ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE

DEPARTMENT OF MEDICAL BIOCHEMISTRY

Evaluation of serum lipid profiles, uric acid and high sensitivity C-reactive protein levels among pregnancy-induced hypertension

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This is to verify that the thesis entitled "Evaluation of serum lipid profiles, uric acid and high-sensitivity C-reactive protein levels among pregnancy-induced hypertension" is submitted for the partial fulfillment of the requirements for the degree of Master of Science in Medical Biochemistry to the Graduate Program of the Department of Medical Biochemistry, School of Medicine, College of Health Science, Addis Ababa University and has been carried out by Bilisuma Girma Areda under our supervision.

This thesis complies with regulations of the University and meets the accepted standards with respect to originality and quality.

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ABBREVIATIONS AND ACRONYMS

ACOG…….American College of Obstetricians and Gynecologists

ANC……Antenatal care

AURH…….Ambo University Referral Hospital

BP…….....Blood Pressure

CI…….Confidence Interval

DBP…….Diastolic Blood Pressure

HELLP……Hemolysis, Elevation of Liver enzymes, Low Platelet count

HDL-C…….....High-Density Lipoprotein-Cholesterol

Hs-CRP..…….High sensitivity C-Reactive Protein

IL-6…….....Interleukins-6

JNC…….....Joint National Committee

LDL-C…….....Low-Density Lipoprotein-Cholesterol

MMHg……...Millimeter Mercury

NICE……...National Institute for Health and Clinical Excellence

NTP…….....Normotensive Pregnant

PIH……..Pregnancy-induced Hypertension

SBP…….....Systolic Blood Pressure

SOGC…….....Society of Obstetricians and Gynecologists of Canada

SOMANZ……Society of Obstetric Medicine of Australia and New Zealand

TC……Total Cholesterol

TG……Triglyceride

VLDL-C…….....Very-low Density Lipoprotein Cholesterol

WHO…….....World Health Organization

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ABSTRACT

Background: Pregnancy-induced hypertension is characterized by an elevation of blood pressure ≥140/90 mmHg as well as the presence/absence of proteinuria and/or edema during pregnancy. Pregnancy-induced hypertension in women is the main problems in developing countries including Ethiopia. Since it is one of the major contributors to maternal and prenatal mortality, the biochemical profiling of these cases are required to provide adequate information to clinicians, health researchers and policy-makers in seeking of potential interventions.

Objective: We aimed to evaluate serum lipid profiles, uric acid and high sensitivity C-reactive protein levels among pregnancy-induced hypertension and compared to normotensive pregnant women attending at Ambo University Referral Hospital, Oromia Region, Western Ethiopia.

Methods and Materials: A case-control study design and convenient sampling method were used to evaluate serum lipid profile, uric acid and high sensitivity C-reactive protein among pregnancy-induced hypertension and compared to normotensive pregnant women attending at Ambo University Referral Hospital. After we obtained informed consent from pregnant women who visited at ANC service clinic in Ambo University Referral Hospital, about two spoonsful of (3-5mL) blood was collected and automated Cobas c311 analyzer for Clinical Chemistry was used for laboratory analysis. Then data was analyzed by SPSS version 25. While Student's t-test was used to compare the mean value of continuous variables, Ch-square was used to compare the relationship of categorical variables between two groups. Significance level was set at the $P< 0.05$ and confidence interval of 95%.

Result: Our result showed that while the mean±SD of serum lipid profiles (TC, TG, LDL-C, TC/HDL-C, TG/HDL-C, LDL-C/HDL-C), uric acid and hs-CRP were significantly elevated in pregnancy-induced hypertension, HDL-C was decreased in pregnancy-induced hypertension compared to normotensive pregnant women ($P<0.05$).

Conclusion: The lipid profiles (except HDL-C, which was significantly decreased), uric acid and hs-CRP were significantly increased in pregnancy-induced hypertension than normotensive pregnant women, indicating that dyslipidemia, hyperuricemia and inflammation could be an integral part in the pathogenesis of pregnancy-induced hypertension. Therefore, we should consider these potential biomarkers to further research in seeking of interventions in PIH patients.

Key word: Pregnancy-induced hypertension, lipid profiles, uric acid, inflammation, Ethiopia.

1. INTRODUCTION

1.1. Background

Hypertension in pregnancy is defined as an elevation of systolic blood pressure (BP≥140 mmHg) or diastolic blood pressure (BP ≥90 mmHg). Either elevation of diastolic or systolic blood pressure was important with the identification of pregnancy-induced hypertension and reduction was thought of as beneficiary in reducing risk of hypertension (Kacica *et al*., 2013). Pregnancy-induced hypertension is characterized by high blood pressure, with/without protein in urine and pathological edema during pregnancy (Parmar *et al*., 2012).

Pregnancy-induced hypertension is the third common complications in pregnancy next to hemorrhage and infection and a serious contributor to maternal and perinatal morbidity and mortality (NICE, 2010). World health organization (WHO) states that severe hypertension in pregnancy will increase both the mother's (WHO, 2011) and fetus's risks (WHO, 2011 and Latha and Ganesan, 2013) such as poor placenta transfer, growth restriction, preterm birth, placenta abortion and neonatal death.

Varies risk factors are known for the event of pregnancy-induced hypertension; but, its pathophysiology and etiology is not to be well understood in most cases. Placenta implantation with abnormal tissue layer invasion of uterine vessels and immunologic intolerance between maternal, placenta and foetal tissues are a number of the etiological factors for PIH (Payne *et al*., 2014). Placenta ischemia is the main factors responsible for the diseases process. This could as a result of various factors such as vasospasm, vascular endothelial activation, vascular endothelial dysfunction, accumulation of activated inflammatory mediator molecules and diminished prostacyclin to thromboxane ratio (Latha and Ganesan, 2013).

The metabolic modification of lipids are believed to extend the chance of the risk of pregnancy-induced hypertension by the inducement of endothelial cell dysfunction secondary to oxidative stress, metabolic syndrome (insulin resistance, central obesity, high blood pressure and atherogenic dyslipidemia) and/or dysregulation of lipoprotein lipase that breaks down lipids (von Versen-Hoeynck and Powers, 2007). As a study showed that lipid profile ratios reflect balance between the risks and protecting lipoprotein capability, and they are a higher predictor of cardiovascular risk than lipid profile parameters alone. Lipid profile parameters combined into

ratios that reflect the proportion of atherogenic to anti-atherogenic lipid and lipoproteins. Those lipid ratios embody TC/HDL-C, TG/HDL-C and LDL-C (Millán *et al*., 2009).

Uric acid is one of the foremost consistent and earliest notable change in PIH and has been indicated as a higher predictor of maternal and fetal risk than blood pressure level (Hawkins *et al*., 2012). The potential origin of uric acid is renal dysfunction, excessive tissue breakdown, acidosis and excessive activity of the xanthine oxidase enzyme. Elevated serum uric acid is not a straightforward marker for the disease's severity rather contributes directly on to the pathological process of the disorder. Uric acid has a potential effects on maternal vasculature, placenta development and placental function specifically through alteration of endothelial cell function and repair, induction of inflammation and alteration of vascular tone (Hawkins *et al*., 2012).

High sensitivity C-reactive protein defined as an acute phase reactant protein produced in the liver by stimulation of interleukin-6. Hs-CRP can be a marker for tissue damage and inflammation. An increased level of inflammatory markers (interleukins-6, tumor necrosis factor-α and C-reactive proteins) play a key role in vascular inflammation in hypertensive patients at the start and advance stages (Dawri *et al*., 2014). Pregnancy-induced hypertension case is often diagnosed in late pregnancy when blood pressure is elevated with/without protein urea and/or edema is presented (NICE, 2010). In distinction, a study proved that an early detection of the disease and treatment decreases the pregnancy induced-hypertension crisis within the mother and reduces the fetal complications (Tagetti and Fava, 2019). This will be double through understanding of its risk factors, pathological process and clinical presentation. Therefore, medical management of PIH is often custom-made not solely by the amount of elevated blood pressure with proteinuria but also by the degree of overall risk factors for an early detection of the case (Parmar *et al*., 2012).

1.2. Statement of the Problem

Pregnancy-induced hypertension is the major contributors to maternal and perinatal morbidity and mortality worldwide (Lowe *et al*., 2015). In the year of 2014, WHO, reported that 14% of maternal death worldwide due to PIH and with an estimated at least one women dies every seven minute from its complication (Payne *et al*., 2014). In addition, this report indicated that while the prevalence of PIH in Latin America and Caribbean countries was 22.1%, it was found 9.1% in Africa and Asian regions. Unfortunately, this was highly pronounced in Sub-Saharan Africa with a prevalence of 16% (Say *et al*., 2014).

In developing countries including Ethiopia, the maternal and perinatal morbidity and mortality much higher when compared with developed countries because of low level health services utilization and poor quality of maternal and neonatal care (Payne *et al*., 2014). For instance, a research report in Ghana shown that 30% of maternal mortality was due to hypertensive disorder of pregnancy (Adu-Bonsaffoh *et al*., 2014). In Ethiopia, 19% of maternal morbidity and mortality are attributed to hypertensive disorder of pregnancy according to a systematic review report (Berhan and Berhan, 2014). The prevalence of maternal mortality due to PIH in Ambo town, West Shewa Zone of the Oromia Region, Western Ethiopia, was reported to be 12.3% (Garomssa and Dwivedi, 2008).

Pregnancy-induced hypertension complicate 3-10% of all pregnancies worldwide, around 6% of all pregnancies in Ethiopia and it is a major cause of maternal and perinatal complication (Lowe *et al*., 2015 and Mersha *et al*., 2019). According to a systematic and meta-analysis study report in Ethiopia, the prevalence of maternal death was 4% and perinatal mortality was 25% as well as HELLP syndrome and low birth weight complication were 13% and 37%, respectively (Mersha *et al*., 2019).

Several risk factors (modifiable and non-modifiable factors) may play a role in the development of PIH (Lowe *et al*., 2015). A research conducted on varies genetic and environmental risk factors of PIH indicated that aging, parity, gravidity, chronic history of hypertension, history of diabetes mellitus, history of renal diseases, family history of hypertension, obesity, dyslipidemia, hyperuricemia, systemic inflammation and other factors are associated with pregnancy induced hypertension (Lai *et al*., 2017 and Lowe *et al*., 2015). Dyslipidemia is one of the modifiable risk

factor that hurt the vascular endothelium, which results in reduced placenta perfusion, in turn, leads to PIH (Ghooshchi *et al*., 2014).

Both uric acid (Bainbridge and Roberts, 2008) and hs-CRP (Farzadnia *et al*., 2013) are mediator of inflammation and a risk factor in the pathogenesis of PIH. The study conducted by (Sarmah, 2015) on evaluation of serum uric acid levels among PIH women and study conducted by (Farzadnia *et al*., 2013) on evaluation of serum hs-CRP levels among PIH women showed that a significant elevation in PIH compared to NTP women.

Limited research studies have been performed on serum lipid profile, uric acid and high sensitivity C-reactive protein among PIH women in several countries. However, there is a data information gap on the condition in Ethiopia. Moreover, there are not comprehensive reports done on the evaluation of serum lipid profile, uric acid and high sensitivity C-reactive protein among PIH women in Ethiopia in a generally and in our study area in particular. The early management and prevention of PIH can help to reduce its complication by reducing risk factors and systemic manifestation. The management and prevention of the PIH and its complications need to the early detection and screening biomarkers. Therefore, the problems /challenges of PIH, its complication and in support of the mission "No Woman or Child should Die of Pregnancy" in Ethiopia has initiated us to design this research.

1.3. Significance of the Study

It is a known fact that pregnancy-induced hypertension is the serious reason for maternal and prenatal morbidity and mortality worldwide and the majority of PIH is associated with dyslipidemia and systemic inflammation. This problem is agitating and causing a major concern in resource-limited countries including Ethiopia. Unfortunately, because of low socioeconomic states and limited antenatal care services (ANC), pregnant women with hypertension will be diagnosed after complication of pregnancy. Therefore, evaluation of serum lipid profile, lipid profile ratios, uric acid and hs-CRP among pregnant women during antenatal care (ANC) are important within the early detection of the diseases to avoid complication and death.

Sustainable Development Goals (SDG) of Ethiopian regarding health delivery system is targeted to reduce maternal mortality 267per 100,000 live birth rate in 2030. PIH is a major reason for maternal mortality rate in Ethiopia. Therefore, this study helps clinicians, health researchers and policy-makers to give much attention to serum lipid profiles, lipid profile ratios, uric acid and hs-CRP level of pregnant women during ANC services. Our findings will be useful in providing an insight for researchers in the future.

1.4. Hypothesis

Null hypothesis: There is no significant difference in the mean levels of the lipid profiles, lipid profile ratios, uric acid and hs-CRP between PIH and NTP women.

Alternative hypothesis: There is a significant difference in the mean levels of the lipid profile, lipid profile ratios, uric acid and hs-CRP between PIH and NTP women.

2. LITERATURE REVIEW

2.1. Overview of pregnancy induced hypertension

A research report indicated that pregnancy-induced hypertension (PIH) as a major contributor to maternal and perinatal morbidity and mortality worldwide (Payne *et al*., 2014). Pregnancy induced-hypertension effect about 10% of all pregnant women worldwide and attribute 14% of maternal deaths globally. In 2011, WHO report indicated that PIH was the second leading cause of maternal mortality (15%) in the United States of American. In Africa and Asian countries maternal mortality due to PIH were 9.1% and in fact about 16% were in sub-Saharan countries (WHO, 2011). Pregnancy-induced hypertension represents the most common medical complications of pregnancy with an announced incidence of 5-10% worldwide (WHO, 2014).

Hypertensive disorder of pregnancy is a spectrum of conditions characterized by an elevated blood pressure and classified into: Chronic hypertension, gestational hypertension, pre-eclampsia and its severe complication, eclampsia and pre-eclampsia superimposed on chronic hypertension (Lowe *et al*., 2015).

The well-defined classification and stratification of hypertension in pregnancy reflects the pathophysiology of the constituents as well as the risks and potential outcomes for both mother and baby. This classification promotes accurate and effective communication among health care providers and furthermore serves as the basis for management (James *et al*., 2014).

Gestational hypertension is characterized by the blood pressure ≥140/ 90 mmHg in normotensive mothers following 20 weeks of gestation. Proteinuria and other features noted with pre-eclampsia are missing in gestational hypertension. Majority of the cases usually resolved after 12 weeks of postpartum (Lai *et al*., 2017). It may also change to chronic hypertension when hypertension does not regain normal condition. Additionally, there is a probability of gestational hypertension developing into pre-eclampsia and cause perinatal complication unless strictly diagnosed and managed (ACOG, 2013).

Chronic hypertension is defined as a blood pressure ≥140/90 mmHg, predate to pregnancy or before 20 weeks of gestation. This condition is usually without proteinuria and other features of pre-eclampsia. Chronic hypertension may persist beyond 12 weeks' postpartum and associated with superimposed pre-eclampsia (Lai *et al*., 2017).

Pre-eclampsia is distinguished by elevation of blood pressure (PB≥140/90 mmHg) after 20 weeks of gestation with significant proteinuria or specifically gestational hypertension with new-onset proteinuria. It can also occur without proteinuria, with hepatic and hematopoietic dysfunction. Pre-eclampsia is one of the leading causes of maternal mortality and morbidity among pregnant women in the world (ACOG, 2013).

Pre-eclampsia can be mild or severe form. Mild preeclampsia characterized by blood pressure between 140/90 mmHg and 160/110 mmHg after 20 weeks of gestation with proteinuria ≥0.3 g in urine and serum protein/creatinine ratio of 0.3 mg/dL (Woelkers *et al*., 2015). Severe pre-eclampsia in pregnancy is characterized blood pressure ≥160/110 mmHg or both. Additionally, the presence of any one of the following criteria; cerebral or visual disturbance, epigastric or right upper quadrant pain, oliguria, pulmonary edema, impaired liver function, thrombocytopenia or intrauterine growth restriction rule out pre-eclampsia (ACOG, 2013).

Pre-eclampsia syndrome superimposed on chronic hypertension is where pre-eclampsia occurs in already existing chronic hypertension patients. In this case, hypertension may take place before or early pregnancy followed proteinuria after 20 weeks of gestation. The maternal and fetal complications are more severe. The proteinuria disappeared after 12 weeks of postpartum but hypertension may be persisting beyond (ACOG, 2013).

Eclampsia is defined as convulsions occurring in a woman with established pre-eclampsia. This type of hypertensive disorder of pregnancy develops nearly at the end of pregnancy or after delivery (Woelkers *et al*., 2015).

2.2. Pathophysiology of pregnancy-induced hypertension

Even though pregnancy-induced hypertension is one of a major contributor of maternal and perinatal morbidity and mortality, the mechanisms responsible for the pathogenesis are unclear. What understood about PIH is that the diseases stem from an abnormality in the placenta. The initial event in the PIH is supposed to be due to reduced placental perfusion lead to various maternal vascular endothelial dysfunction by mechanisms remain not well defined. Despite the mechanisms lead to the reduction of placental perfusion in PIH may be multiples factors, the study done on pregnant women indicate that an abnormal cytotrophoblast invasion, placental infarct,

sclerotic narrowing of arteries and arterioles, abnormal uterine spiral artery remodeling are an important factor (Granger *et al*., 2001).

Maternal features of PIH include vasospasm, activation of the coagulation system, activation of pro-inflammatory cytokines, oxidative stress, and change in humoral and autacoid system related blood volume and blood pressures control which promote the overt symptoms of the diseases (Anjum *et al*., 2013).

Pre-eclampsia hypertension is usually associated with the offset of the vasodilator effect of normal pregnancy and an increase in vascular resistance. Normal pregnancy is associated with hypovolemia and decreased vasoactive peptides and amines whereas the pre-eclamptic women become hyper-responsive to vasoactive peptides and amines (ACOG, 2013).

The ischemia developed in pregnancy-induced hypertension promotes the formation of ischemic pro-inflammatory cytokines and coagulation factors. These factors from ischemia released on maternal endothelial system cause vascular endothelial dysfunction that enhance formation of vasoconstrictors (endothelin-1 and thromboxane), increased vascular sensitivity to angiotensin II, increased free-radical (superoxide) and decreased formation of vasodilators (nitric oxide and prostacyclin). The overall accumulative effect of these factors result in the hypertension observed in pregnant women (Bainbridge and Roberts, 2008)

A change of renal function in normotensive pregnant women occurs to meet the metabolic demand of the mother and fetus. In contrast to normotensive pregnant women, in PIH women an abnormal renal function is observed in these patients as a result of renal lesion that causes hypertrophy of the intra-capillary cells (Bainbridge and Roberts, 2008). This resulted in decrease of a renal blood flow and glomerular filtration rate. The reduced glomerular filtration rate is responsible for the increased blood urea nitrogen, uric acid and protein urea and creatinine level. The podocytes damage of glomerulus causes the secretion of specific podocyte protein in the urine leading to proteinuria (Ramana, 2014).

Neurological signs observed in pre-eclampsia are including headache, cortical blindness, scotomata, hyperreflexia and seizure. The seizures differentiate eclampsia from pre-eclampsia and other form of pregnancy-induced hypertension (James *et al*., 2014). Neurological manifestation eclampsia resulting from hypertension causes cerebral-auto regulatory dysfunction, blood-brain

barrier (BBB) disruption and passage of damaging protein and serum constituents into the brain (Cipolla *et al*., 2010).

2.3. Lipid Profiles Level in Normotensive Pregnant Women

Normotensive pregnant women are associated with the predicted change in lipid metabolism and increase lipid serum concentration as gestational age progress. During the early stage of gestation, there is a marked accumulation of lipid and hypertrophy of maternal adipocytes. This hyperlipidemia in normal pregnancy is not atherogenic because it is under hormonal control. Maternal hormone (progesterone and estrogen) secreted by corpus lutum and later by placenta continues to rise throughout pregnancy (Wild *et al*., 2015).

In health pregnancy, estrogen and progesterone hormones increase insulin receptor expression, insulin biosynthesis and beta cells (β cells) survive. An increase in maternal production of those hormones lead to diminishing lipolysis but increasing lipogenesis, which is the production of lipid that transported across the placenta and metabolized to meet energy demand for fetus (Paradisi *et al*., 2010).

2.4. Lipid Profiles Level in Pregnancy-induced Hypertension

Different factors promote the risks of hypertension and cardiovascular diseases, in which an elevated blood pressure is among the many. Elevated blood pressure may arise as sequel other complication; such as, diabetes, obesity, smoking, alcohol, aging, high salt intake, sedentary life styles and dyslipidemia. Those complications cause to endothelial dysfunction and inflammation that lead to pregnancy-induced hypertension (Alghatrif *et al*., 2013).

A research evidences have indicated that pregnancy-induced hypertension shared certain pathophysiology feature with cardiovascular disease (CVD). Additionally, dyslipidemia, which is a strong indicator of cardiovascular disease (CVD), can also be an important indicator of pregnancy-induced hypertension. Dyslipidemia adversely affects the functional and structural wall of arteries and promotes atherosclerosis. This change impairs blood pressure regulation, which is , in turn, leads to hypertension (Otsuka *et al*., 2016).

Biochemically, lipoproteins are composed of complex variable proteins and lipid compositions, so that they are responsible for transporting of lipid throughout the body. Plasma lipoproteins are spherical macromolecules made up of hydrophobic core contains phospholipid, fat-soluble

antioxidants and vitamins and cholesteryl ester and a hydrophilic coat that contains free cholesterol, phospholipid and Apo-lipoprotein molecules. This lipoprotein complexes include high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and chylomicrons (CM) (Jiram *et al.*, 2012). The generic lipoprotein particles and lipoprotein classes are illustrated in Figure 1 and 2 below, respectively.

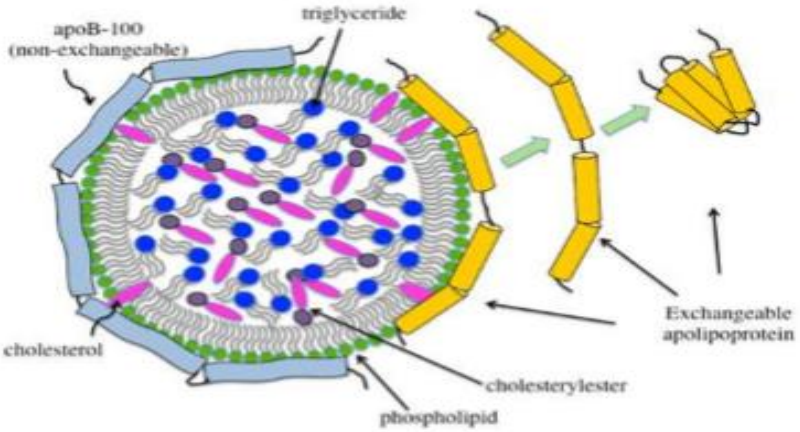


Figure 1**:** Pictorial representation of a generic lipoprotein particle (adopted from Jairam *et al*., 2012)

Lipoproteins have a spherical shape with a monolayer amphipathic lipids and proteins encircling a core of neutral lipids. Apo-100 (pale blue) is a single large polypeptide and is a none-exchangeable component of lipoprotein like VLDL and LDL. Exchangeable apo-lipoproteins can exist in lipid-free and lipid-bound states (Jairam *et al*., 2012).

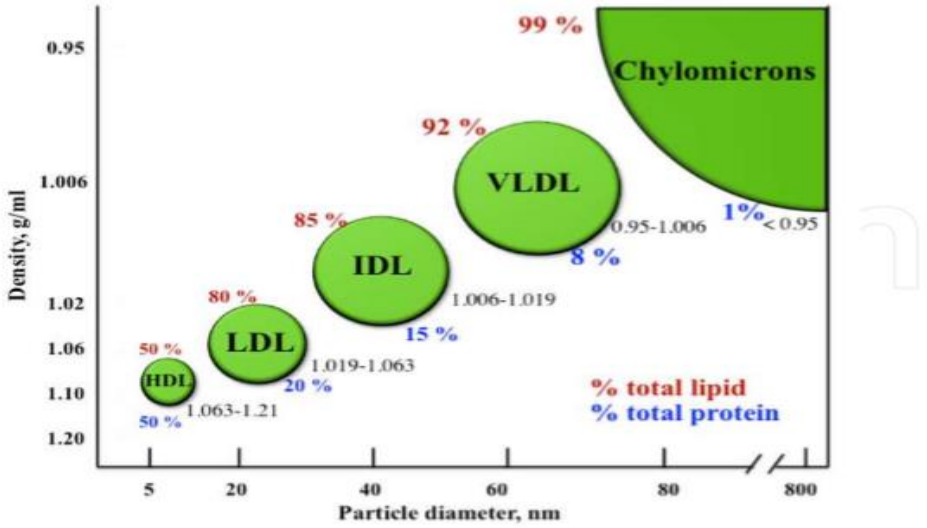


Figure 2: lipoprotein classes (adopted from Jairam *et al*., 2012)

The classification of the major types of lipoprotein is based on their density obtained by flotation ultracentrifugation analysis. Density range for each class is shown. The total lipid proportion is indicated by red color whereas total protein is indicated by blue color. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, IDL: Intermediate-density lipoprotein, VLDL: Very low-density lipoprotein (Jairam *et al*., 2012)

The lipoprotein maintain their lipid-soluble component when transporting lipids in the blood vessels and providing efficient mechanism for transporting their lipid contents to or from body tissues. In human, transportation mechanism is less an efficient compared with other animals and venerable to modification then lead to gradual deposition dyslipidemia on the wall of endothelial tissues. In particular, the small size LDL-C protein, due to inflammation, leads to the potential life threating plaque formation, causing the narrowing of blood vessels (Hegele, 2009).

Low-density lipoprotein-cholesterol (LDL-C) is pro-atherogenic particle, which is associated with apo-lipoprotein B-100 (apo-100), less triacylglycerol than their precursor VLDL, and has a high concentration of cholesterol and cholesterol esters. LDL-C particles are mainly synthesized in the liver and their main function is to provide cholesterol to the peripheral tissues where they are taken via LDL receptor by receptor-mediated endocytosis. Oxidation of small size LDL particles due to oxidative stress leads to endothelial cell injure and endothelial vascular dysfunction that are important in the pathogenesis of hypertension and also genetic defect of LDL receptor cause inherited hyperlipidemias (Harvey and Ferrier, 2011).

High-density lipoprotein-cholesterol (HDL-C) is ant-atherogenic particles synthesized in both liver and intestine and their main function is to reverse transport of peripheral cholesterol to liver. HDL-C particles contain Apo-lipoprotein A-1 (ApoA-1), they acquired cholesterol, and phospholipids that are released from cells through cholesterol–phospholipid transporter ABCA1 mediated process. Hence, HD-C plays an important role in protective from the development of atherosclerosis by scavenging cholesterol efflux from macrophages (Feingold and Grunfeld, 2018).

Serum lipid profiles are measured for cardiovascular risks including, hypertension. The test panel includes four basic parameters (TC, TG, HDL-C and LDL-C) and three their ratios (TC/HDL-C,

TG/HDL-C and LDL-C/HDL-C). Increased serum levels of TC, TG, LDL-C and decreased serum levels of HDL-C are known to be associated with major risk factors for pregnancy-induced hypertension (Ghooshchi *et al*., 2014).

Descriptive type of observational study done from 2016 to 2017 in India indicated that women with PIH have higher TC, TG, LDL-C, VLDL-C, and lower HDL-C levels compared to NTP women. Hence, antenatal screening for serum lipids levels can be useful in an early detection of PIH (De *et al*., 2006). Another study done in similar country on evaluation of TC, TG, and LDL-C were significantly elevated and HDL-C was significantly reduced in gestational hypertension when compared to NTP women (Latha and Ganesan, 2013)

2.5. Serum Uric Acid Relation with Pregnancy-induced Hypertension

Serum uric acid is formed from purine degradation reaction catalyzed by xanthine dehydrogenase or xanthine oxidase (XDH/XO) enzymes. Xanthine dehydrogenase (XDH) is oxidized to xanthine oxidase (XO) in the presence of several stimuli including ischemia. Xanthine oxidase is responsible for couple production of uric acid with the production of free radicals (super oxidase) and is implicated as a contributor to oxidative stress (Santillan *et al*., 2018).

XDH/XO found in most tissues but concentrated mainly in the live and gut. Xanthine oxidase (XO) circulation increased in ischemic tissues damage and it can bind to endothelium and lead to local oxidative injury. Unlike other mammal, human do not possess uricase enzyme so that their uric acid excretion mainly on renal clearance. Uric acid minimal soluble and its concentration is maintained in normal range in healthy individuals (less than 6mg/dL). Even in a low concentration, uric acid serve as a plasma antioxidant capable of scavenging free radicals (superoxide, hydroxyl radical and singlet oxygen) and it also reduces rosylation of tyrosine residues on proteins by peroxynitrite and is a capability to mainnittaining the integrity of superoxide dismutase enzyme (Latha and Ganesan, 2013)

Conversely, uric acid itself becomes a pro-oxidant (urate radical) where there is compromised antioxidant availability, particular reduced vitamin C. Uric acid is also a potent mediator of inflammation. It increases a production of monocyte chemo-attractant protein-1(MCP-1) mRNA and protein in vascular smooth muscle. Furthermore, uric acid stimulates human monocytes to produce pro-inflammatory cytokines IL-1β, IL-6 and TNF-α which are also elevated in pre-

eclamptic women as well as an experimental-induced hyperuricemic model animal (Bainbridge and Roberts, 2008)

Normal placenta structures are responsible for transportation of required gases (oxygen) and nutrient to the developing fetus. However, in pre-eclamptic mothers, uric acid damages the placenta vascular structure and enters to the smooth muscle via organic ion transporter then it activates the intracellular mitogen activated protein (p38) and nuclear transcription factors (NFK-B). This stimulates overproduction and expression of platelet-derived growth factors, thromboxane, angiotensin II, inflammatory markers C-reactive protein, and pro-inflammatory cytokines result in loss of the endothelial cell structure and function (Al-Jameil *et al*., 2014 and Masoura *et al*., 2015).

In normal physiology, uric acid is transformed to urate free radical and act as anti-oxidant. Urate radical is quickly recycled back to uric aci in the presence of the ascorbate. However, in a setting limits of ascorbate, uric acid is converted to urate radicals and cause to oxidative modification of the placenta protein and lipids (Lam *et al*., 2005).

Furthermore, increased level of uric acid causes decrease of production of nitrogen monoxide (NO) which is an important for maintaining an optimum placental perfusion and up regulates Cox-2 genes expression with increases production of thromboxane (Masoura *et al*., 2015).

A comparative study done to evaluate serum uric acid level showed that significant increases of serum uric acid in gestational hypertension and pre-eclampsia when compared with normotensive NTP women. It suggested that monitoring of serum uric acid concentration during pregnancy may help in the early detection and intervention of PIH and prevent the maternal and fetus complication outcomes (Sarmah, 2015).

A case-control study done on the association of serum uric acid with preeclampsia indicated hyperuricemia associated with pre-eclampsia compared to normotensive pregnant women (Sultana *et al*., 2013). Another prospective case-control study conducted on evaluation of lipid profile, and uric acid in pre-eclampsia reported that increased serum uric acid level in pre-eclampsia and its association was significant as compared with normotensive pregnant women. In pre-eclampsia, glomerular endothelial lesions lead to diminished renal blood flow, and glomerular filtration rate

but increased tubular reabsorption. Due to placenta hypoxia, placenta cell destruction is increased which, in turn, increase serum uric acid (Enaruna *et al*., 2014).

2.6. High Sensitivity C-reactive protein and Pregnancy-induced Hypertension

C-reactive proteins is the most sensitive positive acute-phase reactant protein produced by the liver through stimulation of cytokines mainly interleukin-6 (IL-6). It is a marker, mediator of inflammation and tissue injure, and it used to monitor the course of infection and inflammatory diseases. Inflammation has associated with endothelial cell dysfunction and related with renin-angiotensin system impairment. Research report indicated that hypertension might be in part an inflammatory condition (Dawri *et al*., 2014). As a component inflammatory mediator, high concentration of serum CRP raises blood pressure by lowering nitric oxide and increasing endothelin-1 production causing vasoconstriction (Paternoster *et al.*, 2006).

The study revealed that an early onset of pre-eclampsia-related maternal syndrome caused by oxidative stress in placenta associated with spiral arteries diseases. Because pre-eclampsia characterized by intensive inflammation response, an elevated level of CRP and cytokines including IL-6, and TNF-α play a major role in causing the vascular endothelial cell damage (Farzadnia *et al.*, 2013).

A prospective case-control research done on pregnancy-associated plasma protein-A and C-reactive protein levels in preeclampsia and NTP women at the third trimester in Turkey shown that serum hs-CRP was increased significantly in pre-eclampsia as compared with normotensive pregnant women (Deveci *et al*., 2009). When the inflammation or tissue destruction is resolved, hs-CRP levels fall, making it a useful marker for monitoring disease activity.

3. OBJECTIVE OF THE STUDY

3.1. General Objective

- To evaluate serum lipid profile, lipid profile ratios, uric acid and high-sensitivity C-reactive protein levels among pregnancy-induced hypertension and compare with normotensive pregnant women attending at Ambo University Referral Hospital, Oromia Region, Western Ethiopia, 2020 G.C.

3.2. Specific Objectives

- To compare the levels of serum lipid profiles (TC, LDL-C, HDL-C and TG) among pregnancy-induced hypertension and normotensive pregnant women.
- To compare lipid profile ratios (TC/HDL-C, TG/HDL-C and LDL-C/HDL-C) level among pregnancy-induced hypertension and normotensive pregnant women
- To compare serum uric acid level among pregnancy-induced hypertension and normotensive pregnant women
- To compare high sensitivity C-reactive protein level among pregnancy-induced hypertension and normotensive pregnant women

4. METHODS AND MATERIALS

4.1. Study Area and Period

The study was conducted in the Department of Medical Biochemistry, School of Medicine, College of Health Science, Addis Ababa University, in collaboration with the Ambo University Referral Hospital found in Oromia Region, Western Ethiopia from August to November 2020. Ambo University Referral Hospital serves as a referral center and also play an important role in teaching students in medical fields. According to annual report of 2019, Ambo University Referral Hospital provides an antenatal care (ANC) services and delivery services for 3423 and 3978 women, respectively.

4.2. Study Design

A case-control study was designed to evaluate serum lipid profiles, lipid profile ratios, uric acid and high-sensitivity C-reactive protein level among pregnancy-induced hypertensive women attending at Ambo University Referral Hospital, Oromia Region, Western Ethiopia from August to November, 2020 G.C.

4.3. Population

4.3.1. Sources population

Sources of the population were all pregnant women who attended ANC services clinic in the Ambo University Referral Hospital.

4.3.2. Study population

The study population were all confirmed pregnancy-induced hypertension and normotensive pregnant women after 20 weeks of a gestational age who attended ANC services clinic in the Ambo University Referral Hospital during study period until desired sample size was achieved.

4.4. Eligibility Criteria

4.4.1. Inclusion criteria

- PIH confirmed pregnant women after 20 weeks of gestational age for cases.
- NTP pregnant women after 20 weeks of gestational age for controls.

4.4.2. Exclusion criteria

Based on the recorded information (patient medical history, clinical data, ultrasound and laboratory investigations), PIH and NTP women experienced with the specifics below were excluded:

- Preexisting hypertension, renal and cardiovascular diseases
- Diabetes mellitus and gestational diabetes
- Pregnant mothers on lipid lowering drugs
- Gout
- History of alcohol abuse, khat chewing and smoking
- Obese women
- Systemic lupus erythematosus (SLE)
- Pregnant women with a known history of dyslipidemia
- Rheumatoid arthritis
- thyroid disorders
- Multiple pregnancies
- Cancers
- Asthma
- Infection (like HBV, HIV and UTI)

4.5. Sample Size Determination

Sample size was determined based on the specific mean± standard deviation (SD) for each groups in Ethiopia were not found. Therefore, the mean±SD of serum HDL-C for case was 39.68±7.5 and for that of healthy control was 43.72±7.35 taken from a study done in Indian entitle "Study of serum lipid profile in pregnancy and its correlation with pre-eclampsia,"(Nidhi *et al*.,2019). The sample size was determined by using the G* Power software statistical power analyses for Windows (version 3.1.2.9) with the following assumption: 95% of confidence interval, 80% of power, 1:1 ratio, two independent means±SD and the critical value ($Z\ \alpha/_2$) at 95% (α=0.05).

The minimum sample size computed based on the above assumption was 55 PIH and 55 NTP women. However, considering 10% of non-respondents rate, 10% of this value was added so that it made our sample size up to 61 PIH and 61 NTP women. Finally, to increase the validity of our data we deliberately increased by 9 PIH and 9 NTP women (more than 16% from the original sample size) and the total sample size became 70 PIH and 70 NTP women. Therefore, in this study total of 140 pregnant women were enrolled.

4.6. Sampling Technique

The convenient sampling technique was used to select, eligible and consented, 70 PIH women after 20 weeks of gestation for cases. Then each eligible and consented, 70 NTP women after 20

weeks of gestation following PIH women from the same population was selected as a control group. The two groups were matched for age and gestational age.

4.7. Variables

4.7.1. Dependent variables

- Lipid profiles (TG,TC, HDL-C and LDL-C)
- Lipid profile ratios (TC/HDL-C, TG/HDL-C and LDL-C/HDL-C ratio)
- Uric acid
- High sensitivity C-reactive protein (hs-CRP)

4.7.2. Independent variables

- Gestational age
- Age
- Gravidity
- Parity
- Family history of hypertension
- History of multi-partners
- Blood pressure

4.8. Blood Sample and Data Collection

After we explain details with regard the study, we obtained an informed consent from the study participants to fill up the questionnaires and donate blood samples for only this research purpose. The questionnaires were filled through face to face interview and blood pressure (two consecutive reading at least 4 hours apart, and the mean of the two was taken) was measured at the same time, by midwifery professionals. Medical records of the study participants were reviewed from integrated Antenatal, Labor, Delivery, Newborn and Postnatal Care Card. The detailed history and physical examination of the study participants were obtained by General Practionar (GP) about preexisting hypertension, liver diseases, renal disease and cardiovascular diseases, diabetes mellitus, gestational diabetes, gout, known dyslipidemia, rheumatoid arthritis and infection (like HBV, HIV, UTI). The study participants body mass index and circumference was measeared to exclude obese pregnant women from the study.

4.8.1. Blood Sample Collection and Processing

About 3-5mL volume of blood was withdrawn from the ante cubital vein by well experienced and trained medical laboratory technologists. A total of 140 blood samples (each form PIH and NTP women) were collected and transferred to a labelled serum separator tube (SST).

The collected blood sample was allowed to keep for 30 minutes to form complete clotting and clot retraction. Then serum sample was separated by centrifugation at 4000 rpm for five minutes by Centrifuge Humax 4K (Human, 2017, Germany).The serum sample was stored in Refigrater 0593 (Techno Diagnostics, 2017, USA) at -20^{0}C temperature until analyzed. While lipid profiles (TG, TC, HDL-C and LDL-C) and uric acid levels were measured by Cobas c311 analyzer for Clinical Chemistry (Roche, 2020, Germany), serum high sensitivity C-reactive protein (hs-CRP) was analyzed by Flouresence Immunoassay based Finecare^{TM} FIA meter (Wondfo, 2018, China) at Ambo University Referral Hospital Laboratory. Finally, serum lipid profile ratios (TC/HDL-C,TG/HDL-C and LDL-C/HDL-C) were calculated.

4.8.2. Blood pressure measurement

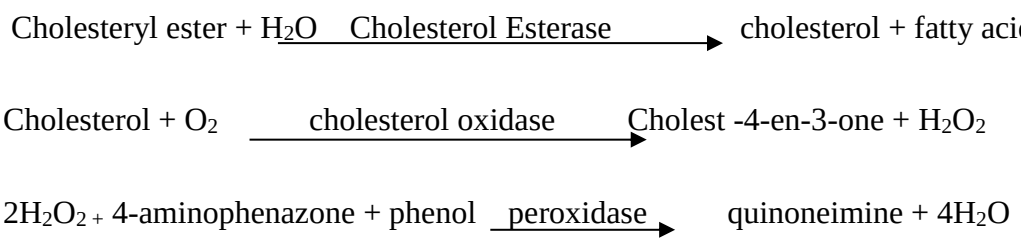
The blood pressure was measured with a mercury sphygmomanometer by the data collector.The study participants were allowed to sit and rest for about five minutes. Cuff of Accoson mercury sphygmomanometer was applied around the upper left arm at the level of the heart.The systolic blood pressure was accepted as the first sound heard (Korotkoff sound 1) and the diastolic blood pressure the disappearance of sounds completely (korotkoff sound 5) (Lowe et al., 2015). Elevated blood pressure was repeated after at least 4 hours and the average was taken. The cut-off points for elevated systolic and diastolic blood pressure was 140 mmHg or above and 90 mmHg or above, respectively (James *et al*., 2014).

4.9. Test Principle of Laboratory Analytes

Determination of serum total cholesterol level

Principles of the Method: Total cholesterol determination is based on the enzymatically hyrodolysis of cholesterol esters and oxidation of the 3-OH group of cholesterol through a seriseof a couple reactions**.** The estrase enyme removed ester group from esterified cholesterol to form free-cholesterol. The cholesterol oxidase enzyme oxidized free-cholesterol to form hydrogen peroxide which is further reacts with phenol and 4-amino-antipyrines by the catalytic action of the peroxidase enzyme to produce a red colored quinoneimine dye complex. The color intensity of the

quinoneimine dye produced is directly proportional to the cholesterol concentrations found in the serum sample (Röschlau et al., 1975). The reaction steps are illustrated as follows



Procedure: Two microliter (2µL) serum sample will be loaded into the sample cups then placed on the sample disk. The sample disk spins to orient the appropriate racks into the lane of the sample probe for specimen sampling. About one drop (47µL) of the reaction reagent that contains different enzymes and chemicals (4-Aminophenazone, phenol, peroxidase, cholesterol esterase, cholesterol oxidase) will be loaded into reagent bottle stand for total cholesterol and placed on a reagent disk. Then total cholesterol (as parameter to be tested) will entered on the screen menu of the machine. While the sample probe was loaded the sample from the sample disk and transferred into cuvettes that found in the reaction disk, the reagent probe was loaded the reagent from the reagent disk, and transferred it into reaction disk. The reaction disk is a large rotatable disk holding reusable cuvettes and is using ultra sonic mixing technology to mix thoroughly the serum sample within the reagent. Then the cuvettes are moving into water bath for incubation at 37^0C for five minutes. Furthermore, the reaction is going to be spin the cells to all reaction stations including the photometer light path. Finally, the light will be passed through the cuvettes and absorbance of the sample will be measured at 500nm wavelength.

Determination of serum triglycerides level

Principle of the Method: Triglyceride determination is an enzymatic assay method. Conjugated protein lipases enzyme hydrolysis triglyceride to glycerol and free-fatty acids. Glycerol kinases (GK) enzyme phosphorylate glycerol to glycerol-3-phosphate (G-3-P) and adenosine diphosphate (ADP) within the presence of ATP. Glycerol phosphate oxidases (GPO) oxidize glycerol-3-phosphate to dihydroxy-acetone phosphate (DHAP) and hydrogen peroxide (H_2O_2). Furthermore, hydrogen peroxide (H_2O_2) reacts with 4-amnioantipyrine and phenol by the action of peroxidase enzymes to form red colored complex. The color intensity of red color dyestuff is directly

proportional to the triglyceride concentration found in the serum sample (Klotzsch and Mcnamara, 1990). The reaction steps will be illustrated as follows.

Triglycerides $\xrightarrow{\text{Lipoprotein lipase (LPL)}}$ glycerol + fatty acids

Glycerol + ATP $\xrightarrow{\text{Glycerol kinase}}$ glycerol-3-phosphate + ADP

Glycerol-3-phosphate + O_2 $\xrightarrow{\text{GPO}}$ dihydroxyacetone phosphate + H_2O_2

H_2O_2 + 4-aminoantipyrine $\xrightarrow{\text{POD}}$ quinoneimine +HCl +H_2O + 4-chlorophenol

Procedure: Two micro liter of serum sample will be loaded and mixed in a cuvette with 120µL of triglyceride mono-reagent 1(R1) then incubated at room temperature for ten minutes. Finally, the optical density will be read at 540nm wavelength and it will be directly proportional to triglyceride concentration found in the serum sample.

Determination of high-density lipoprotein cholesterol (HDL-C) level

Non- HDL-C lipoprotein such as LDL-C, VLDL-C and chylomicrons combined with magnesium and dextrasulfate forming a water-soluble complex, which are resistant to polyethylene glycol-modified (PEG) enzyme. Only HDL-C can react with coupled polyethylene glycol-cholesterol esterase and polyethylene glycol-cholesterol oxidase enzyme because the enzymatic action of those enzymes towards non HDL-C are blocked. Then cholesterol esters are hydrolyzed to free cholesterol and fatty acids by cholesterol esterase. In the presence of oxygen, free cholesterol is oxidized by cholesterol oxidase to form 4-cholestenone and hydrogen peroxide. Finally, hydrogen peroxide reacts with 4-amino-antipyrines and sodium N-(2-hydroxy-3-sulfopropyl)-3, 5-dimethoxyaniline (HSDA) to form a purple-blue dye by the action of the peroxidase enzyme. The absorbance of light formed from the blue dye is directly proportional to the HDL-C concentration found in the serum sample (Jacobs Jr *et al*., 1990). The reaction steps will be illustrated as follows

HDL-cholesterol esters + H_2O $\xrightarrow[\text{esterase}]{\text{PEG cholestrol}}$ cholesterol + free fatty acids

Cholesterol + O_2 $\xrightarrow[\text{oxidase}]{\text{PEG cholesterol}}$ cholestenone + H_2O_2

$2H_2O_2$ + 4-amino – antipyrines + HSDA* + H^+ + H_2O $\xrightarrow{\text{Peroxidase}}$ purple-blue pigment + $5H_2O$

Procedure: About 2.4µL serum samples will be loaded into the sample cubs and placed on the sample disk. The sample disk spins to orient the appropriate raks into the lane of the sample probe for specimen sampling. About 120mL reagent 1 and 40µL reagent 2 will be loaded into reagent bottle stand for HDL-C and placed on the reagent disks. Then HDL-C (as parameter to be tested) will entered on the screen menu of the machine. While the sample probe was loaded the sample from the sample disk and transferred into cuvettes that found in the reaction disk, the reagent probe was loaded the reagent from the reagent disk and transferred it into reaction disk. Ultra sonic mixing technology is used to mix the serum sample within the reagents. Then the cuvettes are moving into water bath for incubation at 37^0C for five minutes. Furthermore, the reaction is going to be spin the cells to all reaction stations including the photometer light path. Finally, the light will be passed through the cuvettes and absorbance of the sample will be measured at 500nm wavelength.

Determination of serum Low-density lipoprotein (LDL) cholesterol level

Principles of the method: It is based on the direct determination of LDL-C takes advantage of the selective micellary solubilization of LDL-C by a non-ionic detergent and the interaction of a sugar compound, and lipoproteins (VLDL, and chylomicrons). Once a detergent is enclosed within the enzymatic method for sterol determination (cholesterol esterase, sterol enzyme coupling reaction), the relative reactivity's of sterol within the conjugated protein fractions increase during this order: alpha-lipoprotein (HDL) < chylomicrons < VLDL < beta-lipoprotein (LDL). In the presence of Mg^{++}, a sugar compound markedly reduces the accelerator reaction of the sterol measure in VLDL and chylomicrons. The combination of a sugar compound with detergent allows the selective determination of LDL-cholesterol in body fluid.

LDL-cholesterol esters+ H2O $\xrightarrow{\text{Cholesterol esterase}}$ Cholesterol + free fatty acids (selective micellar solubilization) detergent

Cholesterol esters are hydrolyzed to cholesterol and fatty acids by cholesterol esterase.

LDL-Cholesterol + O_2 $\xrightarrow{\text{cholesterol oxidase}}$ Δ^4-cholestenone + H_2O_2

Cholesterol is oxidized to Δ^4-cholestenone and hydrogen peroxide by cholesterol oxidase in the presence of oxygen.

$2H_2O_2$ + 4-amino-antipyrines +HSDA + H_2O + H^+ $\xrightarrow{\text{peroxidase}}$ Purple-blue color + 5 H_2O

The hydrogen peroxide reacts with 4-amino-antipyrines and HSDA to form a purple-blue dye by the catalytic action of peroxidase enzyme. The absorbance of the light from purple-blue dye is directly proportional to the LDL-C cholesterol concentration found in the serum sample (Jacobs Jr *et al.*, 1990, Röschlau *et al*., 1975).

Determination of serum Uric acid concentration

Principle of the method: Serum uric acid will be measured by uricase or PAP method. Uric acid is oxidized to allantoin and hydrogen peroxide (H_2O_2) by uricase enzyme. Phenolic compound and 4-amino-antipyrines react with hydrogen peroxide to form red colored quinoneimine dye complex by the catalytic action of peroxidase enzyme.

Absorbance of light from red color will be measured at 520nm wavelength and directily proportional to the uric acid concentration found in the serum sample (Latha, 2013). The reaction steps will be illustrated as follows:

Uric acid +H_2O $\xrightarrow{\text{uricase}}$ allantoin +H_2O_2

H_2O_2 + phenolic compound + 4-amino-antipyrines $\xrightarrow{\text{peroxidase}}$ red color quinoneimine dye +H_2O

Procedure: About 20 micro liter of serum sample was mixed in a cuvette with about 120mµ of R1 and 40mµ of R2 then incubated at 37^0C for five minutes, or at room temperature for 15 minutes. Absorbance of light from red color will be measured at 520nm wavelength and it proportional to the uric acid concentration found in the serum sample.

Determination of serum high sensitivity C-reactive protein level

Principle of the method: High sensetivity C-reactive protein level was measured by fluorescence immunoassay using Finecare^{TM} FIA meter (Wondrfo, China). The finecare^{TM} hs-CRP rapid test uses a sandwich method, when sample is added to the sample well of test cartridge, the fluorescence tagged hs-CRP antibody bind to hs-CRP antigen in blood specimen. A mixture of sample migrates on the nitrocellulose matrix of the test strip by capillary action.Then, the complexes of tagged hs-CRP antibody and CRP are captured to CRP antibody that has been

immobilized on the test strip. Theferore, hs-CRP antigens in a blood specimen combined with hs-CRP antibody on the test strip to form fluorescent complex. The signal intesity of the fluorescence detector antibody indicates the cocentration levels of the CRP captured. The finecare^{TM} FIA meter shows CRP concentration in a blood specimen.The results of Finecare^{TM} hs-CRP rapid test is displayed as mg/L. The working range and detection limit of hs-CRP are 0.5-200mg/L and 0.5 mg/L.The normal refernce value for hs-CRP in healthy individuals are expected to be <1.0 mg/L

4.10. Interpretation of the Results

The results for lipid profiles were interprated by using the cut off value which is established by the National Cholesterol Education program (**Table 1**) (NIH, 2001). The TC/ HDL-C ratio >5 (Emerson, 2003), TG/HDL-C ratio>4.5 and LDL-C/HDL-C ratio >3.5 (Salazar *et al*., 2012) was taken as a baseline values for interpretation of the lipid profile ratios. Uric acid normal reference value was 2.6- 6 mg/dL and its ≥6 mg/dL was considered as an abnormal values (Desideri et al., 2014). While hsCRP below 1mg/L was considered as a normal, 1-3mg/L was considered as moderate increased and >3mg/L was considered as a high value (Mazurek *et al*., 2011). Therefore, after the tests have been analyzed the result interpreted based on the normal reference value established.

Table 1: Normal reference value for the lipid profile tests established by the National Cholesterol education program (total cholesterol, triglyceride, LDL-cholesterol and HDL-cholesterol)

	Parameters			
Normal reference range	TC	TG	LDL-C	HDL-C
	<200 mg/dL	<150 mg/dL	<130 mg/dL	<40 mg/dL

4.11. Data Quality Assurance

4.11.1. Data collection quality control measures

Data was collected using semi-structured questionnaires.The questionnaires were prepared in English and translated into Afan Oromo and then consistency was checked via back translated to English by speaker fluent for both language. Training was provided for the data collector on the study objective, procedures, confidentiality, respondents' right, and informed consent. In addition,

pretest was conducted among 7 respondents (5% of total required sample sizes) whose found outside of the study area to check the acceptability of the questionnaires whether it can pool the necessary information, and the interview was formalized with how to record, and group the necessary information. Reliability analysis was done by using Cronbatch's alpha model on scale to check internal consistency. Cronbatch's alpha for 8 items was 58%. The data collection process was supervised by principal investigator and principal advisor. The filled questionnaires were checked daily for completeness, logical errors, unclear information, or irrelevant information.

4.11.2. Pre-analytical phase

The blood samples collection and storage was adherence with the standard operation procedures (SOP) and laboratory manual to ensure sample quality. Participants were well-prepared and serum separator tube (SST) was coded with the collection date, medical record number (MRN) and unique identification number. After processed, serum sample stored at below -20^0C and this temperature was monitored daily.

4.11.3. Analytic phase

Laboratory analysis was done at Ambo University Referral Hospital Laboratory, clinical chemistry section. According to Laboratory schedule, calibration and daily maintenance was performed. Internal laboratory quality control was run to ensuring accuracy and reliability of laboratory testing before running pateint sample.The control result was interpreted using a Levey-Jenning's chart. The control result was fallen within the acceptable ranges (mean±2SD). After the sample towed and mixed throughout it was run by senior Laboratory Technologists.

4.11.4. Post analytical phase

The printed results was checked for unit of reporting, correctnesses of medical registration number (MRN) and unique identification card number. Then the printed out or recorded (in the absence of printer paper) results were approved by laboratory quality officer. Lipid profile ratios were calculated and recorded on the result form provided.

4.12. Data Processing and Analysis

All the data was checked for the completeness, cleaning, processing and analysis of the data obtained from laboratory analysis of the blood sample. The data was coded and entered to Epi-data statistical software (version 3.1, 2008) and then it was exported to SPSS software (version 25.0, 2013, USA) for analysis. While the difference between two groups were compared using the independent student's t-test, the difference between categorical variables between two groups

were compared using the chi-square for independence and fisher exact t-test. The percentage (%) distribution was done for both continuous and categorical variables. Then the result was presented by tables and figures. The P value <0.05 at 95% of confidence level was considered as a statistically significant.

4.13. Ethical Consideration

Data collection proceeded after receiving an ethical clearance and official letters from the Research and Ethics Review Committee of Department of Medical Biochemistry, School of Medicine, College of Health Science, Addis Ababa University (DRERC), by approval letter with Ref. No. of SOM/BCHM/091/2012, meeting No. of DRERC 02/20 and protocol No. of M.Sc. 06/20 issued on March 12 /2020 G.C. The collaboration letter for data collection was also received from Ambo University Referral Hospital. The informed written consent was obtained from the study participants before enrollment into the study. They were informed there were not any incentive, or harm for their participation in this study. Data and laboratory sample was collected after the study participants gave full consent by signing on the consent form. Confidentiality, accountability and academic honesty was maintained throughout the study. Finally, all necessary precautions were undertaken to prevent COVID-19 pandemic transmission during data collection.

4.14. Operational Definition

Lipid profile: An assessement of the levels of fats in a patient's blood. It includes trigylceride, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol .

Lipid ratios: The pattern of atherogenic to anti-atherogenic lipid ratios in a pateint's blood. It includes the ratio of trigylceride to high-density lipoprotein cholesterol, total cholesterol to high-density lipoprotein-cholesterol and low-density lipoprotein to high-density lipoprotein-cholesterol.

Normotensive pregnant women: Pregnant women's with blood pressure ≤140/90 mmHg after 20 weeks of gestation

Pregnancy- induced hypertension: Pregnant women's with blood pressure ≥140/90 mmHg and with or without proteinuria after 20 weeks of gestation. Pregnancy-induced hypertension includes gestational hypertension, pre-eclampsia, pre-eclampsia superimposed on chronic hypertension and eclampsia

4.15. Result Dissemination

The result of the study will be submitted and presented to the Department of Medical Biochemistry, College of Health Science, School of Medicine, Addis Ababa University and will be disseminated to the School Library of Addis Ababa University.This finding also disseminatted to Ambo University Referral Hospital. Finally, it will be published in an international reputable journal and presentation at a scientific meeting.

5. RESULTS

5.1. Age and Gestational Age distribution between PIH and NTP Women

One hundred and forty (70 of each with PIH and NTP) consented pregnant women with the age between 18-39 years were participated in this study. Only 17.1% participants from PIH and 12.8% participants from NTP women found at an extreme age (≤19 and ≥35 years). The minimum and maximum gestational age of the study participants were 22 and 40 weeks, respectively. From PIH women, 82.9% of them were preterm and solely 17.1% of them were term. From NTP group, 91.4% were preterm and solely 8.6% of them were term. The age and gestational age distribution was showed in **Table 2** below.

Table 2: Age and gestational age distribution between PIH and NTP women at AURH, Oromia Region,Western Ethiopia, from August to December 2020 (n=140)

Variables		PIH (n=70)	NTP (n=70)
		%	%
Age	≤19	7.10	7.10
	20-24	27.1	31.4
	25-29	30.0	30.0
	30-34	25.7	25.7
	35-39	10.0	5.70
GA (weeks)	Preterm	82.9	91.4
	Term	17.1	8.60

5.2. Comparison of Age, Gestational Age and Blood Pressure between PIH and NTP Women

The mean±SD of the age and gestational age of PIH was found 27.56±5.23 years and 34.23±4.25 weeks, respectively whereas the mean±SD of the age and gestational age of NTP was found 26.73±4.94 years and 30.66±4.78 weeks, respectively. While the age distribution between group was not showed statistical significance with P>0.05 level; the gestational age distribution was showed statistical significance with p<0.05 level. In PIH group, while the mean±SD of SBP and DBP of PIH was found 151.86±10.20 and 101.67±7.67 mmHg, respectively; the SBP and DBP of NTP group was found 106.97±6.35 and 78.79±7.58 mmHg, respectively. In both cases, the data was showed that statistical significant.

Table 3: Comparison of the age, gestational age and blood pressure between PIH and NTP women at AURH, Oromia Region, Western Ethiopia, from August to December 2020 (n=140)

Variables	PIH (n=70)	NTP (n=70)	T value	P value	95% CI
Mean Age	27.56± 5.23	26.73±4.94	-.979	0.329	-2.54,0.859
Mean GA(weeks)	34.23±4.25	30.66+4.78	-4.669	0.000*	-5.08,-2.06
SBP(mm Hg)	151.86±10.20	106.97±6.35	-31.269	0.000*	-47.73,-42.04
DBP(mm Hg)	101.67±7.67	78.79±7.58	-22.285	0.000*	-26.07,-21.81

The * indicates $p<0.05$

5.3. Comparison of Obstetric History between PIH and NTP Women

From the PIH group, it was found nulliparous (37.1%), primipara (25.7%), and multipara (37.1%). On the other hand, from NTP group, it was found nulliparous (40%), primipara (27.1%), and multipara (32.9%). Sixty percent of PIH group were primigravida and 40% were multigravida whereas 44.3% of NTP group were primgravida and 55.7% were multigravida. Solely 5.7% of PIH had history multi-partner and the remaining had no history. In distinction to this, only 2.9% from NTP group had a history of multi-partner and 97.1% had not. There was no statistically significant ($p>0.05$) difference in parity, gravidity and history of multi-partner between two groups. During this study, the majority of PIH group has had a negative family history of high blood pressure. Only 8.6% of the PIH groups have had a positive family history of high blood pressure. From NTP group only 2.9% of the study participants have had a positive family history of high blood pressure and the remaining 97.1% of them had not a family history of high blood pressure (**Table 4**). This difference between groups were statistical significant with $p<0.05$.

Table 4: Obstetric history distribution between PIH and NTP women at AURH, Oromia Region, Western Ethiopia, from August to December 2020 (n=140)

Variables	Category	PIH (n=70)	NTP (n=70)	P value	95% CI
		%	%		
Parity	Nulliparous	37.1	40.0	0.538	0.58, 2.85
	Primipara	25.7	27.1		
	Multipara	37.1	32.9		
Gravidity	Primigravida	60.0	44.3	0.271	0.27, 1.04
	Multigravida	40.0	55.7		
History of multi-partner	Yes	5.70	2.90	0.360	0.07, 2.56
	No	94.3	97.1		
Family history of high BP	Yes	8.60	2.90	0.030*	0.056,1.57
	No	91.4	90.0		
	Don't know	0.00	7.10		

5.4. Biochemical Parameters

5.4.1. Comparison of serum lipid profiles, uric acid, hs-CRP and glucose between PIH and NTP women

Our result showed (**Table 5**) that while the mean±SD of serum lipid profiles (TC,TG, LDL-C), hs-CRP, blood sugar and uric acid were significantly elevated in pregnancy-induced hypertension, HDL-C was decreased in pregnancy-induced hypertension when compared to normotensive pregnant women ($P<0.05$).

Table 5: Comparison of serum level of lipid profiles, uric acid, hs-CRP and glucose between PIH and NTP women at AURH, Oromia Region, Western Ethiopia, from August to December 2020 (n=140)

Parameters(mg/dL)	Groups	Mean±SD	Minimum	Maximum	Range	P(2tailed)	95% CI
TC	PIH	184.80±54.07	105.0	453.7	348.7	0.000*	-47.40,-16.13
	NTP	153.03±38.12	78.40	245.0	166.6		
TG	PIH	236.25±71.76	108.5	413.00	304.5	0.000*	-80.51,-32.60
	NTP	179.68±71.57	80.50	389.5	309.0		
HDL-C	PIH	35.52± 11.53	12.00	61.20	49.20	0.000*	2.72, 9.44
	NTP	41.60± 8.29	26.00	65.00	39.00		
LDL-C	PIH	130.20±50.31	58.80	300.0	241.2	0.000*	-59.06,-31.45
	NTP	84.94± 29.46	19.60	171.0	151.4		
Uric Acid	PIH	6.65±1.97	2.900	11.90	9.000	0.000*	-3.40,-2.30
	NTP	3.80±1.20	1.900	8.600	6.700		
hs-CRP (mg/L)	PIH	12.25±14.12	0.400	70.90	70.50	0.000*	-14.47,-7.71
	NTP	1.16±1.36	0.100	7.200	7.100		
Glucose	PIH	90.86 ±21.34	72.00	167.0	105.0	0.015*	-13.24, -1.48
	NTP	83.50±12.71	71.40	126.0	58.60		

5.4.2. Categorical values of serum lipid profiles and uric acid between PIH and NTP women

Out of the PIH group, it was found above the baseline value for TC (31.4%), TG (88.6%) and LDL-C (37.1%) whereas out of the NTP group, it was found above the baseline value for TC (14.3%), TG (57.1%) and LDL-C (32.9%). While from PIH, it was found below baseline value for HDL-C (67.1%), from NTP women, it was found below baseline value for HDL-C (42.9%). About 75.7% of the PIH group found above the baseline value for uric acid levels but 24.3% of them found a below the baseline value. Conversely, only 7.1% of the NTP group found above the baseline value for uric acid levels and the remaining found a below the baseline value.

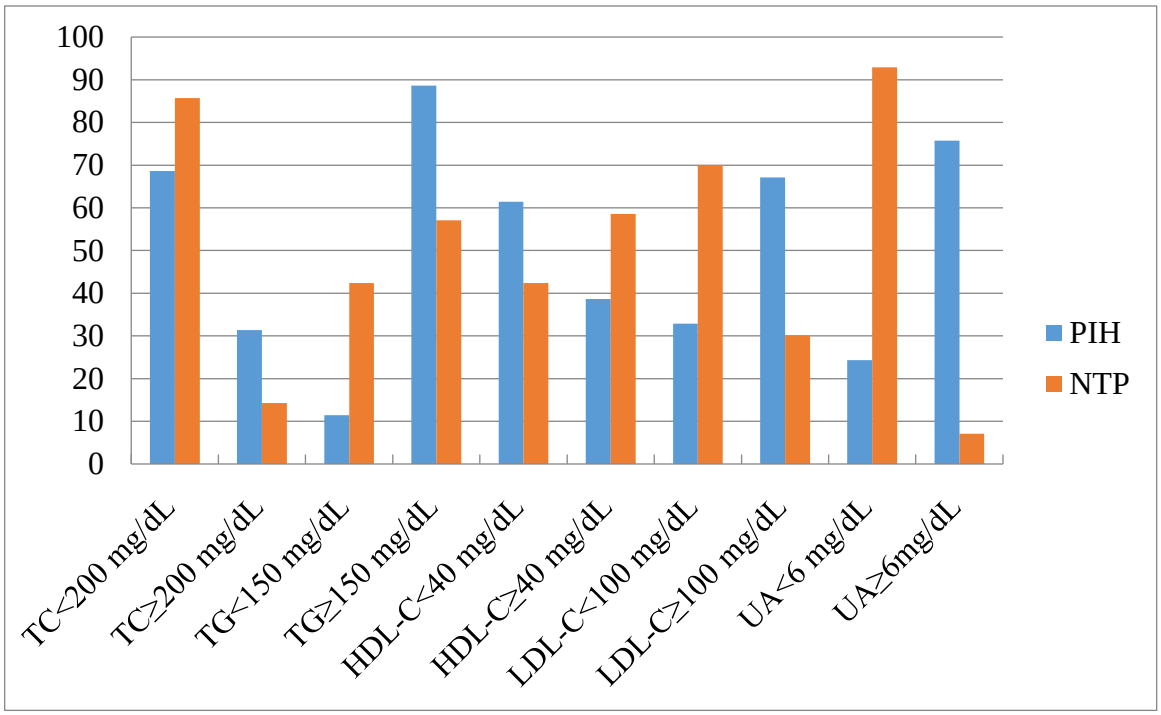


Figure 3: Categorical values of serum lipid profiles and uric acid between PIH and NTP women at AURH, Oromia Region, Western Ethiopia, from August to December 2020 (n=140)

5.4.3. Comparison of serum lipid profile ratios between PIH and NTP women

The ratio of the lipid profile is a vital in predicting cardiovascular risks. The mean value of TC/HDL-C, TG/HDL-C and LDL-C/HDL-C for PIH were 5.92±3.13, 7.43±3.79 and 4.37±2.53, respectively. In contrast, the mean values of TC/HDL-C, TG/HDL-C and LDL-C/HDL-C for NTP women were 3.93±1.03, 4.37±1.84 and 2.57±1.08, respectively. Therefore, the ratios of these lipid profiles were significantly higher in PIH compared to NTP women (**Table 6**).

Table 6: Comparison of serum lipid profile ratios between PIH and NTP women at AURH, Oromia Region, Western Ethiopia, from August to December 2020 (n=140)

Parameters	Groups	Mean±sd	Minimum	Maximum	Range	P value	95% CI.
TC/HDL-C	PIH	5.92±3.13	2.60	20.0	17.4	0.000*	-2.77,-1.21
	NTP	3.93±1.03	1.20	7.80	5.60		
TG/HDL-C	PIH	7.43±3.79	2.30	20.0	17.7	0.000*	-4.06,-2.06
	NTP	4.37±1.84	1.26	9.00	7.74		
LDL-C/HDL-C	PIH	4.37±2.53	1.10	13.7	12.6	0.000*	-2.45,-1.15
	NTP	2.57±1.08	0.50	6.10	5.60		

5.4.4. Categorical values of lipid profile ratios between PIH and NTP women

For PIH cases, the ratios were found higher than the baseline: TC/HDL-C by 51.4%; TG/HLD-C by 74.3%; and LDL-C/HDL-C by 67.1%. On the other hand, for the NTP cases, the ratios were found higher than the baseline: TC/HDL-C by 11.4%; TG/HDL-C by 29%; and LDL-C/HDL-C by 28.3%. From each group the remaining study participants were below the baseline value for the listed parameters.

5.4.5. Categorical value of serum hs-CRP between PIH and NTP women

The levels of high sensitivity C-reactive protein (hs-CRP) were classified as low, moderate and high risk to evaluate inflammatory status of the study participants. Among PIH women in this study, 11.4%, 35.7% and 52.9% fall in <1mg/dL, 1-3mg/dL and >3mg/L levels of hs-CRP, respectively. The normotensive pergnant women (NTP) showed that 72.9%, 14.3% and 12.9% were found in <1mg/L, 1-3mg/L and >3mg/L levels of hs-CRP, respectively (**Figure 5).**

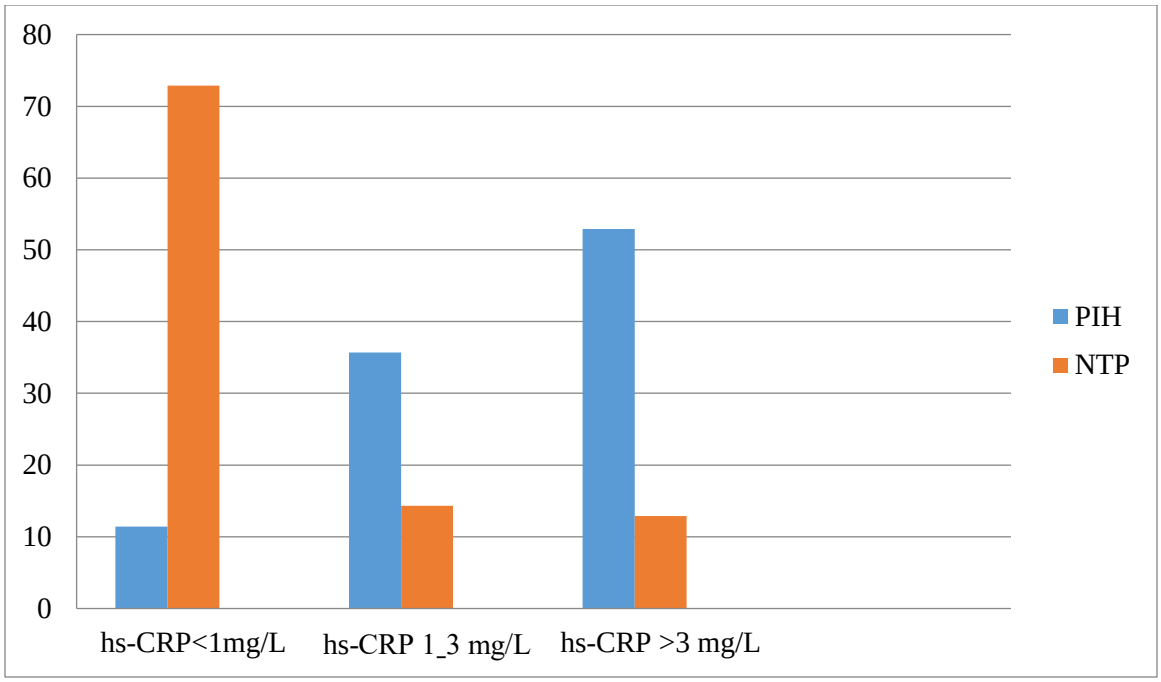


Figure 4: Categorical levels of serum hs-CRP between PIH and NTP women at AURH, Oromia Region, Western Ethiopia, from August to December 2020 (n=140)

6. DISCUSSION

Pregnancy-induced hypertension (PIH) is a common complication pregnancy that contributes to maternal and perinatal morbidity and mortality (NICE, 2010). Various risk factors known for the event of PIH but etiology and pathophysiology are yet not fully understood. Abnormal placental implantation and immunologic intolerance between maternal, placenta and fetus are some famed etiologic factors (Sava *et al*., 2018). An altered lipid profiles (dyslipidemia) (Wild *et al*., 2015), hyperuricemia (Bainbridge and Roberts, 2008) and oxidative stress and inflammation (Harmon et al., 2016) are the molecular mediators that cause endothelia dysfunction results in high blood pressure. To fill the gap and in seeking of potential biomarkers for possible intervention, the current study aimed to profile lipids, uric acid and hs-CRP from 140 study participants age- and gestational-matched PIH and NTP women.

Normotensive pregnant women (NTP) are associated with notable change in lipid metabolism and increased blood lipid concentration as the gestational age progress (Wild *et al*., 2015). This lipidemia in traditional physiological state is not atherogenic as a result of it's under hormonal control. A maternal secretion like steroid hormone (estrogen) secreted by the corpus lutum and later by placenta features are very important role up to the mark of lipid metabolism throughout the traditional course of physiological state (Paradisi *et al.*, 2010). Estrogen could be a principal modulator of hypertriglyceridemia causing hepatic biosynthesis of endogenous triglycerides carried by VLDL. This method may also be modulated by hyperinsulinemia throughout the physiological state (Wild *et al*., 2015).

In contrast to NTP women, blood lipid concentration were increased several folds and become atherogenic dyslipidemia in PIH cases (Wild *et al*., 2015). This is often similar inside our study that the serum lipid profiles were statistically significantly elevated in PIH women compared to NTP women ($p<0.05$). In pre-eclampsia, change in lipid metabolism causes to endothelial dysfunction that reduces vasodilator molecules and rises vasoconstriction molecules as well as will increase pro-inflammatory molecules and oxidative stress (Mcelwain *et al.*, 2020).

In this study, TC was significantly elevated in PIH (184.80±54.07 mg/dL) when compared to NTP women (153.03±38.12 mg/dL) ($p<0.05$). About 31.4 percent of the PIH was found above the base-line value (<200mg/dL).This finding is in agreement with the study done by a few researchers (Thathagari and Kumar, 2018, Gohil *et al*., 2011 and Blessy PPS *et al*., 2019). Insulin resistance

in hypertension disorder of pregnancy could be contributing suppression of lipoprotein lipase activity and will increase free fatty acid mobilization from visceral adipocytes (Ghooshchi *et al*., 2014). This could highlight hypercholesterolemia in hypertension disorder of pregnancy.

Regarding TG, our result is in line with the previous study (Bishoni *et al*., 2019 and Latha and Ganesan, 2013).The mean value of TG levels was higher in PIH (236.25±71.76 mg/dL) compared to NTP (179.6±71.57 mg/dL),which is statistically significant ($p<0.05$). An elevation of serum TG may be due to decreased in hepatic lipase activity responsible for an endogenous biosynthesis of TG and diminished lipoprotein lipase activity that keeps TG in adipocyte tissue (Wild *et al*., 2015). This might contribute to an endothelial pathology directly predisposed in uterine vessels or indirectly via generating small dense LDL-C and/or it should be a lot related with hypercoagulability (Latha and Ganesan, 2013).

Among the PIH cases, 65.7% of them showed higher LDL-C above the baseline value and the mean value of LDL-C was found a high in PIH (130.20±50.31 mg/dL) compared to NTP women (84.94±29.46 mg/dL) ($p<0.001$. This study is in agreement with the report (Blessy PPS *et al*., 2019, Latha and Ganesan, 2013 and Singh *et al.*, 2013). LDL-cholesterol principally synthesized within the liver and its main function is providing cholesterol to peripheral tissues. Small dense LDL particles are more atherogenic because they have increased ability to infiltrate tissues (Jairam *et al*., 2012). Small dense LDL-C is additionally more venerable to oxidation than traditional LDL-C. Its oxidation due to oxidative stress in endothelial cells cause reduction of prostacyclin to thromboxane A-2 ratio, and scale back other vasodilator molecules. Additionally, it up-regulates pro-inflammatory cytokines and intracellular vascular adhesion molecules. Small dense LDL-C peroxidation involved in the foam cell formation in the intima of endothelial cell. These results in endothelial cell dysfunction that lead to hypertension (Harvey and Ferrier, 2011).

In this study, we have also evaluated whether serum HDL-C as risk factors for PIH. The mean value of HDL-C was significantly lower in PIH (35.52±11.53 mg/dL) than NTP cases (41.60±8.29 mg/dL) ($p<0.05$). When compared with baseline value, 67.1% of the study participants in PIH had HDL-C value below the baseline value. This finding is comparable with study done by (Rathore *et al*., 2019 and Singh *et al.*, 2015). The significant lowered of serum HDL-C is because of the reverse impact of atherogenic lipoprotein and inflammatory burden. HDL-C plays vital role in protective from endothelial cell damage by scavenging cholesterol discharged from macrophages

(Feingold and Grunfeld, 2018). Decreasing of the HDL-C concentration in PIH reduces the stimulation of nitric oxide (NO) that ends up in placental endothelial cell dysfunction. Impairment of endothelial could be a generally features of pre-eclampsia and eclampsia. The reduction levels of HDL-C is not only due to hypo-estrogenemia but also due to insulin resistance (Wild *et al*., 2015).

The mean value of lipid profile ratios include TC/HDL-C, TG/HDL-C and LDL-C/HDL-C were significantly elevated among PIH (5.92±3.13, 7.43±3.79 and 4.37±2.53, respectively) compared to NTP women (3.93±1.03, 4.37±1.84 and 2.57±1.08, respectively) ($p<0.05$). This result is in agreement with the study of (Blessy PPS *et al*., 2019 and Anjum *et al*., 2013). The lipid profile ratios (TC/HDL-C and LDL-C/HDL-C) are more predictive than isolated parameters to indicate future cardiovascular risk and prognostic state. Those ratios reflect the balance between the risk and protecting lipoprotein protein capability (Millán *et al*., 2009). The study done by (Sniderman *et al*., 2011) showed that lipid ratios as a good predictor of the cardiovascular risk assessment than isolated lipid parameters.

In the present study, the mean serum uric acid level was significantly increased in PIH (6.65±1.97 mg/dL) cases compared to NTP (3.80±1.20 mg/dL) ($P<0.05$), which is in agreement with the previous study of (Agarwal *et al.*, 2014, Sarmah, 2015). Uric acid is a mediator of inflammation and freelance risk factors within the pathological process of PIH (Bainbridge and Roberts, 2008).

Placental/maternal tissue ischemia activates xanthine oxidase which results in overrun of uric acid with free radicals including superoxide (O^{2-}) and is concerned as a contributor to oxidative stress (Santillan *et al.*, 2018). In the reduced state of ant-oxidants (vitamin C), an increase level of uric acid becomes pro-oxidant (urate radicals). This hyperuricemia activates the immune cells to pro-inflammatory cytokines and chemo-attractant molecules that play a task in endothelial cell dysfunction (Mishra *et al*., 2016). In contrast to this, low level of uric acid or within the presence of ample anti-oxidant, uric acid by itself is a plasma anti-oxidant scavenging free-radicals and maintaining the integrity of anti-oxidant enzymes (Latha and Ganesan, 2013). Previous study on pre-eclampsia indicated that, uric acid damages placenta tube structures and enters to sleek muscles result in the production of vasoconstrictor molecules, platelet-derived growth factors and inflammatory marker (C-reactive protein) leads to functional and structural loss of endothelial cells (Masoura *et al*., 2015). Elevation of uric acid could predate symptom and vital sign of

elevation by several weeks. Thus, its evaluation is better indicators of the onset of pre-eclampsia and predicts the development of eclampsia (Sahijwani *et al*., 2012).

Inflammatory marker high-sensitive C-reactive protein level was significantly ($p<0.05$) higher in PIH (12.25±14.12 mg/dL) compared to NTP women (1.16±1.36 mg/dL) and it is comparable result was reported by (Deveci *et al.,* 2009). An elevation of hs-CRP in PIH reveals the presence of systematic inflammation. An experimental study result showed that hs-CRP levels in PIH was significantly increased when compared to NTP women and it also increased with aggravation of PIH (Veerbeek *et al*., 2015).

Study done by (Veerbeek *et al.,* 2015) proved that immune imbalance and cytokines, particularly inflammatory factors, play a vital role in immune regulation as their association with PIH. The extent of hs-CRP directly reflects the state of the body's inflammatory response. With the severity of pre-eclampsia, the concentration of hs-CRP in peripheral blood is elevated. Therefore, assessing serum hs-CRP will be serving as a monitoring biomarker for the hypertensive disorder of pregnancy (Kong *et al.*, 2018). Inflammation shares a pathophysiologic role in PIH. Therefore, as an element of inflammatory mediator's, high concentration of C-reactive protein raises blood pressure by lowering nitric oxide and increasing endothelin-1 production inflicting constriction that, in turn, is causing vascular endothelial cell damage (Harmon *et al.*, 2016).

7. CONCLUSION

Our study confirmed that dsylipidemia indicators (increased levels of TC, TG, LDL-C, TC/HDL-C, TG/HDL-C, LDL-C/HDL-C and decreased levels of HDL-C), hyperuricemia indicator (elevated uric acid), and a potential inflammatory marker (increased hs-CRP) were highly pronounced in the PIH than NTP women. As a result, in an addition to being potential biomarkers to understand the pathophysiology of the PIH, these biomarkers will be used as a potential intervention to reduce the risk of women during their pregnancy. We believe this study benefits clinicians, researchers and policy makers who are striving to protect the death of pregnancy-induced hypertension mortality in the world, particularly in our country. Moreover, the outcome of this study provides an insight for those in the forefront on the mission of "No Woman or Child should Die of Pregnancy in Ethiopia."

8. RECOMMENDATION

The monitoring of serum lipid profiles, lipid profile ratios, uric acid and hs-CRP for pregnant women who come during antenatal care services (ANC) could help for the early detection of women with PIH cases. Evaluation of dyslipidemia, hyperuricemia and inflammation in pregnancy-induced hypertensive women should be given attention to prevent PIH and its future complications. This study should be conduct on large scale to confirm dyslipidemia, systematic inflammation and hyperuricemia as risk factors for PIH and as a future predictor of cardiovascular risk. It is better to integrate evaluation of the serum lipid profile, lipid profile ratios, uric acid and hs-CRP as a component of routine laboratory tests during antenatal care service (ANC).

9. STRENGTH AND LIMITATION OF THE STUDY

9.1. Strength of the Study

- The comprehensive evaluation of serum lipid profile, lipid profile ratios, uric acid and hs-CRP in PIH compared to NTP women were attempted for the first time in Ethiopia.
- Even though the data collection period was overlapped with the outbreak of COVID-19 pandemic, we were overcame the challenge of this pandemic by strictly adherence to the recommended preventive measures to protect ourselves and study participants during sample collection and laboratory works.

9.2. Limitation of the Study

- This study could not include others biomarkers (hormonal analysis) that may associated with PIH.
- Nutrition status (dietary habit) of study participants were not assessed.

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11. ANNEXES

11.1. Participants Information Sheet

Thank you very much for your participation in this study supervised by Department of Medical Biochemistry, School of Medicine, College of Health Sciences, Addis Ababa University. We are kindly requesting you to read the information provided and respond to these questions with no pressure.

Research title: Evaluation of serum lipid profiles, uric acid and high sensitivity C-reactive protein levels among pregnancy-induced hypertension attending at Ambo University Referral Hospital, Oromia Region, Western Ethiopia.

Sponsoring organization: Addis Ababa University, College of Health Science, Department of Medical Biochemistry

Principal investigator: Bilisma Girma Areda (BSC). Advisor: Solomon Tebeje Gizaw (Ph.D.).

Objectives of research project: we have prepared this information sheet at Addis Ababa University for the project with the objectives of evaluation of serum lipid profiles, uric acid and high sensitivity C-reactive protein levels among pregnancy-induced hypertension and compared with normotensive pregnant women.

Study procedures: We are going to be asked kindly you if you are volunteer to participate in this research project. If you are volunteers, we will give you verbal or in written information with regards the project. We would like to collect general health information about you and withdraw about 3-5 mL of blood specimen for laboratory investigations. Important information including blood pressure, gestational age, age, parity, gravidity and related current and prior medical history will be recorded from chart and physical examination or by asking you.

Discomfort, Risk and benefits: There will be no risk and only minimal discomfort with minor pain around injected areas following blood drawing that can relieve after some time. Laboratory technologist professionals in the hospital will draw the blood sample by using aseptic techniques. There is no any direct payment or incentives for your participation in this research. However, laboratory investigation payments are going to be covered by the project fund. The result of this study could be highly benefit for the future prevention and care of pregnancy-induced hypertension women.

Confidentiality and Rights: All of the data collection process will be done by well-experienced and trained health professional. All data record about your health status will be access for this study remained confidential. All information data will be documented only with unique codes for each study participant and no name will be recorded. You have full right of accepting or denying of participating in this study without being forced by someone. You are free to cease your participation at any time due to any reasons. Your decision will not affect your right to receiving best medical care that the hospital provides. Please be free to ask us any questions at any time if you have any question with regard this study.

Contact information: If you have any questions or for further clarification you can contact us through our phone and E-mail address provided below.

Principal investigator: Bilisuma Girma, **Mobile**: 0910566384. **E-mail**: bileke2014@gmail.com

Advisor: Dr Solomon Tebeje, Mobile: 0911731148. **E-mail**: solomon.tebeje@aau.edu.et

11.2. Consent Form

A. Consent form (English version)

Dear participants,

I am a Msc Medical Biochemistry student in Addis Ababa University, carrying out a study on evaluation of serum lipid profiles, uric acid and high sensitivity C-reactive protein levels among pregnancy-induced hypertension attending at Ambo University Referral Hospital, Oromia Region, Western Ethiopia. This study is an important because an abnormal elevation of lipid profiles, uric acid and high sensitivity C-reactive protein are the possible cause of pregnancy-induced hypertension and the data information obtained from this study can be useful in screening and the early detection of at risk women in pregnancy.

I_____ hereby give my consent for providing the requested information and blood sample.

Signature of participants ----------

Date_____

B. Consent form (Afaan oromo version)

Kabajamoo maamiloota,

Ani barataan digirii lammaffaa muummee barnoota 'Medical Biochemistry' Addis Ababaa yunivarsiiti yoon ta'u qorannoo koo kanan hojjedhu haadholii ulfaa dhiibba dhiigaa qabaatani hospitaalaa rifaraalaa yunivarsiitii Ambootti yaalama jiran irratti. Kunis lippiidii piroofaayelii, yuuriki asiidii fi C ri'aktivii pirootiin dhiigaa isaanii safaruufi.

Ogeessa leenji'een ibsa gaha erga siniif laanneen booda gaaffilee muraasa isin gaafachun itt aansinemoo dhiibba dhiigaa keessaani fi ulfaatiina qaama keessaani safarra. Akkasumas pirootiin fincaa'an keessaani qoranna. Odeeffannoo isin irraa arganne foormii yaadannoof qophaa'e irratti kan galmessine keenyu ta'a. lippiidii piroofaayelii, yuuriki asiidii fi C ri'aktivii pirootiini safaruuf dhiigaa miilileetirii shan (5mL) isin irraa yoo fudhannu kaffaltii hin qabu. Odeeffannoon nuuf kennitan hunduu qaama biraaf dabarfamee hin laatamu (iccitiin ni eeggama).Hirmaannan keessan fedhii keessan irratti kan hundaa'e waan ta'eef yeroo barbaddanitti hirmaannaa keessan addaan kutunis ta'e ba'uun isin hin adabsiisu. Maaloo, qorannoo kana keessaatti hirmachuuf heyyamamoo yoo taatan deebii gaaffilee armaan gadii guutuun nu gargaara.

Qorataan	Mallattoo hirmaata	Mallattoo gaafata
Blisuma Girma	----------	----------

11.3. Questionnaires

A. Questionnaires (English version)

Evaluation of serum lipid profiles, uric acid and high sensitivity C-reactive protein levels among pregnancy-induced hypertension attending at Ambo University Referral Hospital.

Card number----------

1. Age (year)----------
2. Gravidae: primegravidae □ multigravidas □
3. Number of fetus : single □ multiple □
4. Parity : 0 □ 1-4 □ c.≥5 □
5. History of multi-partner : Yes □ No □
6. Gestational age (weeks) _____

7. Systolic blood pressure 1_____ 2_____ mean_____
8. Diastolic blood pressure 1_____2_____mean _____
9. Family history of high blood pressure : No □ Yes □ Don't know □

Thank you

Name of interviewer ----------date---------- sign----------

Name of supervisor----------date---------- sign----------

B. Questionnaires (Afan oromo version)

Haadholii ulfaa dhiibba dhiigaa qabaatani hospitaalaa rifaraalaa yunivarsiitii Ambootti yaalama jiran irraa lippiidii piroofaayelii, yuuriki asiidii fi C ri'aktivii pirootiin dhiigaa isaani qorachuuf.

Lakkoofsaa kaardi----------

1. Umuri (waggaa)----------
2. Daa'imaa meeqaa garatti baata? Tokko □ Baay'ee □
3. Yeroo meeqaf ulfooftan? Tokko qofa □ Baay'ee □
4. Ijjoollee dhalataan: 0 □ 1-4 □ c.≥5 □
5. Seenaa jalaallee baay'ee jijjiruu qabdu ? eeyyen □ lakki □
6. Turtii erga ulfoofte jiru (torbanin) _____
7. Systolic blood pressure 1_____ 2_____ avereejjii _____
8. Diastolic blood pressure 1_____2_____avereejjii _____
9. Pirootiin fincaan keessa jiru: hin jiru □ xiqqoo □ 1^{+}□ 2^{+}□ 3^{+} □ 4^{+}□
10. Maatii keessan keessaa namni dhiibbaa dhiigaa qabu jira?: lakki □ eeyyen□hin beeku□

Galatooma.

Maqaa nama gaafate ----------guyyaa---------- mallattoo----------

Maqaa to'aata----------guyyaa---------- mallattoo----------

11.4. Laboratory Result Recording Format

Name_____
Age_____
Code_____

1. Lipid profile fractions (mg/dL): Triglycerides----------

Total cholesterol----------

Low-density lipoprotein cholesterol ----------

High-density lipoprotein cholesterol ----------

Total cholesterol/HDL-cholesterol ratio----------

Triglyceride/HDL-cholesterol ratio----------

LDL-cholesterol/ HDL-cholesterol ratio----------

2. Uric acid level (mg/dL) ----------
3. High sensitivity C- reactive protein (mg/L) ----------

Name of laboratory technologist ----------date ---------- sign----------

Name of supervisor ----------date---------- sign----------

DECLARATION

I, the undersigned, declare that this thesis paper entitled "**Evaluation of serum lipid profiles, uric acid and high sensitivity C-reactive protein levels among pregnancy-induced hypertension attending at Ambo University Referral Hospital, Oromia Region, Western Ethiopia"** is my original work and all source of materials used for thesis has been duly acknowledged**.**

Principal investigator	Signature	Date
Bilisuma Girma Areda (BSc, MSc candidate)	_____	_____
Advisor	Signature	Date
Solomon Tebeje Gizaw (PhD)	_____	_____

Date of submission_____

Place: Addis Ababa, Ethiopia