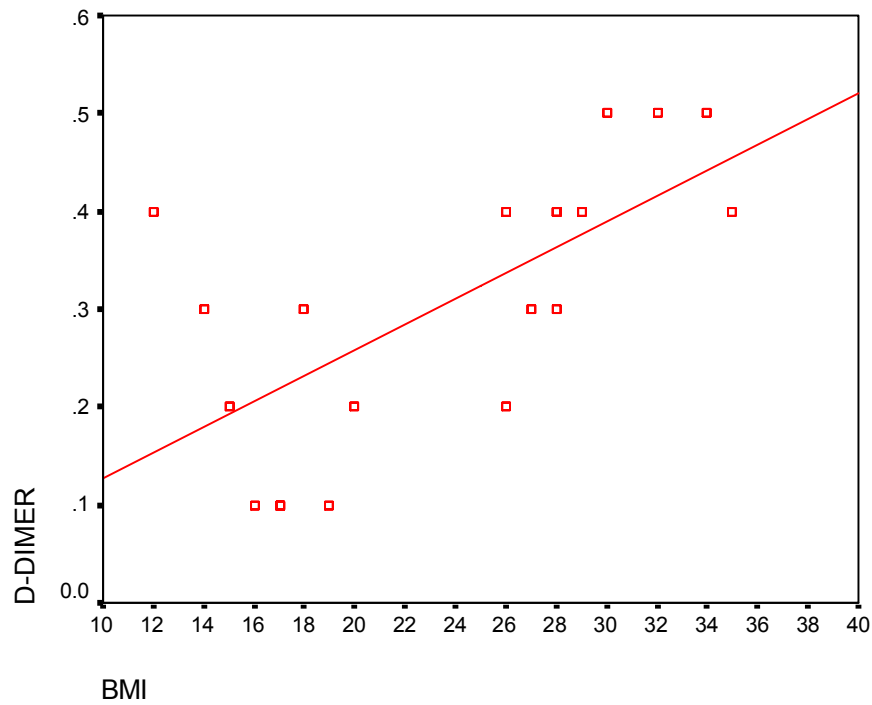
P-value ≤ 0.05 is considered significant.

Figure (4.1):



A scatter plot Shows significant moderate positive correlation between the levels of D-dimer and the duration of hypertension appearance ($r=0.835$, $p=0.000$).

Figure (4.2):



A scatter plot Shows significant moderate positive correlation between the levels of D-dimer and BMI ($r=0.673$, $p=0.003$).

Chapter five

5. Discussion, Conclusion and Recommendation

5.1 Discussion:

Hypertension is the most common medical complication of pregnancy, affecting 10% to 15% of all pregnancies in the develop world, where it is the second leading cause of maternal death and markedly increase the incidence of preterm birth. Intrauterine growth restriction, placental abruption, and parental mortality.

During pregnancy, maternal coagulation is enhanced so that excessive postpartum bleeding usually does not occur. Maternal hypercoagulability results from increase production of thrombotic factors in intrinsic and extrinsic pathways (Woodhams,.1989).

In this study the level of D-dimer was found to be significantly increased in preeclamptic women when compared with normotensive pregnant women.

The results with a study done by;(Nolan.*et al*.,1993), found that D- dimer significantly greater than those of controlsbecause pregnancy is ahypercoagulation state lead to alteration of normal hemostasis.

Also study results showed a significant correlation between duration of hypertension and level of D-dime.This study results matched the study results donein American by ;(Sara.*et al*.,1994) .

This study showed a significant correlation between body mass index and levels of D-dimer. These finding were contrary to the observation of (O'Brien.*et al*.,2003).

The result of this study suggest that; Preeclampsiais associate with raised level of D-dimer and hence with increase risks of developing eclampsia and other possible complications.

5.2 Conclusion:

From this study, it is concluded that:

- 1-The level of D-dimer is significantly increased in preeclamptic pregnant women.
- 2-There are significant correlations between the levels of D-dimer and the duration of hypertension appearance .
- 3- There are significant correlation between level of D-dimer and BMI.

5.3 Recommendation:

- 1- Pregnant women should be screened for D-dimer, as it is useful indicator for early diagnosis of preeclampsia.
- 2- Further studies to evaluate the value of D-dimer in prognosis and management follow up of preeclampsia and eclampsia recommended to be done.

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Appendices

Sudan University of Science and Technology
College of Graduate Studies
Master Degree

Appendix (I): Questionnaire

Topic: Assessment of plasma D-dimer level in hypertensive preeclamptic pregnant women in Khartoum state

General information:

- (i) Serial No.....
- (ii) Age:.....
- (iii) Gestation:.....
- (iv) Weight.....
- (v) Height.....
- (vi) Is there any one of the family have preeclampsia:.....

Clinical information:

Diabetes Mellitus : Yes () No ()
Hypoparathyroidism : Yes () No ()
Other chronic disease : Yes () No ()

.....

Investigation Results:

D-dimer =.....ng/ml

BMI=.....Kg/m²