Biochemical Changes in Sudanese Women with Pre-eclampsia

A thesis submitted for fulfillment of the requirements of M.Sc in Medical Laboratory Sciences
(Chemical Pathology)

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيم

ق ال اٰمَّة

﴿هُوَ الَّذِي يُصَوِّرُكُمْ فِي الَّدَرْسِ كَيْفَ يَشَاءُ لََ إِلَٰهَ إِلََّ هُوَ الْعَزِيزُ الْحَكِيمُ﴾

صدق اٰمَّة العظيم

صلح الله العظيم

ال عمران: الآية (6)
DEDICATION

This Research is lovingly dedicated to my respective parents who have been my constant source of inspiration. They have given me the drive and discipline to tackle any task with enthusiasm and determination. Without their love and support this work would not have been made possible.
ACKNOWLEDGEMENT

I take this opportunity to express my profound gratitude and deep regards to my guide (Professor Elstayeb Mohamed Ahmed Tayrah) for his exemplary guidance, monitoring and constant encouragement throughout this work. The blessing help and guidance given by his time to time that carried me a long way in the journey of life on which I am about to embark. I also take this opportunity to express a deep sense of gratitude to my parents and my colleagues, for their cordial support, valuable encourage, which helped me in completing this task through various stages.
Abstract

This case control study which was conducted in Omdurman Maternity Hospital and Ribat University Hospital in Khartoum State, during the period from September 2013 to July 2015.

Objectives of the study: The aim of this study was to evaluate the biochemical changes which occur in the serum of pregnant women with pre-eclampsia including renal functions (urea, creatinine, sodium, potassium, and uric acid), liver functions (total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), and complete blood count (CBC).

Materials and methods: Blood samples were collected from 120 pregnant women with pre-eclampsia beside 75 normal pregnant women which served as control group. Serum urea, creatinine, uric acid, total protein, albumin, ALT, AST, ALP were measured using automated chemical analyzer (Mindary BS - 210). Serum sodium and potassium were measured using (ion selective electrode). Complete blood count (CBC) was done using full automated hematology analyzer (Sysmex).  Data were analyzed using IBM SPSS (version 20).

Results: The study revealed that the mean age of the women with pre-eclampsia was (28.1±6.5 years), while in the women with normal pregnancy was (29.2±6.4 years). The mean weight in the pre-eclampsic women was (79.3±9.0 Kg), while in the control group was (77.4±5.8 Kg). The study observed a significant increase {P value (0.000)} in the mean of both diastolic and systolic blood pressure in the pre-eclampsic women, which were (152.3±17.7 mmHg) and (106.5±11.5 mmHg), versus (122.8±5.6 mmHg) and (78.9±3.3 mmHg) respectively for the control group. Serum creatinine level was significant increased in pre-eclampsic women when compared to the control group (0.7±0.4 mg/dl) versus (0.4±0.3 mg/dl) with
value (0.000). Serum uric acid in the women with pre-eclampsia was (7.0±2.1mg/dl) versus 5.0±1.4mg/dl) in the women with normal pregnancy; there was a significant increase with P. value (0.000). The mean of serum ALP in the women with pre-eclampsia was (130.7±46.1 U/L) versus (83.9±17.7U/L) in the women with normal pregnancy, there was a significant increase with P. value (0.000). The mean of serum AST in the women with pre-eclampsia was (63.9±112.2 U/L) versus (29.6±12.1 U/L) in the women with normal pregnancy; there was a significant increase with P.value (0.01). The mean of serum ALT in the women with pre-eclampsia was (32.1±49.9 U/L) versus (18.2±8.6 U/L) in the women with normal pregnancy there was significant increase with P.value (0.003). The mean WBCs in the women with pre-eclampsia was (9.4±4.2) versus (8.2±2.8) in the women with normal pregnancy; there was a significant increase with P.value (0.015). The mean of PLTs in the women with pre-eclampsia was (211.2±93.1) versus (245.4±66.0) in the women with normal pregnancy; there was a significant decrease with P.value (0.003).

**Conclusion:** in pre-eclampsic Sudanese women; serum creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and white blood cell count significantly increase, while platelets count significantly decrease.
مستخلص الدراسة

اجريت هذه الدراسة بولاية الخرطوم بمستشفى الولادة بمصدرمان ومستشفى الرباط الجامعي خلال الفترة من سبتمبر 2013 و يوليو 2015.

هدف البحث: هدفت هذه الدراسة على دراسة التغيرات الكيميائية التي تحدث في مصل النساء الحوامل المصابات بتسمم الحمل أو بمقدمات الارتعاج.

المواد والطريقة: تم جمع عينات الدم من 120 من النساء الحوامل المصابات بتسمم الحمل بالإضافة إلى 75 من النساء الحوامل بحمل طبيعي ومماثلات لهن في العمر لاستخدامهن في عملية المقارنة. تم قياس البولينا والكرياتينين والبروتين الكلي والزال والفوسفاتازات الكلية والألانين والألانين ونافلة أمين الأسبارتات مستخدمين جهاز التحليل الكيميائي التلقائي (مندري210).

كما تم إجراء تحليل صورة الدم الكاملة مستخدمين جهاز تحليل الدم الآليوماتيكي. وكذلك تم قياس الصوديوم والبوتاسيوم مستخدمين جهاز التحليل الأيوني.

استخدم البرنامج الإحصائي IBM SPSS للتحليل الإحصائي.

النتائج: اوضحت الدراسة على ان متوسط الاعمار عند النساء الحوامل والمصابات بتسمم الحمل هو (28.1±6.5) مقابل (29.2±5.2) سنة عند العينات الضابطة، كما ظهرت ان متوسط الوزان عند النساء الحوامل المصابات بتسمم الحمل هو (9.0±5.8) مقابل (77.4±5.6) كجم للعينات الضابطة. ووجدت الدراسة ان هناك زيادة ذات دلالة معنوية عند النساء الحوامل والمصابات بتسمم الحمل (الكلش) في مستوى كل: الكرياتينين (0.7±0.4mg/dl) مقابل (0.4±0.3mg/dl) والفسفاتازات الكلية (130.7±46.1 U/L) مقابل (12.1±5.0 mg/dl) والفوسفاتازات الكلية (17.67±112.2 U/L) مقابل (29.6±8.6 U/L) ونافلة أمين الأسبارتات (83.9±63.9 U/L) مقابل (21.2±32.1 U/L) ووكريات الدم البيضاء (9.4±4.2) مقابل (8.2±4.2) مقارنة بالجموعة الضابطة.
كما توجد هناك انخفاض ذو دلالة معنوية في مستوى الصفائح الدموية في الحوامل المصابات بتسمم الحمل

(211.3±93.4) مقابل (66.0±45.4) مقارنة بالمجموعة الضابطة.

الخلاصة: عند النساء السودانيات الحوامل والمصابات بداء تسمم الحمل، هناك زيادة معنوية في مستوى الكرياتينين وحمض البوريك والفسفاتاز القلوية والألانين ألانين وناقلة أمين الإسبارتا وكريات الدم البيضاء مقارنة بالمجموعات الضابطة. كما تظهر عندهن انخفاض ذو دلالة معنوية في عدد الصفائح الدموية.
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Abbreviations

BMI: Body mass index
BP: Blood pressure
GFR: Glomerular filtration rate
GH: Gestational hypertension
IFCC: International Federation of Clinical Chemistry and Laboratory Medicine
LFT: Liver function tests
PIH: Pregnancy-induced hypertension
RFT: Renal function tests
CHAPTER ONE

Introduction & literature review
1. Introduction and literature review

1.1. Introduction to Preeclampsia

Eclampsia is a Greek; means "shining forth" is an acute and life-threatening complication of pregnancy, characterized by the appearance of tonic–clonic seizures, usually in a patient who has developed pre-eclampsia. Pre-eclampsia and eclampsia are collectively called hypertensive disorder of pregnancy and toxemia of pregnancy. Eclampsia includes seizures and coma that happen during pregnancy but are not due to preexisting or organic brain disorders (Chesley, 1971).

Eclampsia refers to the occurrence of one or more generalized convulsions and/or coma in the setting of pre-eclampsia and in the absence of other neurologic conditions. The clinical manifestations can appear anytime from the second trimester to the puerperium. In the past, eclampsia was thought to be the end result of preeclampsia, however; it is now clear that seizures should be considered merely one of several clinical manifestations of severe pre-eclampsia, rather than a separate disease. Despite advances in detection and management, pre-eclampsia/eclampsia remains a common cause of maternal death (Douglas and Redman, 1994).

An eclamptic seizure occurs in 2 to 3 percent of severely pre-eclamptic women not receiving anti-seizure prophylaxis; the seizure rate is estimated to be between 0 and 0.6 percent in women with mild pre-eclampsia (Sibai, 2004). The incidence of eclampsia has been relatively stable at 1.6 to 10 cases per 10,000 deliveries in developed countries (Douglas and Redman, 1994; Tan et al, 2006). In developing countries, however, the incidence varies widely: from 6 to 157 cases per 10,000 deliveries (Miguillet al, 2008).
Pre-eclampsia is a medical condition characterized by high blood pressure and significant amounts of protein in the urine of a pregnant woman. If left untreated, it can develop into eclampsia, the life-threatening occurrence of seizures during pregnancy (Chesley, 1971).

There are many different causes for the condition. It appears likely that there are substances from the placenta that can cause endothelial dysfunction in the maternal blood vessels of susceptible women. While blood pressure elevation is the most visible sign of the disease, it involves generalized damage to the maternal endothelium, kidneys, and liver, with the release of vasoconstrictive factors being a consequence of the original damage. An outdated medical term for pre-eclampsia is toxemia of pregnancy, since it was thought that the condition was caused by toxins (Sibai, 2004). The pathophysiologic processes underlying this disorder are described as occurring in two stages (Roberts and Hubel, 1999).

The first stage is characterized by reduced placental perfusion, possibly related to abnormal placentation, with impaired trophoblast invasion and inadequate remodeling of the uterine spiral arteries. The second stage refers to the maternal systemic manifestations characterized by inflammatory, metabolic, and thrombotic responses that converge to alter vascular function, which can result in multiorgan damage (Roberts and Gammill 2005; Steegers et al., 2010).

Many factors have been associated with an increased risk of developing preeclampsia including prior history or family history of preeclampsia, nulliparity, multigestational pregnancy, long time interval between pregnancies, obesity, age >40 years, diabetes mellitus, and preexisting history of other medical conditions such as chronic hypertension and renal disease, among others (Duckitt and Harrington 2005; Van Rijn et al., 2006).
Pre-eclampsia may develop from 20th week of gestation (it is considered early onset before 32 weeks, which is associated with an increased morbidity). Its progress differs among patients; most cases are diagnosed before labor typically would begin. Pre-eclampsia may also occur up to six weeks after delivery. Apart from Caesarean section and induction of labor (and therefore delivery of the placenta), there is no known cure. It is the most common of the dangerous pregnancy complications; it may affect both the mother and fetus (Sibai, 2004).

The hypertensive disorders during pregnancy affect up to 8.0% of all pregnancies (Sullivan and Martin, 1995).

Over the years, a lot of interest has been directed at studies on the role of serum uric acid, urea and creatinine in the pathogenesis of pregnancy induced hypertension (Egwuatu, 1986; Mustaphi, et al, 1996). At the same time hypertensive disorders account for 21% (Mustaphi et al, 1999) of cases of thrombocytopenia in pregnancy and the risk of anemia may also increase with the severity of hypertensive disorders (Mustaphi and Ananth, 2009). Thus; though the roles of serum urea, uric acid and creatinine have been studied by many researchers, there is a constant ongoing search for better predictors and prognostic factors to assess the progress and severity of the disease, hematological parameters being one among them (Mustaphi and Nanda, 2013; Sivakumar et al, 2007).
1.2. Literature review of Preeclampsia

In the 18th century, Boissier de Sauvages distinguished eclampsia from epilepsy. Along with the distinction he made in disease classification, de Sauvages offered his views on the cause of convulsions. He believed that convulsions resulted from nature trying to free the organism of any morbid element (Temkin, 1971).

Theories on disease causation continued to be proposed and thoroughly discussed in the writings of 19th century physicians. In the work entitled introduction to the practice of midwifery; Denman (1821) focused much attention on the labors affected by convulsions. Although Denman attributed convulsions to certain customs and manners associated with living in large cities and towns, he noted that the greatest risk of convulsions came from the uterus. According to Denman, as the uterus expanded with pregnancy, greater pressure was placed upon the descending blood vessels. Such an increase in pressure lead to the regurgitation of blood in the head and resulted in an overload of the cerebral vessels and subsequent convulsions (Denman, 1821).

In his 1849 work, parturition and the principles and practice of obstetrics, Dr. William Tyler Smith challenged the theory of cerebral congestion, for he believed that pregnancy was a state of increased fullness in circulation.

Given that contractions during the second stage of labor normally interfered with the circulation of blood, he believed that more cases of convulsions would be observed if such congestion caused convulsions. In contrast, Smith attributed puerperal convulsions to several other causes: (1) any mechanical or emotional stimulus applied in excess to the spinal center; (2) bloodletting; (3) variations in the wind, temperature, and other atmospheric changes; (4) irritation of the uterus, uterine passages, intestinal canal, and the stomach; and (5) toxic elements
As for Smith’s theory on “toxic” elements, he believed that preservation of health during pregnancy depended on the exponential increase in the elimination of wastes (e.g., secretions of the bowels) and debris from the maternal and fetal systems. Failure to do so resulted in a “toxemia” in which morbid elements accumulated in the blood causing irritation to the nervous center (Smith, 1849).

After the introduction of the word “eclampsia,” Bossier de Sauvages (1739) differentiated eclampsia from epilepsy (Chesley, 1978). Eclampsia was acute in nature because convulsions resolved once the precipitating event was removed. Epilepsy was chronic in nature because convulsions recurred over time. Furthermore, eclampsia was not restricted to pregnancy. Severe hemorrhage, various sources of pain, vermicular infestations, and eclampsia associated with pregnancy were several species of eclampsia noted by de Sauvages (Chesley, 1978). At the end of the 18th century and through the 19th century, the classification of pre-eclampsia-eclampsia continued to become more refined as the classic signs and symptoms of pre-eclampsia-eclampsia became more readily recognized. Demanet in (1797) noted a connection between edematous women and eclampsia (Chesley, 1978); while John Lever 1948 discovered albumin in the urine of eclamptic women. The connection between premonitory symptoms during the later months of pregnancy with the development of puerperal convulsions was also recognized in. These premonitory symptoms included headache, temporary loss of vision, severe pain in the stomach, and edema of the hands, arms, neck, and face (Johns, 1843). In 1897, Vaquez and Nobecourt were credited with the discovery of eclamptic hypertension (Chesley, 1978). As a result of these contributions, the concept of the pre-eclamptic state was recognized. Physicians were now aware that
the presence of edema, proteinuria, and headaches should raise concern about the possibility of convulsions (Sinclair and Johnston, 1858).

Although researchers in the 20th century failed to uncover the etiology of preeclampsia, much progress was made in the understanding of pathophysiological changes associated with its development. In the 1960’s, several groups described dramatic differences in placental physiology between placentas from pregnancies affected by preeclampsia versus placentas from pregnancies unaffected by pre-eclampsia. Through the examination of placental bed biopsies, it was discovered that placental trophoblast cells failed to adequately invade maternal spiral arteries and convert the arteries from small muscular vessels into large. With the lack of spiral artery conversion, arterial lumen diameter and dis-tensibility was limited, resulting in restricted blood flow to the placenta and growing fetus (Brosens et al, 1972; Kong et al, 1986; Brosens et al, 1967).

At present, the scientific community has failed to uncover the etiologic mechanisms responsible for the development of pre-eclampsia-eclampsia. As evidenced by the many review articles published in the scientific literature. The theories on disease causation are numerous and diverse, such theories are related to mechanisms involving oxidative stress, immunologic intolerance between the fetoplacental unit and maternal tissue, and angiogenic imbalance (Leeman and Fontaine, 2008). Regardless of the mechanism, a two stage model of pre-eclampsia has been developed to provide a guiding framework for scientists in their search of disease causation (Hladunewich et al, 2007; Roberts and Gammill, 2005).

In 2000, the National High Blood Pressure Education Program published a report with revisions to preeclampsia-eclampsia classification criteria. Preeclampsia is currently classified as a pregnancy-specific syndrome characterized by the
presence of new-onset hypertension in a previously normotensive woman after 20 weeks gestation with proteinuria. Blood pressure (BP) criteria include a systolic BP >140 mm Hg or a diastolic BP >90 mm Hg. Proteinuria is defined as urinary excretion of ≥ 0.3 grams of protein in a 24-hour specimen, which correlates with a random ≥ 1+ urine dipstick in the absence of a urinary tract infection. The presence of edema was dropped from the diagnostic criteria because many pregnant women with normal pregnancies develop edema. Furthermore, eclampsia is classified as the presence of seizures, non-attributable to other causes, in a woman diagnosed with preeclampsia (Roccella, 2000).

Accurate pre-eclampsia statistics are difficult to obtain because the condition ranges from extremely mild to severe, and mild cases are sometimes not included in the official figures. Furthermore, mild cases may have no effect on pregnancy, which is why the figures for pre-eclampsia as a whole are higher than for those that actually complicate pregnancies:

- Around 10% of pregnant women develop pregnancy-induced hypertension or pre-eclampsia (Knight, 2007).
- Worldwide, more than four million women per year will develop pre-eclampsia and over 63,000 maternal deaths were due to pre-eclampsia and eclampsia in 2000.
- Action on pre-eclampsia estimates that every year in the UK pre-eclampsia is responsible for the deaths of 500–600 babies, many due to premature delivery rather than the condition itself. Some six mothers die each year from the complications of pre-eclampsia in the UK.
- A 2005–2006 study showed a promising fall in the numbers of women developing eclampsia since 1992, from 4.9/10,000 to 2.7/10,000. This is the
result of the introduction of management guidelines and protocols for eclampsia and pre-eclampsia (Knight, 2007).

- The risk of women who have had pre-eclampsia developing it again in future pregnancies is 16 percent (one in six), rising to 25 percent (one in four) if they suffered from severe pre-eclampsia, eclampsia or they delivered preterm. This rises further to 55 percent (one in two) if their baby was delivered before 28 weeks.

- Half of the women with severe pre-eclampsia give birth to preterm babies.

- Pre-eclampsia is responsible for 15 percent of all preterm births in the USA. Infants of mothers suffering from pre-eclampsia have a five times higher risk of dying than those of mothers without pre-eclampsia, mainly because of preterm birth (Lain and Roberts, 2002).

Women with preeclampsia are at an increased risk for life-threatening events, including placental abruption, acute renal failure, cerebral hemorrhage, hepatic failure or rupture, pulmonary edema, disseminated intravascular coagulation, and progression to eclampsia. Worldwide, 10 to 15 percent of direct maternal deaths (i.e., resulting from obstetric complications of pregnancy) are associated with preeclampsia/eclampsia (Duley, 2009). In the United States, preeclampsia/eclampsia is one of four leading causes of maternal death, along with hemorrhage, cardiovascular conditions, and thromboembolism (Chang et al, 2003; Mackay et al, 2011). There is approximately one maternal death due to preeclampsia-eclampsia per 100,000 live births, with a case-fatality rate of 6.4 deaths per 10,000 cases (Livingston et al, 2003; Mackay et al, 2001). In the Netherlands between 1993 and 2005, preeclampsia was the most common cause of maternal death, with 3.5 maternal deaths per 100,000 live births (Schutte et al, 2010).
Endothelial dysfunction is responsible for the clinical signs observed in the mother, ie, impairment of the hepatic endothelium contributing to onset of the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome, impairment of the cerebral endothelium inducing refractory neurological disorders, or even eclampsia. Depletion of vascular endothelial growth factor in the podocytes makes the endotheliosis more able to block the slit diaphragms in the basement membrane, adding to decreased glomerular filtration and causing proteinuria. Finally, endothelial dysfunction promotes microangiopathic hemolytic anemia, and vascular hyperpermeability associated with low serum albumin causes edema (Sibai et al., 2005; Mutze et al., 2008).

Preeclampsia is categorized as mild or severe. Mild preeclampsia is defined as blood pressure of at least 140 mm Hg systolic or at least 90 mm Hg diastolic on at least two occasions and at least 4 to 6 hours apart after the 20th week of gestation in women without pre-pregnancy hypertension, with proteinuria (defined as ≥300 mg protein in a 24 hour urine specimen) (Sibai et al., 2005). Severe pre-eclampsia is defined as blood pressure at least 160 or 170 mm Hg systolic, 110 mm Hg diastolic, or both, accompanied by ≥5 g of proteinuria per day. When symptoms such as severe headache, visual disturbance, epigastric pain, vomiting, multi-organ system involvement, fetal morbidity or mortality, onset before 34 or 35 weeks or eclampsia (seizures) are present, pre-eclampsia is also classified as severe. Eclampsia is defined as tonic-clonic seizures in a pregnant or recently delivered woman not attributable to other causes than pre-eclampsia or gestational hypertension, complicates about 1 to 2% of all cases of severe preeclampsia (Steegers et al., 2010). It is important to note that published guidelines for pre-eclampsia diagnostic criteria vary among different professional societies (Steegers et al., 2010).
1.2.1. **Signs and symptoms of Preeclampsia:**

Typically the pregnant woman develops hypertension and proteinuria before the onset of a convulsion, the hallmark of eclampsia (Kane *et al.*, 2013). Other cerebral signs may immediately precede the convulsion, such as nausea, vomiting, headaches, and cortical blindness. If the complication of multi-organ failure ensues, signs and symptoms of those failing organs will appear, such as abdominal pain, jaundice, shortness of breath, and diminished urine output. The fetus may develop intrauterine growth retardation, and with maternal convulsions, bradycardia and fetal distress. Placental bleeding and placental abruption may also occur (ACOG, 2002; Cunningham *et al.*, 1995).

Swelling or edema (especially in the hands and face) was originally considered an important sign for a diagnosis of pre-eclampsia, but in current medical practice only hypertension and proteinuria are necessary for a diagnosis. Pitting edema (unusual swelling, particularly of the hands, feet, or face, notable by leaving an indentation when pressed on) can be significant, and should be reported to a health care provider (Steegers *et al.*, 2010; Al-Jameil *et al.*, 2014).

Although eclampsia is potentially fatal (2% of cases), pre-eclampsia is often asymptomatic, and so its detection depends on signs or investigations. Nonetheless, one symptom is crucially important because it is often misinterpreted: epigastric pain may be confused with heartburn, a common problem of pregnancy. In general, none of the signs of pre-eclampsia are specific, and even convulsions in pregnancy are more likely to have causes other than eclampsia in modern practice. Diagnosis, therefore, depends on finding a coincidence of several pre-eclamptic features, the final proof being their regression after delivery. Some women develop high blood pressure without proteinuria, which is called pregnancy-induced hypertension (PIH) or gestational hypertension.
Both pre-eclampsia and PIH are regarded as very serious conditions and require careful monitoring of mother and baby (Mackay et al., 2001).

1.2.2. Causes of pre-eclampsia:

The pre-eclampsia syndrome is thought in many cases to be caused by a shallowly implanted placenta which becomes hypoxic, leading to an immune reaction characterized by secretion of upregulated inflammatory mediators from the placenta, and acting on the vascular endothelium. The shallow implantation is thought to stem from the maternal immune system's response to the placenta and refers to evidence suggesting a lack of established immunological tolerance in pregnancy. This results in an immune response against paternal antigens from the fetus and its placenta (Burneand Jerome, 2007). In some cases of pre-eclampsia it is thought that the mother lacks the receptors for the proteins the placenta is using to downregulate the maternal immune system's response to it (Moffett and Hiby, 2007). This view is also consistent with evidence showing many miscarriages to be an immunological disorder where the mother's immune system "unleashes a destructive attack on the tissues of the developing child" (BBC, 2007). In many cases of the pre-eclampsia syndrome, however, the maternal response to the placenta appears to have allowed for normal implantation. It is possible that women with higher baseline levels of inflammation stemming from underlying conditions such as chronic hypertension or autoimmune disease may have less tolerance for the inflammatory burden of pregnancy. If severe, pre-eclampsia progresses to fulminant pre-eclampsia, with headaches, visual disturbances, and epigastric pain, and further to the HELLP syndrome and eclampsia. Placental abruption is associated with hypertensive pregnancies. These are life-threatening conditions for both the developing baby and the mother (Courtney et al., 2006).
1.2.3. Epidemiology of preeclampsia:

Preeclampsia is part of the spectrum of hypertensive disorders in pregnancy, which also includes gestational hypertension (GH). GH is defined as elevated blood pressure of at least 140 mm Hg systolic or at least 90 mm Hg diastolic without proteinuria in a woman after 20 weeks’ gestation, which resolves postpartum (Roccella, 2000). Hypertensive disorders in pregnancy affect 8%–12% of all pregnancies, and this rate is even higher in developing countries. About three quarters of cases of pre-eclampsia in women are classified as mild, with onset at or near-term. Adverse outcomes are generally rare in mild pre-eclampsia. However; it is important to note that mild pre-eclampsia is a retrospective diagnosis. Mild hypertension in pregnancy can evolve quickly and unpredictably to fulminant severe pre-eclampsia. African American women appear to be at higher risk for the development of pre-eclampsia, although it is not clear whether this relationship is due to a higher prevalence of hypertension in African American women or other risk factors. Women living at high altitude are also known to be at higher risk for preeclampsia (Sibai et al., 2005).

Pre-eclampsia complicates about 2-8% of all pregnancies and the syndrome results in more than 63,000 maternal deaths every year worldwide (WHO, 2005; Duley, 2009). The maternal mortality rate is highest in low- and middle income countries but pre-eclampsia is also a potentially life threatening condition in high income countries (Khan et al., 2006). Known complications related to pre-eclampsia are eclampsia, abruption placenta with disseminated intravascular coagulopathy, cerebral haemorrhage, pulmonary oedema, hepatic failure, HELLP syndrome and acute renal failure (Duley, 2009; Sibai et al., 2003). Pre-eclampsia increases perinatal mortality five-fold, with most deaths caused by iatrogenic prematurity (Lain and Roberts, 2002). Preterm birth itself is responsible for the majority of neonatal
deaths and nearly one half of all cases of congenital neurologic disability (Goldenberg and Rouse, 1998). In the US pre-eclampsia is responsible for 15% of premature births (Lain and Roberts, 2002). Another risk for the infants is intrauterine growth restriction. A study from Norway reveals that women with pre-eclampsia have a four times higher risk of having an infant small for gestational age (SGA) compared to normal pregnancies. If the disorder occurs in early pregnancy 53% of the infants are SGA (Odegard et al, 2000). Furthermore; to be born SGA; increases the risk of hypertension, diabetes and coronary heart disease as adults (Barker, 2004). Later in life, women who have had pre-eclampsia have an increased risk of early cardiac, cerebrovascular and peripheral arterial diseases and cardiovascular mortality (McDonald et al, 2008). Severe and recurrent hypertensive disorders during pregnancy have a stronger association with ischemic heart disease later in life compared with mild and non-recurrent disease (Wikstrom et al, 2005).

1.2.4. Risk factors of Preeclampsia:

The known risk factors for pre-eclampsia are of multivariate origin. Not all studies have reported the same risks (Pabinger, 2009). One of the strongest risk factors is a previous pregnancy with preeclampsia. The recurrence rate for pre-eclampsia varies widely between studies, but a rate up to 65% is described (Sibai et al, 1991). The risk is related to gestational age at onset, the severity of pre-eclampsia, if the fetus was growth restricted or not and whether there are any underlying medical condition with vascular or renal implications (Dildy et al, 2007) Factors that reduce the risk of pre-eclampsia are a previous normal pregnancy and smoking. However; the damaging effects of smoking on general health and prenatal outcomes outweigh the positive effect of lowered incidence of pre-eclampsia (Dildy et al, 2007).
The epidemiology of pre-eclampsia reflects a wide range of risk factors as well as the complexity and heterogeneity of the disease. Risk factors can be classified into pregnancy-specific characteristics and maternal pre-existing features. The incidence of pre-eclampsia is increasing in the United States and may be related to the higher prevalence of predisposing disorders such as hypertension, diabetes, obesity, and delay in childbearing, as well as to the use of artificial reproductive technologies, which results in a higher rate of multi-fetal gestation (Wallis et al, 2008; Berg et al, 2009).

1.2.4.1. Pregnancy-specific features:

1.2.4.1.1. Parity: Null parity is a strong risk factor that almost triples the risk of preeclampsia, according to a systematic review of controlled studies (Duckitt and Harrington, 2005). It is estimated that two-thirds of all cases occur in first pregnancies that progress beyond the first trimester (Funai et al, 2005). New paternity also increases the risk of pre-eclampsia in a subsequent pregnancy. The association between primiparity and pre-eclampsia suggests an immunological mechanism, such that later pregnancies are protected against those paternal antigens (Redman, 1991). Supporting this concept; previous pregnancy loss, increased duration of sexual activity prior to pregnancy, or prolonged prepregnancy cohabitation confer a lower risk of preeclampsia (Hutcheon et al, 2011). Conversely; the risk of pre-eclampsia is increased with the use of barrier contraceptives, with new paternity, and with donor sperm insemination (Hutcheon et al, 2011; Robillard et al, 1999).

1.2.4.1.2. Placental factors: Excess placental volume, as occurs with hydatidiform moles and multi-fetal gestation, is also associated with the development of preeclampsia (Page, 1939 & Day et al, 2005). The disease process may occur earlier in the pregnancy and have more severe manifestations in such cases. The risk increases progressively with each additional fetus (Day et al, 2005).
1.2.4.1.3. Maternal characteristics:

1.2.4.1.3.1. Age: Extremes of childbearing age have been associated with preeclampsia. However, once adjustments for parity are made in the younger age group (since most first pregnancies occur at a younger age), the association between younger age and preeclampsia is lost (Duckitt and Harrington, 2005; Roberts and Funai, 2009). Multiple studies demonstrate a higher incidence of preeclampsia among older women, independent of parity; however, many of these do not control for pre-existing medical conditions (Wallis et al., 2008; Duckitt and Harrington, 2005). After controlling for baseline differences, women who were 40 years of age or older had almost twice the risk of developing pre-eclampsia (Bianco et al., 1996).

1.2.4.1.3.2 Race: The association between African-American race and preeclampsia has been confounded by the higher prevalence of chronic hypertension, often undiagnosed, in this group, while some studies demonstrate a higher risk of pre-eclampsia among African-American women (Eskenazi et al., 1991; Pabinger, 2009). Larger prospective studies that rigorously defined pre-eclampsia and controlled for other risk factors did not find a significant association between pre-eclampsia and African-American race (Sibai et al., 1995; Sibai et al., 1997). More severe forms of preeclampsia may be associated with maternal nonwhite race (Eskenazi et al., 1991; Pabinger, 2009).

1.2.4.2. Pre-existing conditions: Many of the maternal risk factors for preeclampsia are similar to those for cardiovascular disease. Pre-existing hypertension, diabetes, obesity, and vascular disorders (renal disease, autoimmune conditions) are all associated with pre-eclampsia (Roberts and Funai, 2009; Ness and Roberts, 2009), the risk is correlated with the severity of the underlying disorder. Women with underlying chronic hypertension have a 10–25% risk of developing preeclampsia compared with the general population of pregnant
wome (Caritis et al., 1998; Rey and Couturier, 1994; Sibai et al., 1998), this risk is increased to 31% in women with a longer duration of hypertension (at least 4 years) or more severe hypertension at baseline (Sibai et al., 1998). With pregestational diabetes, the overall risk of developing pre-eclampsia is approximately 21%. However; the risk is 11–12% with diabetes of less than 10 years’ duration, which increases to 36–54% (Hanson and Persson, 1993; Sibai et al., 2000). Among women with longer-standing diabetes associated with microvascular disease, the risk of preeclampsia is estimated at 20–25% in pregnant women with mild renal disease (serum creatinine of <1.5 mg/dl) but increases to greater than 50% in pregnant women with severe renal disease (Jeyabalan and Conrad, 2010). Pre-eclampsia also occurs more frequently among pregnant women with autoimmune conditions such as systemic lupus erythematosus and antiphospholipid antibody syndrome (Duckitt and Harrington, 2005).

1.2.4.2.1. Obesity: Obesity is a risk factor for both pre-eclampsia and cardiovascular disease (Roberts et al., 2011). Exploring common mechanisms may provide insight into the pathophysiology of pre-eclampsia, the potential areas for further investigation, and the possible targets for therapy. Below are few features that are shared by pre-eclampsia and cardiovascular disease, including insulin resistance, inflammation, oxidative stress and vascular dysfunction, and increased levels of adipokines and angiogenic factors (Kaaja, 1998). In the United States; the percentage of women who are overweight or obese has increased by approximately 60% over the past 30 years (Wang et al., 2008). The World Health Organization estimates the prevalence of obese and overweight women (BMI ≥25 kg/m2) to be 77% in the United States, 73% in Mexico, 37% in France, 32% in China, 18% in India, and 69% in South Africa, with wide variation within each continent (WHO, 2011). The high prevalence of obesity and the projected increasing trend have substantial implications for pregnancy, since obesity is associated with infertility,
spontaneous miscarriage, fetal malformations, thromboembolic complications, gestational diabetes, stillbirth, preterm delivery, cesarean section, fetal overgrowth, and hypertensive complications (Yoge and Catalano, 2009). Obesity increases the overall risk of pre-eclampsia by approximately two- to threefold (Bodnar et al., 2005). The risk of pre-eclampsia increases progressively with increasing BMI, even within the normal range. Importantly; it is not only the risk of late or mild forms of pre-eclampsia that is increased, but also the risk of early and severe forms of pre-eclampsia, which are associated with greater perinatal morbidity and mortality (Bodnar et al., 2007; Catov et al., 2007). The increased risk is present in both Caucasian and African-American women (Bodnar et al., 2007). The association between pre-eclampsia risk and obesity has also been demonstrated in varying populations across the globe (Mahomed et al., 1998; Hauger et al., 2008). Supporting the concept that obesity may play a causal role is the finding that weight loss reduces the risk of pre-eclampsia (Magdaleno et al., 2012). Some studies suggest that excessive maternal weight gain is associated with the risk of pre-eclampsia, although these may be confounded by the increase in fluid retention that occurs with pre-eclampsia, thereby contributing to higher weight (Fortner et al., 2009). Although weight loss is discouraged in pregnancy, obesity is a potentially modifiable risk factor for pre-eclampsia. Weight loss prior to pregnancy is encouraged in overweight and obese women to decrease the risk of adverse outcome (Yoge and Catalano, 2009). Elevated body mass index (BMI) is also associated with pre-eclampsia. Given the obesity epidemic in the United States and around the world this is one of the largest attributable and potentially modifiable risk factors for pre-eclampsia.
1.2.4.2.2. **Family history of pre-eclampsia:** A family history of pre-eclampsia nearly triples the risk of preeclampsia (Duckitt and Harrington, 2005).

1.2.4.2.3. **Smoking:** Paradoxically; cigarette smoking during pregnancy is associated with a reduced risk of pre-eclampsia(Conde-Agudelo *et al*, 1999; Wikstrom *et al*, 2010); possibly due to modulation of angiogenic factors(Jeyabalan *et al*, 2008).

1.2.5. **Diagnosis of pre-eclampsia:**

Diagnostic criteria for pre-eclampsia include new onset of elevated blood pressure and proteinuria after 20 weeks of gestation. Features such as edema and blood pressure elevation above the patient’s baseline no longer are diagnostic criteria. Severe pre-eclampsia is indicated by more substantial blood pressure elevations and a greater degree of proteinuria. Other features of severe pre-eclampsia include oliguria, cerebral or visual disturbances, and pulmonary edema or cyanosis. Diagnosis becomes less difficult if physicians understand where pre-eclampsia “fits” into the hypertensive disorders of pregnancy. These disorders include chronic hypertension, preeclampsia-eclampsia, pre-eclampsia superimposed on chronic hypertension, and gestational hypertension. Chronic hypertension is defined by elevated blood pressure that predates the pregnancy, is documented before 20 weeks of gestation, or is present 12 weeks after delivery (Roccella, 2000). In contrast; preeclampsia-eclampsia is defined by elevated blood pressure and proteinuria that occur after 20 weeks of gestation. Eclampsia; a severe complication of pre-eclampsia, is the new onset of seizures in a woman with preeclampsia. Eclamptic seizures are relatively rare and occur in less than 1 percent of women with pre-eclampsia (Witlin andsibai, 1998). There is currently no single reliable, cost-effective screening test for pre-eclampsia. Urinary protein-to-creatinine ratios predict the 24-hour urine total protein level and may provide a
faster, simplified method of estimating proteinuria, providing that the protein values are less than 1 g in 24 hours. The urinary protein-to-creatinine ratio is not sensitive enough to differentiate mild and severe pre-eclampsia if significant proteinuria exists. However; a ratio of less than 0.2 effectively excludes the presence of significant proteinuria. A cutoff ratio of greater than 0.19 is a good predictor of significant proteinuria, with a sensitivity of 90 percent and a specificity of 70 percent. The negative predictive value of the urinary protein-to-creatinine ratio is 87 percent (Rodriquez-Thompson and Lieberman, 2001). A woman who may have signs of early or mild pre-eclampsia should have her blood tested to detect additional signs of pre-eclampsia. A baseline laboratory evaluation should be performed early in pregnancy in women who are at high risk for pre-eclampsia. Tests should include a hepatic enzyme level, a platelet count, a serum creatinine level, and a 12- to 24-hour urine collection for total protein measurement. Once the diagnosis of pre-eclampsia has been made, an expanded set of laboratory tests should be performed. In women who have pre-eclampsia with no suspected progression, all laboratory tests should be conducted weekly, if progression of eclampsia is suspected, the tests should be repeated more frequently (Bethesda, 2000).

1.2.5.1. Uric acid:

Uric acid is synthesized in liver and excreted via kidney, and it is the final products of purine e metabolism. The most common complication of hyperuricemia is the formation of urate crystals, which is called tophus, around the joints. Further causes of elevated blood concentrations of uric acid are renal function disease, starvation, drug abuse, toxicosis, malignant tumor, and increased alcohol and incretion disorders. Reasons of hypouricemia are hereditary metabolic

Uric acid is a waste product formed from the breakdown of some protein-rich foods and the breakdown of cells in the body. It is normally filtered from the blood by the kidneys (Webmed, 2012). The serum uric acid level once was used as an indicator of pre-eclampsia but has been found to lack sensitivity and specificity as a diagnostic tool. However, an elevated serum uric acid level may be of some use in identifying pregnant women with chronic hypertension who have an increased likelihood of having superimposed pre-eclampsia (Lim et al., 1998). Increased uric acid in the blood is often the earliest laboratory finding related to preeclampsia. If the kidneys have been damaged by preeclampsia, uric acid levels in the blood may rise (Webmed, 2012).

1.2.5.2. Hematocrit: A normal hematocrit value for a non-pregnant woman is between 36% and 44%. During pregnancy; the hematocrit value normally decreases (the fluid in the blood (plasma) increases, making red blood cells less concentrated). A high hematocrit value can be a sign of pre-eclampsia. Hematocrit tells the percentage of red blood cells in the blood), a hematocrit value of 42 means that red blood cells make up 42% of the blood volume. Pre-eclampsia often causes the body's tissues to absorb blood plasma. The blood becomes more concentrated, resulting in an abnormally high hematocrit value (Webmed, 2012).

1.2.5.3. Platelets: The number of platelets in the blood may be measured. Pre-eclampsia may cause an abnormally low platelet count. Endothelial dysfunction is responsible for the clinical signs observed in the mother, i.e., impairment of the hepatic endothelium contributing to onset of the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome. Finally; endothelial dysfunction
promotes microangiopathic hemolytic anemia, and vascular hyperpermeability associated with low serum albumin causes edema (Sibai et al, 2005; Mutze et al, 2008).

1.2.5.4. Kidney function tests: These tests check the amount of certain substances found in the blood that are normally removed from the body by the kidneys. These substances, which include blood urea nitrogen and creatinine, increase in the blood if the kidneyshave been damaged (Webmed, 2012).

1.2.5.4.1. Electrolytes: Examples of important electrolytes include sodium, potassium, magnesium, calcium, and chloride. The amounts of electrolytes in the body may change if pre-eclampsia is causing kidney damage or is causing fluid to leak out of blood vessels into surrounding tissues edema (Webmed, 2012).

1.2.5.4.2. Urea:

Urea is a final product of the protein and aminophenole catabolism. Adult produces 16g urea every day. Diseases associated with elevated levels of urea in blood are referred to as uremia or azotmia. Prerenal azotemia may cause by starvation, pyrexia, dehydration, increased protein catabolism, cortisol treatment or decreased renal perfusion (e.g. serious heart failure, lack of water) while creatinine level remains within the reference ranges. Postrenal azotemia may cause by the obstruction of the urinary tract, in this regard, both urea and creatinine levels rise, but urea is in higher extent (Thomase, 1998 & Burtis and Ashwood, 1999).
1.2.5.4.3. Creatinine:

Creatinine is synthesized at constant rate from creatine phosphate during muscle contraction, since the excretion of creatinine in healthy individuals is independent of diet and it is constantly produced, the clearance ratio of creatinine is one of the most sensitive indexes for glomerular filtration rate (GFR) detecting. Many renal diseases such as glomerular nephritis, nephropathysindrome, and serious renal failure will lead to the elevated levels of creatinine in serum. It is a practical method to measure the creatinine level together with the urea level to distinguish the reason of azotemia (Thomase, 1998; Enders and Rude, 1999).

1.2.5.5. Liver function test (LFT):

Abnormalities occur in 3% of the pregnancies, and pre-eclampsia is the most frequent cause (AngelGracia, 2000). The liver diseases peculiar to pregnancy have a characteristic time of onset. In the last trimester liver disease associated with abnormal liver function tests, nausea and/or vomiting and abdominal pain is due to severe pre-eclampsia, HELLP syndrome or acute fatty liver of pregnancy with or without sub-capsular hepatic haematomas, amongst which there is an overlap (Burroughs, 1998). Patients with HELLP syndrome are subsets of those with severe pre-eclampsia who are at increased risk of multiplesystemdysfunctions (Weinstein, 1982). Liver dysfunction during preeclampsia has serious consequences. In pre-eclampsia accompanied by HELLP syndrome, an elevation in liver function test results is noted. Alanineaminotransferaseand aspartate aminotransferase levels may also be elevated, and hyper-bilirubinemia may occur, especially in the presence of hemolysis. Periportalhemorrhagic necrosis in the periphery of the liver lobule is probably the lesion that causes elevated serum liverenzyme levels. Hemorrhage under the liver capsule can be so severe that the
capsule ruptures and, causes life-threatening intra peritoneal bleeding (Simithet et al, 1991).

1.2.5.5.1. Alanine aminotransferase (ALT):
Alanine aminotransferase (EC2.6.1.2, ALT); formerly called glutamic pyruvic transaminase (GPT), is on of liver specific enzymes, it can catalyze the enter conversion of amino acid and akitoacid by transfer of amino groups. Elevated ALT levels can indicate myocardial infraction, muscular dystrophy, especially in hepatobiliary diseases. Measurement of ALT is often used in diagnosis and monitoring treatment of liver diseases and heart diseases. The AST/ALT ratio is often used for differential diagnosis in liver disease if the AST/ALT ratio <1, it indicates mild liver damage otherwise it is associated with severe often chronic liver disease (Thomase, 1998).

1.2.5.5.2. Aspartate aminotransferase (AST):
Aspartate aminotransferase (EC 2.6.1.1, AST); formerly called glutamic oxalacetic transaminase (GOT) is present in both cytoplasm and mitochondria of cells. Belong to the transaminase family, which catalyze the conversion of amino acids and a-oxoglutarate by transfer of amino groups. AST is commonly found in various human tissues. The heart muscle is found to have the most activity of the enzyme, secondly in the brain, liver, gastric mucosa, skeletal muscle and kidneys. The serum AST present low activity in the healthy human body, but when these tissues injury or damage, AST is released into blood and results in high blood AST activity. Measurement of AST in serum and plasma is mainly used for the diagnosis of heart muscle damages, liver damages and skeletal muscle diseases as well as for monitoring the treatment. The AST /ALT ratio is often used for differential diagnosis in liver diseases, while the ratio < 1, it indicates mild liver
damage, otherwise it is associated with severe often chronic liver diseases(Ying-Fuye, et al, 1998; Moss and Henderson, 1999; Sheset al, 1998).

1.2.5.3. Alkaline phosphatase (ALP):

Alkaline phosphatase; it is a hydrolytic enzyme acts optimally at alkaline PH, it is formed in liver and existed in almost all tissues of the body. Under some conditions, such as gestation, budding children, high alkaline phosphatase activities are normal physiological phenomenons. Pathologic high alkaline phosphatase activities may exist in hepatobiliary diseases, bone diseases, bone metastases and hyper parathyrodiscsm. Decreased activity occurs uncommonly and is only observed in about 0.2% old people (Thomase, 1998; Moss and Hendderson, 1999).

1.2.5.4. Total protein:

Serum total protein, including albumin, protein takes charge of transporting substances, including macromolecules and maintaining the plasma osmotic pressure. Hypoproteinemia can be caused by antibody deficiency syndrome, liver cirrhosis, impaired kidney function, diarrhea and nutritional loss. Hyperproteinemia is seldom discovered. Only serious chronic inflammation or self-immunity disease may lead to hyperproteinemia (Thomase, 1998).

1.2.5.5. Albumin:

Albumin is an essential binding and transport protein, which is an important carrier for various substances and a main contributor for the plasma colloid osmotic pressure. Albumin level in serum or plasma is used for monitoring of liver diseases (e.g. liver cirrhosis) and kidney diseases (e.g. nephrotic syndrome), judging the degree of hydropsy. Furthermore, according to detecting the plasma albumin
level, the nutritional status of patient and prognosis of elderly inpatients is attained (Johnson et al, 1999; Thomase, 1998).
1.3. Rationale

Worldwide, 10 to 15 percent of direct maternal deaths (i.e., resulting from obstetric complications of pregnancy) are associated with preeclampsia/eclampsia (Duley, 2009). In the United States, preeclampsia/eclampsia is one of four leading causes of maternal death, along with hemorrhage, cardiovascular conditions, and thromboembolism (Chang et al., 2003, Mackay et al., 2011). Pre-eclampsia is responsible for 15 percent of all preterm births in the USA. Infants of mothers suffering from pre-eclampsia have a five times higher risk of dying than those of mothers without pre-eclampsia, mainly because of preterm birth (Lain and Robert, 2002). Women with pre-eclampsia are at an increased risk for life-threatening events, including placental abruption, acute renal failure, cerebral hemorrhage, hepatic failure or rupture, pulmonary edema, disseminated intravascular coagulation, and progression to eclampsia (Duley, 2009). There is approximately one maternal death due to pre-eclampsia-eclampsia per 100,000 live births, with a case-fatality rate of 6.4 deaths per 10,000 cases (Livingston et al., 2003, Mackay et al., 2001). In the Netherlands between 1993 and 2005, pre-eclampsia was the most common cause of maternal death, with 3.5 maternal deaths per 100,000 live births (Schutte et al., 2010).
1.4. Objectives

1.4.1. General Objectives:
To determine the biochemical changes in Sudanese women with pre-eclampsia.

1.4.2. Specific Objectives:
- To determine blood pressure of subjects under study.
- To evaluate renal function (urea, creatinine, uric acid, sodium, potassium).
- To evaluate liver function (total protein, albumin, ALP, ALT, AST).
- To evaluate (White blood cells, hemoglobin and platelets, PCV, MCH, MCHC, and MCV).
CHAPTER TWO

Materials and methods
2. Materials and methods

2.1. Study duration:

The study was conducted between September 2013 to July 2015

2.2. Study approach:

A case control study conducted to measure serum urea, creatinine, uric acid and electrolyte. Besides assessing liver functions in Sudanese pregnant women.

2.3. Study area:

Maternity Hospital and Ribat University Hospital in Khartoum State.

2.4. Study population:

The test group composed of 120 pregnant women with pre-eclampsia, in addition to 75 normal pregnant women.

2.5. Inclusion Criteria:

Pregnant women diagnosed with pre-eclampsia.

2.6. Exclusion Criteria:

Non pregnant women, non-Sudanese or pregnant suffering from any other diseases.

2.7. Control subject:

Sudanese women with normal pregnancy and apparently healthy.
2.8. **Data collection method and tools:**

Data were collected by using a structural interviewing questionnaire, which is designed to collect and maintain all valuable information from the cases and controls, after filling the informed consent

2.9. **Materials used:**

- Disposable plastic syringes.
- Plain containers.
- Kits of urea, creatinine, uric acid, total protein, albumin, ALP, AST & ALT.
- Ion selective electrode (ISE).

2.10. **Specimen collection:**

Blood samples were collected from 120 pregnant women with pre-eclampsia beside 75 blood samples from normal pregnant women.

Approximately 10 ml of blood were drawn from each subject by disposable plastic syringes in plain containers. The sample preparation was done by the method of centrifugation at 3000 rpm for 10 minutes. Serum was stored at -20 °C till the time of analysis.
2.11. Quality control:

External quality samples used was from (Bio system Spain) and internal quality control samples representing the normal and pathological level of the analyte were used for quality control.

2.12. Data analysis:

Data was analyzed by computer software, by using IBM SPSS statistics version 20. The mean and standard deviation was obtained, t test was used for the comparison studies, P value $\leq 0.05$ was considered significant.

2.13. Ethical consideration.

The approval to this study was obtained from ministry of health and The National Ribat University ethical committee verbal consent from individuals under study was also taken.

2.14. Methods for measurements (RFTs, LFTs, and CBC) (see appendixes)
CHAPTER THREE

Results
3. Results

This case control study which was conducted in Omdurman Maternity Hospital and Ribat University Hospital in Khartoum State and included 120 pregnant women with pre-eclampsia and 75 normal pregnant women which served as control group. The study revealed that the mean age of the women with pre-eclampsia was (28.1 ±6.5 years), while in the women with normal pregnancy was (29.2±6.4 years), (Table 1). The mean weight in the pre-eclamptic women was (79.3±9.0), while in the control group was (77.4±5.8Kg), (Table 1). The mean of diastolic blood pressure in the preeclampsic women was (152.3±17.7mmHg); while in the control group was (122.8±5.6mmHg). There was a significant increase in the diastolic blood pressure in pre-eclamptic women (Table 1) with P.value (0.000). The mean of systolic blood pressure in the preeclampsic women was (106.5±11.5mmHg); while in the control group was (78.9±3.3mmHg); there was a significant increase in the systolic blood pressure in pre eclamptic women with P.value(0.000), (Table 1). The study also revealed that the mean ±SD of urea in the women with pre-eclamsia was (26.3±13.8mg/dl)versus (24.0±9.8mg/dl) in the women with normal pregnancy (Table 2); there was no significant difference in the levels of urea in pre-eclamptic women with P.value (0.190). Serum creatinine in the women with pre-eclampsia was (0.7±0.4mg/dl)versus (0.4±0.3mg/dl) in the women with normal pregnancy (Table2); there was a significant increase in the level of creatinine in pre-eclamptic women with P.value (0.000). The mean of Sodium in the women with pre-eclampsia was (135.9±6.2mmol/l)versus (136.4±5.6mmol/l) in the control group (Table 2); there was no significant difference with P.value (0.744). The mean of potassium in the women with pre-eclampsia was (4.0±0.8mmol/l) versus (4.2±0.9 mmol/l) in the control group (Table2); there was no significant difference with P.value (0.336). The mean serum
uric acid in the women with pre-eclampsia was (7.0±2.1 mg/dl) versus (5.0±1.4 mg/dl) in the women with normal pregnancy (Table 2); there was a significant increase in the level of uric acid in pre-eclamptic women with P.value(0.000). The mean of total protein in the women with pre-eclampsia was (6.1±0.8 g/dl) versus (6.8±0.6 g/dl) in the women with normal pregnancy (Table 2); there was no significant difference in the level of total protein in pre-eclamptic women with P.value (0.264). The mean of albumin in the women with pre-eclampsia was (2.8±0.6 g/dl) versus (3.5±0.5 g/dl) in the women with normal pregnancy (Table 2); there was no significant difference in the levels of albumin in pre-eclamptic women with P.value (0.261). The mean of ALP in the women with pre-eclampsia was (130.7±46.1 U/L) versus (83.9±17.7 U/L) in the women with normal pregnancy (Table 2); there was a significant increase in the level of ALP in pre-eclamptic women with P.value (0.000). The mean of AST in the women with pre-eclampsia was (63.9±112.2 U/L) versus (29.6±12.1 U/L) in the women with normal pregnancy (Table 2); there was a significant increase in the level of AST in pre-eclamptic women with P.value (0.01). The mean of ALT in the women with pre-eclampsia was (32.1±49.9 U/L) versus (18.2±8.6 U/L) in the women with normal pregnancy (Table 2); there was a significant increase in the level of ALT in pre-eclamptic women with P.value (0.003). The mean of Hb in the women with pre-eclampsia was (11.4±1.6) versus (11.8±1.4) in the control group (Table 3); there was no significant change with P.value (0.059). The mean of PCV in the women with pre-eclampsia was (34.7±4.9) versus (35.4±4.8) in the women with normal pregnancy (Table 3); there is no significant difference with P.value (0.376). The mean of MCV in the women with pre-eclampsia was (82.9±6.1) versus (84.0±4.2) in the women with normal pregnancy (Table 3); there was no significant difference with P.value (0.144). The mean of MCH in the women with pre-eclampsia was (28.0±4.0) versus (28.6±2.4) in the women with normal pregnancy (Table 3); there
is no significant difference with P.value (0.248). The mean of MCHC in the women with pre-eclampsia was (32.9±3.0) versus (32.9±2.0) in the women with normal pregnancy (Table 3); there is no significant different with P.value (0.924). The mean of RBC in the women with pre-eclampsia was (3.9±0.8 g/l) versus (4.0±0.7) in the women with normal pregnancy (Table 3); there was no significant different with P.value (0.566). The mean of WBC in the women with pre-eclampsia was (9.4±4.2) versus (8.2±2.8) in the women with normal pregnancy (Table 3); there was a significant increase in the level of WBC in pre-eclamptic women with P.value (0.015). The mean of PLTs in the women with pre-eclampsia was (211.2±93.1) versus (245.4±66.0) in the women with normal pregnancy; there was a significant decrease in the level of platelets in pre eclamptic women with P.value (0.003), (Table 3).
Table (1). Descriptive study of the age, weight, diastolic, systolic blood pressure (one sample T test) in the pre-eclamptic patients and their control groups.

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<td>(diastolic) (mmHg)</td>
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Table (2). Comparative study of urea, creatinine, sodium, potassium, uric acid, total protein, albumin, alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) in pre-eclamptic women and their control.

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Table (3). Comparative study of the hematological parameters (Hb, PCV, MCV, MCH, MCHC, RBC, WBC & PLTs) in pre-eclamptic women and their control.

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<td>WBC (10^9/l)</td>
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<td>PLTs (10^9/l)</td>
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CHAPTER FOUR

Discussion, conclusion and recommendations
4.1. Discussion

In this study, the serum uric acid in the women with pre-eclampsia is significantly higher from that in the women with normal pregnancy; this finding is inconsistent with that reported by Slemons and Bogert (1917), Thomase (1998), and Newman & Price (1999), this hyperuricemia may be due to the uric acid clearance in the kidney; as result or secondary to reduced GFR in these pre-eclamptic women, because increased tubular re-absorption and decreased secretion have been cited as the main reasons for elevated serum uric acid in women with pre-eclampsia as reported by Thangaratinam et al (2006) and Chesley & Williams (1945). In this study, the serum creatinine in the women with pre-eclampsia is significantly higher from that in normal pregnant women. The present study finding agrees the finding of Jeyabalan & Conard (2010) and disagrees with that written by Mohamed Abdulfatah Abdulmunem et al (2005) and Salako et al (2003).

In this study, the platelet count in the women with pre-eclampsia is significantly lower from that in the women with normal pregnancy. The present study agrees with the finding of Srivastava (1995), Jambhulkar (2001) and Joshi et al (2004); while disagree with that reported by Makuyana et al (2002). A white blood cell count is significantly increased in the Sudanese women with pre-eclampsia in the present study this finding is agrees with Terrone et al (2000). In this study the other hematological parameters in the women with pre-eclampsia are not significantly different include Hb, RBC count, PCV, MCV, MCH and MCHC from their normal pregnancy. The present study agrees with that published by Siddiqui et al (2011) and Makuyana et al (2002); while disagrees with the findings of Zafar & Iqbal (2008). In this study, the serum liver enzymes ALP AST and ALT activity in the women with pre-eclampsia are significantly higher from that in normal pregnant women. The present study agree with the finding of Sibai (1991),
Simithet al (1991), and Thomase (1998), some of them concluded that; in pre-eclamptic women hemolysis elevates liver enzymes, which associated with low platelets or(HELP syndrome) is a severe variant of preeclampsia and may warrant expedient delivery to prevent development of life-threatening thrombocytopenia or hemolysis, other researchers like Rathet al (2000), Sibia et al (2005) and Mutze et al (2008) also noticed elevated levels of ALT and AST in severe preeclamptic women. As pre-eclampsia is associated with hypertension and toxemia of pregnancy, in this study both diastolic and systolic blood pressures significantly increase, which are consistent with that reported by Chesley (1971), Rocella (2000) and Sibai (2004).

In this study, the serum urea in the women with pre-eclampsia is not significantly changed from that in the women with normal pregnancy. The present study disagrees with HidajetPaçariziet al (2012) and Tausifzaret al (2011).

In this study, the serum sodium in the women with pre-eclampsia was no significantly from that in the women with normal pregnancy. The present study agrees with that reported by Khan et al (2011), Obembe & Antai (2008). In this study, the serum potassium in the women with pre-eclampsia is not significantly different from that in the women with normal pregnancy. The present study agrees with that written Khan et al (2011); Obembe and Antai (2008). Even the age of the pregnant women is one of the risk factors, in another words; preeclampsia increases above the age of the forty as reported by Biano et al (1996), Duckitt & Harrington (2005) and Van Rijn, et al (2006); in this study the mean age of Sudanese women with preeclampsia included in the study is only (28.1±6.5 years).
4.2. Conclusion

In Sudanese women with pre-eclampsia; both diastolic and systolic blood pressure increase. Serum creatinine, uricacid, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and WBC significantly increase;while platelets count significantly decrease which may predisposethese women to thrombocytopenia.
4.3. Recommendation

This study recommends that; in Sudanese pregnant women:

1. Liver function tests including alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are strongly recommended as routine follow up investigations.

2. Renal function tests including creatinine and uric acid are advised to be a part of antenatal care routine investigations, as early indicators for preeclampsia.

3. Blood pressure should be measured routinely in Sudanese pregnant women.

4. Platelets count should be routine investigation in normal follow up of pregnant women in the antenatal care clinics in Sudan.

5. More research with big sample size is recommended to roll out these findings.
CHAPTER FIVE

References
References:


Kong TY, De Wolf F, Robertson WB, Brosens I (1986). Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and


**Sinclair EB, Johnston G (1858).** Practical midwifery: Comprising an account of 13,748 deliveries which occurred in the Dublin Lying-in Hospital, during a period of seven years, commencing, 1847. Dublin, Ireland: The University Press.


623-625.


Appendixes
Automated method (sysmex-electric impedance):

Sysmex NE-8000:

The sysmex NE-8000 is a multichannel hematology analyzer that reports 23 parameters and generates five histograms and one scattergram. The system uses five separate detectors, four that measure direct current or alternating radio frequency electrical impedance, and one that measures light transmittance. One impedance detector enumerates erythrocytes and platelets. Its results are used to calculate MCV, RDW, MPV, and PDW. Lymphocytes, monocytes, and granulocytes. The other two impedance detectors are for eosinophils and basophils. Hemoglobin is measured photometrically at 540 nm. There are two basic technologies used by the NE-8000. The primary method uses direct current electrical impedance. Platelets and RBCs are counted and sized by this method. Their enumeration includes use of hydrodynamic focusing to improve accuracy and precision of counts. The NE-8000 uses automatic discriminators to separate RBCs from platelets. Differential and WBC technologies in the NE-8000 are based on two principles.

Principle:

Direct current impedance and the use of high-frequency alternating current. The use of radio frequency to assess nuclear characteristics was patented by TOA medical electronics in 1968. In the WBC (lymphocytes, monocytes, and granulocytes), detection system agentle lysing agent is added that increases white blood cell membrane. The lysing agent releases some of the cytoplasm and causes some shrinking of the nucleus. Each altered cell passes through an aperture to the detector block where it is
counted (by resistance to direct current). Cell volume is calculated from the amplitude of the direct current voltage pulse. The computer analyzes these pulses and sorts them into size categorizes. The second technology uses high frequency alternating current (radio frequency {RF} waves) generated by crystals oscillator. The high frequency ac signal is overlaid on a dc signal. Impedance to radio waves depends on mostly on nuclear size, nuclear density, and number of large cytoplasmic granules. The ac voltage pulse resulting from the impedance is proportional to the size and density of nucleus and granularity of the cell.

After each cell has been detected and characterized by both methods, a scattergram of dc pulse amplitude versus rf pulse amplitude is plotted. Lymphocytes, monocyte, and granulocyte are identifiable abnormal cell (nucleated red blood cells (NRBC) atypical lymphocyte, blast, immature granulocytes) can also be identified from their location on the scattergram. Eosinophils and basophils are included in the granulocyte cluster and must be further differentiated. The NE-800 treats whole blood with two special lyse or shrink. The blood dilution are sent to separate detectors that use direct current electrical impedance. The intact unshrunken eosinophils or basophils produce larger voltage pulses than other granulocytes. Histogram for each cell type is generated. Neutrophils are then calculated by subtracting eosinophil and basophil from the total granulocyte count. A recently introduced module for the NE-800 is a side maker with user defined parameter for automated generation of a wedge smear. The side is labeled with a bar code.
**Procedure:**

I-Sample was mixed with diluents reagent.

II-When a blood cell passes through an aperture (sensing zone) Suspended in electrolyte solution.

III-The change in electric impedance was detected.

IV-The change of impedance is in proportion to the volume of the cell detected thus could be separated.

V-And the red blood cell was lysed and the haemoglobin was released and converted into single stable form.

VI-Hemoglobin measure at various wavelength.
The National Ribat University

Biochemical Changes in Sudanese Women with Pre-eclampsia

(Questionnaire)

1. Serial No: ........................................ 2. Age: ..............................................


7. Date of marriage: ..........................

9. Number of pregnancies: ........................

   (a) Life child: □ (b) Dead child: □ (c) Abortion: □

10. History of past pre-eclampsia No ( ) Yes ( ) define: ..........................

11. History of pre-eclampsia in the family: No ( )

   Yes ( ) define: .............................

12. Post-delivery complications: ........................

   ..............................................................................................................

13. Laboratory diagnosis:

    - Renal Function tests:

    Urea ( ) mg/dl, Creatinine ( ) mg/dl, Na⁺ ( ) m.mole/l,

    K⁺ ( ) m.mol/l, Uric acid ( ) mg/dl
Liver Function tests:

AST (  ) U/L, ALT (  ) U/L, T. Bil (  ) mg/dl, D. Bil (  ) mg/dl,
I. Bil (  ) mg/dl, TP (  ) g/dl, Alb (  ) g/dl, Glob (  ) g/dl

Complete blood picture (CBC):

Hb[ ] MCV [ ] MCH [ ] MCHC [ ] RBCs [ ] [ ]
WBCs [ ] Platelet [ ]

Comment…………………………………………………………………...
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*Note: The table content is not fully transcribed due to the quality of the image.*
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<td>Engineer</td>
<td>123 Main St.</td>
</tr>
<tr>
<td>102</td>
<td>Mary</td>
<td>32</td>
<td>Female</td>
<td>Doctor</td>
<td>456 Oak Ave.</td>
</tr>
<tr>
<td>103</td>
<td>Bob</td>
<td>40</td>
<td>Male</td>
<td>IT Specialist</td>
<td>789 Elm Dr.</td>
</tr>
</tbody>
</table>

### Notes
- John is married and has two children.
- Mary has been working in healthcare for 10 years.
- Bob recently joined a new company as their lead IT engineer.
### UREA

**General Name:** Urea Kit (Mindray/CHL) (UV Method)  (Albanova)  (UREA)

**Order Information:**

<table>
<thead>
<tr>
<th>Cat. No.</th>
<th>Package size</th>
</tr>
</thead>
<tbody>
<tr>
<td>URE101</td>
<td>10 x 40 mL</td>
</tr>
<tr>
<td>URE102</td>
<td>10 x 40 mL</td>
</tr>
<tr>
<td>URE103</td>
<td>10 x 40 mL</td>
</tr>
<tr>
<td>URE104</td>
<td>10 x 40 mL</td>
</tr>
</tbody>
</table>

**Intended use:**

To provide test for the quantitative determination of urea concentration in serum, plasma and urine on photometric systems.

**Principle:**

Provide the final products of the protein and amino acid degradation. Each contains 12 reagent mixtures. Citrate buffered with adjusted levels of organic acid and referred to the reference system. Reduced oxalic acid is used to distinguish the regions of citrate. Reduced oxalic acid is used to distinguish the regions of citrate. Reduced oxalic acid is used to distinguish the regions of citrate. Reduced oxalic acid is used to distinguish the regions of citrate. Reduced oxalic acid is used to distinguish the regions of citrate. Reduced oxalic acid is used to distinguish the regions of citrate.

**Concentrations and calculations:**

- R1: 100 µmol/L
- R2: 50 µmol/L

**Storage:**

At the lab at 2-8°C

### CREA

**General Name:** Creatinine Kit (Modified Jaffe Method)  (CREA/CHL) (Chroma)

**Order Information:**

<table>
<thead>
<tr>
<th>Cat. No.</th>
<th>Package size</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRE101</td>
<td>10 x 5 mL</td>
</tr>
<tr>
<td>CRE102</td>
<td>10 x 5 mL</td>
</tr>
<tr>
<td>CRE103</td>
<td>10 x 5 mL</td>
</tr>
<tr>
<td>CRE104</td>
<td>10 x 5 mL</td>
</tr>
</tbody>
</table>

**Intended use:**

To provide test for the quantitative determination of creatinine concentration in serum, plasma and urine on photometric systems.

**Summary:**

Creatinine is synthesized at a constant rate from muscle protein. A balance is maintained between the creatinine rate of synthesis and the rate of elimination. Liver disease is an important factor in the production of creatinine. Creatinine is used as a marker for kidney function. Creatinine is used as a marker for kidney function. Creatinine is used as a marker for kidney function. Creatinine is used as a marker for kidney function. Creatinine is used as a marker for kidney function.

**Concentrations and calculations:**

- R1: 100 µmol/L
- R2: 50 µmol/L

**Storage:**

At the lab at 2-8°C

### ALB

**General Name:** Albunin Kit (Microalbumin Test)  (Chroma)

**Order Information:**

<table>
<thead>
<tr>
<th>Cat. No.</th>
<th>Package size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB101</td>
<td>10 x 40 mL</td>
</tr>
<tr>
<td>ALB102</td>
<td>10 x 40 mL</td>
</tr>
<tr>
<td>ALB103</td>
<td>10 x 40 mL</td>
</tr>
</tbody>
</table>

**Intended use:**

To provide test for the quantitative determination of ALB concentration in serum and plasma on photometric systems.

**Summary:**

Albumin is an essential binding and transport protein, which is an important carrier for various substances and main contributor for the plasma protein profile. Albumin plays a critical role in maintaining osmotic pressure and plasma volume, and is used for the majority of plasma proteins. It regulates the supply of nutrients and the removal of waste products from the blood.

**Concentrations and calculations:**

- R1: 100 µmol/L
- R2: 50 µmol/L

**Storage:**

At the lab at 2-8°C
### UREA

**Common Identifiers:** mg/dL, mmol/L

**Dr. Shangai:** (SHanghai automated distribution Fication Reference Substances)**

**Each laboratory should perform a reference interval for each method based upon its population.**

**Performance Characteristics**

**Empirical Performance range obtained from Moniing System (Table 1).**

**Method Comparison:**

- **Accuracy:**
  - **CGM:**
    - **Units:** mg/dL
    - **Accuracy:**
      - Reference: 0.942, 0.943
      - Method: 0.942, 0.943
      - **Details:**
        - **Accuracy:**
          - **Details:**
            - **Details:**

**Method Comparison:**

- **Accuracy:**
  - **CGM:**
    - **Units:** mg/dL
    - **Accuracy:**
      - Reference: 0.942, 0.943
      - Method: 0.942, 0.943
      - **Details:**
        - **Accuracy:**
          - **Details:**
            - **Details:**

**Graphical symbols**

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### CREA

**Identifications:**

- **Units:** mg/dL, 110, 110, 110

**Accuracy:**

- **Units:** 110, 110, 110

**Sample Type:**

- **Units:** 110, 110, 110

**Method Comparison:**

- **Accuracy:**
  - **CGM:**
    - **Units:** mg/dL
    - **Accuracy:**
      - Reference: 0.942, 0.943
      - Method: 0.942, 0.943
      - **Details:**
        - **Accuracy:**
          - **Details:**
            - **Details:**

**Method Comparison:**

- **Accuracy:**
  - **CGM:**
    - **Units:** mg/dL
    - **Accuracy:**
      - Reference: 0.942, 0.943
      - Method: 0.942, 0.943
      - **Details:**
        - **Accuracy:**
          - **Details:**
            - **Details:**

**Graphical symbols**

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### ALB

**Identifications:**

- **Units:** mg/dL, 110, 110, 110

**Accuracy:**

- **Units:** 110, 110, 110

**Sample Type:**

- **Units:** 110, 110, 110

**Method Comparison:**

- **Accuracy:**
  - **CGM:**
    - **Units:** mg/dL
    - **Accuracy:**
      - Reference: 0.942, 0.943
      - Method: 0.942, 0.943
      - **Details:**
        - **Accuracy:**
          - **Details:**
            - **Details:**

**Method Comparison:**

- **Accuracy:**
  - **CGM:**
    - **Units:** mg/dL
    - **Accuracy:**
      - Reference: 0.942, 0.943
      - Method: 0.942, 0.943
      - **Details:**
        - **Accuracy:**
          - **Details:**
            - **Details:**

**Graphical symbols**

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Website: www.shanghai.com

Tel: +86-21-3485-3000

Fax: +86-21-3485-3000
Agreement consent

After the explanation of the study nature and I had enough time for assurance and all my question were sufficiency answered, I Knew that I have the right to stop this study at any time without losing the right of medical care or any other rights.

I voluntary accept to participate in this study

Signature……………………………………

Date………………………………………
بسم الله الرحمن الرحيم

إقرار موافقه

أما...

بعد أن تم شرح الدراسة وأعطيت فرصة كافية للاستفسار وقد تمت الإجابة علي كل استلائى بصورة واضحة فهمت أن لي الحق عن التوقف عن هذه الدراسة في أي وقت من غير أن أفقد حقي في الرعاية الطبية أو أي حقوق أخرى ووافق طوعاً على ذلك.

التوقيع: 

التاريخ: 