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Inspiring Excellence

TITLE

"ASSOCIATION OF MATERNAL ABO BLOOD GROUP AND RANDOM BLOOD GLUCOSE LEVELS IN PATIENTS OF HYPERTENSIVE DISORDER OF PREGNANCY"

SUBMITTED BY

ANURAG VISHWAKARMA

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Master of Science in Medical Physiology

By

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ANURAG VISHWAKARMA

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Date **ANURAG VISHWAKARMA**

LIST OF ABBREVIATIONS

(-)	Negative
(+)	Positive
ABO-RH	Blood groups types A, B, O and Rhesus
BMI	Body mass index
CAD	Coronary artery disease
IGT	Impaired glucose tolerance
LADA	Latent autoimmune diabetes in adults
MARD	Mild age-related diabetes
MOD	Mild obesity-related diabetes
MODY	Maturity onset diabetes of young
SGLT-2	Sodium glucose cotransport protein – 2
SIDD	Severe insulin deficient diabetes
SIRD	Severe insulin resistant diabetes
UTI	Urinary tract infection
WHO	World Health Organization

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INTRODUCTION

CHAPTER 1

INTRODUCTION

Pre-eclampsia is a multisystem disorder of unknown aetiology, unique to pregnancy. Women with pre-eclampsia usually develop raised blood pressure and proteinuria, but the condition is also associated with abnormalities of the coagulation system, disturbed liver function, renal failure and cerebral ischaemia[1]. It complicates an estimated 2–8% of pregnancies and is a major cause of maternal morbidity, perinatal death and premature delivery, although outcome for most women is good. Eclampsia, the occurrence of one or more convulsions superimposed on the syndrome of pre-eclampsia, occurs less frequently, complicating between 1 in 100–1700 pregnancies in the developing world[2] and about 1 in 2000 pregnancies in Europe and other developed countries. Eclampsia is often a serious and life-threatening condition. Compared to pre-eclampsia it carries a much higher risk of death and serious morbidity for the woman and her baby. In the UK, for example, 1 in 50 of the women who have eclampsia die[3].

Worldwide, over half a million women die each year of pregnancy-related causes, and 99% of these deaths occur in the developing world[4]. Put another way, women in industrialized countries have an average lifetime risk (calculated as the average number of pregnancies multiplied by the risk associated with each pregnancy) of dying from pregnancy-related causes of between 1 in 4000 and 1 in 10,000, whereas women in low income countries have a risk that is between 1 in 15 and 1 in 50. In poor countries, maternal mortality is 100–200 times higher than in Europe and North America. There is no other public health statistic for which the disparity between rich and poor countries is so wide.

Although rare, eclampsia probably accounts for 50,000 maternal deaths a year[5]. In areas where maternal mortality is very high, infection and haemorrhage are the main causes of death6, but as deaths from these causes become less common, those associated with pre-eclampsia and eclampsia assume greater importance. Where overall maternal mortality is high, most deaths are associated with eclampsia5. In places where mortality is low, a greater proportion of deaths are related to pre-eclampsia. There are few reliable data on the maternal morbidity associated with pre-eclampsia and eclampsia, but it is likely that this is also substantial. In the UK, for example, pre-eclampsia accounts for an estimated one-fifth of antenatal admissions[7], two-thirds of referrals to day care assessment units8, and a quarter of obstetric admissions to intensive care units[9]. Although maternal mortality in the UK is low, pre-eclampsia/eclampsia accounts for 10–15% of direct obstet ric deaths10,[11] as it does in many

developing countries5. Reducing the morbidity and mortality associated with these conditions is an important priority.

In India, the incidence of preeclampsia is reported to be 8-10% among the pregnant women. According to a study, the prevalence of hypertensive disorders of pregnancy was 7.8% with preeclampsia in 5.4% of the study population in India.

Preeclampsia is a pregnancy specific hypertensive disease with multisystem involvement. It is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks of gestation and can present as late as 4-6 weeks postpartum (after child birth).

According to the new guidelines given by American Congress of Obstetricians and Gynaecologists (ACOG) in 2013, the diagnosis of preeclampsia does not require the detection of high levels of protein in the urine (proteinuria) along with hypertension. Evidence shows that changes in kidney and liver can occur without signs of proteinuria, and the amount of protein in the urine does not predict how severely the disease will progress.

Preeclampsia is now to be diagnosed by persistent high blood pressure that develops during pregnancy or during the postpartum period and is associated with a lot of protein in the urine or the new development of decreased blood platelets, changes in the kidney or liver function, fluid in the lungs, or signs of brain disorder such as seizures and/or visual disturbances.

HEELP syndrome and eclampsia are the serious complications of the preeclampsia. The majority of deaths related to preeclampsia can be prevented by providing timely and effective care to pregnant women presenting with such complications.

Classification of the hypertensive disorders of pregnancy

Eclampsia and pre-eclampsia are part of a spectrum of conditions associated with raised blood pressure during pregnancy, known as the hypertensive disorders of pregnancy. Attempts to classify these disorders have, in the past, been confusing and sometimes misleading. More recently their classification has been rationalized and simplified to reflect the different situations encountered in clinical practice[12]. Raised blood pressure during pregnancy is generally defined as systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg, and proteinuria as >300 mg/24 h or ≥30 mg/mmol in a single specimen. There is agreement that the terms pregnancy-induced hypertension, or gestational hypertension, refer to raised blood pressure occurring for the first time in the second half of pregnancy, but without proteinuria

(<300 mg/24 h). The term pre-eclampsia is reserved for the new occurrence of hypertension and proteinuria in the second half of pregnancy. The diagnosis of pre-eclampsia is strengthened if there is further indication of multisystem involvement, such as raised serum creatinine or liver enzymes, lowered platelets, or neurological symptoms (hyperreflexia, severe frontal headache, or visual disturbance). Eclampsia is the occurrence of convulsions superimposed on pre-eclampsia. Chronic hypertension is known hypertension before pregnancy. Pre-eclampsia superimposed on chronic hypertension is when a women with chronic hypertension develops new signs or symptoms of pre-eclampsia in the second half of pregnancy.

Women with pregnancy-induced hypertension generally have a good outcome. The risk to them and their baby increases only if they progress to pre-eclampsia, or have very high blood pressure.

Pathophysiology of pre-eclampsia

Although the exact mechanisms which lead to pre-eclampsia are not clear, several factors are known to play a part in determining who will develop this disease. Some women have predisposing factors. These include family history, age and parity. Current thinking is that the primary pathophysiology in pre-eclampsia is placental[13,14]. Pre-eclampsia occurs in women who have an abdominal pregnancy and in those with a hydatidiform mole, indicating that uterine and fetal factors are not essential. In addition, it is more common amongst women who have conditions associated with a large placenta (such as multiple pregnancies and hydrops fetalis), and in women who have microvascular disease (such as diabetes, hypertension and collagen vascular disease). In pre-eclampsia, trophoblastic implantation is abnormal, with reduced placental perfusion. As normal implantation is complete by around 20 weeks, this deficient implantation occurs weeks or months before the disease becomes clinically apparent.

The secondary pathology in pre-eclampsia appears to be endothelial cell injury. The proposed model is that reduced blood supply to the placenta results in production of unknown factors which are released into the maternal circulation and act on endothelial cells, leading to endothelial dysfunction1. This results in vasospasm, with consequent reduction in plasma volume, and activation of the coagulation cascade. These changes antedate other clinical findings1. Recently, there has been interest in oxidative stress as the possible mechanism for this endothelial dysfunction[1,15.]

In Asia and Africa, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy.

ABO blood group

The ABO and Rh-Blood Group System are genetically determined and remain the most important blood groups systems clinically[16,17]. The presence of D antigen confers Rh positive (Rh+), and the absence, Rh negative (Rh-). Furthermore pre-eclampsia is a major contributor to maternal and perinatal morbidity and mortality worldwide[18,19]. These conditions are related to a poor extravillious trophoblast invasion and inadequate remodeling of maternal spiral arteries[20].

The disease mechanisms are thought to be multifactorial involving immunological, genetic factors, and may be related to blood clotting cascade[21,22], and associated with thrombosis of the placental vasculature and thrombophilia[23].

Despite several studies have examined the association between ABO /Rh systems and preeclampsia no consensus exists in relation to the true association between pre-eclampsia and blood groups or to which specific blood group pre-eclampsia is related to, and what the magnitude of the association[24]. Dienst et al., was the first to suggest that isoimmunization to the A or B antigenwas a cause of pre-eclampsia[25]. This finding was supported by Pike and Dickins who reported asignificant excess of group O in pre-eclamptic women[26] which was not found by Clark et al.,[27]. Also, ABO blood group has been associated with several thrombotic disease states; for instance, blood group non-O increased risk for venous thrombosis[27,28] and ABO locus O^1 allele reduced risk for myocardial infarction[27]. Two systematic reviews and meta-analysis of studies analysing ABO blood group system in patients with pre-eclampsia was performed in 2008 and 2013. In the first one no significant association was found[29] however in the later review, the analyses revealed an association between AB blood group and pre-eclampsia[30], as reported in a large study in 2012[31]. Also, many authors reported these associations over the last century; eventually they were related only to one allele, or even only to Rhesus group[32,33,34]. Nevertheless, the association is not seen in all studies and there are very few large population-based studies[35,36].

Random glucose level

Gestational diabetes and hypertensive disorders are common pregnancy complications among pregnant women worldwide because it shares metabolic and cardiovascular risk factors. Pregnant women with gestational diabetes are known to have insulin resistance pre-pregnancy and during pregnancy. Typically, they were diagnosed between 24 and 28week of gestation using glucose tolerance test. Elevated of postprandial blood glucose more than 120mg/dL or fasting blood glucose more than 95mg/dL is considered poor glycemic control leading to pregnancy complications, particularly

hypertensive disorders. The purpose of this review is to examine the association of gestational diabetes and hypertensive disorders among pregnant women and its outcomes. Inclusion criteria for recruited studied paper is the study of association of gestational diabetes and hypertensive disorders among pregnant women published within 5 year, 2016-2020. Exclusion criteria are 1) The study of association of pre-gestational diabetes, type 1 and type 2 diabetes and hypertensive disorders, 2) It is not printed in English.

There are four categories of hypertensive disorders in pregnancy: 1) Gestational hypertension, 2) Preeclampsia- eclampsia, 3) Preeclampsia superimposed chronic hypertension, and 4) Chronic hypertension. It can be classified into two groups of manifestation: Before 20week of gestation and after 20week of gestation. Pregnant women are usually diagnosed of chronic hypertension before 20week of gestation. Another groups developed hypertension after 20 week of gestation. Gestational hypertension is diagnosed when pregnant women develop hypertension, blood presser of 140/90mmHg or over after 20 week of gestation and without proteinuria. It is also named as transient hypertension of pregnancy. Elevated blood pressure and present of proteinuria are considered preeclampsia without severe features or with severe features.

Pregnant women with gestational diabetes who developed preeclampsia-eclampsia are overweight or obese, usually they were diagnosed after 24-28 week of gestation because of occurring peak of insulin resistance and endothelial dysfunction. Placental hormones act against insulin action in order to preserve blood glucose for developing fetus. In addition, prior insulin resistance due to oxidative stress leads to hyperinsulinemia and beta-cell dysfunction. Prolonged hyperglycemia, insulin resistance, and dyslipidemia also affect endothelial function leading to atherosclerosis, thickening and stiffness of vascular, vasoconstriction and its related complications.

Gestational diabetes and hypertensive disorders affect pregnancy outcomes including preterm labor and birth, macrosomia, maternal death, and perinatal death. Maternal gestational diabetes and hypertensive disorders are associated with large for gestational age fetus and macrosomia. Stillbirth rates in pregnant women with hypertensive disorders is 21.9 per1,000 birth. In addition, women with a history of gestational diabetes and hypertensive disorders are at risk for development of chronic hypertension later in their lives.

Primary prevention by raising awareness of healthier dietary pattern and doing regular exercise before conception and during the first half of pregnancy would be suggested for all pregnant women. The

moderate intensity of prenatal exercise including brisk walking, water aerobics, stationary cycling, resistance training can prevent the development of gestational diabetes and hypertensive disorders among pregnant women. Early detection and management of gestational diabetes and hypertensive disorders in pregnancy would be helpful to delay development maternal and newborn complications. Lastly, modification of healthy behaviors is recommended for women with a history of gestational diabetes and hypertensive disorders in order to improve metabolic imbalance and cardiovascular pathogenesis. As a result, maternal and newborn complications will be decreased.

REVIEW OF LITERATURE

CHAPTER 2

REVIEW OF LITERATURE

The major cause of maternal, fetal morbidity and mortality is Preeclampsia. In pathogenesis of Preeclampsia, altered lipid metabolism seems important.

DEFINITION17

National High Blood Pressure Education Program (NHBPEP) 2000 & ACOG (2002) defines Gestational Hypertension as,

Systolic pressure of more than equal to 140 mmHg, Diastolic pressure of more than equal to 90mmHg after 20 weeks of gestation, measured 4 to 6 hours apart in a previously normotensive women.

Severe Hypertension in pregnancy is defined as,

a) Systolic BP greater than or equal to 160 mmHg or
b) Diastolic BP greater than or equal to 110 mmHg

This represents a cut off level of BP beyond which cerebral auto regulation stops functioning, because of which complications like cerebral hemorrhage and hypertensive encephalopathy may happen.

CLASSIFICATION OF HYPERTENSIVE DISORDERS IN PREGNANCY

NHBPEP classifies as,

1. Gestational Hypertension
2. Preeclampsia
3. Eclampsia
4. Super imposed Preeclampsia on Chronic Hypertension
5. Chronic Hypertension

1. GESTATIONAL HYPERTENSION

Systolic BP of greater than or equal to 140mmHg or Diastolic BP of greater than or equal to 90mmHg without proteinuria and other imminent symptoms &signs and BP returns to normal before 12 weeks post-partum.

2. PREECLAMPSIA

Systolic BP of greater than or equal to 140mmHg or Diastolic BP of greater than or equal to 90mmHg with proteinuria of more than 300mg in 24 hours i.e more than 1+ in dipstick test.

3. ECLAMPSIA

Generalised tonic clonic seizures with preeclampsia, which cannot be contributed by other causes.

4. SUPER IMPOSED PREECLAMPSIA ON CHRONIC HYPERTENSION

It is diagnosed by

a) In chronic hypertension patient whenever there is sudden increase in blood pressure or, proteinuria, platelet count.

a) In chronic hypertension patient whenever there new onset of proteinuria of more than 300mg/24 hours.

5. CHRONIC HYPERTENSION

Systolic BP of greater than or equal to 140mmHg or Diastolic BP of greater than or equal to 90mmHg before 20 weeks not including gestational trophoblastic disease, twin . Hypertension diagnosed after 20 weeks of gestation and persisting after 12 weeks post partum.

ASSOCIATION OF DYSLIPIDEMIA AND PREECLAMPSIA

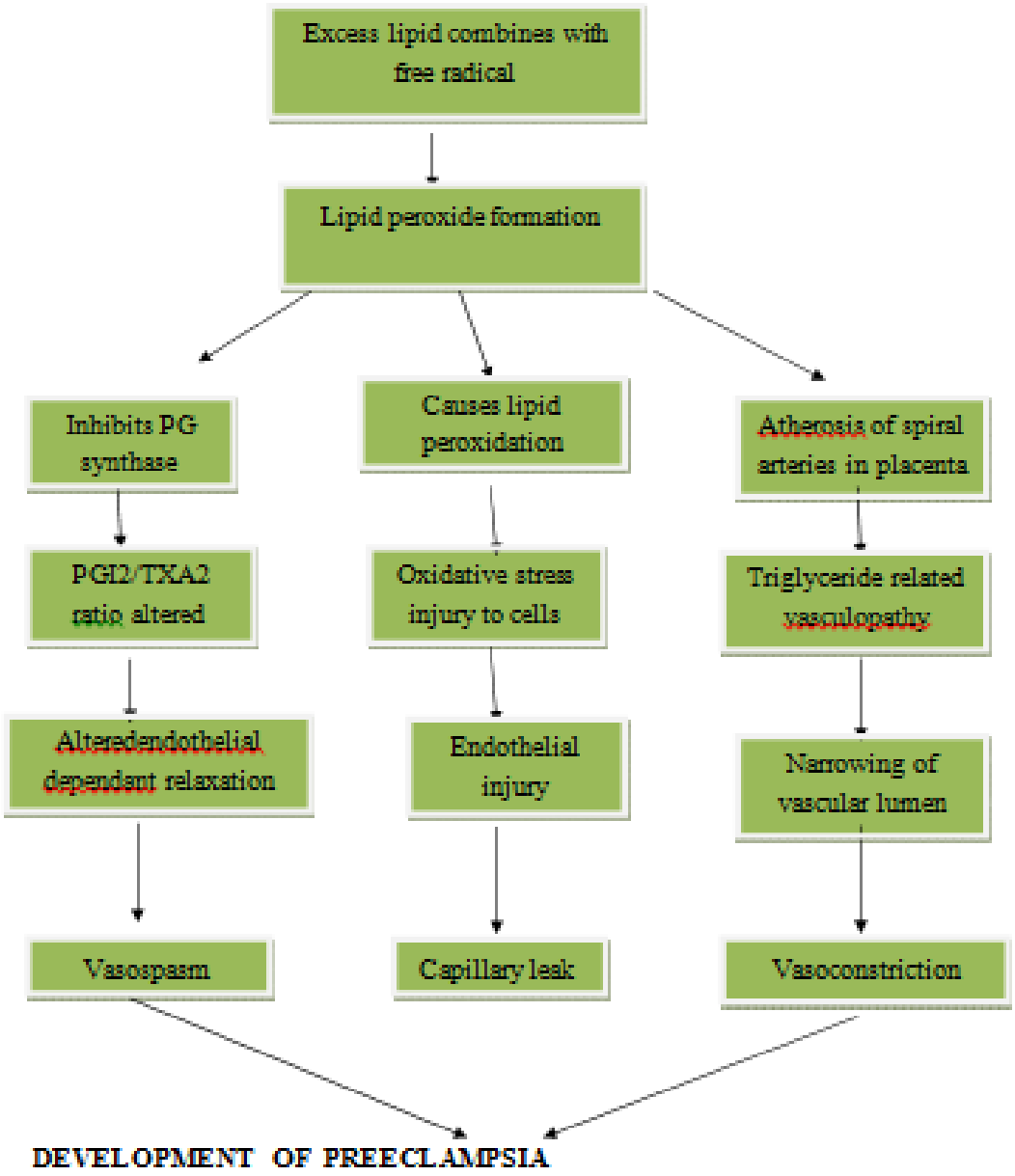

Figure-1.Role of altered lipid profile in the pathogenesis of preeclampsia

The changes in lipid profile are due to changes in hepatic and adipose tissue metabolism that alter circulating concentrations of TG, fatty acids, cholesterol and phospholipids and it is attributed to higher concentration of estrogen and state of relative insulin resistance[56], and also characterised by increased hepatic lipase activity and decreased lipoprotein lipase activity, leading to increase in circulating triglycerides. Because of reduction in adipose tissue lipoprotein lipase activity, there is reduction in clearance of triglyceride rich lipoproteins.

NORMAL PREGNANCY ASSOCIATED WITH HYPERTRIGLYCERIDEMIA

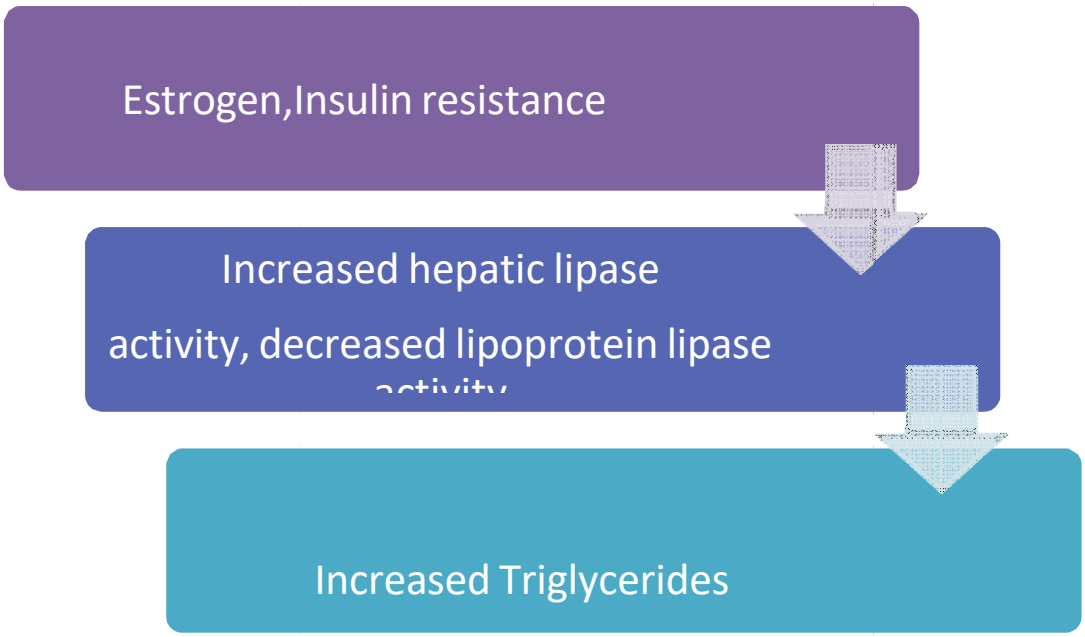

Figure-2:Cause of altered lipid profile in normal pregnancy

There was increasing evidence that in pathophysiologic mechanism of preeclampsia, lipid metabolism and circulating lipids play a major role, because lipid peroxides and oxidative imbalance act as cytotoxic and lead to endothelial injury. Compared to normal pregnant women, women with preeclampsia have elevated lipid peroxides, and also severity of preeclampsia has a correlation with lipid peroxide levels. In particular levels of antioxidant in plasma and antioxidant activity are low in preeclamptic women. Normally lipid peroxidation was under control by variety of antioxidant mechanisms. But in women with preeclampsia, the balance of oxidant-antioxidant system was impaired. In women with preeclampsia, lipid peroxide production by placental tissue also elevated that lead to elevated concentration of lipid peroxides. Lipids interacts with oxygen free radical and forms lipid peroxide, which are unstable,highly reactive and damaging compounds[61]. They are toxic to the cells, enzymes by

stimulating peroxidation reactions. In preeclampsia, the causal factor implicated is uncontrolled lipid peroxidation.

Elevated lipid peroxides act by modulating prostocyclin synthesis, alter important biochemical reactions in the cell and lead to endothelial cell dysfunction. Lipid peroxides alter the ratio between prostacyclin and thromboxane A2 by inhibiting prostacyclin synthase. In preeclampsia ,major clinical symptoms are due to this imbalance between prostacyclin and thromboxane. Lipid peroxides lead to impaired endothelial dependent relaxation by altering prostacyclin mechanism.In preeclampsia , proteinuria is explained by endothelial cells damage by lipid peroxides in kidney. Oxidative stress causes endothelial dysfunction. In cell membrane unsaturated lipids and thiol containing proteins are susceptible to free radical attack[64].There is lot of evidence supports that in preeclampsia , there is increased free radical activity and free radicals will cause lipid peroxidaion. Severity of preeclampsia has positive correlation with high levels of oxidation products. During pregnancy, the increase in lipid peroxides and increase in preeclampsia were confined to lipoprotein bound factors. Free & LDL bound lipid peroxides exhibit cytotoxicity on endothelial cells[64]. In preeclamptic women, atherogenic lipid profile is seen,which is characterised by increase in triglycerides and small dense LDL. Increase in triglycerides predispose to preeclampsia by placental vasculopathy[67].

According to study conducted by Anne Catherine, he observed that higher concentration of phospholipid , lipid peroxides and TC in placental deciduas basalis tissue derived from women with Preeclampsia. Atherosis of spiral arteries in placental layers heighten the risk of placental disease. As Preeclampsia is multicausal disease,one of the plausible etiological facto is 'TRIGLYCERIDE RELATED VASCULOPATHY".

In women with PIH, vascular changes in the placental bed is described as "acute atherosis" due to lipid laden macrophages (foam cells) in atherosclerotic plaque.

ACUTE ATHEROSIS:

In preeclampsia distinct pathological lesion of decidual arterioles are termed as acute atherosis. The arteriopathy involves the spiral and myometrial arteries region,where physiologic transformation changes were absent. Acute atherosis resembles atherosclerotic lesions of coronary arteries by showing endothelial disruption,platelet aggregation and accumulation of foam cells(lipid laden macrophages). In

preeclampsia,acute atherosis of spiral areries have two outstanding features. They are vessel wall necrosis and fatty change in intimal cells,which are analogous in systemic arterial disease.

It is essential to explain why some women in pregnancy develop preeclampsia, while others not , that is because of the existence maternal predisposing factors and abnormal lipid metabolism could be one of the factor.

Alteration in lipid promote oxidative stress in preeclampsia.In pathogenesis of preeclampsia, insulin resistance syndrome, (syndrome X-includes dyslipidemia, resistance to insulin mediated glucose uptake, obesity) have an important role.

Multiple factors converge at particular point of oxidative stress and result in endothelial dysfunction, clinical features of preeclampsia. Primary or secondary maternal dyslipidemia lead to decrease of antioxidants results in preeclampsia.

Women with preeclampsia also predisposed to develop cardiovascular manifestation and coronary heart disease in later life5.In subsequent pregnancies also, They are prone to develop metabolic and hypertensive complications. In particular, if preeclampsia diagnosed early in index pregnancy, the risk of recurrence is high.This was supported by Sibai and colleagues that nulliparous women diagnosed preeclampsia before 30 weeks have 40% recurrence risk in subsequent pregnancy. Compared to recurrence in nulliparous women developing preeclampsia, the recurrence risk is high in multiparous women developing preeclampsia. So, to prevent maternal and fetal morbidity and mortality, preeclampsia to be predicted as early as possible.

Saleh R et al noted inflammatory and atherosclerotic lesions in the placenta of preeclamptic women Presence of dyslipidemia in gestational hypertension and preeclampsia can aggravate the atherosclerotic plaque formation in uterine spiral arteries leading to narrowing of their lumen. This leads to significant reduction in the blood flow and placental ischemia thus setting up a vicious cycle of placental ischemia _ inflammation _ insulin resistance _ dyslipidemia _ atherosclerosis _ placental ischemia

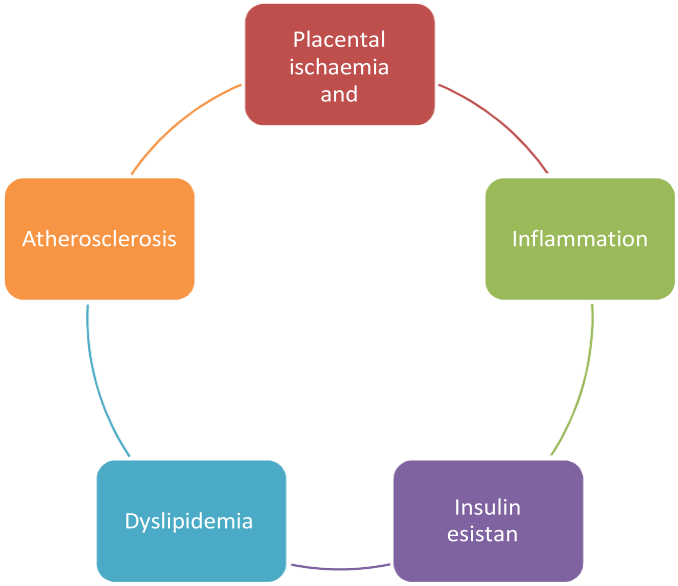

Figure-3: Dyslipidemia and preeclampsia STUDIES RELATED TO LIPID PROFILE &PREECLAMPSIA

ABO-RH Blood Groups System

The basis of blood grouping is RBCs antigens and consist of proteins and carbohydrates attached to lipids or proteins. ABO is the most studied group in the human population out of more than 100 blood group systems involving over 500 antigens. But it was more than a century ago in 1900 that Karl Landsteiner of the University of Vienna identified that RBCs contain antigens on their surfaces and that blood plasma contains antibodies targeted to particular antigens.

ABO antigens are highly expressed on human tissues and most epithelial and endothelial cells. The blood type of an individual defined by small carbohydrate epitopes depends on the presence or absence of genes A and B. The gene is located on chromosome 9q34 and consists of 7 exons spread over 18 kb called ABO blood groups.

ABO system is based upon the presence or absence of the two agglutinogens, the A and B agglutinogens on the surface of RBCs. When only type A agglutinogen is present, the blood is type A. When only type B agglutinogen is present, the blood is type B. When both A and B agglutinogens are present, the blood is type AB. When neither A nor B agglutinogen is present, the blood is type O.

Even after Karl Landsteiner's discovery in 1900, transfusion reactions were still prevalent. It took another 40 years until 1940 when Landsteiner and Weiner discovered the RH factor that transfusion medicine involved less risk.49 Currently there are more than 50 antigens in the RH blood group system

but the principal RH antigens of medical interest are D, C, E, c and e. A person with Rhesus antigen is referred to as RH (+) while individuals lacking the antigen are RH (-).

When a RH (-) person is exposed to RH (+) blood, antibodies will be produced, which causes potentially fatal hemolytic reactions. Immunogenicity of the RH factor along with A, B antigens made it mandatory for pre-transfusion testing.

Identification of any association between diseases and blood groups is an excellent source for genetic researches in human. The membranes of RBC have several hundreds of isotopes that their structure is under control of genes that are located on different chromosomes.

The Multinational Pancreatic Cancer Consortium successfully identified susceptibility loci in the ABO gene for pancreatic cancer pathogenesis.[75] Other studies have shown an association between gastric cancer and blood group A related to a higher susceptibility of Helicobacter pylori infection. Different hypothetical models such as inflammation, immune system surveillance and cell membrane signalling have been developed to explain the mechanism of cancer susceptibility among people with varying blood groups.[76] This Chinese study found out that blood type B individuals are susceptible to esophageal and biliary cancer. T2DM is also significantly associated with gastric, biliary and especially pancreatic cancer.

Blood group AB was a protective factor against gestational DM in pregnant Chinese women. In two large independent populations in USA, non-O blood group was associated with a decreased risk of skin cancer and this association was statistically significant for non-melanoma skin cancer.[78] Another study done in China found the synergism between blood group A and hepatitis B virus (HBV) in the development of pancreatic cancer. There was higher incidence of nasopharyngeal carcinoma and distant metastasis in blood types A or AB.[80] In one of the cancer hospital in Iran, the investigators found a relationship between blood group AB and Acute lymphoblastic leukemia.

In a study done in the United States, frequency of blood group O was 45%, A 41%, B 10%, and AB 4% respectivley.10 Similar study done in India showed blood group O more common with frequency of 37.12%, followed by B 32.26%, A 22.88%, and AB 7.74%. In the Rhesus type, 94.61% were RH (+) and rest were RH (-).

The study carried out in TUTH and NMCTH showed that the frequency of distribution of A, B, AB and O was 28.5%, 27.3%, 8.7% and 35.5% respectively and only 0.8 % of them were was found to be RH (-).

A descriptive cross-sectional study done in department of anatomy in collaboration with the clinical pathology laboratory and out-patient DM clinic, Isra university, Hyderabad and department of physiology, university of Sindh and outpatients of Liaquat university of medical and health sciences, Hyderabad from January 2001 to December 2001 supported the hypothesis that T2DM and blood groups are interrelated because of the broad genetic immunologic basis and concluded that frequency of blood groups B and O was significantly higher and lower respectively.

A case control study conducted at Kepala Batas hospital, Penang, Malaysia in 2009, involving 70 patients with T2DM and 140 healthy controls showed negative association between blood groups A and O and concluded that these groups have less chances of diabetes.

The risk of T2DM was found to be 35% in blood groups B and RH (+) compared with the universal donor blood group O and RH (-) in a large prospective E3N cohort study done in France between 1990 and 2008.

Okon et al. studied a total of 224 diabetics and 221 non-diabetics (control) in a case control study in Nigeria and found out blood group O (-) and A (+) had risk of DM.

Rahman et al. from Bangladesh conducted a study from diabetics (2312) for ABO blood groupings and the results was compared with normal (8936) subjects in 1976. The data were analyzed statistically to detect any possibility of an association between ABO blood groups and DM. No such association was apparent in the subjects studied.

Meo et al. did meta-analysis and found out blood group B was associated with high incidence of T2DM and blood group O had a minimum association. Blood group A and AB were almost equally distributed in both diabetic and non-diabetic population. No any relationship was evident with RH factor.

Table-1. Global comparison of ABO blood groups among diabetic population

Global comparison of distribution of ABO blood groups among diabetic population						
Country	**Total sample size**	**ABO Blood groups (%)**				**Year**
		A	**B**	**AB**	**O**	
Nigeria	224	33.03	11.60	5.35	52.67	2008
India	511	27.98	38.55	9.0	24.46	2008
Malaysia	70	15.17	35.71	14.29	34.29	2009
Algeria	280	28.28	13.92	3.92	52.85	2011
Pakistan	201	20.37	28.86	14.92	30.85	2011
Iraq	920	35.98	16.30	4.13	43.58	2012
Japan	114	33.70	26.90	6.70	32.70	2013
Qatar	1633	29	25.7	6.8	38.5	2013

Studies found that blood group O was most commonly associated with diabetes in the studies done in Pakistan, Nigeria, Algeria, Iraq and Qatar. Blood group A and O was most commonly associated with diabetics in the studies done in Japan. Blood group B is the most common blood group in Indian studies.

Table-2. Association of ABO-RH blood groups with T2DM in various studies[86]

Authors name andyear	Type of study	Blood groups	Association with diabetes
Kamil et al. 2010	Case-control study	B, A and O	Blood group B was more in T2DM patients Blood group A and O had lesschances of DM
Okan et al. 2006	Cross-sectional study	O (-) A (+) O (+)	Blood group A (+) and O (-) was more susceptible to DM Blood group O (+) was markedly lower in diabetics than controls
Karagoz et al. 2015	Retrospective	AB O	AB: higher risk of GDM O: higher risk of DM
Fagherazzi et al. 2015	Prospective cohort	O A, B	O: low risk of T2DM A or B: increased risk of T2DM
Bener et al. 2014	Case-control	BO	B more common and O less common in diabetics
Qureshi et al. 2014	Descriptive cross-sectional	BO	B more common and O less common
Joseph et al. 1964		AB, B	High frequency for B and lessfor AB
Zhang et al. 2015	Prospective population-based cohort	A, B or OAB	AB protects GDM and A, B orO risk for GDM
Qi et al. 2010	Cross-sectional	B, O	B low risk compared with O
Waseem et al. 2012	Cross-sectional	AB A, B B	AB and RH (-) more common in diabetics; A, B low risk for DM
Hadeal et al. 2008	Prospective randomized	B	B associated with DM
Moinzadeh et al. 2014	Cross-sectional	B	B (+) more common
Sindhu et al. 1988	Cross-sectional	A, AB	A, AB and RH (+) have high association

AIM AND OBJECTIVES

CHAPTER 3

AIM AND OBJECTIVES

AIM

To determine the association between maternal ABO blood group and random blood glucose levels in patients of hypertensive disorder of pregnancy in the Lucknow region.

OBJECTIVES

1. To record blood pressure of subjects.
2. To estimate the random blood glucose levels of subjects.
3. To determine the association of ABO blood group with hypertension in pregnancy

NULL HYPOTHESIS (H0)

There is no association maternal ABO blood group and random blood glucose in patients with hypertensive disorder of pregnancy.

ALTERNATIVE HYPOTHESIS (H1)

There is association of maternal ABO blood group and random blood glucose in patients with hypertensive disorder of pregnancy.

MATERIAL AND METHODS

CHAPTER 4

MATERIAL AND METHODS

TYPE OF STUDY:

Cross-sectional Study.

PLACE OF STUDY:

The study will be performed in the Department of Physiology at Integral Institute Medical Science & Research, Lucknow (U.P.).

DURATION OF STUDY:

6 months (January2022 to June 2022).

SAMPLE SIZE:

The sample size will be calculated using the formula:

$$N = \frac{Z_{\alpha/2} P(1-P)}{d^2}$$

N = 128 cases

Z1−α/2 = Critical value and a standard value for the corresponding level of confidence. (At 95% CI or 5% level of significance (type-I error) it is 1.96)

p = Prevalence 52.5% (Semin Hematol 2004) d = Margin of error or precision 5%

Non -response = 10% (Daniel WW; 1999)

The study will include 183 cases diagnosed with diabetes and hypertension of pregnancy.

INCLUSION CRITERIA:

1. Pregnant females between 15-45 years of age
2. BP should be more than or equal to140 mm Hg systolic and diastolic more than or equal to 90 mm Hg on 2 occasions more than 6 hours apart.

3. Only those pregnant females who give a signed the informed consent form.

EXCLUSION CRITERIA:

1. Pregnant women having chronic disease in the prepregnancy state (chronic hypertension)
2. All pregnant women having any other medical, surgical complication or having history of any drug use, multi-fetal pregnancy and smoking.
3. All pregnant females who do not give consent.

COLLECTION OF DATA

1. Data of pregnant females attending the antenatal clinic of IIMS&R will be taken after obtaining an informed consent form.
2. 3 ml blood will be taken in an EDTA vial using all aseptic precaution for estimation of blood group and random blood glucose levels.
3. Blood group will be analysed using the agglutination methods.
4. 1.5ml of blood was collected using all asceptic precaution in the fluoride vials of estimation of gluscose by using Erba Chem-5 plus.
5. Arterial blood pressure by a digital sphygmomanometer will be estimated in Department of Physiology of IIMS&R, Lucknow.

STATISCAL ANALYSIS:

The results will be presented in mean ±SD. The Pearson's coefficient will be used to assess the correlation among the different study parameters. The p-value < 0.05 will be considered significant. All the analysis will be carried out by using Statistical Package for Social Sciences (SPSS) version 22.

SIGNIFICANCE OF THE STUDY

The significance of this study will be to assess the association of maternal blood group and hypertensive disorder of pregnancy to correlate and address these issues with overall health status of people. It has been found that DM has a link to ABO blood groups, and that those with Group-B have a higher risk of developing diabetes. These findings, on the other hand, aren't important enough to draw a firm judgment. This could be the case have any other genetic characteristics that may need to be investigated further. The present study will be beneficial in determining a possible association between diabetes and hypertension of pregnancy in the general population.

RESULTS

AND

OBSERVATION

CHAPTER 4

RESULTS AND OBSERVATION

A total of 183 participants were included in the final analysis, out of which 100 were Normal controls and the remaining 83 were pregnant ladies with gestational hypertension (PIH) cases. Among 83 PIH cases majority were having pre- eclampsia (38.25%). 9 cases have severe eclampsia (4.91%), only 1 case (0.005%) with eclampsia and 3 cases were with chronic hypertension (0.016%) as per Table – 1.

Majority of the Gestational hypertension cases were distributed between 21 years to 25 years and 26 to 30 years (37.30% and 45.80%). Only one case is reported above 35 years (1.20%). The association of age and gestational hypertension was statistically not significant (P=0.361). Majority of the PIH cases have Gravida 1 (48.20%) and Para 0 (61.40%).But the association was not statistically significant (P =0.348 and 0.205).In most of the pregnant women pregnancy was continued, abortions were less than 20% both in Cases and controls but the association was not statistically significant (P = 0.339) as per Table – 2.

Majority of the study participants i.e. nearly 40.4% have O group, 33.3% pregnant women were from B group, 20.2% were belongs to A group only 6.0% were having ABO blood group. Nearly 95.1% study population were RH positive (Table - 3).

Almost equal distribution of cases and controls in B group (33.70%: 33.00%). Slightly higher percentage of controls (21% and 42%) were belongs A and O blood groups than the Gestational hypertensive cases (19.30% and 38.6%) respectively. But the cases from ABO blood group are double than the controls (8.4%: 4%). Most of the cases were RH positive group (97.6%) but in controls slightly lower (93%) than cases. But the association of blood groups gestational hypertension was not statistically significant (P = 0.15) as per Table – 5.

Few existing studies have evidenced that gestational hypertensive disorders are related with Mothers blood group. As per available literature pregnant women with non AB blood groups have high risk of gestational hypertensive dis orders, but its etiology is uncertain [9, 10, 12, 17, 18, 20-22]. Our study has

focused on effect of pregnant women blood group on gestational hypertensive disorders and its association with RhD group.

Current study findings reveal that among 183 study participants 100 are normal controls and 83 pregnant ladies are of gestational hypertension. 38.25% cases are with pre-eclampsia, 4.91% were severed eclampsia cases, 0.005% were eclampsia cases and 0.016% are with chronic hypertension. Similar findings were reported by Hutcheon, et al. [6] and Lee, et al. In the study of

Hutcheon, et al. [6], 3% of cases were pre- eclampsia and remaining all other hypertensive disorders were observed in10% of cases. In the study of Lee, et al. [18] out of total study participants (n = 641926) 6.1% of people were with gestational hypertensive disorders. Among the gestational hypertensive disorders 4.6% were with pre-eclampsia and 1.3% were with severe pre-eclampsia.

Table - 3: Description of study population (N=183).

Parameter	Frequency	Percentage
Normal	100	54.6
Gestational hypertension	83	45.40
Pre eclampsia	70	38.25
Severe pre eclampsia	9	4.91
Eclampsia	1	0.0054
Chronic hypertension	3	0.016

Table -4: Comparison of demographic and obstetric parameters between the study groups.

Parameter	Normal (N=100)	PIH (N=83)	P value
I. Age groups (Years)			
20 and < 20	6 (6.00%)	4 (4.80%)	0.361
21 to 25	47 (47.00%)	31 (37.30%)	
26 to 30	31 (31.00%)	38 (45.80%)	
31 to 35	15 (15.00%)	9 (10.80%)	
> 35	1 (1.00%)	1 (1.20%)	
II. Gravida rev			
1	44 (44.00%)	40 (48.20%)	0.348
2	41 (41.00%)	26 (31.30%)	
3	15 (15.00%)	17 (20.50%)	
III. Para			
0	53 (53.00%)	51 (61.40%)	0.205
1	44 (44.00%)	29 (34.90%)	
2	1 (1.00%)	3 (3.60%)	
3	2 (2.00%)	0 (0.00%)	
IV. Abortions			
0	84 (84.00%)	67 (80.70%)	0.339
1	13 (13.00%)	13 (15.70%)	
2	1 (1.00%)	3 (3.60%)	
3	2 (2.00%)	0 (0.00%)	

In the current study, 83.1% of the gestational hypertension cases were distributed between the age of 21 to 30 years only one case present above 35 years. Association of maternal age and PIH was not statistically significant (P = 0.361). Association of gravida, para of mother with PIH also not statistically significant (P=0.348 and 0.205). Abortions of PIH cases also only 20%.and the association was not statistically significant (P=0.339). Similar observations were found in the studies of Spinnilo, et al. [23] and Hiltunen, et al. [17]. In the study of Spinnilo, et al. maternal age was 27.7±5.2 and only one primi gravid pregnancy was reported.

In the current study, nearly 40.4% of the study participants are belongs to O group, B and A group pregnant women are 33.3%, 20.2% respectively whereas 6.0% were having ABO blood group. Nearly 95.1% study population were RH positive. In B blood group both cases and controls are nearly in same distribution (33.70%:33.00%). But the gestational hypertension cases are slightly lower than controls (21% and 42%) in A and O blood groups (19.30% and 38.6%) respectively. But the cases from ABO blood group are double than the controls (8.4%: 4%). Most of the PIH cases were RH positive group (97.6%) but in controls slightly lower (93%). The association of blood groups both ABO and RHD with gestational hypertension was not statistically significant (P=0.639 and P=0.153).

Table - 5: Descriptive analysis of type of gestational hypertension and ABO and RH blood group in study population

Parameter	Frequency	Percent
ABO		
A	37	20.2
AB	11	6.0
B	61	33.3
O	74	40.4
RH		
RH Positive	174	95.1
RH negative	9	4.9

Table -6: Association between gestational hypertension and ABO/ Rh blood group.

Parameter	Normal	PIH	P value
I.ABO			
A	21 (21.00%)	16 (19.30%)	0.639
AB	4 (4.00%)	7 (8.40%)	
B	33 (33.00%)	28 (33.70%)	
O	42 (42.00%)	32 (38.60%)	
II.RH			
RH Positive	93 (93.00%)	81 (97.60%)	0.153
RH Negative	7 (7.00%)	2 (2.40%)	

Our Study findings are comparable with the findings of Lee, et al. [24] and Hiltunen, et al. [17]. Lee, et al. [24] in their study concluded that non-O blood groups have high risk of pre eclamsia than O group, odds ratio are significantly higher. AB blood group has high sensitivity for PE and severe pre-eclampsia (OR=1.10, 95% CI 1.04-1.16) and (OR = 1.18, 95% CI 1.07–1.30).When compared to Rhd negative pageants RhD positive were have high risk of PE (OR = 1.07, 95%CI 1.03–1.10).

In the study of Hiltunen, et al. [17] 41.9% were from A blood group,16.1% pregnant from B group,12.9% from AB blood group and from O group 29.1% were involved.87.1% PIH cases were RhD positive. AB blood group had significantly high risk of PE than other blood groups. The association of PE with AB blood group was having adjusted OR: 2.03; and 95% CI = 1.49 to3.9.

Table - 7: Association between gestational hypertension and Random Blood Glucose Level.

Parameter	Normal	PIH	P value
RBG levels			
≤ 100	24 (24.00%)	30 (36.14%)	0.488 0.011
101-140	46 (46.00%)	13 (15.6%)	
> 140	30 (30.00%)	40 (48.19%)	

In the current study, nearly 24% of the study participants are belongs to ≤ 100 RBG, 101-140, > 140 are 46%, 30% respectively. Majority of the patients with normal hypertension had RBG levels > 140 mg/dl (30.00%) and 101-140 mg/dl (46.0%) only a small proportion had RBG ≤ 100 mg/ dl (30%) (table 7). Admission RBG levels > 140 mg/dl showed a significant association with increased risk of hypertension.

DISSCUSSION

DISSCUSSION

In the current study, 83.1% of the gestational hypertension cases were distributed between the age of 21 to 30 years only one case present above 35 years. Association of maternal age and PIH was not statistically significant (P = 0.361). Association of gravida, para of mother with PIH also not statistically significant (P=0.348 and 0.205). Abortions of PIH cases also only 20%.and the association was not statistically significant (P=0.339). Similar observations were found in the studies of Spinnilo, et al.

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CONCLUSION

Conclusion

The study shows an association between ABO blood group and the occurrence of DM, with B blood group women having the highest risk. Admission RBG levels > 140 mg/dl showed a significant association with increased risk of hypertension.

The results of our study showed that admission RBG levels > 140 mg/dl were independently associated with an increased risk of hypertension in pregnant women, which is in accordance with previous findings. In agreement with previous reports, hypertension and DM were also associated with an increased risk of Pregnancy induced hypertension.

Thus, special attention should be given to pregnant women carrying the B, AB and O blood group in order to prevent the development of PIH. The results of this study suggest there is an association between types of ABO groups and RH with hypertensive disorders during pregnancy.

High blood pressure can be dangerous for pregnant women and their un has borne babies. Unhealthy lifestyle choices may lead to high blood pressure during pregnancy. Being overweight or obese, or not staying active, are major risk factors for high blood pressure.

Women experiencing their first pregnancy are more likely to have high blood pressure. Fortunately, there's a lower chance of this condition in subsequent pregnancies with the same partner. Women carrying multiples are more likely to develop hypertension, as their body is under additional stress. Maternal age is also a factor, with pregnant women over the age of 40 being more at risk. According to the American Society for Reproductive Medicine, using assistive technologies (such as IVF) during the conception process can increase the chances of high blood pressure in a pregnant woman. Women who had high blood pressure before pregnancy are at higher risk for related complications during pregnancy than those with normal blood pressure.

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ANNEXURE

APPENDICES

CONSENT FORM

I……age…… D/o……Address……

……. agree to participate in the research work

Topic "ASSOCIATION OF MATERNAL ABO BLOOD GROUP AND RANDOM BLOOD GLUCOSE LEVELS IN PATIENTS IN HYPERTENSIVE DISORDER OF PREGNANCY IN LUCKNOW"

I have known the details of the research work very well and I give my consent for the same.

Date:

Signature/thumb impression of the patients: Name of research scholar

Signature/thumb impression of the witness: Signature of research scholar:

INFORMATION SHEET (FOR CASES)

I, Anurag vishwakarma of Medical Physiology is a research scholar in

IIMS&R.I am associated with your treating doctor panel.

You are a newly diagnosed case of hypertension of pregnancy

For this study, I will take few drops of your blood sample for the estimation of blood group andrandom blood glucose levels

The blood will be used for estimation of blood group and random blood glucose levels and not forany other purpose.

I will also measure your blood pressure with

Sphygmomanometer.You will be neither charged for any of

the above test nor be paid.

Your identity will be kept confidential and information and result of your blood test will not berevealed to any other except you if you, so desire.

The result of this test may or may not be helpful for your treatment but may improve the knowledgeand understanding of disease and the knowledge may be helpful in future.

After having the all above information would you like to participate in our study? YES NO

SIGNATURE / THUMB

IMPRESSIONDATE:

सूचना पत्र

1. मै अनुराग विश्वकर्मा आईआईएमएसआर लखनऊ में शोध विद्यार्थी हू।
2. इस परीक्षण के लिए ना ही शुल्क लिया अथवा दिया जायेगा
3. इस दौरान आपके द्वारा दी सारी जानकारी परीक्षण गोपनीय रखा जायेगा।
4. आप अगर चाहेंगे तो उसका परिणाम आपको बताया जायेगा।
5. आप इस अध्ययन में अपनी स्वेच्छा से शामिल अथवा इंकार कर सकते हैं।
6. इससे आपके इलाज पर कोई दुष्प्रभाव नही पडेगा।
7. इस समस्त तत्व को समझते हुए क्या अध्यन में योगदान देने की सहमति प्रदान करते है हां/नहीं।

स्वीकृति/सहमति पत्र

मै..... उम्र ..... वर्ष पुत्र/पुत्री/पत्नी.....
..... निवासी.....
.....

मुझे अध्ययन शीर्षक "गर्भावस्था के उच्च रक्तचाप से ग्रस्त विकार के रोगियो मे मातृ रक्त समूह का संघ और यादृच्छिक रक्त शर्करा का स्तर।"

अतः मै सूचित करता/करती हूँ एवं लिखित सहमति देता/देता हूँ कि मेरे रक्त/पेशाब का नमूना केवल ऊपर कहे गये अध्ययन के लिए एकत्रित किया जाए।

रोगी के हस्ताक्षर/अंगूठे के निशान

शोध छात्र के हस्ताक्षर

गवाह के हस्ताक्षर/अंगूठे के निशान

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INTEGRAL UNIVESITY, LUCKNOW

II CASE REPORT PERFORMA

Registration No/Date: OPD IPDName (in capital):

Father Name/Husband's Name:

Mother Name:

Date of Birth:

Age:

Sex: Male Female

Marital status:

Permanent Address:

Current Address:

Mobile no.

Category: GEN OBC SC STNationality

Mather Tongue:

Social/Economical Status: Annual income (approx.):

Educational level: Uneducated / Metric /Graduate /

Postgraduate / Ph.D.Vegetarian / Non-Vegetarian:

Physical Activity: Sedentary / Moderate / Active

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INTEGRAL UNIVESITY, LUCKNOW

III DEMOGRAPHICS

1. **Age:** **years**
2. **Sex:** **Male** **Female**
3. **Religion:**
4. **Height:** **cm**
5. **Weight:** **Kg**
6. **Body Mass Index (BMI):** **kg/m^2**
7. **Waist Hip Ratio:**

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I.INCLUSION AND EXCLUSION

CRITERIAINCLUSION CRIETRIA

1. Subject with hypertension of pregnancy ☐☐

2. Age group between 15-45 years. ☐☐

EXCLUSION CRITERIA

1. Healthy subjects. ☐☐

2. Any serious medical condition other than hypertension of pregnancy.

☐☐☐ 3.Drug addicts and alcoholic subjects. ☐☐

Subject is eligible for the study, if all**INCLUSION**criteria are**YES** and all **EXCLUSION**

criteria are**NO**

INVESTIGATOR'STATEMENT

I have verified the data entered in the case report form and have determined that it is complete,accurate and compatible with the source documents.

Investigator's name

Investigator's signature
Date

II. WORKING PROFORMA

1. Registration No.: **Date** **OPD** ☐ **IPD** ☐

2. Contact No:

3. Name: ☐☐☐ **Age** **Sex**: a) Male b) Female

4. Father 's Name:

5. Place of Residence: a) Urban b) Rural

6. Address:

7. Marital status: a) Unmarried b) Married c) Divorced d) Widow

8. Education:

9. Occupation:

10. Diet: a) Vegetarian b) Non-Vegetarian

11. Height:

12. Weight:

III. Family history

1. Mother **2. Father**

a) Mother suffers from Thyroid Disorders:

Yes, No Unknown

b) Father suffers from Thyroid Disorders.

Yes, No Unknown

3. No. of siblings:

How many of them suffering from Hypertension?

IV. MEDICAL HISTORY

1. Duration of Hypertension:

Yes **No**

2. Hypertension complications:

3. Smoker/tobacco consumer:

4. Alcohol consumer:

5. Treatment:

If yes, specify:

- Duration of treatment:

3. Patient complications; - **Low** **Fair** **High**