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PREDICTORS OF POTENTIALLY HIGH RISK FOR PREECLAMPSIA AMONG PREGNANT WOMEN ATTENDING ANTENATAL CLINICS AT SELECTED HOSPITALS IN ACCRA

BY

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DECLARATION

I, Heckel Amoabeng Abban, author of this thesis, do hereby declare that the entire content of this work was produced by me with the exception of cited references under the able supervision of Prof. Matilda Steiner – Asiedu, Dr Seth Adu –Afarwuah, Dr. Frederick Vuvor all of the Department of Nutrition and Food Science, University of Ghana, Legon - Accra and Dr. Timothy Senuyeme of University of Ghana Hospital, Legon – Accra.

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ABSTRACT

Introduction: Preeclampsia/Toxemia (PE) is a genuine hypertension condition related with maternal and infant ill health and death during pregnancy. Preeclamptics as well as their babies/children develop health conditions including cardiovascular disease as well as growth conditions well along in life. In Ghana, prevalence of PE has been known to be as low as 2.5% in Ghana Police hospital and as high as 48.8% in Komfo Anokye Teaching Hospital. Most of the studies carried out on PE has been case control and hence do not have enough data on the possible exposures at the early stages of pregnancy which may have led to the developing of PE. Also only a few studies has been carried out on the predictors associated with preeclampsia.

Objective: This current prospective cohort study sought to determine the factors at the various stages of pregnancy; ≤ 20 weeks gestation through 28 – 32 weeks and during 6 weeks postpartum which may predispose the pregnant women to a potentially high risk for PE.

Methodology: This was prospective cohort study involving 403 pregnant women who were recruited at ≤ 20 weeks gestation. Nonetheless, 21 participants dropped out between weeks 28 and 32, and 24 participants also dropped out at 6 weeks postpartum leaving 358 participants in the study. The study took place at the Ghana Police Hospital, Cantonment, and the University of Ghana Hospital, Legon, both in Accra. The entire study lasted for 21 months (May, 2018 – Feb.2020). Structured questionnaires that had been pre-tested were used to obtain information on the participants' backgrounds, lifestyle practices, gynecological factors, dietary factors, stress status, BMI, biochemical data (haemoglobin, proteinuria), clinical data (blood pressure), family history of chronic conditions, morbidities among other factors. The criteria used for potentially high risk for preeclampsia was having at least a systolic

blood pressure of ≥130 mmHg or diastolic blood pressure of ≥80 mmHg or oedema or proteiunuria. Background categorical variables were computed as frequencies and percentages, whereas continuous variables were enumerated as median (interquartile range; Q1, Q3) or means ± SD, as appropriate. The predictors of possibly high risk for PE were investigated using binary logistic regression and finally path analysis was run to determine the path way through which the predictors operate.

Results: The age on average of expectant mothers is 31 ± 5 years, a greater number 194 (48%) of expectant mothers had attained tertiary education, median gestational age at first time ante natal booking was 14 (12, 17) weeks, Akan ethnicity was dominating 166 (41.0%) and 347 (86.0%) of the women were married. Prevalence of serum vitamin D and calcium deficiencies were 48.3% and 53.2% respectively with 34.0% being at a potentially high risk for PE. Predictors of potentially high risk for PE were the following; estimated pre – pregnancy body mass index (≥ 30 kg/m^2) AOR = 3.6 (95% CI = 1.01 – 11.750) p value 0.040 and estimated pre- pregnancy weight (> 71 kg) AOR = 3.4 (95% CI = 1.250 - 12.703) p 0.019. From path analysis, path relationship for anthropometric indices (estimated pre – pregnancy BMI and estimated pre- pregnancy weight) and potentially high risk for preeclampsia shows a favorable and significant direct association (β = 0.519; t-value = 8.545; p-value = 0.001).

Conclusion: Predictors of potentially high risk for PE among the participants were estimated pre-pregnancy BMI and estimated pre-pregnancy weight (weight measured at the first antenatal clinic). In contrast to findings of most studies, serum vitamin D and calcium deficiencies had no association with PE.

DEDICATION

I dedicate this work to my entire family who believed in me and supported me to undertake this academic pursuit.

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LIST OF ABBREVIATIONS

anti-AT1-AA	Anti- angiotensin II type 1 receptor autoantibody
AT1	Angiotensin II type 1
AT1-AA	Angiotensin II receptor 1 Autoantibodies
CBS	Cystathionine β-synthase
CHP	Chronic Hypertension in Pregnancy
CO	Carbon Monoxide
COPP	Cobalt Protoporphyrin
CSE or Cth	Cystathionine-γ-lyase
DIC -	Disseminated Intravascular Coagulation
ET-1	Endothelin-1
ET-1163	Endothelin – 1163
G. S.S.	Ghana Statistical Service
G.H.S.	Ghana Health Service
GSH-Px	Glutathione Peroxidase
H_2S	Hydrogen Sulphide
HDP	Hypertensive Disoders in Pregnancy
HELLP	Hemolysis, Elevated Liver Enzymes and Low Platelets
HIF	Hypoxia-inducible factors
HLA-C	Human Leukocyte Antigen-C
Hmox1 or HO-1	Haem oxygenase 1
HO	Heme oxygenase
IL-10	Interleukin -10
KATH	Komfo Anokye Teaching Hospital
KBTH	Korle Bu Teaching Hospital
KIR	Killer cell Ig-like Receptors
MBRN	Medical Birth Registry of Norway
MDC	NSW Midwives Data Collection
MHCs	self-Major Histocompatibility Complexes

NSW	New South Wales
PE	Preeclampsia
PIGF	placental growth factor
PIH	pregnancy-induced hypertension
RAAS	Renin–angiotensin–aldosterone system
ROS	Reactive Oxygen Species
sFlt 1	soluble fms-like tyrosinekinase
SLE	systemic lupus erythematosus
SOD	Superoxide dismutase
TAS	Total Antioxidant Status
Th 2	T helper type 2 phenotype
uNK	uterine Natural Killer
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background Information

Preeclampsia (PE) is a pregnancy–induced hypertensive disorder characterised by blood pressure of more than 140/90 mmHg, significant proteinuria with or without oedema or signs of damage of an essential organ such as the kidney (Lorquet *et al.*, 2010; Mayo Foundation for Medical Education and Research, 1998 - 2017; Rudra *et al.*, 2011). Mostly, the symptoms of the condition become evident after gestational age of 20 weeks among women who used to have regular blood pressure readings (Abalos *et al.*, 2013; James *et al.*, 2010; Jeyabalan, 2013).

Hypertensive pregnancy has been recognised as a complication of pregnancy for ages but its aetiology remains unclear to date. There are two stages to the pathophysiologic processes that underpin this illness; reduced placental perfusion, presumably related to aberrant placenta placement with decreased invasion of the trophoblast and deficient modification of the spiral arteries of the uterus was the initial phase whilst the final phase is linked to maternal disease symptoms, with inflammatory, metabolic, and thrombotic responses convergent to alter vascular function, potentially leading to multi-organ damage (Roberts and Gammill, 2005; Steegers *et al.*, 2010). Also Tomimatsu and colleagues decribed this two-stage process with the claim that " predisposing immunological, genetic and preexisting maternal risk factors may affect abnormal cytotrophoblast invasion of spiral arteries (abnormal placentation) (first stage) and the second stage involving a reduction of the uteroplacental perfusion which induces placental release of antiangiogenic factors (soluble fms-like

tyrosinekinase 1 (sFlt 1) into the maternal circulation, which antagonizes proangioangenic factors leading to endothelial dysfunction. Preexisting maternal health conditions such as chronic hypertension, systemic lupus erythematosus (SLE) and obesity also contribute to endothelial dysfunction" (Tomimatsu *et al.*, 2019) (Fig 1.1).

Hippocrates (O'Dowd and Philipp, 1994) recorded the frequency of seizures in expectant mothers as right on time as the fourth century B.C., subsequently the term eclampsia, which is gotten from the Greek word eclampsia, which in a real sense signifies "streak forward," inferring an unexpected turn of events. Toxemia was consequently authored after it was found that hypertension and albuminuria flagged the improvement of seizures in these expectant mothers. The term pregnancy-actuated hypertension (PIH) is most generally utilized at present, since not all preeclamptics go along these lines foster eclampsia (Lewis and Chamberlain, 1990).

Research has shown that 10 million women develop PE worldwide yearly, of which 76,000 die as a result of it and other hypertensive related disorders, with 500,000 babies dying in a year (Kuklina *et al.*, 2009). Preeclampsia is found in 1.8 % to 16.7 % of pregnant women in underdeveloped nations (Ige and Osungbade, 2011). In 2007, the WHO estimated that 10 – 25% maternal deaths were caused by PE (WHO, 2007). Furthermore, a study by (Nour, 2008) indicated that PE alone has nearly 12% of direct influence on maternal death. PE is estimated to affect 3.4 % of the American populace (Ananth *et al.*, 2013).

In comparison to their counterparts in the developed world, women in poor countries are seven times more likely to suffer preeclampsia (WHO, 2007). Preeclampsia has been known to be the number one cause of maternal deaths in Latin America (Preeclampsia Foundation, 2010) with a prevalence of 8.9% recorded in Brazil in a descriptive and retrospective analysis of data acquired from medical histories of pregnant women who were with and without preeclampsia admitted at the Guilherme Álvaro Reference Hospital Santos/SP – Brazil (Bergamo *et al*., 2015). In Asia, a research on singleton births in Australia, showed the prevalence of PE was 3.3 %, according to data taken from the New South Wales (NSW) Department of Health that collects mother and newborn data for all births weighing more than 400 grams or occurring after 20 weeks of pregnancy, accounting for more than one-third of all births in Australia) (Thornton *et al.*, 2013), 12% among non pre-gestational diabetic patients and 18.2 % among pre-gestational diabetic patients in Bangladesh in a cross-sectional research in which participants were sourced from selected hospitals in Dhaka city (Jahan *et al.*, 2015) and 4.7% was found in a review of medical files of 7013 singleton women who were pregnant and gave birth in the hospital between 2008 and 2009 in Bangkok, Thailand (Pitakkarnku *et al*., 2011).

In Ghana, prevalence of PE has been found to be 7.0% in a longitudinal study involving 11784 nulliparous pregnant women at the Out Patient Department who were followed up from 14 – 16 gestational weeks till delivery at the Korle Bu Teaching hospital (Obed and Aniteye, 2006), 6.6% in a retrospective observational hospital-based study among referral and Out Patient Department pregnant women in Komfo Anokye Teaching hospital (Owiredu *et al.*, 2010), 2.5% in an unmatched case control study in the Police hospital among referral and Out Patient Department

pregnant women who delivered at the facility (Otu-Nyarko *et al.*, 2015), 7.9% in Korle Bu Teaching hospital (Adu-Bonsaffoh *et al.*, 2017a) and 3 in 10 in a study with mismatched participants involving all referrals and regular ante natal clients deliveries at the Regional hospital in Accra (Aseidu *et al.*, 2019).

Though the aetiology of PE is unknown, major risk factors include history of PE (personal or family), obesity, chronic hypertension, first pregnancy, multiple pregnancies, new paternity, age, interval between pregnancies, history of certain health conditions and in vitro fertilization (Mayo Foundation for Medical Education and Research, 1998 – 2017). Turpin et al. (2008) found preeclamptics to have a higher prevalence for obesity, hypertension and high fasting blood glucose. Reports from (Wei *et al.*, 2013; Zhao *et al.*, 2017) studies specified that maternal 25-hydroxyvitamin D insufficiency between 23 and 28 weeks of pregnancy is linked to an elevated tendency for severe PE development. Shand et al. 2010 also discovered 25 hydroxyvitamin D deficiency to be frequent among preeclamptics.

In America, total dietary fibre consumption was linked to lower pregnancy-related dyslipidaemia, a culprit for PE (Qiu *et al.*, 2008). Pre-pregnancy maternal BMI ($\geq$ 25 kgm-^{2}) a known modifiable risk factor for PE, has been recognized to increase one's risk for PE development by approximately three fold (Eiland *et al.*, 2011). Low serum calcium levels as well as their dysregulation, have a role in the development of PE (Rashid *et al.*, 2015).

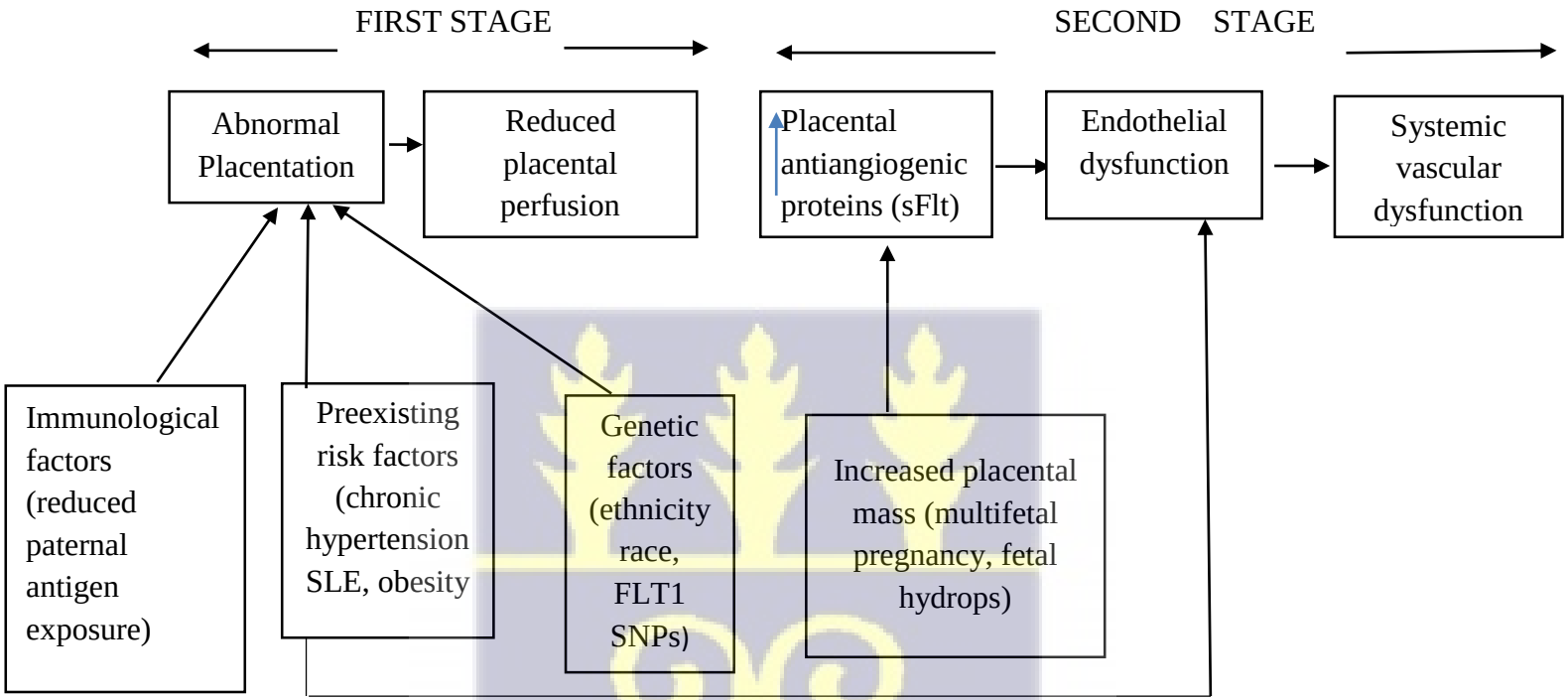

Figure 1.1: The Two Stage Pathophysiological Process Underlying PE

1.2 Research Problem

Preeclampsia is one of the main culprits of pregnancy-related deaths globally (Cousens *et al.*, 2011). The major risk factors have been known to be medical, maternal, socioeconomic, parity, family history among others (Mayo Foundation, 1978 – 2017). In Ghana, medically, abnormal functioning of the endothelial contribute greatly to PE development as indicated by decreased serum vascular endothelial growth factor levels (Adu-Bonsaffoh *et al.*, 2017b) and systolic blood pressure of 130 mmHg at initial booking has been linked with PE (Otu-Nyarko *et al.*, 2015). Maternally, parity of one (Otu-Nyarko *et al.*, 2015) and high percentage body fat (Yeboah *et al.*, 2017) increase ones risk of developing PE. In addition lower levels of serum calcium and magnesium, abnormal lipid levels (Ephraim *et al.*, 2014a), serum nitric oxide upregulation as evidenced by elevated serum nitric oxide metabolite (Adu-Bonsaffoh *et al.*, 2015) had been reported to be associated with PE. However in the western world, total dietary fibre intake was found to be associated with reduced pregnancy-related dyslipidaemia as a cause for preeclampsia (Qiu *et al.*, 2008) and calcium deficiency as well as their deregulation influence the onset of PE (Rashid *et al.*, 2015), further more, WHO recommmends daily supplementation of calcium for pregnant women living in areas of low calcium intake (WHO, 2011).

In Ghana, however, the few studies having been carried out indicated that even though pregnancy-related hypertensive disorders of which PE is one significant reason for maternal deaths particularly in our tertiary medical clinics; 31.7% of maternal deaths recorded in a retrospective descriptive study carried out at KorleBu Teaching hospital was attributed to pregnancy-related hypertensive disorders with eclampsia contrbuting 23.8% (Adu-Bonsaffoh *et al.*, 2013), 3 out of 10 maternal deaths recorded

were due to PE (Adu - Bonsaffoh *et al.*, 2014), hypertensive disorders of which PE is one was found to be the second utmost culprit of mortality in a retrospective study in which 280 maternal deaths were recorded at Tamale Teaching hospital (Gumanga *et al.*, 2011) findings from a retrospective review study in Komfo Anokye Teaching hospital by Lee et al. (2012) indicated that hypertensive disorders are the number one culprit of maternal mortality (26.4%).

Nutritionally, Agyare et al. (2018) in a longitudinal study among pregnant women found initiation of iron and folic acid after completing first trimester compare with the first trimester to be significantly associated with more than three fold increase risk of developing oedema as a risk factor for PE. Darkwa et al. (2017a), in a situational control study found among expectant mothers in their first trimester an adequately low amount of sodium and potassium levels in the blood among women who foster toxemia contrast with expectant mothers with normal blood pressure. In a comparative cross sectional study among pregnant women who were > 30 weeks gestational age, an insignificant contrast in serum magnesium and overall calcium among preeclamptic and ordinary expectant mothers was found (Darkwa *et al.*, 2017b); Ephraim et al. (2014b) found obesity to be a predictor of PE and high percentage body fat was recorded among preeclamptics compared to non preeclamptics (Yeboah *et al.*, 2017). Most of these studies were case control and hence do not have enough data on the possible exposures at the early stages of pregnancy which may have led to the developing of PE, therefore this current study which is prospective cohort aspires to determine the factors at the very early stages of pregnancy (≤ 20 weeks gestation) and 28 – 32 weeks which may predispose the pregnant women to be at a potentially high risk for PE. The outcome of this study

will add onto the knowledge already known about PE and also serve as a basis for further research into PE.

1.3 Research Questions

i. What is the prevalence of potentially high risk for PE among pregnant women attending antenatal clinic at University of Ghana and the Ghana Police hospitals?

ii. What are the factors associated with potentially high risk for PE among the pregnant women?

iii. What are the pathways through which these factors operate?

1.4 Objectives

Main Objective

To identify the factors linked with potentially high risk for PE among pregnant women attending antenatal clinic at selected hospitals in Accra, and to identify the pathways through which the factors operate.

Specific Objectives

i. To determine the prevalence of potentially high risk for PE (presence of at least high systolic blood pressure (≥ 130 mmHg) or high diastolic blood pressure (≥ 80 mmHg) or oedema or proteinuria) among pregnant women attending antenatal clinics at University of Ghana and the Ghana Police hospitals in Accra.

ii. To determine the factors associated with potentially high risk for PE among the pregnant women.

iii. To identify the pathways through which these factors operate.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Hypertensive Disorders in Pregnancy (HDP)

Pregnancy induced hypertension (HDP) is defined as a systolic blood pressure (SBP) of >140 mmHg and a diastolic blood pressure (DBP) >90 mmHg, or a 30/15 mmHg increase in first or pre-pregnancy blood pressure, proteinuria, and/or edema (Lawrence and Patricia, 2008). It can occur during pregnancy, at birth, or even after delivery, with health concerns such as heart, liver, and renal disease, as well as fetal difficulties (NHBPEPWG, 2000). According to Ghulmiyyah and Sibai (2012), HDP affects 8–10% of all pregnancies globally, resulting in 14% maternal fatalities (Say *et al.*, 2014). HDP is the leading cause of maternal deaths in Ghana's tertiary institutions, according to clinical investigations (Lee *et al.*, 2012; Adu-Bonsaffoh *et al.*, 2013). Adu-Bonsaffoh et al. (2017a) discovered problems in pregnant women out of 1856 who gave birth at Korle Bu Teaching Hospital (KBTH), suggesting a prevalence of 21.4 %.

In an analysis involving 82 studies and 854 304 pregnant women, Noubiap et al. (2019) discovered a prevalence of 49.8% (95 percent Confidence Interval (95% CI) = 32.3 – 70.7), 14.7 % (95% CI = 11.6 – 18.2), 9.2% (95% CI = 4.2 – 16.0), 44.0% (95% CI = 36.7 – 52.0), 22.1% (95% CI = 14.8 – 30.8), 14.7% (95% CI = 8.1 – 23.2) and 2.2% (95% CI = 1.2 – 3.4) for gestational hypertension, chronic hypertension, superimposed PE, PE, severe PE, eclampsia and Haemolysis, Elevated liver enzymes, Low Platelet count (HELLP) syndrome respectively. At the continent level, Central and Western Africa had a greater prevalence, with a consistent trend of increasing

HDP prevalence with increased affluence. Among the Americans, the prevalence of hypertensive disorders in pregnancy and PE was about 10% and 3%, respectively (Amro *et al.*, 2016).

2.1.1 Chronic Hypertension in Pregnancy

Chronic hypertension in pregnancy (CHP) is "hypertension that develops before pregnancy or before 20 weeks of gestation; having a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg or use of antihypertensive medication before pregnancy or having high blood pressure after 12 weeks of delivery" (ACOG Committee on Practice Bulletins–Obstetrics, 2002). It's been linked to a slew of pregnancy-related issues. In a study conducted in Ghana, Dassah et al. (2019) discovered a prevalence of persistent high blood pressure in pregnancy of 5.3 % among 451 pregnant women. Furthermore, Firoza and colleagues found a prevalence of chronic hypertension to be 1.6 % (95% CI = 0.12 – 0.20) with a prevalence in middle-income and high-income countries of 0.6 % (95% CI = 0.004 – 0.009) and 1.7 % (95% CI = 0.013 – 0.022) respectively (Firoza *et al.*, 2018).

2.1.2 Gestational Hypertension (GH)

This is one of the pregnancy-induced hypertension that arises after 20 weeks with no urine protein or symptoms of renal impairment (Mayo Foundation for Medical Research, 1998–2019). In a prevalence study conducted at Komfo Anokye Teaching Hospital in Ghana, Dassah and colleagues discovered that 32.4 % of pregnant women had gestational hypertension (Dassah *et al.*, 2019). Shen et al. (2017) discovered a 3.75% frequency of GH in 8085 pregnant women at the Ottawa Hospital and Kingston General Hospital in the United States of America.

2.1.3 Preeclampsia: Forms and Prevalence

Preeclampsia (PE) was previously known as Toxemia, a hypertensive disorder in pregnancy associated with blood pressure greater than 140 mmHg/90 mmHg recorded every 4–6 hours and symptoms of damage to an essential organ such as the liver or kidney (Mayo Foundation for Medical Education and Research, 1998–2019). PE can occur anytime between 48 hours and 6 weeks after delivery (Mayo Foundation for Medical Research, 1998–2020). Severe headache, impaired vision/light sensitivity/loss of vision, protein in urine and upper abdominal pain (below the right side ribs), nausea, vomiting, decreased urine output, decreased level of platelets and shortness of breath are some of the most common symptoms (Mayo Foundation for Medical Education and Research, 1998 – 2019).

PE has been classified into two types: mild and severe. The mild type as having SBP ≥140 mmHg and DBP ≥90 mmHg, as well as proteinuria of 0.3g in a 24-hour period whereas the severe form is defined by SBP ≥ 160 mmHg and DBP ≥110 mmHg on two instances of not less than 6 hours interval and proteinuria of 5 g in 24 hour urine specimen or having 3+ in two urine samples obtained randomly at not less than 4 hrs interval, oliguria of 500 ml in 24 hours (Schroeder, 2002). Preeclampsia is expected to affect 4.6 % of pregnant women worldwide (95% CI = 2.7% – 8.2%) (Abalos *et al.*, 2013). PE is prevalent in underdeveloped nations at a rate of 2 to 17 % (Lakew *et al.*, 2013), with African women accounting for 10% of the total (Nakimuli *et al.*, 2014). Browne et al. (2015) showed that 1.7 % of the 789 women who finished the research in Accra, Ghana had PE, based on a cohort study enrolling 1010 women who were 17 weeks pregnant. Furthermore, in a prevalence research conducted at Komfo Anokye Teaching Hospital, Dassah and colleagues discovered a prevalence of 48.8% of

pregnant women with PE (Dassah *et al.*, 2019). PE was found to be 8.8% prevalent among Nigerian women according to Musa and colleagues (Musa *et al.*, 2018). Preeclampsia was discovered to have a 2.23 % incidence rate in Ethiopia's Dilla University Referral Hospital (Vata *et al.*, 2015). Additionally, Belay and Wudad (2019) discovered a prevalence of PE of 12.4 % in a prevalence investigation at the Mettu Karl referral hospital in Ethiopia. PE affects one in every 25 pregnancies in the United States (ACOG, 2013; S. Preventive Serivices Task Force, 2017).

2.1.3.1 Pathogenesis and Pathophysiology of Preeclampsia

Preeclampsia has been dubbed the "disease of theories" due to the numerous theories that have been linked to it. Lack of balance in the formation of new vessels, inflammation, and oxidative stress take on the role of the "accelerator," while the "braking system" includes safeguarding the functional process of haem oxygenase 1 and cystathionine-lyase. Carbon (II) oxide (CO) as well as Hydrogen sulphide (H_2S) is produced by the enzymes haem oxygenase 1 and cystathionine-lyase. PE is caused by the brake system's failure to function properly. Preeclampsia is a condition that causes the accelerator and brake systems to fail. CO and H_2S are therefore important to the development of PE as a result of their unrivaled potential to lower anti-angiogenic factors sFlt-1 and solubilized type I membrane glycoprotein while simultaneously promoting PlGF and endothelial NOS activity (Ahmed and Ramma, 2015). The development of PE occurs in 2 phases; abnormal placentation in the first trimester and maternal disease manifestation in the mid and later stages of pregnancy (second and third trimesters), with antiangiogenic agents being used concurrently (Redman and Sargent, 2005; Romero and Chaiworapongsa, 2013).

In a healthy pregnancy, cytotrophoblasts "migrate into the maternal uterine spiral arteries to establish vascular sinuses at the fetal-maternal interface to supply nutrition for the foetus". This leads to a greater modification of the spiral arterioles into higher flow arteries (Brosens *et al.*, 1967; Brosens *et al.*, 2011). Preeclamptic cytotrophoblasts are unable to transition to invasive endothelial subtype from the proliferative epithelial state, resulting in inadequate spiral artery remodeling (Zhou *et al.*, 1997). This inadequate remodeling cause narrow maternal artery, which are prone to atherosis and therefore placenta ischaemia (Brosens and Renaer, 1972). Anomalies in the trophoblasts can also cause shallow placentation and insufficient spiral artery transformation, resulting in placental ischemia and the maternal syndrome of preeclampsia (Zhou *et al.*, 1997). This lack of blood flow in the placenta is linked to decidual vasculopathy and is linked to a poorer clinical outcome, higher diastolic blood pressure, kidney malfunction, and neonatal death (Stevens *et al.*, 2013).

Furthermore, during the early phases of placentation, trophoblast proliferation is aided by a hypoxic (low oxygen) environment. Before invasion, the blastocyst is supported by proliferating trophoblasts, which also fix the tips of the spiral arteries within the deciduas (Burton *et al.*, 2001). These trophoblastic-spiral artery plugs break down over time, causing an intervillous gap to be formed. The newly developed sinuses allow maternal blood to enter, increasing oxygen tension and causing oxidative stress, as well as boosting trophoblast distinction to an invasive phenotype and modify the spiral arteries (Jauniaux *et al.*, 2000). Hypoxia-inducible factors (HIF) 1 and -2, which are indicators of cellular oxygen improvement expressed at elevated amounts in proliferative trophoblasts and placenta in PE (Rajakumar *et al.*, 2004). HIF-1

upregulation was also detected in pregnant mice which were linked to high blood pressure and proteinuria according to Tal and colleagues (Tal *et al.*, 2010).

Oxidative Stress

Imbalance between antioxidant and free radicals in cells and tissues causes a disruption in redox signaling and regulation, as well as molecular damage (Ďuraková, 2010). Oxidative stress can occur due to irregular low amount of oxygen and re-oxygenation as a result of inadequate spiral artery invasion. Molecular analysis of preeclamptic placentas reveals an imbalance of free radicals. Furthermore, there was an increase in preeclamptic ex vivo preeclamptic trophoblast, ROS-producing enzymes and activity (Many *et al.*, 2000) and impede the Wnt/-catenin signaling pathway, which promotes trophoblast invasion (Zhuang *et al.*, 2015).

According to Huang and colleagues, the imbalance of both antioxidant and free radicals may influence the expression of antiangiogenic factors (Huang *et al.*, 2013). Women suffering from preeclampsia have reduced placental antioxidant systems, as demonstrated by decreased appearance of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) than that of non-preeclamptics (Vaughan and Walsh, 2002), although according to Poston et al. (2006) and Roberts et al. (2010) vitamin E and C supplementation had no influence on disease severity .

In a study in Sokoto, Nigeria, preeclamptics had a higher mean value of oxidative stress indicators malondialdehyde (MDA) and GSH-Px peroxidase than non-preeclamptic women (3.44 ± 1.25 and 71.53 ± 26.02) (3.024 ± 1.08 and 62.58 ± 22.45) ($p < 0.001$) respectively with superoxide dismutase be lower in pregnant

women with preeclampsia compare with the non preeclamptics (13.00 ± 15.27) versus (57.21 ± 38.08) $p < 0.001$ respectively (Shehu *et al.*, 2020). In Clinical Center of Vojvodina in Novi Sad, Serbia study, preeclamptic pregnant women had higher values of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) than the non-preeclamptics 45.6 (13.6 – 77.5) vs 29.7 (9.0 -70.5) $p < 0.0001$ and 634.712 (35.0 – 995.3) vs 519.46 (253.6 – 827.1) p 0.0058 respectively however, mean total antioxidant status (TAS) was lower among the preeclamptics than with the non-preeclamptics 0.97 (0.2 – 5.3) vs. 1.9 (0.35 – 5.03) p 0.0075 respectively (Bogavac *et al.*, 2017).

Haem Oxygenase and Other Abnormalities

Studies are continuously demonstrating that "haem oxygenase (HO), the haem degradation catalyst," plays a crucial role in the mother and fetus' vascular tasks, as well as placental growth and function (Cudmore *et al.*, 2007; George *et al.*, 2012; George and Granger, 2013).The haem oxyenase is of two forms; HO-2, which is involved in spiral artery invasion (McCaig and Lyall, 2009), and HO-1, which is significantly expressed in non-invasive trophoblastic phenotypes(Bilban *et al.*, 2009). In an animal investigation, a rodent model with low uterine tissue perfusion pressure was given cobalt protoporphyrin (COPP), a HO-1 inducer, which reduced blood pressure and resulted in a pro-angiogenic change in the placenta's VEGF/sFLT1 ratio (George *et al.*, 2011).

Natural Killer Cells/Tissues and Abnormal Placentation

The involvement of uterine Natural Killer (uNK) in the process that leads in considerable change of endometrial cells is well defined (Bulmer *et al.*, 2010) and it

may contribute to the poor placentation seen in preeclampsia. It is not cytotoxic (Koopman *et al.,* 2003; Moffett and Colucci, 2014). The uNK cells determine the extent of placentation, spiral artery modification and trophoblastic invasion (Lash *et al.*, 2006; Moffett-King, 2002). It expresses killer cell Ig-like receptors, (KIR) (Parham and Moffett, 2013) while fetal invasive extra villous trophoblasts express the main KIR ligand, polymorphic human leukocyte antigen-C (HLA-C) and self-major histocompatibility complexes (MHCs) (Apps *et al.,* 2009). The individual separation of maternal KIR and HLA loci (Parham and Moffett, 2013) along with the extra villous trophoblast HLA-C from paternal side to pregnancy leads to a unique combination of KIR (maternal) and HLA-C (fetal) which may influence the success of placentation (Moffett and Colucci, 2014). .

Maternal Syndrome Manifestation at the Later Part of Second and Third Trimesters with Associated Excessive Antiangiogenic Factors Imbalance in Circulating Angiogenic Factors

Angiogenesis is the growth of more blood vessels from a vascular bed (Folkman and Shing, 1992) and is controlled by an equilibrium between the pro-angiogenesis and anti-genesis factors (Folkman, 1992; Folkman and Shing, 1992). According to Alon et al. (1995), VEGF, PlGF and transforming growth factor-β (TGF-β) make up the pro-angiogenic factors. Vascular endothelial growth factor is required for the proper endothelial cell function, particularly in pitted endothelial in primary organs affected by preeclampsia such as the brain, liver and kidneys (Esser *et al.*, 1998) and is abundantly demonstrated by glomerular podocytes, whose receptors are found on glomerular endothelial cells (Maharaj *et al.,* 2006).

PlGF plays a critical role in angiogenesis and binds to VEGFR1/sFLT1 rather than VEGFR2 (De Falco, 2012). Antiangiogenic factor soluble fms-like tyrosine kinase-1 (sFlt1) on the other hand, is made up of Flt1's extracellular ligand-binding domain but lacks the transmembrane and intracellular signaling domains. The solubilized fms-like tyrosine kinase-1 (sFlt1) is made available through the bloodstream, where it attaches to VEGF and PlGF and antagonizes them (Kendall and Thomas, 1993).There is a lot of evidence that sFlt-1 plays a major role in preeclampsia development; high amounts of sFlt-1 were observed in serum or plasma (Koga *et al.*, 2003; Maynard *et al.*, 2003) and preeclamptic placentas had high expression of SFlt-1 and mRNA (Tsatsaris *et al.*, 2003), administration of exogenous sFLT1 delivery to rodents causes hypertension, proteinuria, glomerular endotheliosis, and other symptoms associated with PE (Maynard *et al.*, 2003; Lu *et al.*, 2007). Reduction in sFLT1 levels or antagonizing sFLT1 in preeclampsia animal models improves clinical symptoms (Li *et al.*, 2007; Bergmann *et al.*, 2010; Kumasawa *et al.*, 2011).

In preeclamptics, (Maynard *et al.*, 2003; Levine *et al.*, 2004) discovered an elevated circulating levels of sFLT1 with a decrease in free PlGF levels, indicating a protein imbalance between antiangiogenic and proangiogenic proteins. Preeclamptic women's serum and urinary PIGF levels were shown to be low at diagnosis and as the condition progressed, which could be due to both lower expression of PlGF and free PlGF as a result of its attachment to sFLT-1 and an increase in affected women (Levine *et al.*, 2004). The concentration of serum Endoglin (sENG) was significantly higher among pregnant women who developed PE early in pregnancy than in those who developed PE later in pregnancy in an observational descriptive cross sectional study involving 13 early-onset preeclamptics, 13 late-onset preeclamptics and 13 normal pregnant

women in the University Hospital and Surabaya hospitals in Indonesia (47.7 ± 40.2, 13.5 ± 9.5, 6.1 ± 1.5 ngmL^{-1}; p = < 0.0001) (Akbar *et al.,* 2017).

There was a significant difference in serum VEGF and PlGF values among the preeclamptics and non-preeclamptics (p.05), with preeclamptics having lower serum VEGF and PlGF levels than non-preeclamptics (Nasrolahi *et al.,* 2018). Cim et al. (2017) discovered that in a study involving 40 late-onset preeclamptics at 32 weeks and 40 non-preeclamptics, sENG and SFlt-1 were higher but not significantly higher among the preeclamptics; elevated levels of sENG were noticed in preeclamptics. Among 88 pregnant women who gave birth at Oslo University Hospital, Moe and colleagues discovered that free moving autoantibodies against VEGF and PlGF were significantly declined in preeclamptics in contrast with non-preeclamptics (p value 0.05); independently, only AA-VEGFA and AA-VEGFR-1 were found to be associated with PE and AA-VEGF was also found to be a significant predictor of PE, with an AUC of 0.735 (Moe *et al.,* 2017). In a case-control research, Ding and colleagues discovered significantly elevated values of sFlt-1 and sFlt-1/PlGF, as well as low levels of PIGF (Ding *et al.,* 2018).

Adu-Bonsaffoh and colleagues discovered a significant decrease in serum levels of free VEGF among preeclamptics and non-preeclamptics, but not among non-pregnant women, 4.71 pg/ml (3.41, 7.93) and 84.06 pgml^{-1} (p value 0.001) respectively. Compared to late-onset preeclamptics, early-onset preeclamptics had a significantly reduced free VEGFof 3.89 (2.60, 5.67 pgml^{-1}) with p value 0.001 (Adu-Bonsaffoh *et al.,* 2017b).

Inflammatory Cytokines and Immune Cell Alterations

The cytokine interleukin -10 (IL-10) promotes T cells to develop into T helper type 2 cells (Th 2). It has been shown to be a significant mitigator of the maternal disease by counterbalancing pro-inflammatory cytokines, AT1-AA, placental reactive oxygen speciesand endothelin-1 (EDN1) (Harmon *et al.*, 2015). According to Weel et al. (2016), several cell types of preeclamptics, including uterine and circulating NKs, are dysregulated in the equilibrium of IL-10 and proinflammatory cytokines. Normal pregnancy has interrelationship with a shift in T-cell phenotype from Th1 to Th2 (Saito and Sakai, 2003; Wegmann *et al.*, 1993) and preeclampsia-related pregnancy has been linked to insufficient trophoblast invasion (Sowmya *et al.*, 2014).

Renin-Angiostensin Pathway Downward - Regulation

During normal pregnancy, maternal blood volume increases and total resistance decreases, especially in the early stages, and to avoid a drop in blood pressure, the Renin-angiotensin-aldosterone system is turned on, causing sodium and water retention. Moreover, in preeclampsia, intravascular blood volume as well as cardiac output are lowered, and total peripheral aversion was elevated (Verdonk *et al.*, 2014). Despite a decrease in circulating renin and angiotensin II, angiotensin II sensitivity increased during and before the diagnose of PE (Brown *et al.*, 1997; Gant *et al.*, 1973).

Autoantibodies to angiotensin II type 1 have been found to recreate the bulk of the key symptoms of preeclampsia; vasoconstriction via endothelin-1163 (ET-1163) activation (LaMarca *et al.*, 2009): endothelial cell mortification and death in the endothelial cells of the umbilical vein (Yang *et al.*, 2014). In response to placental

abnormality, there is activation of tissue factor release which contributes to clot formation (Dechend *et al.*, 2000), decrease of trophoblast invasion in human cell culture models (Xia *et al.*, 2003) and rise in the release of reactive oxygen species in culture models (Dechend *et al.*, 2003). Anti-AT1-AA can cause the placenta to produce antiangiogenic factors like sFLT1 and sENG (Parrish *et al.*, 2010). Its activity is stronger in preeclamptics sera, as are CD19+CD5+ cells (surface glycoproteins expressed by Tcells), showing that B lymphocytes contribute to the functioning of the immune system (Herse and LaMarca, 2013). Increased levels of an oxidized angiotensinogen, which is more easily cleaved by renin, have also been linked to the pathogenesis of preeclampsia (Zhou *et al.*, 2010).

Hydrogen Sulphide, Cystathionine β-synthase and Cystathionine γ-lyase Downward - Regulation

Hydrogen sulphide (H_2S) is a gas molecule that creates a signaling effect in the endothelial cells of humans and animals to bring about a vaso-relaxant effects and play a role in in uterine contractions (Papapetropoulos *et al.*, 2009; You *et al.*, 2011; Zhao *et al.*, 2001). H_2S generated by the body possesses angiogenic and non-inflammatory qualities effects at the endothelial-leukocyte interface (Papapetropoulos *et al.*, 2009; Zanardo *et al.*, 2006). The enzymes cystathionine-lyase (CSE) and cystathionine-synthase (CBS) are required for the generation of H_2S (Holwerda *et al.*, 2012) and are found in foetal endothelial cells of the stem and chorionic villi with Hofbauer cells expressing CBS mRNA (Holwerda *et al.*, 2012).

Cystathionine-synthase mRNA, on the other hand, is down-regulated in early-onset PE (Holwerda *et al.*, 2012). In comparison to healthy pregnancy, Wang and

colleagues discovered a reduction in CSE mRNA expression in preeclamptic placental tissue and in women with small for gestational age newborns and this decrease was equivalent to a decrease in H_2S levels in the maternal circulation (Wang *et al.*, 2013). Furthermore, in pregnant mice, suppression of enzymes cystathionine-lyase by DL-propargylglycine (PAG) caused hypertension and an increase in circulating fms-like kinase-1, endoglobin, and placental anomalies, whereas administration of GYY4137, which suppresses PAG's action, decreasced circulating sFlt-1 and sENG levels and restored foetal growth (Wang *et al.*, 2013). Deregulation of the enzymes cystathionine-lyase /hydrogen sulphide system also harmed spiral artery remodelling and placental development,according to data from an in vitro investigation. In addition, inhibiting enzymes cystathionine-lyase with PAG lowered Placental growth factor synthesis in placental explants from first-trimester pregnancies (Wang *et al.*, 2013).

2.1.3.2 Risk Factors of Preeclampsia

According to research, maternal gynecological history, estimated pre-pregnancy weight and BMI, high blood pressure at first booking, ethnicity/race, marital status/new paternity, maternal previous history of PE and other health conditions, family history of PE and chronic health conditions, seasonality/environmental conditions, lifestyle practices, and nutritional factors all play a role (Mayo Foundation for Medicaal Education and Research, 1998 – 2019). Their links to PE have been demonstrated here in a number of researches.

Primiparous/Nulliparous Pregnancy

According to findings from after a cross sectional scholarship encompassing 340 expectant mothers who gave birth at East Kalimantan hospital, Indonesia, there is a significant correlation linking primigravidae and the incidence of PE and eclampsia, with a p- value of 0.002 and a prevalence ratio of 1.998 (95% CI = 1.3 – 3.1) with a higher tendency of 1.9 times when compared to multigravid (Fatimah *et al.,* 2017). Primiparity was found to be independently linked with PE OR = 4.51 (95% CI = 2.7652 – 7.3609) with a p value of 0.0001 in a study including 180 preeclamptics and 180 non-preeclamptics at Jaipur, India (Verma *et al.,* 2017).

Hercus and fellow researchers in a survey at McEwin Hospital, Australia, observed that mothers with increase birth coupled with longer birth intervals had a significantly higher tendency of developing PE in subsequent pregnancies, with OR = 1.39 (p 0.042) and OR = 2.05 (p = .002) at 3 and 4 years respectively (Hercus *et al.,* 2020). Women with parity of one or more had a higher risk of getting PE in a case study involving 112 cases and 112 controls, with OR = 3.389 (95% CI = 1.936 – 5.934) (Rosmala *et al.,* 2019). Primiparity was a risk factor for PE development (Ferreira *et al.,* 2019).

Primiparous women have a higher tendency of developing late-onset PE RRR 0.71 in a retrospective population-based study (You *et al.,* 2018). In a comprehensive review and meta-analysis encompassing fifty-one papers, Meazaw et al. (2020) discovered that primiparous women have a higher tendency of getting PE OR = 2.52 (95% CI =1.19 – 3.86). Primiparous women were shown to be at a higher potential of acquiring PE than non-primaparous women in a hospital-based study in Nairobi County, Kenya

AOR=2.1 (95% CI = 1.1–4.2) p 0.031 (Logan *et al.*, 2020). Nulliparous women were found to be at a higher potential of risk developing PE in contrast to non-nulliparous women OR = 1.59 (95% CI = 1.11 – 2.29); AOR = 3.83 (95% CI = 0.72 – 20.40) in a nested case-control study in Hospital Universitario, Bogotá, Colombia (Ayala-Ramrez *et al.*, 2020).

Similarly, in a study at Paropakar Hospital in Kathmandu, Nepal, primiparous pregnant women had a higher risk of PE than non primiparous expectant mothers with an adjusted odds ratio of 2.12 and a 95% CI range of 1.25 – 3.60 (Das *et al.*, 2019). To buttress this, a case control study conducted at the Police Hospital in Accra, Ghana, found out that having one child decreased ones tendency of developing PE with odds ratio of 0.5 (95% CI of 0.27 – 0.91) p 0.05 (Otu-Nyarko *et al.*, 2015). Furthermore, another case-control study involving 69 non-preeclamptics and 65 preeclamptics undertaken at Korle Bu Teaching Hospital, found primigravidity to be associated with PE (AOR = 6.6, 95 % CI = 2.4–18.2) (Obiri *et al.*, 2020).

Multiple Pregnancies

In a study in Norway (SSB), expectant mothers of twin pregnancies were 3 to 4 times higher at risk of having PE than their singleton counterparts OR = 3.78 (95% CI = 3.59 – 3.96). Twin pregnancy remained a risk factor for PE AOR = 4.07 (95% CI= 3.65 – 4.54) even after adjusting for other variables (Laine *et al.*, 2019). Furthermore, Henry and colleagues discovered preterm severe PE was more common in twin pregnancies than in singleton pregnancies (2.4% vs 0.4%, P<0.001), RR = 5.70 (95% CI = 4.47 to 7.26) (Henry *et al.*, 2013). This was also discovered in Endeshaw and colleagues study in Bahir Dar city, Ethiopia where women with multiple gestation

have a higher tendency of developing PE than those with single gestation AOR = 4.05 (95% CI = 1.57 – 12.27) (Endeshaw *et al.*, 2016).

Furthermore multiple pregnancy was linked with a higher potential of having PE compare with singleton pregnancy Adjusted OR = 5.73 (95 % CI = 1.13 – 29.10) p value 0.04 (Pandey and Pandey, 2017). Das et al. (2019) in a study in Paropakar, Kathmandu, Nepal involving 4820 pregnant women, found pregnant women carrying multiple fetuses to be at a higher tendency for PE than those carrying single foetus AOR = 8.49 (95% CI = 2.92 – 24.72).

Estimated Pre-Pregnancy Overweight/Obesity

Obesity defined as a BMI of 30 or higher, has been shown to have negative consequences on pregnancy and its outcomes, including preeclampsia (Mayo Foundation, 1998 – 2019). Mohammadi et al. (2019) discovered that overweight and obese pregnant women had an increase chance of getting PE compared to those with normal BMI OR = 1.47 (95% CI = 1.06 – 2.02) and OR = 3.67 (95% CI = 2.57–5.24) respectively. In a case-control study involving 100 preeclamptics and 100 controls conducted in hospital at Dakshina Kannada district, Karnataka, South India, Kumar and colleagues discovered that pregnant women who were overweight had a significant likelihood of developing PE AOR = 7.56 (95% CI = 1.32 – 43.37) p value 0.02 (Kumar *et al.*, 2010).

Overweight/obesity were risk factors for preeclampsia OR = 1.81 (95% CI = 1.37 – 2.39) in a study by Yawen and colleagues on pre-pregnancy BMI as well as the likelihood of developing preeclampsia across a subgroup of expectant mothers in

Landzhou, China (Yawen *et al.*, 2017). Furthermore, a link was found between pre pregnancy overweight AOR = 1.4 (95% CI= 1.2 – 1.8),obesity AOR =1.8 (95% CI = 1.3 – 2.4) and the risk of preeclampsia (Mrema *et al.*, 2018). Women who were obese class II and III were shown to have a 4 times higher risk of slight to reasonable preeclampsia AOR = 4.0 (95 % CI = 3.7– 4.4) in a population-based cohort research (Sohlberg *et al.*, 2012). Another study in Budi Kemuliaan hospital in Jakarta, Indonesia, found that having a high BMI was linked to PE AOR = 1.09 (95% CI = 1.04 – 1.14) p <0.01 (Savitri *et al.*, 2016).

Cuifang et al. (2016) found pregnant women with low BMI to have 28% decreased risk of developing PE compare to normal BMI whilst pooled OR for overweight and obese women were at an increased risk of 1.64 (95% CI = 1.54 – 1.76) and 2.86 (95% CI = 2.56 – 3.19) respectively. Ayala-Ramírez et al. (2020) found pre-gestational underweight, overweight and obese expectant mothers to have a higher tendency for PE development than those with normal BMI AOR = 2.9 (95% CI = 0.2 – 28.36), AOR = 2.37 (95% CI = 0.79 – 7.10) and AOR = 21.0 (95% CI = 1.90 – 232.58) respectively. An open study in Jos , Nigeria; BMI at booking of ≥ 25 kg/m2 was found to be a risk factor for PE RR=3.9 (95% CI = 1.5 – 10.0) (Musa *et al.*, 2018). In a study in Sokoto, Nigeria prevalence of PE was found to be 6% with obesity been a significant predictor (Singh *et al.*, 2014). Verma and colleagues in a study in Jaipur, India found pre-obese and obese expectant mothers to have significantly higher likelihood for PE development than those with normal BMI OR = 3.23 (95% CI = 1.6626 – 6.2925) with p value of 0.0005 and OR = 8.28 (95% CI = 2.4889 – 27.5537) with a p value of 0.006 respectively (Verma *et al.*, 2017).

In a study in a municipality in the state of Piauí, Brazil; prevalence of obesity among those who developed PE was 8 (8.6%) (Ferreira *et al.*, 2019). Meazaw and colleagues found high maternal body mass index to be linked with higher tendency of developing PE than those with normal body mass index OR = 1.69 (95% CI =1.17, 2.21) (Meazaw *et al.*, 2020). In a case control study carried out in Bundelkhand Medical College Hospital Sagar Madhya Pradesh, maternal body mass index > 25 kg/m^2 was found to be linked with an elevated tendency for PE development AOR = 7.65 (95% CI = 1.32 – 43.47) p 0.02 (Pandey and Pandey, 2017). Shao et al. (2017) in a birth cohort study in China, found overweight/obese pregnant women were at a higher tendency of developing PE (OR = 1.81; 95% CI = 1.37–2.39) compared with those with normal pre-pregnancy body mass index.

In a meta-analysis to determine the link amongst overweight/obesity and PE, overweight was found to be associated with PE among 13 random-effect model studies OR = 1.71 (95% CI = 1.52 – 1.91) than with normal body mass index likewise obesity OR = 2.48 (95% CI = 2.05 – 2.90) (He *et al.*, 2020). Canto-Cetina et al (2018) also found overweight or obese expectant mothers to be at a higher likelihood of developing PE compared with those with normal body mass index (Canto-Cetina *et al.*, 2018).

In a study in Goma, in the eastern Democratic Republic of Congo, pre-pregnancy overweight and obesity was linked with a higher potential of developing PE compared with those of normal body mass index OR = 2.82 (95% CI = 1.28 – 6.21) p = 0.010 (Richard *et al.*, 2020). Poorolajal and Jenabi in a meta-analysis found pregnant women with excess weight to be at an elevated risk for PE development than those

who had normal BMI OR = 1.73 (95% CI = 1.59 – 1.87; 21 studies; I^2 = 62.3%) and OR = 3.15 (95% CI = 2.96 – 3.35; 22 studies; I^2 = 36.0%) for overweight and obesity respectively (Poorolajal and Jenabi, 2016). In Ghana, a study found obese pregnant women to be at 7 times increase risk (95% CI = 1.9 – 27.7) of developing PE compared with those who had normal BMI (Owiredu *et al.*, 2012).

Excessive Gestational Weight Gain

Shao and colleagues in a birth cohort study China, found women who gained excessive weight during pregnancy to be at a higher likelihood of developing PE OR = 2.28 (95% CI = 1.70 – 3.05) than those who gained healthy weight (Shao *et al.*, 2017). In a prospective cohort study based on the obstetrical practices of Baystate Health, Massachusetts, USA, pregnant women who gained weight above the Institute of Medicine (IOM) guidelines had a higher tendency for PE development than those who gained within IOM guidelines AOR = 3.33 (95% CI = 1.15 – 9.65) p = 0.02 (Chasan-Taber *et al.*, 2016).

Short/Long Inter-Pregnancy Interval

Findings from a systematic review and meta-analysis indicated that pregnant women with inter-pregnancy interval of more than 4 years have an increase tendency of developing PE again than those with inter- pregnancy interval of 2 – 4 years AOR = 1.10 [95 % CI = 1.02 – 1.19) I2 0 %] (Cormick *et al.*, 2016).

Extremes of Maternal Age

Extremes of age is a predictor of PE; that is, ages less than 18 years and more than 35 years (Carson, 2018). In a registry constructed revision involving data in Finland, prevalence of PE was 9.4% among women in their advanced age (> 35years) and 6.4% among women less than 35 years (Lamminpää *et al.*, 2012). A prospective study among 220 Indians in BGH, Jharkhand, Indian found prevalence of PE to be 56.1% among the under 20 years, 40.0% among the 20 – 30 years and a positive correlation for 30 years and above (Neha *et al.*, 2016). In a study in Japan, women who were 45 years and above were at an elevated risk for PE development than those who were 30 – 34 years aRR = 1.86 (95% CI =1.43 – 2.42) and severe PE aRR = 2.03 (95% CI =1.31–3.13) (Ogawa *et al.*, 2017).

In a study conducted by Tessema and colleagues in Ethiopia, pregnant women age 35 years or more were found to be at an increased risk of developing PE compared with those who were younger AOR = 4.5 (95% CI = 1.56 – 12.8) (Tessema *et al.*, 2015). In a study in Taiwan, older age was strongly associated with early- onset and vice versa PE RRR = 1.41 (95% CI = 1.29 – 1.54) (You *et al.*, 2018). In Bahir Dar, Ethiopia, older maternal age was linked to a higher risk of developing PE than younger mothers AOR= 4.79 (95% CI = 1.031 – 22.18) (Endeshaw *et al.*, 2016). Goyal et al. (2020) in a matched case control study conducted in associated group of hospitals, Rajasthan, India, found pregnant women age 30 years and above to be at a higher tendency for PE development than their younger counterparts OR = 1.667 (95% CI = 0.992 –2.799) but it was not significant.

Furthermore, in a hospital-based unmatched case control study among pregnant women who delivered and were admitted in hospitals in Nairobi County, Kenya, advanced maternal age of 35 – 49 years was linked with an elevated risk of developing PE than those who are younger AOR= 5.9 (95% CI = 1.1 – 33.3) p value 0.042 (Logan *et al.*, 2020). Ayala-Ramírez and colleagues in their study in Bogotá, Colombia, found maternal age of ≥ 35 years to be related with a higher tendency of developing PE than the younger pregnant women AOR = 4.57 (95% CI = 0.94 – 22.06) but it was not significant (Ayala-Ramírez *et al.*, 2020). On the contrary, Das and colleagues in a study found pregnant women 35 years and older to have a higher chance of developing PE compared with those between the ages of 20 – 24 years AOR = 3.27 (95% CI = 1.42 –7.52) (Das *et al.*, 2019) and it was significant. In Ghana, Otu-Nyarko and colleagues found maternal age of 25 years or more to be a predictor of PE OR = 2.42 (95% CI = 1.11 – 5.28) p <0.05 (Otu-Nyarko *et al.*, 2015).

Short Parental Height

In a study involving 99968 pregnant women and their spouse, the tallest mothers (>172 cm) were at 30% decreased tendency of PE development risk than the shortest women; adjusted OR = 0.74 (CI = 0.66 – 0.82) whilst paternal height was not associated with PE. Findings from an analysis indicated the potential of paternal height to be protective against PE OR = 0.88 (CI = 0.80 – 0.96), but this protection was lost after adjustment for maternal height (Lee and Magnus, 2018). Furthermore, in a study based in Nordic countries, shortest women were at an elevated tendency of developing PE; odds ratio of 1.11 (95% CI1.06 – 1.15) (Sohlberg *et al.*, 2012).

Short Duration of Sperm Exposure/Short Cohabitation

In an analytic case control study carried out at maternity Hospital in Kashan city, Iran involving primigravid women who delivered at the facility, many preeclamptics had short duration of sperm exposure than the controls (29.2 versus 14.2 for <3 months without barrier methods, AOR = 2.6 (95% CI =1.32 – 5.13) and (45 versus 29.2 for <6 months, AOR = 2.4 (95% CI=1.35 – 4.32) (Sadat *et al.,* 2012). Similarly, Mekie and colleagues in a matched case control involving nulliparous women who delivered in three hospitals of West Amhara Zones, Ethiopia, short duration of cohabitation was identified to be linked with expanded risk for developing PE compared with longer duration of cohabitation PE AOR = 2.13 (95% CI = 1.10 – 4.1) (Mekie *et al.*, 2020).

High Maternal Blood Pressure at First Antenatal Clinic Booking

Maternal SBP of ≥130 mmHg and DBP of ≥90 mmHg at first time booking at the antenatal clinic significantly increased the chance of getting PE; odds ratio 6.38 (95% CI of 3.03 – 13.33), p value < 0.0001 and odds ratio 3.31 (95% CI of 1.83 – 5.97), p value < 0.0001 respectively (Otu-Nyarko *et al.*, 2015).

Non – White Races

In a study of 271,569 inpatient delivery hospitalizations in Hawaii, PE rates for non-white race recorded between 2.0 % for Chinese to 4.6 % for Filipinos; native Hawaiians age <35 years and non-obese OR = 1.54 (95 % CI = 1.43 – 1.66), age ≥35 years and non-obese OR = 2.31 (95 % CI = 2.00 – 2.68), other Pacific Islanders age <35 years and non-obese OR = 1.40 (95 % CI = 1.27 – 1.54), age ≥35 years and non-obese OR = 2.18 (95 % 1.79- 2.64), Filipinos age < 35 years and non-obese OR = 1.55 (95 % CI = 1.43 – 1.67), age ≥ 35 years and non-obese OR = 2.26 (95 % 1.67 –

2.60) (Nakagawa *et al.*, 2016). Between 2002 and 2008, the Consortium on Safe Labor conducted a study found that non-Hispanic black women had a higher risk of developing mild PE AOR=1.26. Hispanic women and Asian/Pacific Islanders, respectively, had increased odds of remaining normotensive (AOR=1.22 (95 % CI = 1.12 – 1.33) and AOR=1.55 (95 % CI = 1.31–1.84) (Ghosh *et al.*, 2014).

Anderson and colleagues found the odds of developing PE to be different among women from different countries; AOR = 1.25 (95 % CI = 0.99–1.27), adjusted odds ratio of 0.56 (95% CI of 0.41–0.76), adjusted odds ratio of 1.51 (CI = 1.16–1.96), and AOR = 1.20 (CI = 0.92–1.56) among Chinese, Mori, Pacific and Indian women respectively in City Hospital, Auckland, New Zealand (Anderson *et al.*, 2012). Breathett and colleagues confirmed this in a study in which PE occurred much more among African Americans than the Caucasians in the National Hospital Discharge Survey (1979–2006) involving 4,644 African Americans and 12,131 Caucasians who had PE and delivered, from a POR of 0.98 (95 % CI = 0.96, 1.0) to a POR of 1.75 (95 % CI = 1.73, 1.78) (Breathett *et al.*, 2014). Furthermore, expectant mothers of the black race had an increased chance of developing PE than expectant mothers of the white race in a study involving expectant mothers of both black and white race based in California (Ross *et al.*, 2019).

Low Socioeconomic Status

Analysis on data gathered on pregnant women from lower socioeconomic status household indicated a higher tendency of developing PE (odds ratio = 1.26 and 95% CI = 1.01 – 1.57) compared with those from higher socioeconomic households (Choe *et al.*, 2016).

Unmarried Women/New Partner

In a hospital-based cross-sectional study conducted by Tessema et al. (2015) at Dessie referral hospital in Ethiopia, unmarried women had a higher tendency of developing PE than the married ones. Hercus and colleagues in south Australia observed that women with history of healthy pregnancy had a significantly elevated tendency of developing PE in future pregnancy with new paternity OR = 2.27 p .015 (Hercus *et al.*, 2020). In a nested case- control study in Bogotá, Colombia, unmarried women had a higher chance of developing PE than the married ones OR = 1.06 (95% CI = 0.65 – 1.73) (Ayala-Ramírez *et al.*, 2020).

History of PE and Other Maternal Health Conditions

Musa and colleagues found in prospective open-cohort study in the antenatal clinic Jos, Nigeria, that previous history of preeclampsia is a predictor of PE RR=5.1 (95% CI = 2.2 – 12.1) (Musa *et al.*, 2018). Tessema and colleagues found in a study conducted in Ethiopia that women with known high blood pressure have a higher tendency of developing PE than the non-hypertensive AOR = 4.3 (95% CI = 1.33 – 13.9) (Tessema *et al.*, 2015). Kumar et al. (2010) in a study in South India found maternal history of chronic hypertension and diabetes to be significantly linked with PE AOR = 6.69 (95% CI = 1.37 – 32.75) p value 0.02 and PE AOR = 8.66 (95% CI = 1.01 – 76.26) p value 0.05 respectively.

Ahmed and colleagues in a study found history of diabetes and hypertension to be significantly associated with PE OR = 5.923 (95% CI = 1.519 – 23.091) p value 0.010 and OR = 7.838 (95% CI = 1.048 – 58.628) p value 0.045 respectively (Ahmed *et al.*, 2018). In a retrospective study involving 42,500 known chronic hypertension patients

who had singleton deliveries at two centers in Melbourne, Australia; previous preeclampsia and hypertension duration were most strongly associated with any severity of preeclampsia OR = 5.45(95% CI = 1.89 – 12.71) and OR = 2.4 (95% CI = 1.76 – 4.92) respectively (Brumby *et al.*, 2018).

In an age-matched case control study involving 112 cases and 112 controls, participants with known hypertension have a greater tendency of developing PE OR = 5.071 (95% CI = 2.819 – 9.120) (Rosmala *et al.*, 2019). In addition, a retrospective study in Piauí, Brazil, prevalence of chronic hypertension and diabetes mellitus among the preeclamptics were 4 (4.3%) and 8 (8.6%) respectively (Ferreira *et al.*, 2019). Tangren et al. (2018) also in a study at Massachusetts General Hospital, USA, women with recovered acute kidney injury (r-AKI) had a higher rate of PE than those without previous r-AKI (22% versus 9%; P<0.001). As the severity of r-AKI increases the risk of preeclampsia for stages 2 and 3 AKI also increases AOR = 3.5 (95% CI = 2.1 – 5.7) and AOR = 6.5 (95% CI = 3.5 – 12.0) respectively, but not for stage 1 AOR = 1.7 (95% CI = 0.9 – 3.2).

Ndoni and colleagues in a retrospective cross sectional study involving data collected from medical records of pregnant women at Tirana, Albania found pre-existing hypertension, renal disease and diabetes mellitus to be 7.8% vs. 2.3% (p = 0.02), 1.9% vs. 1.1% and 5.8% vs. 4.6% respectively (Ndoni *et al.*, 2016). In study in Taiwan, chronic hypertension was strongly associated with early-onset PE RRR 1.71 (95% CI = 1.55 – 1.88) (You *et al.*, 2018). In a retrospective analysis of countywide records on 271,569 admitted patients who delivered in hospitals in Hawaii, Nakagawa and his colleagues discovered that pre-gestational diabetes and chronic hypertension

were independently associated with PE OR = 3.41 (95% CI = 3.02 – 3.85) and OR = 5.98 (95% CI = 4.98 – 7.18) respectively (Nakagawa *et al.,* 2016). In a study in UK, chronic hypertension was found to be linked with a higher tendency of developing PE OR = 5.76 (95% CI = 4.93 – 6.73) (Panaitescu *et al.*, 2017).

In a multicenter trial, 216 women (28%) out of 774 with chronic hypertension developed superimposed PE; 87 (11%) had superimposed PE with severe features and 129 (17%) had superimposed PE without severe features (Moussa *et al.,* 2017). Findings from systematic review and meta-analysis involving 795221 from 55 countries indicated that chronic hypertension was associated with incidence of 26% for superimposed PE (Bramham *et al.*, 2014). A study in Dr. Soetomo, East Java hospital, Indonesia found stage 2 of chronic hypertension to be associated with urinary protein of +3 (67% vs 21.5%, p = 0.001) and +4 (12.3% vs 0.4%, p = 0.001) (Akhar *et al.,* 2019).

Vestgaard and colleagues in a systematic review, found PE to be 17% among diabetes type 1 patients 5 times more than the background population with associated clinical predictors such as diabetic nephropathy (OR = 3.7 – 23.5), microalbuminuria (OR = 3.8 –11.7), diabetic retinopathy (OR 1.9 – 2.9) and pre-existing hypertension (OR = 3.8 –17.1) (Vestgaard *et al.,* 2018). In a study in Bahir Dar city, Ethiopia consisting of 453 expectant mothers family history of preexisting hypertension and diabetes mellitus were linked with increased risk of developing PE AOR=11.16 (95% CI = 5.41 – 41.43) and AOR = 6.17 (95% CI = 2.11 – 20.33) respectively (Endeshaw *et al.,* 2016).

Meazaw and colleagues found history of maternal PE/eclampsia was linked with increased danger of developing PE (odds ratio = 5.6 and 95% CI range = 1.82 – 9.28) compared with those who have never developed PE/Eclampsia (Meazaw *et al.*, 2020). In a study in Nairobi County, Kenya, history of hypertension was linked with a higher risk of developing PE AOR = 7.1 (95% CI = 2.6 – 19.3), p = 0.001 (Logan *et al.*, 2020). Gutaj et al. (2017) in Poznan, Poland found prevalence of PE to be 9.7% with duration of disease related with a higher chance of developing PE OR = 1.11(95% CI = 1.03 – 1.12) p 0.009. In Bogotá, Colombia, age of menarche of 12 years or more was found to be linked with a higher risk of developing PE = OR 1.7 (95% CI = 1.18 – 2.46) ; AOR = 1.13 (95% CI = 0.44 – 3.90), migraine was found to be related with the elevated risk of developing PE = OR 1.33 (95% CI = 0.65 – 2.71), polycystic ovary was also found to be linked to expanded risk in developing PE OR = 2.07 (95% CI = 0.49 – 8.80), history of PE and intra uterine growth restriction were also related with a higher tendency of of developing PE OR = 6.58 (95% CI = 2.89 – 14.97); AOR = 30.78 (95% CI = 2.65 – 356.73) and OR = 4.54 (95% CI = 1.85 – 11.13); AOR = 11.10 (95% CI = 1.60 – 76.76) respectively (Ayala-Ramírez *et al.*, 2020).

In a case control study in Madhya Pradesh, India, chronic hypertension, diabetes and renal disease were found to be connected with a higher risk of developing PE AOR 6.69 (95% CI 1.37 – 32.75) p 0.02, AOR = 8.66 (95% CI = 1.01 – 76.26) p 0.05 and AOR = 5.60 (95% CI = 1.12- 28.04) p 0.04 respectively (Pandey and Pandey, 2017). Das et al. (2019) in a study in Kathmandu, Nepal involving 4820 pregnant women, found pregnant women who were hypertensive and/or gestational diabetics to have a

higher tendency of developing PE than non-hypertensive or diabetics AOR = 13.64 (95% CI = 4.45 – 41.81) and AOR = 11.79 (95% CI = 3.20 – 43.41) respectively.

In a case control study carried out by Pan and colleagues, matured ovarian teratoma, uterine fibroids and pre-gestational hypothyroidism were establish to be related with high risk for PE with adjusted odds ratios of 7.69 (95% CI = 1.58 – 37.53), 2.24 (95% CI = 1.28 – 3.92) and 5.17 (95% CI = 2.43 –11.00) respectively (Pan *et al.*, 2019). Bernardes and colleagues investigated to determine the risk of recurrence of PE and how the maximum diastolic blood pressure of the previous pregnancies can lead to the development of PE, previous early PE was associated with a risk proportional to that of the maximum diastolic blood pressure recorded in that pregnancy; the recurrence risk for 90 and 100 mmHg and above 110 mmHg were 15% (95% CI = 11.1 – 20.6%) and 26.6% (95% CI = 21.6 – 32.3%) respectively whilst pregnant women who recorded high diastolic blood pressure but no PE in their initial pregnancy were at an expanded risk of 2.2% (95% CI = 2.0 – 2.4%) and 6.3% (95% CI = 5.3 –7.5%) for DBP within the range of 90 to 100 mmHg and above 110 mmHg respectively (Bernardes *et al.*, 2016). In Goma, in the eastern Democratic Republic of Congo, history of maternal PE was connected with an increased tendency of developing PE OR = 12.30 (95% CI = 1.92 – 18.98) p = 0.008 (Richard *et al.*, 2020).

Anaemia

In Bahir Dar City, Ethiopia, anaemia in the first trimester is a predictor of PE AOR 2.80 (95% CI = 1.09 – 7.21) (Endeshaw *et al.*, 2014). Meazaw and colleagues found in fifty- one studies that anaemia during pregnancy was linked with a higher tendency for developing PE with OR = 3.22 (95 % Confidence Interval = 2.70, 3.75)

(Meazaw *et al.*, 2020). In Bogotá, Colombia, anaemia was observed to be linked with higher chance for PE OR = 5.00 (95% CI = 0.55 – 45.11) (Ayala-Ramírez *et al.*, 2020).

The outcome of a survey by the World Health Organization Global indicated that nulliparous and multiparous pregnant women with severe anemia had a high tendency of becoming preeclamptic AOR = 3.74 (95% CI = 2.90 – 4.81) and AOR = 3.45 (95% CI = 2.79 – 4.25) respectively (Chen *et al.*, 2018). In Ghana, an age-matched case control carried out at Obstetrics and Gynaecology Departments Komfo Anokye Teaching hospital and Ridge Regional hospital (Greater Accra Regional hospital), preeclamptics, mean hemoglobin (Hb) was significantly lower among the preeclamptics (10.01 ± 0.73) than the non preeclamptics (13.76 ± 0.80) ($p < 0.001$) (Yeboah *et al.*, 2017).

Family History of PE and Chronic Disease Conditions

Tessema and colleagues in a study in Ethiopia found women having genetically related hypertension and diabetes mellitus to be at an increased risk of developing PE AOR = 7.19 (95% CI = 3.24 – 15.2) and AOR = 2.4 (95% CI = 1.09–5.6) respectively (Tessema *et al.*, 2015). In Jaipur, India, family history of hypertension denoted a significant linked with preeclampsia; AOR = 2.28 (95% CI of 1.27 – 4.09) and p value of 0.007 (Verma *et al.*, 2017). Also Kumar and colleagues found a link between genetically related hypertension and PE in Karnataka, India AOR = 5.48 (95% CI = 1.09 – 27.55) with p value of 0.04 (Kumar *et al.*, 2010).

Inheritable PE/eclampsia was found to be linked with a high tendency of developing PE OR =1.68 (95% CI = 1.26, 2.11) in a systematic and meta-analysis carried out by Meazaw et al. (2020). In Bogotá, Colombia, genetically related PE was found to be connected with a higher risk of developing PE = OR 1.51 (95% CI = 0.97 – 2.37) but was linked with a reduced chance of development of preeclampsia when other factors were included in the model; AOR = 0.91 (95% confidence Interval = 0.20 – 4.12), family history of intrauterine growth restriction was a predictor of PE OR = 1.09 (95% CI = 0.53 – 2.24), family history of cardiovascular disease was found to be related with the elevated risk of developing PE OR = 1.20 (95% CI = 0.74 – 1.96), family history of abortions was linked with a higher tendency of PE development risk PE OR =1.98 (95% CI = 1.09 – 3.60) but upon modification, the association was lost adjusted OR = 0.96 (95% CI = 0.17 – 5.15), family history of stillbirth was linked with a higher tendency of developing PE OR = 1.48 (95% CI = 0.65 – 3.38), family history of preterm was connected with a higher risk of developing PE OR = 1.27 (95% CI = 0.76 – 2.12), family history of diabetes was linked with a stronger tendency of developing PE OR = 1.68 (95% CI = 1.12 – 2.52); AOR= 3.41 (95% CI = 1.09 – 10.67) and history of cancer was linked with a decreased chance of developing PE OR = 0.75 (95% CI = 0.47 – 1.20) (Ayala-Ramírez *et al.*, 2020). In a history of genetically-related high blood pressure was found to be linked with a higher potential of developing PE AOR = 5.84 (95% CI = 1.09 – 27.55) p 0.04 (Pandey & Pandey, 2017).

Low Levels of Vitamins and Minerals

As indicated by discoveries from an EVITA study including 2327 hopeful moms in Pittsburgh, the tendency of developing toxemia diminishes as the Vitamin D fixation

builds (50 nmol per L) and afterward levels at values lower than p = 0.05 while those with groupings of <25 nmol/L, 25 -49.9 nmol/L, and 50 - 74.9 nmol/L had an adjusted danger of toxemia of 2.4 (95% CI = 1.2–4.8), 1.1 (95% CI = 0.69–1.7), and 1.3 (95% CI = 0.89–1.8), individually, when contrasted with those with 75 nmol/L (Baca *et al.*, 2016). Among Canadian cohorts, a fundamentally lower 25 hydroxyvitamin D fixation at a mean gestational age of 14 weeks contrasted non-preeclamptics; mean ± SD 25 hydroxyvitamin D 47.2 ± 17.7 versus 52.3 ± 17.2 nmol/L, P < .0001. Pregnant women with 25 hydroxyvitamin D <30 nmol/L contrasted with those with no less than 50 nmol/L had a more serious danger of developing PE AOR = 2.23 (95% CI = 1.29–3.83) (Achkar *et al.*, 2015).

An associate report completed by Zhao and partners discovered that the expectant mothers who became preeclamptic had impressively less 25 hydroxyvitamin D in blood serum contrasted the individuals who didn't. Once more, pregnant women with serum 25 hydroxyvitamin D inadequacy at 23–28 weeks of growth were strongly connected with expanded chances for extreme PE in the wake of adapting to significant confounders AOR = 3.16 (95% CI = 1.77–5.65) (Zhao *et al.*, 2017). Serum 25 hydroxyvitamin D concentrations in early pregnancy were 56% significantly less among the preeclamptics than the controls; mean of 9.79 ± 4.09 $ngml^{-1}$ (95% CI = 8.71–10.88 $ngml^{-1}$) vs 22.26 ± 15.28 $ngml^{-1}$ (95% CI = 20.0 – 24.52 ng/ml) p <0.001. Vitamin D deficient mothers were at 17 times higher risk of developing PE than their counterparts at early pregnancy and at term (p < 0.001; RR = 17.93). Serum 25 hydroxyvitamin D deficiency was seen as an independent risk factor for PE (Jain *et al.*, 2015).

Wei and colleagues in a prospective cohort study carried in seventeen urban obstetric hospitals, Canada among pregnant women who were participants in a trial of vitamin C and E supplementation for the prevention of PE; a strong positive correlation was seen in maternal 25(OH)D concentrations between the two gestational age windows (r = 0.69, p < 0.0001), mean maternal 25 hydroxyvitamin D concentrations at 24-26 weeks of gestation were significantly lower in women who subsequently developed PE compared with those who did not (mean ± SD: 48.9 ± 16.8 versus 57.0 ± 19.1 nmol/L, p = 0.03), women with 25 hydroxyvitaminD < 50 nmol/L at 24 – 26 weeks gestation experienced an increased risk of PE AOR = 3.24 (95% CI = 1.37 – 7.69), whereas the association was not statistically significant for maternal 25(OH)D level at 12 – 18 weeks of gestation (Wei *et al.*, 2012).

In study in America, the risk of developing PE increased by approximately 3 fold (95% CI = 1.28 – 6.41) for women with vitamin D concentration of < 20 ng per ml (Scholl *et al.*, 2013). Prevalence of low calcium among preeclamptics was 66 (60%) (Saeed *et al.*, 2017). Bodnar et al. (2014) in a case cohort study among women enrolled at 12 U.S. sites in the Collaborative Perinatal Project, found Maternal 25(OH)D 50 – <75 $nmolL^{-1}$ to be linked with a decrease in the absolute and relative risk of PE and mild PE than 25 hydroxyvitamin D <30 $nmolL^{-1}$, but the effects were no longer present after adjustment for confounders. For severe PE, 25 hydroxyvitamin D ≥50 $nmolL^{-1}$ was linked with a decrease of 3 cases per 1,000 pregnancies adjusted RD = −0.003 (95% CI = −0.005 – 0.0002) and a 40% reduction in risk aRR = 0.65 (95% CI = 0.43 – 0.98) than 25hydroxyvitamin D <50 nmol/L.

In a study in Qazvin, Iran, mean serum vitamin D level was 27.7 ± 15.3, 22.9 ± 15.9, and 27.6 ± 16.6 for normal, mild PE and severe PE groups respectively (P > 0.05), also vitamin D deficiency was not different between the groups. Calcium deficiency was more frequent among severe preeclamptic group than their counterparts (25.9% vs. 6.6%, p 0.017) and was linked with severe PE OR = 6.7 (95% CI = 1.45 – 30.79) p 0.015 (Hashemipour *et al.,* 2017). In a study by Benachi and colleagues comprising of 83 preeclampsia cases and 319 non preeclamptics, the mean 25 hydroxyviamin D values recorded in the first trimester were $20.1 \pm 9.3\ ngmL^{-1}$ in PE cases and $22.3 \pm 11.1\ ngmL^{-1}$ in non preeclamptic ($p = 0.09$). The chance for PE with 25 hydroxyvitamin D level $\geq 30\ ngmL^{-1}$ in the first trimester was low and insignificant OR = 0.57 (95% CI = 0.30 –1.01) p = 0.09. High levels of 25 hydroxyvitamin D however during the 3rd trimester was linked with a sufficiently low chance of PE OR 0.43 (95% CI = 0.23 –0.80) p = 0.008. For women with 25 hydroxyvitamin D levels <30 ng/mL both in the first and 3rd trimesters ("low-low") as references, the odds ratio for PE was 0.59 (95% CI = 0.31–1.14) p = 0.12 for "low-high" or "high-low" women and 0.34 (95% CI = 0.13 – 0.86) p = 0.02 for "high-high" women (Benachi *et al.,* 2020).

PE was significantly increase in the folic acid group than the control group in crude analyses 17.2% versus 9.9%, relative risk of 1.75 (95 % CI = 1.06 –2.88), p value 0.029. Multivariable analyses nullified this effect, rendering it not statistically remarkable RR = 1.58, p value 0.079 (Corsi *et al.,* 2020). In a nested case - control and meta-analysis, 25 hydroxyvitamin D concentrations were significantly lower in preeclamptics than controls; median (IQR), preeclamptics versus controls: 43.3 (35.5, 55.2) versus 47.5 (37.6, 60.4) nmol/L, p = .014. For women with 25 hydroxyvitamin

D <50.0 nmol/L, had a 65% increase in preeclampsia risk (95% CI = 1.02 – 2.69) as compared with women with 25 hydroxyvitamin D concentrations from 50.0 to 74.9 nmol/L. The meta-analysis showed that low 25 hydroxyvitamin D were linked with a significantly increased risk of developing PE by 62% pooled OR = 1.62 (95% CI = 1.36 –1.94) and the risk effect of low 25 hydroxyvitamin D existed in most subgroups (Yuan *et al.,* 2019).

In a study in Osun State, Nigeria, mean serum concentrations of zinc, copper, selenium, manganese and magnesium were significantly lower $p < 0.05$ among preeclamptics than the control group (Akinloye *et al.*, 2010). In addition, Okoror and colleagues in a study found levels of serum Ca^{2+} to be 7.73 + 1.24 verses 9.17 + 0.77; $p < 0.001$, Ca^{2+} - Mg^{2+} ratio 3.36 + 0.60 verses 3.83 + 0.41; $p = 0.001$ and Mg^{2+} 2.35 + 0.35 verses 2.41 + 0.16; P=0.469 to be lower among cases. A negative correlation was established between the Serum Ca^{2+} level and SBP (r = -0.45, p 0.05) and DBP (r =0.50, p 0.010). Hypocalcemia was a risk factor for PE AOR = 7.63 (95% CI = 1.64 – 35.37) (Okoror *et al.*, 2020).

Darkwa et al. (2017a) in a study in Accra, Ghana found mean serum magnesium and total calcium levels in preeclamptics to be 0.70 ± 0.15 and 2.13±0.30 mmol/L and mean serum magnesium and total calcium levels among controls to be 0.76 ± 0.14 and 2.13 ± 0.35 mmol/L with significant difference. Furthermore, Darkwa and colleagues also found a significantly decreased $p < 0.001$ serum sodium levels in preeclamptics mean = 136.13; SD = 4.17 mmol/L compared to normotensive pregnant women (mean = 142.17; SD = 5.66 mmol/L). There was a significantly decreased ($p < 0.001$) serum potassium levels in preeclamptics (mean = 3.45; SD = 0.54 $mmolL^{-1}$) than

normotensive pregnant women (mean = 3.98; SD = 0.36 mmolL^{-1}) (Darkwa *et al.*, 2017a).

A meta-analysis carried out by Fu et al. (2018) results showed that vitamins supplementation could decrease the risk of PE (RR = 0.74, 95%CI = 0.64–0.86), findings of analysis of non-randomized controlled trial (RCT) indicated a significant link between vitamins supplementation with risk of developing PE (RR = 0.60, 95% CI = 0.42 – 0.85) and a vice versa was found for the randomized controlled trial studies. Furthermore, subgroup analysis by vitamin type among RCT studies indicated that vitamin D and multivitamin supplementation could significantly decrease the risk of PE (RR = 0.41, 95% CI = 0.22 – 0.78) and (RR = 0.69, 95% CI = 0.51– 0.93) respectively. Hovedenak and Haram in their literature review on the effect of vitamin and mineral supplementation on pregnancy outcome indicated that calcium, vitamin D and vitamin B6 deficiency as well as low selenium and vitamin C is associated with PE and supplementation of these minerals and vitamins may be beneficial with exception of vitamin E supplementation which findings claim may have harmful effect on pregnancy outcome (Hovdenak and Haram, 2012).

From a Cochrane Database Systematic review, calcium supplementation caused a decrease in the average risk of hypertension and the average risk for PE RR0.65, 95% CI = 0.53 to 0.81) and (13 trials, 15,730 women: RR 0.45, 95% CI 0.31 to 0.65) respectively with the impact been strongest among women who are at a potentially high risk (RR 0.22, 95% CI 0.12 – 0.42), and those with low baseline calcium intake (RR 0.36, 95% CI 0.20 – 0.65) (Hofmeyr *et al.*, 2014). In a clinical preliminary which expected to decide the impact of nutrient Vitamin D enhancement on lessening the

likelihood of intermittent toxemia, 72 patients were set in the benchmark group (2.8% had twin pregnancies) while 70 patients were randomized to the intercession bunch (all had singleton pregnancies). The intercession bunch got a 50000 IU pearl nutrient Vitamin D3 once every two weeks while the benchmark group was managed with control treatment until the 36th seven day stretch of pregnancy. The patients in intercession bunch had altogether decrease (p 0.036) likelihood of creating toxemia than patients in the benchmark group. The danger of toxemia for the benchmark group was 1.94 times elevated compared to that for the intercession bunch (95% CI = 1.02 – 3.71) (Sasan *et al.*, 2017).

The results of a systematic review and meta-analysis involving twenty-seven RCTs with 28,000 women by Khaing *et al.* (2017) indicated that calcium, vitamin D and calcium plus vitamin D have the tendency to reduce PE development. In the mean serum level of 25 hydroxyvitamin D in PE group was significantly lower than that in the healthy group (15.27 ± 3.52 vs. 23.84 ± 6.93, $p < 0.001$) and women deficient in 25 hydroxyvitamin D had an increased tendency of developing PE (odds ratio $= 4.79$ and 95% CI $= 1.45 – 9.87$) at $P = 0.01$ (Pashapour *et al.*, 2019). Mardali and colleagues found serum vitamin B_{12} level lower among preeclamptic women compare with non-preeclamptic (mean, -15.24 $pgmL^{-1}$ $p < 0.015$) (Mardali *et al.*, 2020).

In a study conducted in Sokoto, Northwestern Nigeria, a significant reduction levels of vitamins A and C were found among the women with PE (1.52 ± 1.68 and 0.14 ± 1.33) $p < 0.0001$ (Shehu *et al.*, 2020). In a study at Bydgoszcz, Poland, preeclamptics had a lower level of serum 25 hydroxyvitamin D compared with the controls (14.75 vs. 22.10 ng/mL, p 0.0021) and low level of serum hydroxyvitamin D was also found

to be a significant predictor on the receiver operating characteristics analysis (AUC = 0.70, $p < 0.01$) (Domaracki *et al.*, 2016). In a randomized controlled study, mean maternal 25[OH]D level increased significantly among the pregnant women in the group who received 4000IU compared with those in the group 1 who received 400IU (group 2 from 16.3 ± 5 nmol/mL to 72.3 ± 30.9 nmol/mL and group 1 from 17.5 ± 6.7 nmolMl^{-1} to 35.3 ± 20.7 nmolmL^{-1}) $p > 0.0001$.The relative risk reduction for attaining ≥75 nmolL^{-1} before delivery was significantly higher RRR 93.2 (95% CI 79–98] for those treated with 4000 IU. Fewer cases of PE were reported among the group 2 pregnant women compared with the those in group 1 (8.6% versus 1.2%; $p < 0.05$) of the total incidence of 4.3% (Ali *et al.*, 2019).

Hamedanian and colleagues carried out case-control study involving pregnant women recruited among referrals to Kamali and Alborz General Hospital, Karaj City, Iran, found serum vitamin D level to be lower among the preeclamptics compared with non preeclamptics (6.12 (4.57 – 11.21) vs 5.18 (7.67 – 18.83) whiles serum phosphorous level was higher among the preeclamptics compared with the non preeclamptics 4.08 ± 0.84 vs 3.92 ± 0.71 (Hamedanian *et al.*, 2019).In a study conducted in Ibadan, Nigeria, preclamptic women had significantly decrease levels ($p < .05$) of Vitamin D at 20 weeks, 30 weeks and postpartum (24.5±4.6 vs 36.59±5.1), (23.8±3.9 vs 34.14±3.7), and (21.7±5.5 vs 32.62±3.2) respectively compared with the non-preeclamptic group (Sonuga *et al.*, 2017). In India, the total serum calcium level was <8.2 mg/dL and was found to be linked with a higher tendency of developing PE than with controls OR = 10.8 (95% CI = 7.437 – 7.806) $p < 0.05$ (MiSra *et al.*, 2020).

Xiao and colleagues in a study in Wuxi, Jiangsu Province, China, found the mean serum vitamin D level among the women with PE to be significantly lower compared with those who were not preeclamptic 33.05 ± 4.10 vs 38.06 ± 6.28 with vitamin D deficiency been associated with increased risk for PE = OR 2.83 (95% CI = 1.32 – 6.08) (Xiao *et al.*, 2017). Kumari et al. (2017) in a case-control study carried out at the BRD Medical College, Gorakhpur, Uttar Pradesh, India, found the mean serum vitamin D among the preeclamptics to be significantly lower than that of the controls 11.53 ± 6.22 ng/ml vs 24.25 ± 14.44 ng/ml $p < 0.05$.

In USA, the mean serum 25 hydroxyvitamin D was lower among the preeclamptics compared with the non preeclamptics (29.99 ng/mL; 95% CI: 29.40 – 30.58 ng/mL) and (33.7 ng/mL; 95% CI: 33.20 – 34.30 ng/mL) respectively and pregnant women with vitamin D deficiency were at a higher tendency of developing PE OR = 2.18 (95% CI =1.80 –2.64) (Serrano *et al.*, 2018).

In the Democratic Republic of Congo a study involving expectant mothers recruited from seven hospitals, the median serum 25 hydroxyvitamin D level among the women who developed PE were less than that of the non preeclamptics (21.7 [(IQR) = 19.2 – 24.1] $ngml^{-1}$ versus 28.5 [IQR = 24.9 – 31.4] $ngml^{-1}$); ($p < 0.001$) and vitamin D deficiency was identified to be linked with a surge in the development of PE OR = 2.77 (95% CI =1.22 – 6.31) p = 0.015 (Richard *et al.*, 2020).

In a similar study carried out at the Medical center Imo state, Nigeria, selenium level in serum was found to be lesser among the preeclamptics compared with non preeclaamptics (0.67±0.27µmol/l) and (1.20±0.46µmol/l) respectively $p < 0.001$ (Eze

et al., 2020). Fasanu et al. (2020) in a study conducted in Osun State, Nigeria also reported the preeclamptics to have had a significantly reduce plasma calcium level than that of the non preeclamptics 1.65 ± 0.37 $mmolL^{-1}$ and 2.09 ± 0.36 $mmolL^{-1}$ $p < 0.001$ respectively and this observation was similar to report of a study involving expectant mothers of Nigeria's Ebonyi state where serum calcium and magnesium concentrations were shown to be significantly below values recorded for preeclamptics visa vie that of the non preeclamptics (13.9 [3.3] vs. 14.0 [5.7] μgdl^{-1}) $p < 0.0001$ and (3.22 [1.05] vs. 4.15 [0.78]) respectively (Ugwuja *et al.*, 2016).

In Ghana, an age-matched case control carried out at Komfo Anokye Teaching hospital and Ridge Regional hospital (Greater Accra Regional hospital), preeclamptics also had significantly lower levels of serum calcium and magnesium compared with the non preeclamptics (1.53 ± 0.90, 2.36 ± 0.17) and (0.56 ± 0.08, 0.88 ± 0.08) respectively ($p < 0.001$) (Yeboah *et al.*, 2017).

Poor Dietary Intake

Among 65,220 singleton pregnancies in the Danish National Birth Cohort recruited into a prospective cohort study, 1302 developed PE of which 301 were severe. Women in the top quintile of docosahexaenoic acid intake had a reduce tendency of developing PE RR = 0.67 (95% CI = 0.51–0.89) and severe preeclampsia RR = 0.46 (95% CI = 0.25 – 0.83) than women in the bottom quintile. Women who were able to meet ≥250 mg/day intake of eicosapentaenoic acid (EPA) + DHA had a lesser risk of severe PE RR = 0.77 (95% CI = 0.60 – 0.99), but not of PE RR = 0.93 (95% CI = 0.82 –1.05). On the other hand, alpha-linolenic acid intake was linked with elevated risk of severe PE RR = 1.71 (95% CI = 1.07 – 2.75) (Arvizu *et al.*, 2019).

In Bahir Dar City Administration, Ethiopia, women who took coffee when pregnant had an elevated odds of developing PE (AOR = 2.16, 95% CI = 1.32, 3.53), fruit, vegetable consumption as well as folate intake were found to reduce the likelihood developing PE AOR = 0.37 (95% CI = 0.19, 0.73), AOR = 0.45 (95% CI = 0.22, 0.91), AOR = 0.19 (95% CI = 0.10, 0.37) respectively (Endeshaw *et al.*, 2014). Yusuf and colleagues found saturated fat and fat consumption was highly linked with the development of PE whilst the consumption of fruits and olive oil were protective against the development of PE OR = 6.40, (95% CI = 1.85 – 22.17), OR = 3.35 (95% CI = 1.0 –11.54) OR = 0.16 (95% CI = 0.47– 0.55) and OR = 0.20 (95% CI = 0.05 – 0.78) respectively (Yusuf *et al.*, 2019).

Summer/Pollution

Discoveries from Janani and Changaee review examination led among in excess of 8,000 expectant mothers showed that the occurrence of PE was most elevated among expectant mothers who delivered in July and August at prevalence of 4.7% and 4.5% respectively (Janani and Changaee, 2017). For a situation control study in Kinshasa urinary discharges of 14 metals were altogether elevated in preeclamptics than in non preeclamptics lead: GM 61 µg/day (25th–75th %ile 8–345) in preeclamptics versus 9 µg/day (25th–75th %ile 3–21) in non preeclamptics ($p < 0 \cdot 001$) and this happened uniquely in the harmattan (Moyene *et al.*, 2016).

Wang and colleagues found the risk of PE increasing with increasing quartiles of particulate matter 10 microns and sulphide dioxide exposure and significant interaction between particulate matter 10 microns and dew point on PE with negative consequences of particulate matter 10 microns rising with dew point. A null link

between particulate matter 10 micron and PE under dew point < 5th %ile was also observed. The risk of PE rose by 23% (95% CI = 19 – 26%) for 5th < dew point < 95th %ile, and by 34% (16 – 55%) for dew point > 95th %ile. Effect of air pollution on the development of PE is more pronounced in autumn/winter period (Wang *et al.*, 2018).

Auger and colleagues in a population-based study in Montreal discovered that PE was higher in women who were exposed to higher levels of environmental noise pollution (LAeq24h 65 dB(A) = 37.9 per 1000 vs. 50 dB(A) = 27.9 per 1000). A LAeq24h of 65.0 dB (A) insignificantly linked with PE development risk odds ratio = 1.09 (95 % CI = 0.99 –1.20) when compared to 50 dB (A). However, for the severe form of PE, the odds ratio was 1.29 and with early onset odds ratio was 1.71 PE, associations were found, with results consistent across all noise indicators (Auger *et al.*, 2018).

In a retrospective cohort study involving 110064 women who gave birth in hospitals in the Norwegian cities of Stavanger and Bergen, 2799 developed late-onset PE (2.5 %) and 348 developed early-onset PE (0.3 %); pre-gestational allergy was found to increase the tendency of developing early-onset PE with an odds ratio of 1.7 and to reduce the danger of PE onset occurring late OR = 0.8 (95 % CI = 0.8–0.9) (Sande *et al.*, 2018). The lead concentration in the blood was linked with PE OR = 9.81 p 0.005 (Poropat *et al.*, 2018).

Maternal exposure to particulate matter 2.5 microns (per 10 $\mu g/m^3$ increment) elevated the chance of developing PE OR = 1.32 (95% CI = 1.10 - 1.58%) and the pregnant women were more susceptible during the third trimester (Yu *et al.*, 2020).

Assibey-Mensah et al. (2020) in a retrospective cohort study extracted from medical records of 20 596 live births to female residents of Monroe County who delivered at either Strong Memorial Hospital or Highland Hospital in Rochester, NY, found every 3.64 µg/m^3 rise in fine particle concentration to be linked with a higher tendency of developing early-onset PE during the first trimester, second trimester and third trimester to be OR = 1.35 (95% CI = 1.08 –1.68]), OR = 1.51 (95% CI = 1.23 – 1.86), OR = 1.25 (95% CI = 1.06 –1.46) respectively.

In a study in Taiyuan, China among pregnant women who came to deliver, chromium, mercury and arsenic were found to be linked with a higher tendency of developing PE OR = 1.76 (95% CI = 1.18 – 2.62 for middle vs low); OR = 1.90(95% CI = 1.22 – 2.93 for high vs low), OR = 1.60 (95% CI = 1.08 – 2.38 for high vs low) and OR = 1.64, 95% CI = 1.07, 2.52 for the middle vs. low) respectively (Wang *et al.*, 2020). Eugene and Isaac in a case series observational study which was carried out in Niger Delta University Teaching Hospital, found the prevalence of PE/ eclampsia to be 6.7% and 7.9% during the wet and dry seasons respectively (Eugene and Isaac, 2020).

In a study in Sweden, women in the highest quintile of black carbon exposure were at an elevated risk of developing PE than those in the lowest quintile in the third trimester AOR = 1.35 (95% CI = 1.11–1.63),for the entire pregnancy, every increment of 5 µg/m^3 of the locally emitted particulate matter 2.5 microns was linked with a higher risk for PE development AOR = 2.74 (95% CI = 1.68, 4.47) (Mandakh *et al.*, 2020). Song et al. (2017) found out that preeclamptics had a higher serum copper level standardized mean ratio compared with the non preeclamptics (95% CI): 1.05

(0.34, 1.77), Z = 2.88, P for Z = 0.004; I^2 = 96.9%, P for I^2< 0.0001. In a study in Massachusetts, USA, urinary chromium was linked with PE HR = 3.48 (95% CI = 1.02 – 11.8) (Bommarito *et al.*, 2019).

Smoking, Low Physical Activity and Anxiety

Nakagawa and partners in an examination in Hawaii, discovered smoking to be independently connected with an expanded danger of developing preeclampsia OR = 1.199 (5% CI = 1.07 – 1.33) (Nakagawa *et al.*, 2016). In a Makassar City, Indonesia, 17 (68%) were presented to tobacco smoke; the link between tobacco smoke openness and toxemia was measurably noted (p 0.046) (Eriyantia *et al.*, 2020).

Kharkova and partners in an investigation in Russia, discovered a dose reaction connection; quantity of cigarettes smoked/day of pregnancy and the danger of developing toxemia/eclampsia, there was no distinction in this danger among women who smoked previously and during pregnancy and the individuals who did as such before but not during pregnancy AOR = 1.10 (95% CI = 0.91–1.32) (Kharkova *et al.*, 2017). Do and partners in a prospective investigation of 189 pregnant women with prior diabetes who developed PE in early pregnancy detailed a higher stationary conduct (15 MET-h/week (7 – 18) versus 7 (4 – 15) p 0.04) adapting to parity, diastolic pulse and smoking, the affiliation was change (p = 0.13) (Do *et al.*, 2020).

For a situation control study including equivalent numbers of preeclamptics and healthy mothers alluded to Health centers, a significant alliance among anxiety and PE (P< 0.001) was seen among 26.7% of the expectant mothers who developed PE and 10.7% of healthy expectant mothers. Anxiety has the propensity of expanding the

rate at which an eager mother can foster PE 2.90 times with a odds proportion of 2.90 and a 95% CI 1.46 – 4.26) (Kordi *et al.*, 2017). Endeshaw and partners in a study in Bahir Dar city, Ethiopia discovered absence of physical activity to be unequivocally connected with PE development with an adjusted odds proportion of 3.33 (95% Confidence Interval of 1.35 – 8.17) (Endeshaw *et al.*, 2016). In a settled case-control study in San Ignacio, Bogotá, Colombia smoking during pregnancy was connected with decreased inclination for PE advancement OR = 0.96 (95% Confidence Interval of 0.58 – 1.59) (Ayala-Ramírez *et al.*, 2020).

Blood Group O, A and AB

In a study carried out at Khartoum, Sudan pregnant women with blood group O were at an increased risk of developing PE compared with non-blood group O pregnant women OR = 1.78 (95% CI = 1.088 – 2.934) p = 0.022 (Elmugabil *et al.*, 2016). Mukhtar and colleagues found in a study in Kano, Nigeria, expectant mothers with blood group A and AB to be at a higher risk of developing PE OR = 1.243 (95% CI = 0.561 – 2.754) p 0.59 and OR = 1.699 (95% CI= 0.546 – 5.281) p 0.36 respectively whilespregnant women with blood group B were less likely to develop PE compared with pregnant women with blood group O (Mukhtar *et al.*, 2019) .

Infections

Bellos and colleagues in a systematic review to determine the correlation between PE and infection by involving fourteen studies comprising of 9787 women, Helicobacter pylori IgG seropositivity was significantly highly prevalent in preeclamptics than non preeclamptics (9391 women, OR= 2.32 (95% CI = 1.55, 3.46) with the frequency of anti-CagA antibodies also higher among preeclamptics (3275 women, OR = 3.97,

95% CI [1.55, 10.19]) (Bellos *et al.*, 2018). In Bahir Dar city, Ethiopia, urinary tract infections during the current conception is linked with greater than before risk of developing PE AOR = 6.58 (95% CI = 2.93 – 14.73) (Endeshaw *et al.*, 2016).

Hill and colleagues in a retrospective cohort found C. trachomatis infection to be significantly linked with term preeclampsia adjusted RR 1.88 (95% CI 1.38 – 2.57) (Hill *et al.*, 2020). In a meta-analysis by Yan et al. urinary tract infection was found to increase ones risk of developing preeclampsia OR = 1.31 (95% CI = 1.22–1.40) (Yan *et al.*, 2018). On the contrary, Ayala-Ramírez and colleagues in a study in Bogotá, Colombia, found urinary tract infection to be related with an elevated risk of developing preeclampsia OR = 1.05 (95% CI = 0.71 – 1.55) but it was not significant (Ayala-Ramírez *et al.*, 2020). Das and colleagues in a retrospective study carried out in Paropakar Maternity and Women's Hospital, Kathmandu, Nepal found pregnant women with urinary tract infection to be at an elevated risk of developing PE than those who do not have it AOR = 6.89 (95% CI = 1.28 – 36.95) (Das *et al.*, 2019).

Kaduma and colleagues in a study in Mwanza city, Tanzania among admitted pregnant women found preeclamptics having 8 fold odds of having significant bacteriuria than the non preeclamptics OR=7.7 (95% CI 4.11 –14.49); p-value <0.001 (Kaduma *et al.*, 2019). In a Khartoum, Sudan study, maternal serum IgG seropositivity for rubella (92.2% versus 34.4%, $p < 0.001$) and HSV-2 (87.8% versus57.8%, $p < 0.001$) to be significantly higher in preeclamptics than in the non preeclamptics. Pregnant women with rubella and HSV-2 had a high tendency of developing PE than the controls OR = 4.93 (95% CI = 2.082 –11.692) $P < 0.001$ and

OR = 5.54 (95% CI = 2.48 – 12.38) p < 0.001 IgG seropositivity respectively (Alshareef *et al.,* 2017).

In a study, pregnant women with periodontal disease were found to have a significantly increased tendency of developing PE OR = 2.79 (95% CI = 2.01–3.01) p <0.0001(Wei *et al.,* 2013). Shetty and colleagues found out that pregnant women with periodontitis at enrollment or within 48 hours of delivery may be at an increased risk of developing PE; Odds = 5.78 (95 % CI = 2.41 –13.89) and OR = 20.15 (95% CI = 4.55 –89.29) respectively (Shetty *et al.,* 2010). Politano et al. (2011) in a case control study involving pregnant women at two reference hospitals in Campinas, São Paulo, Brazil, found women who have developed periodontitis to be at a higher risk of developing PE AOR = 3.73 (95% CI = 1.32 –10.58. Silva and colleagues in study conducted in Recife, Brazil found women who developed periodontitis to be at a significantly elevated risk of developing PE AOR = 8.60 (95% CI = 3.92 – 18.88) p <0.001 (da Silva *et al.,* 2012).

In Naples, Italy pregnant women infected with human immunodeficiency virus were at a notably higher risk for PE;AOR = 2.68 (95% CI = 1.96 – 3.64) with (4.0% than 2.0%; adjusted OR = 2.03, 95% CI = 1.26 – 3.28) (3.5% than 1.4%; adjusted OR = 2.50, 95% CI = 1.51–4.15) (6.6% than 2.6%; adjusted OR = 2.64, 95% CI = 1.82 – 3.85) been increased risk of developing preeclampsia with severe features, early onset PE and late onset PE respectively (Sansone *et al.,* 2016). Pregnant women who had developed Hepatitis has been found to be at a higher risk of developing PE than those who do not have hepatitis OR = 2.86 (95% CI = 1.41–5.79) p 0.003 (Ahmed *et al.,* 2018).

Assisted Reproductive Technology

Blazquez et al. (2018) observation involving 433 expectant mothers who were impregnated through assisted reproductive technology (oocyte and sperm donation and only oocyte donation), found that those impregnated by donation of both oocyte and sperm were at an increased risk of early PE than those impregnated by the donation of only oocyte with an OR = 3.02 (95% CI = 1.11–8.24; p = 0.031) but there was no difference in the risk of developing term PE (OR = 0.26, 95% CI = 0.03–1.98; p = 0.19). There was a significantly higher incidence of preeclampsia among women who conceived by means of in vitro fertilization than those with spontaneous pregnancies (6.1% vs. 1.0%, p < 0.01). Severe PE was more common among women in the singleton in vitro fertilization-preeclampsia group than in singleton who conceived spontaneously-preeclampsia group (40% vs. 24.1%, p 0.025) (Gui *et al.*, 2020).

Masoudian and colleagues indicated that the risk of preeclampsia was higher in oocyte-donation pregnancies than other methods of assisted reproductive technology OR = 2.54 (95% CI = 1.98 – 3.24) p < .0001 or natural conception OR = 4.34 (95% CI = 3.10 – 6.06) p < .0001 (Masoudian *et al.*, 2016). A significant increase in preeclampsia was found among women who conceived by assisted reproductive technology than those who conceived spontaneously (RR = 1.71, 95% CI = 1.11 – 2.62, p = 0.015) (Almasi-Hashiani *et al.*, 2019).

Furthermore a systematic and meta-analysis carried out by Omani-Samani et al. (2020) indicated considerable heterogeneity among studies (Q = 15 415.61, df = 71, p < .001, I^2=99.5%) and the pooled estimate of preeclampsia risk using the

random effects model was 10.8% (95% CI = 9.10 – 12.5). Schwarze and colleagues' review and analysis found pregnant women who conceived by means of donor oocytes to be at a notably higher risk of developing PE RR 2.62 (95% CI = 2.13 – 3.21) (Schwarze *et al.*, 2018). Allen and colleagues found pregnant women who conceived by means of a donor sperm to have a higher tendency of developing PE compare with pregnant women who conceived with partners' sperm relative risk 1.49 (95% CI =1.05 2.09) (Allen *et al.*, 2020).

2.2 Oedema in Pregnancy

The triad of severe preeclampsia is often described as a combination of hypertension, oedema and proteinuria but oedema does not necessarily denote abnormality even though oedema has been noted to be linked with a higher risk of preeclampsia (MacGillivray and Campbell, 1980). Agyare et al. (2018) carried out a longitudinal study in Accra, Ghana, the prevalence of oedema at any point during pregnancy was 33.7% and oedema was significantly associated with mean systolic blood pressure (p-value 0.006) but not mean diastolic blood pressure (p-value 0.74). Timing of initiation of iron and folic acid supplementation and gestational weight gain were the nutritional factors significantly associated with oedema at $\alpha < 0.2$ in the bivariate analyses and in the multivariate logistic model, the initiation of iron and folic acid supplementation after completing the first trimester (compared to the first trimester) was linked with more than 3-fold higher odds (95% CI) of developing oedema at any point during pregnancy AOR = 3.3 (95 % CI =1.1, 10.1); p-value 0.034.

2.3 Other Previous Works Carried Out in Ghana

In Ho, Ghana, first trimester serum leptin level (p <0.0001) and body fat %age (p <0.0001) were notably elevated in those who developed preeclampsia than those who did not; with triglycerides (p 0.8600), total cholesterol (p 0.5620), high-density lipoprotein (p 0.5880), low-density lipoprotein (p 0.4870) and very low-density lipoprotein (p 0.6540) showing no significant difference between preeclamptics and non preeclamptics (Yeboah *et al.*, 2017).

Ababio and colleagues observed that the factor V Leiden mutation was more in preeclampsia and hypertensive patients. Elevated white blood cells, uric acid and a three-fold increment of AST/ALT ratio was also observed in preeclamptics when stratified by factor V Leiden exons (exon 8 and 10) (Ababio *et al.*, 2019).

Tetteh et al. (2013) found pre-eclamptic group had notably (p = 0.0006) elevated urinary isoprostane excretion (2.81 ± 0.14 ng/mg creatinine) compared with the control group (2.01 ± 0.18 ng/mg creatinine) and a notably (p = 0.0008) reduced total antioxidant power (1.68 ± 0.05 mM) compared with the control group (1.89 ± 0.04 mM). The difference in the plasma levels of nitric oxide in preeclamptic (Mean = 1178.78; SD = 89.70 nM) compared to healthy pregnant women (Mean = 1365.43; SD = 95.46 nM) were not statistically significant (p-value = 0.160) (Darkwa *et al.*, 2018).

Fondjo and colleagues found prevalence of inadequate and adequate knowledge of preeclampsia to be 88.6% (mean 55.5 ± 4.3%) and 11.4% (mean 76.3 ± 5.9%), respectively. For participants with adequate knowledge of PE, 9.1% (mean 67.4 ±

6.9%) and 2.3% (mean 85.2 ± 5.1%) had moderate and high knowledge, respectively. Being older (> 35 years old) [cOR = 3.09, 95%CI (0.88 – 10.88), p = 0.049] and having a higher level of education (> SHS education) [cOR = 4.45, 95%CI (2.18 – 9.10), p < 0.0001] elevated the individual's chances of having adequate knowledge of PE. After controlling for potential confounders in multivariate logistic regression analysis, we found higher level of education to be independently linked with adequate knowledge of PE OR = 2.87 (95% CI = 1.31 – 6.30) p 0.008 (Fondjo *et al.*, 2019).

In a case control study carried out among 69 non-preeclamptics and 65 preeclamptics, placental malaria (PM) was 64 (48.1%) and 21 (15.8%) respectively for active and past infections and these proportions were notably greater in the preeclamptic group than the non-preeclamptic group. Further multivariate analyses showed placental pathology, active PM and past PM are to be associated with PE AOR = 3.0 (95% CI = 1.2 – 7.5), AOR = 6.7 (95% CI = 2.3 – 19.1) and AOR = 12.4 (95% CI = 3.0 – 51.0) respectively (Obiri *et al.*, 2020).

In summary, PE is a hypertensive disorder that is developed during pregnancy with associated symptoms; high SBP (≥ 140 mmHg), high DBP (≥ 90 mmHg), proteinuria (+ 3) and sometimes oedema. Theories have been stated relating it to a car with accelerator and brake where the accelerators are imbalance in angiogenic milieu, inflammations and oxidative stress whilst the brake system comprises of haem oxygenase and cysthathionine. A malfunction in the braking components leads to the development of PE. Primiparity, nulliparity, multiple pregnancies, estimated overweight/obesity condition at the pre-pregnancy stage, disproportionate weight added from the time of conception until birth, short/long pregnancy interval, extremes

of maternal age, short parental height, short duration of sperm exposure/short cohabitation, high blood pressure reading at first ante natal clinic booking, non-white race, low socioeconomic status, unmarried status (women), personal and family history of PE and other chronic health conditions, anaemia, low level of vitamins and minerals, poor dietary intake, summer/pollution, smoking , low physical activity, anxiety, blood group O, infections and assisted reproductive technologies among other factors have been found to increase ones risk of developing PE significantly or insignificantly.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Research Design and Setting

The research was designed as prospective cohort study. The study took place at the Ghana Police Hospital, Cantonment, and the University of Ghana Hospital, Legon, both in Accra. These two hospitals are highly patronized by people of different socioeconomic status from the different suburbs of Accra. The Police Hospital was established for Police personnel and their dependents in 1976. Since1980, the hospital has rendered services to civilians, who currently constitute over 80% of out-patient attendees. The hospital is made up of the following departments and units: Out Patient Department, Records, X-ray and Laboratory, Anesthesia, Public Health, Physiotherapy, Pharmacy, Dental, Ear, Nose and Throat, Intensive Care, Pediatrics, Operating Theatre, Accident and Emergency, Dialysis, Obstetrics and Gynecology. The department of Obstetrics and Gynecology is headed by a Consultant (Ghana Police Service, 2017).

The University of Ghana Hospital was initially built to offer services to the University community. However, in 1976/77 as the community started developing, the residents of its fast-growing environs began to seek health care from the Hospital. In recognition of the extension of services to people outside the University community in 1976/77, the Ministry of Health (MOH) readily accepted to assist the hospital yearly with drugs, supplies equipment and instruments. This arrangement worked quite well until 1986/87 when the "cash-and- carry" system was introduced and the assistance to the hospital ceased. The Hospital readily continues to offer its services to these people. The hospital now serves as a District Hospital. It is made up of the following

departments and units: Out Patient Department, Records; X-ray, Laboratory, Anesthesia, Public Health, Physiotherapy, Pharmacy, Dental, Ear, Nose and Throat, Pediatrics, Operating Theatre, Public Health, Accident and Emergency and Obstetrics and Gynecology. The department of Obstetrics and Gynecology is headed by a Consultant (University of Ghana Health Service).

3.2 Subject Recruitment and Selection

The number of pregnant women recruited into the study was 403; 269 from Ghana Police Hospital and 134 from University of Ghana Hospital based on the number of attendees on a weekly basis. The entire study lasted for 21 months (May, 2018 – Feb. 2020). The women were contacted on arrival at the Outpatient waiting area and their consent requested after briefing them on the study. Participants who were willing to partake in the study were taken through screening interview in which they were asked if they have or have ever developed any of the following health conditions: diabetes mellitus, hypertension, renal disorders, liver disorders, gestational hypertension and PE. Women were eligible if they have not ever developed any of the disease conditions mentioned and were at 20 weeks or less of gestation and intended to attend antenatal clinics at the Police and University of Ghana Hospitals till 6 weeks postpartum. Pregnant women were followed up at 28 – 32 weeks (midline) to collect dietary, lifestyle, anthropometric, biochemical, clinical data and also to find out if they have developed gestational hypertension, oedema of any form (hands, face or feet) or PE and at 6 weeks postpartum to collect anthropometric data, clinical data and biochemical data (haemoglobin level) and also to find out if they have developed PE. Pregnant women were considered to have met the study's exit criteria when they developed preeclampsia.

3.3 Sample Size Determination

Using Cochran's sample size formula for an alpha (significance level) of 0.05.

$n = z^2 \times p\,(1-p)/\,d^2$

Where:

n = required sample size

z = standard value from statistical table representing confidence level

d = desired level of precision or margin error expressed in proportion of one

p = the estimated proportion or the prevalence of an attribute that is present in the population.

In this present study,

Z = 1.96 for a confidence interval of 95%

d = 5%

p = 38.0% (Adu-Bonsaffoh *et al.*, 2017a)

$n = (1.96)^{2*}\,(38.0\%)\,(1 - 38.0\%)/\,(0.05)^2 = 362$

With attrition rate of 10%, adjusted sample size was 403. One hundred and thirty four (134) and two hundred and sixty nine (269) participants were recruited from University of Ghana Hospital and Ghana Police Hospital respectively. This was based on the number of pregnant women who patronize the facilities on a weekly basis.

From Fig 3.1, 21 participants out of the 403 participants recruited into the study at 20 weeks or less gestational age dropped out of the study by 28 – 32 weeks gestation for the following reasons: miscarriage (3), transfer from place of work (6), partners' lack of interest (5), diagnose of preeclampsia (3) and change of facility (4) reducing the number of participants from 403 to 382. Further reduction of 24 participants from the 382 participants at the 28 – 32 weeks was observed at the 6 weeks postpartum

bringing the number of participants remaining in the study to 358 due to the following reasons: travelling to the hometown to deliver (9), change of facility (11) and loss to follow up (4).

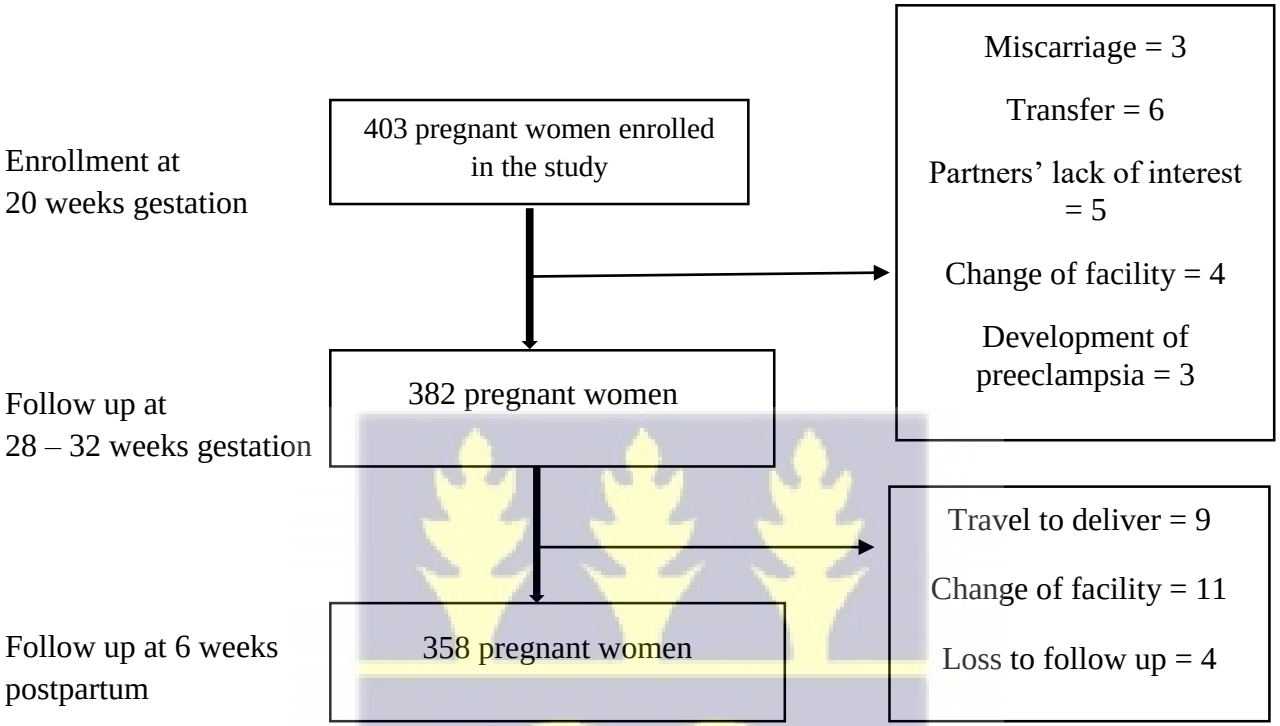

Figure 3.1 A Flow Chart of Loss to Follow up

3.4 Data Collection

Data were collected at baseline, midline and endline. Data collection at baseline and midline were in 4 parts: In-person interviews, anthropometric, clinical and biochemical measurements. At endline, anthropometric, clinical and biochemical measurements (urine protein and haemoglobin level) were taken.

3.4.1 Interviews

A pre-tested closed-ended questionnaire (Appendix 3) was administered by in–person interview to obtain information on biodata, maternal factors, anthropometric data, lifestyle practices, dietary intake, dietary pattern, family health history and biochemical data.

Biodata: Information on participants' age, education, occupation, marital status and ethnicity were collected.

Health: Maternal gynaecological, medical and family health histories were taken.

Lifestyle Practices: Information on the participants' alcohol and tobacco usage were collected with questionnaire modified from (Sallis *et al.*, 1985).

Dietary Intake/Pattern: Dietary intake were determined using questionnaire modified after Perinatal food frequency questionnaire 2004 (http://www. lapublichealth. org/mch/cpsp/forms/PFFQ_Eng&Span_Blank.pdf).

3.4.2 Anthropometric Data

Anthropometric data collected were body weight and height. For the weight measurement, the participants were allowed to mount the Camry weighing scale (Zhongshan Camry Electronic, Zhongshan, Guangdong, China) (Appendix 4) with cleaned and dried feet and looking straight, weight measurement was recorded to the nearest 0.1kg.

Height measurement was taken with participant mounting the foot board of the stadiometer (model: HM200P Charder USA) (Appendix 5) with bare feet, heel, head and buttocks touching the body of the stadiometer and taken in a deep breath. Height was measured to the nearest 0.1m. The BMI was determined based on the standard of World Health Organization (1995) (Appendix 6).

3.4.3 Biochemical Data

Biochemical data such as haemoglobin levels, urine protein and glucose levels were obtained from the hospital records of the participants. Sera collected were used to determine 25- Hydroxyvitamin D, magnesium and calcium levels.

Serum Collection and Preparation: About 3mls of whole venous blood samples were drawn from research participant by qualified phlebotomists from both hospitals. The drawn blood sample were kept in a serum separation tube and allowed to stand undisturbed for 30-45 mins to clot. The samples were then centrifuged at 4000 rpm for 5 mins. The sera were fetched into eppendorf tubes and then kept in the medical refrigerator at -20 ºC at the hospitals.

Determination of Serum 25 Hydroxyvitamin D

Determination of 25hydroxyvitamin D was carried out using a modified procedure after Aksnes (Aksnes, 1994) at the Nutrition Department Laboratory of the Noguchi Institute of Medical Research and reference standard of Holicks, 2007 (Mayo Foundation for Medical Education and Research (Mayo Clinic Laboratories), 1995 – 2020.; Ross *et al.*, 2011) (Appendix 7).

Extraction of Serum 25-Hydroxyvitamin D

A measure of 1ml of methanol was added onto to 0.5 mL of test (serum). The samples were vortexed to mix for 1min. The samples were then centrifuged at 5500 rpm for 10 mins. The supernatant was isolated and 3 mL of hexane added and vortex at 3000 rpm for 5 mins. The resultant arrangement was dried under nitrogen gas and the dried item settled in 0.2 mL methanol.

Chromatography Analysis

Agilent series 1100 HPLC system (Agilent Technologies, Massachusetts, USA) was used. Separation was carried out on a LiChrospher60 RP select B column at 40ºC. The developer used was a compound of acetonitrile, methanol and water in the ratio of 85%: 13%: 2% respectively. Concentrations of 25 (OH) D_3 (range; catalogue Number. H-4014; Sigma Aldrich Germany) were used to draw the standard curve.

Measurement of Calcium and Magnesium in the serum

The serum magnesium and calcium were measured using an automated electrolyte analyzer Selectra PROS (ELITechGroup Clinical Systems, France) (Appendix 8) at the University of Ghana Hospital Laboratory. It operates on the principle of

photometry. The sample was mixed with Xylidyl and Arsenazo III reagents respectively to produce a reaction that resulted in color formation. The intensity of the colour produced was related to the concentration of the analyte present.

3.4.4 Clinical Data

Systolic and diastolic blood pressure readings were recorded from participants' medical records on each antenatal visit. The systolic and diastolic blood pressures were determined using the standard of American Heart Association (2021) and ACOG (2002) (Appendix 9).

3.5 Quality Assurance

The questionnaire was pretested at the Madina Polyclinic. Based on the responses, the needed modifications were made concerning the questions asked, the length of time needed to administer a questionnaire, and even how to relate with the pregnant women in order to obtain the necessary information. The body weighing scale was calibrated frequently in order to ensure accuracy. Field assistants were given the necessary training in questionnaire administration and right usage of the necessary instruments.

3.6 Data Capture and Statistical Analysis

Collected data were entered into SPSS version 22 (Chicago, USA), cleaned and statistically analyzed. Background categorical variables were summarized as frequencies and percentages, whereas background continuous variables were summarized as median (Q1, Q3) or means ± SD, as appropriate.

Creation of Independent Binary Variable

Independent binary variables were meaningfully created out of each independent variable based on appropriate referenced rationale that is one category "have no or weak association with the dependent variable" whilst the other category "have a positive association with the dependent variable" (Table 3.1).

Table 3.1 Independent Binary Variables, Definitions and Rationale

#	Variable	Definition	Rationale
1	Age	Coded 1 if the participant's age was ≤ 35 years and 0 if otherwise	Risk for PE is higher for women age ≥ 36 years (MFMER, 1998 – 2018)
2	Education	Coded 1 if the participant's highest educational level attained was tertiary education and 0 if otherwise	Women of higher educational level are highly knowledgeable in PE (Fondjo *et al.*, 2019)
3	Occupation	Coded 1 if the participant was employed by the government and 0 if otherwise	Government employees have regular income and have the opportunity to attend ANC (Personal communication). Most of the women fell in this category
4	Income	Coded 1 if the participant's income was > 1400 Ghc and 0 if otherwise	The minimum salary in Ghana is Ghc 1280 (Salary Explorer, 2021)
5	Ethnicity	Coded 1 if the participant was an Akan and 0 if otherwise	Majority of the women were Akans
6	Marital status	Coded 1 if the participant was married and 0 if otherwise	Unmarried women tend to be at a higher risk for PE (Tessema *et al.*, 2015)
7	Hours of sleep	Coded 1 if the participant slept for ≥ 8 hours and 0 if otherwise	8 hours or more has been recommended for a healthy living (MFMER, 1998 – 2020)
8	Regular exposure sunlight	Coded 1 if the participant's daily activities usually involved walking/working in the direct sunlight for 5 days/week before and during pregnancy and 0 if otherwise	Sunlight exposure time required for adequate vitamin D synthesis vary by individual and environmental factors, such as skin pigmentation and latitude. It is possible that women exposed to direct sunlight throughout the 5 working days of the week may more likely be able to maintain adequate plasma vitamin D levels than women not exposed to direct sunlight throughout the 5 working days of the week.

Table 3.1 Independent Binary Variables, Definitions and Rationale continued

#	Variable	Definition	Rationale
9	Pica practice	Coded 1 if the participant practice pica and 0 if otherwise	Pica practice has been associated with increased risk for hypertension (Barton *et al.,* 1992; Motawei *et al.,* 2013)
10	Alcohol intake	Coded 1 if the participant has drunk alcohol in the past 1 year and 0 if otherwise	Prevalence of women of childbearing age who drunk alcohol was 37.6% (Adeyiga *et al.,* 2014).
11	Number of meals	Coded 1 if the participant ate ≤ 3 meals a day and 0 if otherwise	Taking more than three meals/day can lead to obesity and obesity is a risk factor for PE (Mrema *et al.,* 2018).
12	Time of eating	Coded 1 if the participant ate supper usually before 7 pm during pregnancy and 0 if otherwise	Most of the women slept between 9 - 10 pm hence eating before 7 pm will give them some time to stay awake before sleeping to maintain healthy weight than sleeping right after eating which can lead to excessive weight gain. Overweight/obesity is linked to eating dinner within 2 hours of going to bed at least 3 times per week. (Okada *et al.,* 2019).
13	Amount of water drank in a day	Coded 1 if the participant usually drank 10 cups	Pregnant women need 10 cups of fluid/per day (Mayo Clinic, 1998 - 2020).
14	Dark green vegetables in a week	Coded 1 if the participant ate dark green vegetables at least once a week and 0 if otherwise	Dietary fibre, vitamins and minerals are associated with reduced risk for PE (Grum *et al.,* 2018).
15	Vitamin A rich fruits	Coded 1 if the participant ate vitamin A rich fruits at least once a week and 0 if otherwise	Dietary fibre, vitamins and minerals are associated with reduced risk for PE (Grum *et al.,* 2018)

Table 3.1 Independent Binary Variables, Definitions and Rationale continued

#	Variable	Definition	Rationale
16	Other fruits	Coded 1 if the participant ate other fruits at least once a week and 0 if otherwise	Dietary fibre, vitamins and minerals are associated with reduced risk for PE (Grum *et al.*, 2018)
17	Other vegetables	Coded 1 if the woman eats other vegetables at least once a week and 0 if otherwise	Dietary fibre, vitamins and minerals are associated with reduced risk for PE (Grum *et al.*, 2018)
18	Beans and nuts	Coded 1 if the participant ate beans and nuts at least once a week and 0 if otherwise	Intake of beans has been found to be associated with lower risk for PE (Agrawal, 2014)
19	Artificial spices in cooking	Coded 1 if the participant used artificial spices in preparing meals regularly and 0 if otherwise	Artificial spices are high in sodium and high sodium intake is a risk factor for hypertension (Naqvi *et al.*, 2010)
20	Age at first birth	Coded 1 if the participant had her first child at ≥ 35 years and 0 if otherwise	Women ≥ 35 years are at increased risk of PE (Lamminpää *et al.*, 2012)
21	Primiparity	Coded 1 if the participant had at least one child and 0 if otherwise	Primiparity is associated with PE (Das *et al.*, 2019)
22	Miscarriage	Coded 1 if the participant has ever had mis- carriage and 0 if otherwise	Prior miscarriage is associated with increased risk for PE (Gunnarsdottir *et al.*, 2014).
23	Contraceptive use	Coded 1 if the participant used contraceptives before current pregnancy and 0 if otherwise	Contraceptives used prior to current pregnancy is associated with increased risk for PE (Setiawan, 2016)

Table 3.1 Independent Binary Variables, Definitions and Rationale continued

#	Variable	Definition	Rationale
24	Vaginal discharge	Coded 1 if the participant has ever had an offensive discharge during this pregnancy and 0 if otherwise	Maternal infection is associated with an increased risk for PE (Minassian *et al.*, 2013).
25	Haemoglobin level	Coded 1 if the participant was anemic at baseline and 0 if otherwise	Anemia is associated with increased risk for PE (Ali *et al.*, 2011).
26	Serum vitamin D	Coded 1 if the participant was deficient in serum vitamin D (< 20 ng/ml) and 0 if otherwise	Vitamin D deficiency is associated with the development of PE (Djekic-Ivankovic *et al.*, 2017).
27	Serum calcium	Coded 1 if the participant was deficient in serum calcium (< 2.2 mmol) and 0 if otherwise	Women who had PE were found to be deficient in serum calcium (Ephraim *et al.*, 2014).
28	Serum magnesium	Coded 1 if the participant was deficient in serum magnesium (< 0.66) and 0 if otherwise	Women who had PE were found to be deficient in serum magnesium (Ephraim *et al.*, 2014)
29	Sickle cell	Coded 1 if the participant had sickle cells disease and 0 if otherwise	Sickle cells disease increased the risk of developing PE (Prophet *et al.*, 2018)
30	Pre-pregnancy Body mass index	Coded 1 if the participant's BMI is ≥ 25 and 0 if otherwise	Overweight and obese are risk factors for PE (Mrema *et al.*, 2018).
31	Sweets	Coded 1 if the participant ate sweets on a regular basis and 0 if otherwise	There has not been any study linking intake of sweets to the development of PE
32	Hypertension disorder in pregnancy (family history)	Coded 1 if participant had family history of hypertension disorder in pregnancy and 0 if otherwise	Women whose mother and/or sister had PE are at an increased risk for PE (Serrano *et al.*, 2020)
33	Family records on diabetes	Coded 1 if participant had family record of diabetes and 0 if otherwise	Diabetic record in family history of increased ones chance of developing PE (Barrett *et al.*, 2014)

Table 3.1 Independent Binary Variables, Definitions and Rationale continued

#	Variable	Definition	Rationale
34	Abdominal/ Upper abdominal pains	Coded 1 if participant had abdominal pains and 0 if otherwise	Upper abdominal pain is a sign associated with PE (MFMER, 1998-2020)
35	Headache	Coded 1 if participant had headaches and 0 if otherwise	Headache is a sign associated with PE (MFMER, 1998-2020)
36	Maternal height	Coded 1 if participant's height was < 164 cm and 0 if otherwise	Maternal height < 164 cm is associated with increased risk for PE (Lee and Magnus, 2018)
37	Estimated Pre –pregnancy weight	Coded 1 if participant's weight was < 71 kg and 0 if otherwise	There has been no study associating PE with estimated pre - pregnancy weight
38	Gestational age at first antenatal booking	Coded 1 if participant's gestational age was ≤14 weeks and 0 if otherwise	The mean gestational age at first antenatal booking. There has been no study associating PE with gestational age at first booking
39	Calcium supplement	Coded 1 if participant was given calcium supplement and 0 if otherwise	Calcium supplementation was associated with reduce risk for PE (Sun *et al.*, 2019).
40	Vit D supplement	Coded 1 if participant was given Vit D supplement and 0 if otherwise	Vit D supplementation is linked with lower chance for PE (Fu *et al.*, 2018)

Creation of Dependent Variable

The main dependent variable, namely: potentially high risk for PE; having at least a high SBP (≥ 130 mmHg) or a high DBP (≥ 80 mmHg) or oedema or proteinuria. Any participant who had at least a high systolic blood pressure or a high diastolic blood pressure or an oedema or proteinuria is said to be at a potentially high risk of developing PE. High systolic blood pressure, high diastolic blood pressure,

proteinuria and oedema are all risk factors that put one at a potentially high risk of developing PE

Correlation Test to Determine the Relationship between the Independent Binary Variables and the Dependent Variable

A Spearman correlation was run between the created independent binary variables and the dependent variable (potentially high risk for PE; having at least a high systolic blood pressure (≥ 130 mmHg) or high diastolic blood pressure (≥ 80 mmHg) or presence of oedema or presence of proteinuria). Variables that significantly correlated with the dependent variable at $P < 0.05$ were selected to be run in the logistic regression model to determine the association between the independent variables and the dependent variable. The selected variables were analyzed to check for multicollinearity at a variance of inflation factor (VIF) > 5.

Selection of Independent Variable to be run in the Binary Logistic Regression Model

The variables for the logistic regression model for predicting potentially high risk for PE were selected as follows: The variables that correlated significantly with the dependent variable as well as other variables that did not correlate significantly with the dependent variable but has been proven severally in research to be associated with the dependent variable were selected and analysed using binary logistic regression model to predict their association with the dependent variable.

Structural Equation Modeling

Initial Confirmatory Factor Analysis (CFA) of Initial Measurement Model

The estimation model fit of the information collected was assessed and tested for fitness, validity and reliability. Assessing model fit involves two main criteria: absolute fit and comparative fit (Bagozzi and Yi, 2012). Common absolute fit criteria include the following: Root-Mean-Squared-Error of Approximation (**RMSEA ≤ 0.08**), Goodness-of-Fit-Index (**GFI ≥ 0.90**) and Normed Fit Index (**NFI ≥ 0.90**). The absolute fit is based on the contrasts between the noticed and the covariance matrix (Hair Jr *et al.*, 2014). The comparative fit, on the other hand, considers whether, in accounting for the observed data, the model being used is better than other alternative models with a criteria: normed fit index **(NFI) (> 0.9),** Tucker Lewis index **(TLI) (> 0.9)** and comparative fit index **(CFI) (> 0.9)** are some of the criteria used in the comparative fit (Hair Jr *et al.*, 2014).

Reliability and Validity

Pearson's correlation test was run to check the dependability and legitimacy of the research instruments. The dependability was determined by the Cronbach's alpha and the composite reliability; the Cronbach's alpha has a threshold of 0.6 as a minimum and the composite reliability has an acceptable minimum of 0.5 (Sarstedt *et al.*, 2017). Validity comprises of discriminant and convergent validity. Discriminant validity was assessed based on the Fornell-Lacker criterion and cross loadings, where the square root of average variance extracted (AVE) was greater than the correlation shared between the construct and the other constructs. It assesses the uniqueness of each construct, and that the scale items do not relate more to other constructs than to the construct they are meant to measure. It is indicated by the low correlation between the

measure of interest and the measures of other constructs (Hair Jr *et al.*, 2014). The convergent validity also was determined by the AVE loadings and it should have a minimum of 0.5 to be acceptable (Sarstedt *et al.*, 2017).

Structural Model

After establishing that the construct measures were dependable and valid, assessment of the structural model results was carried out to specify how the latent variables were related and interacted with each other. According to Kline (2015), the structural model assessed the statistical test and examination of the hypothesised relationships between the latent variables. Thus, the structural model conducted in this study intends to test the hypothetical propositions based on the conceptual framework (Fig 3.2) for this research.

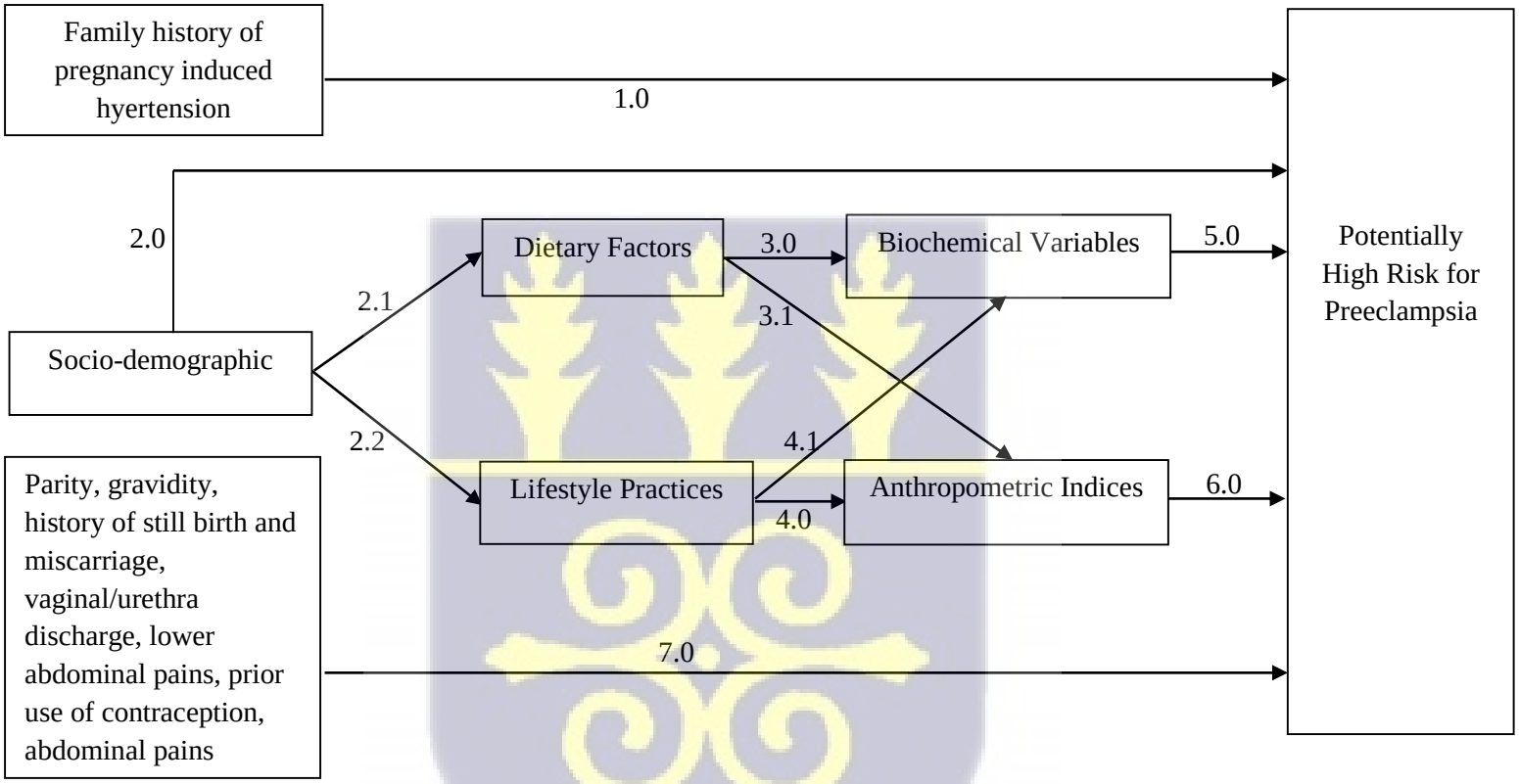

Figure 3.2: Proposed Conceptual Model of Potentially High Risk for PE

Figure 3.2 above was the proposed conceptual model tested during data analysis. It shows the various pathways through which potentially high risk for preeclampsia (outcome variable) may be influenced by the various variables; socio-demographic characteristics, maternal factors, family history of medical conditions, dietary factors and lifestyle practices. The figures in the diagram represent the pathways of influence of the different variables on the outcome variable. It was proposed that socio-demographic characteristics might influence potentially high risk for preeclampsia directly (2.0) and indirectly through dietary factors (2.1) and lifestyle practices (2.2). Maternal medical health and gynecological factors were proposed might influence potentially high risk for preeclampsia directly (7.0). Family history of medical conditions might influence potentially high risk for preeclampsia directly (1.1). Dietary factors might affect potentially high risk for preeclampsia indirectly through biochemical variables (3.0) and anthropometric indices (3.1). Lifestyle practices might affect high risk for preeclampsia indirectly through biochemical variables (4.1) and anthropometric indices (4.0). Anthropometric indices and biochemistry might directly influence potentially high risk for preeclampsia (6.0) and (5.0) respectively.

3.7 Ethical Consideration

Ethical clearance (Appendix 1) was sought from the Ethics Committee for Basic and Applied Sciences, University of Ghana. Permits were also sought from the offices responsible for research activities at the two hospitals before the commencement of the study. Volunteers were educated on the purpose of the research along with thorough explanation on the body measurements and samples to be taken. Afterwards, they were served with printed copies of the Consent forms (Appendix 2) in which the purpose of the research study, body measurements and samples requires were clearly

stated. Risks and discomforts that were envisaged and measures that were put in place to manage them were also spelt out. Furthermore, confidentiality concerning their data, their right to participate or opt out without being penalized was stated. In addition, volunteers were given opportunity to ask questions and the appropriate answers given. They were recruited into the study after they had given their consent and signed or thumb-printed the consent forms.

CHAPTER FOUR

4.0 RESULTS

4.1 Preamble

Information on socio-demographic parameters, lifestyle practices, dietary intake, maternal factors, anthropometry, clinical and biochemical were collected for all the 403 participants at baseline. At midline, data on lifestyle practices, dietary intake, maternal factors, anthropometric, clinical and biochemical were collected for 382 participants (21 participants dropped out of the 403 participants (baseline) of the study). Data on clinical, biochemical and anthropometry were collected at endline for the remaining 358 participants (24 participants dropped out of the 382 participants (midline) of the study).

4.2 Socio-demographic Characteristics

Table 4.1 shows the socio-demographic parameters of all the 403 pregnant women. Mean ± SD age of the women was 30.6 ± 4.7 years with majority of them 341 (84.6%) being in the age range of 20 – 35 years. Almost one-half of the number of participants, that is 194 (48.1%), had obtained tertiary education (Teachers' training, Nursing training or University education) with 22 (5.5%) having had no formal education or had only primary school education. A total of 166 (41.0%) were self-employed with 47 (11.7%) being unemployed. A majority of the women were married 347 (86.1%) with 166 (41.2%) being Akans. A total of 122 (30.3%) of the pregnant women had a monthly income of less than Ghc 500 with 111 (27.5%) having an income more than Ghc 1000 a month. A total of 133 (33.1%) of their partners had a monthly income of more than Ghc 1000.

Table 4.1 Socio-demographic Characteristics of Pregnant Women at Baseline

Characteristics	[1]n (%)
Age (year)	30.6 ± 4.7
≤ 19	1 (0.2)
20 – 35	341 (84.6)
≥ 36	61 (15.2)
Ethnicity	
Krobo	4 (1.0)
Akan	166 (41.2)
Ga/Adangbe	71 (17.6)
Ewe	73 (18.1)
Northern ethnicities	83 (20.6)
[1]Other	6 (1.5)
Marital status	
Single	27 (6.7)
Married	347 (86.1)
Co-habiting	25 (6.2)
Divorced/Widowed	4 (1.0)
Highest educational level attained	
None/Primary	22 (5.5)
[1]JHS/MSLC	77 (19.1)
[2]SHS/GCE (OL/AL)/Tech/Voc	110 (27.3)
[3]Tertiary	194 (48.1)
Occupation	
Unemployed	47 (11.7)
[1]Self employed	166 (41.2)
[2]Public servants	124 (30.8)
[3]Other	66 (16.4)
Income of women (Ghc)	
< 500	122 (30.3)
500 – 1000	73 (15.1)
≥ 1001	111 (27.5)
Non response	97 (27.1)

Table 4.1 Socio-demographic Characteristics of Pregnant Women at Baseline continued

Characteristics	[1]n (%)
Income of partners (Ghc)	
< 500	34 (8.4)
500 – 1000	34 (8.4)
≥ 1001	133 (33.1)
Don't know	202 (50.1)

[1]n = 403. JHS/MSLC denotes Junior High School/Middle School Leavers Certificate [2]SHS/GCE (OL/AL)/Tech/Voc denotes Senior High School/ General Certificate Examination (Ordinary level/Advance Level)/ Technical School level/Vocational Education [3]Tertiary denotes Teachers' and Nurses' Training Colleges, Polytechnics, University and higher learning Institutions [1]Other denotes Nzema, Guan etc [2]Public servants denote Government employed professionals (teachers, nurses, medical doctors, pharmacists, lecturers, researches, administrators, police officers etc) [3]Other denotes private hired jobs [1]Self employed denotes traders, beauticians, fashion designers, food vendors etc

4.3 Dietary Characteristics of Pregnant Women at Baseline and Midline

Consumption of different food items was high at both baseline and midline with midline recording higher frequencies compare to baseline except the consumption of organ meat and beans and nuts (Fig 4.1). Table 4.2 shows that majority of the pregnant women had 1-3 meals in a day at baseline 311 (77.2%) and 214 (53.1%) had four or more meals in a day at midline with means of 3.1 ± 0.8 and 3.7 ± 0.9 respectively. Majority of the participants drank 10 or more cups of water in day 292 (72.5%) and 352 (92.1%) at baseline and midline respectively with means and SDs of 13.1 ± 6.1 and 15.8 ± 4.8 respectively.

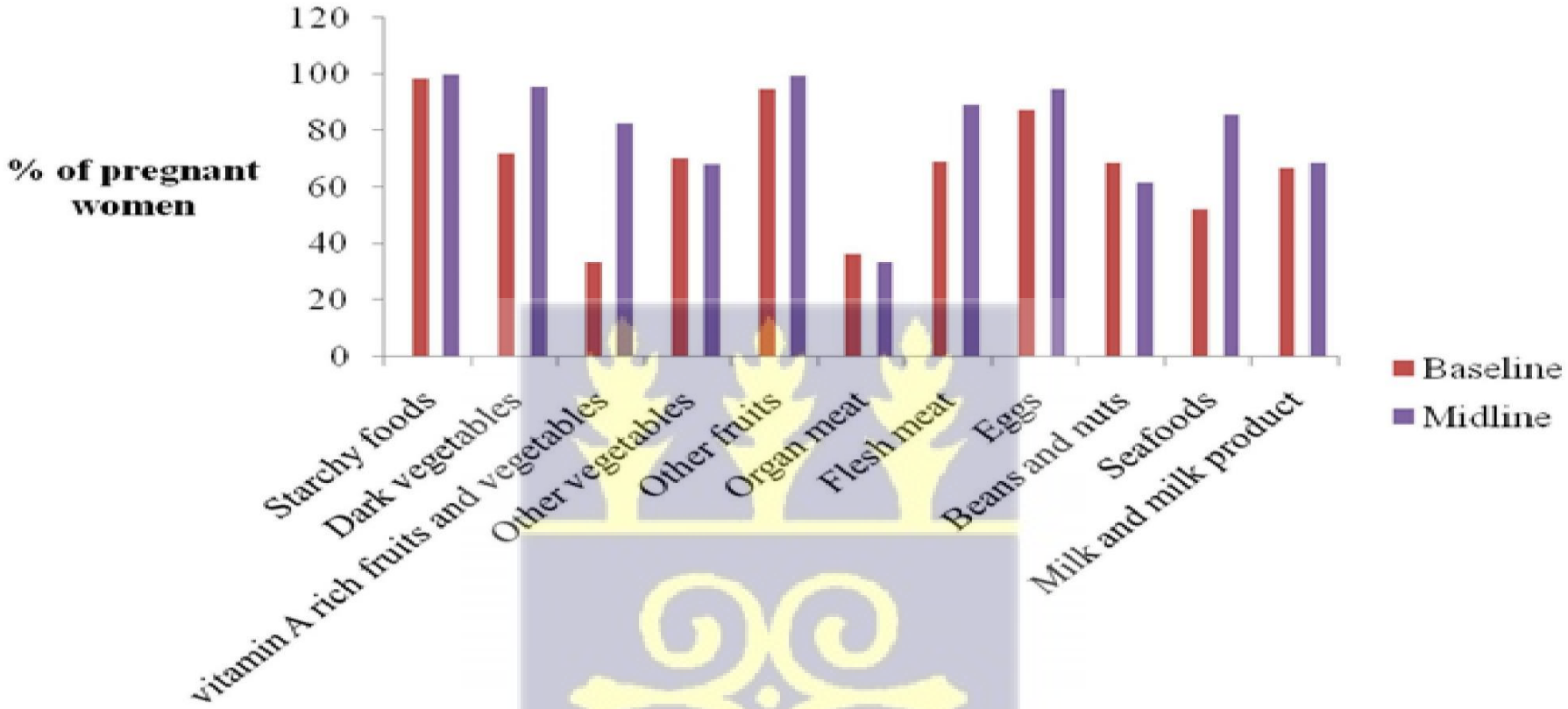

Figure 4.1 Percentages of Food Items Consumed in a Week at Baseline and Midline

Table 4.2 Dietary Characteristics of Pregnant Women at Baseline and Midline

Parameter	[1]n (%)
Number of times of eating in a day	
Baseline ([1]n = 403)	**3.1 ± 0.8[a]**
1-3	311 (77.2)
≥ 4	92 (22.8)
Midline ([1]n = 382)	**3.7 ± 0.9[a]**
1-3	168 (44.0)
≥ 4	214 (56.0)
Amount of water drank in a day (cups)	
Baseline ([1]n = 403)	**13.1 ± 6.1[a]**
< 10	111 (27.5)
≥ 10	292 (72.5)
Midline ([1]n = 382)	**15.8 ± 4.8[a]**
< 10	30 (7.9)
≥ 10	352 (92.1)

[a]values in means ± SD [1]n = 403 at baseline [1]n = 382 at midline

4.4 Body Mass Index and Blood Pressure measurements of the Pregnant Women

At baseline (Table 4.3) 186 (46.2%) of the women were overweight and 110 (27.3%) were obese with a median estimated pre-pregnancy BMI of 27.1 kg/m^2 (24.7, 30.5). A median value of 110 mmHg (109,117) systolic blood pressure (SBP) and 70 mmHg (60, 73) diastolic blood pressure (DBP) were also recorded respectively at enrolment. At midline, the median SBP and DBP were 120 mmHg (88, 141) and 75 mmHg (70, 95) with 119 mmHg (110, 120) and 70 mmHg (66, 75) been the median SBP and DBP at 6 weeks respectively. Prevalence of preeclampsia and potentially high risk for preeclampsia were 3 (0.8%) and 130 (34%) with oedema being 40 (10.5%) and gestational hypertension being 9 (2.4%).

Table 4.3 Body Mass Index and Blood Pressure Measurement of the Pregnant Women at Baseline, Midline and Endline

Measurement	[1]n (%)
Weight at enrolment ([1]n = 403)	**71 (62, 77)[a]**
Weight at 28-32 weeks ([1]n = 382)	**78 (70, 85)[a]**
Weight at 6 weeks postpartum ([1]n = 358)	**75 (68, 84)[a]**
Estimated pre-pregnancy BMI (kg/m^2)	**27.1 (24.7, 30.5)[a]**
Underweight	5 (1.2)
Normal	102 (25.3)
Overweight	186 (46.2)
Obesity	110 (27.3)
SBP (mmHg) at ≤ 20 weeks gestational age	**110 (109, 117)[a]**
SBP (mmHg) at 28 – 32 gestational age	**120 (88, 141)[a]**
Non- Hypertension (≤ 129 mmHg)	310 (81.2)
Stage 1 Hypertension (130 mmHg – 139 mmHg)	57 (14.9)
Stage 2 Hypertension (≥ 140 mmHg)	15 (3.9)
SBP (mmHg) at 6 weeks postpartum	**119 (110, 120)[a]**
Non - Hypertensive (≤ 129 mmHg)	358 (100.0)
DBP (mmHg) at ≤ 20 weeks gestational age	**70 (60, 73)[a]**
DBP (mmHg) at 28 – 32 gestational weeks	**75 (70, 95)[a]**
Non –Hypertension (< 80 mmHg)	368 (96.3)
Stage 1 Hypertension (80 mmHg – 89 mmHg)	5 (1.3)
Stage 2 Hypertension (≥ 90 mmHg)	9 (2.4)
DBP (mmHg) at 6 weeks postpartum	**70 (66, 75)[a]**
Non – Hypertension	358 (100.0)
Potentially high risk for preeclampsia	130 (34.0)
Preeclampsia	3 (0.8)
Oedema	40 (10.5)
Gestational hypertension	9 (2.4)

Stage 1 Hypertension (systolic blood pressure) : 130 -139 ; Stage 2 Hypertension (systolic blood pressure) : ≥ 140 mmHg; Stage 1 Hypertension (diastolic blood pressure): 80 – 89; Stage 2 hypertension (diastolic blood pressure) : ≥ 90 mmHg ; SBP : systolic blood pressure; DBP : diastolic blood pressure Baseline: ≤ 20 weeks Midline: 28 – 32 weeks End line: 6 weeks postpartum
[a]values in median (IQR) [1]n = 403 at baseline; [1]n = 382 at midline [1]n = 358 at endline

4.5 Lifestyle Characteristics of Pregnant Women

Table 4.4 depicts the lifestyle practices of the pregnant women. Among the 403 participants at baseline 1 (0.2%) and 14 (3.5%) have ever smoked or drunk alcohol respectively. Majority 248 (61.5%) of them slept for 8 hrs or more with a median sleeping hours of 8 (7, 9) before and during pregnancy. More than the average number of participants 332 (82.4%) used public transport system and 328 (81.4%) had 5 days or more of the sun exposure in a week. A few of them 40 (9.9%) practiced pica which was mainly on ice cubes. At midline, majority 255 (66.8%) of the women slept for 8 hrs or more during the night. Public transportation system remains the major 328 (85.9%) means of moving around. A total of 318 (83.2) had 5 or more days of sun exposure. Pica practice remains low 21 (5.8%).

Table 4.4 Lifestyle Characteristics at Baseline and Midline

Characteristics	Baseline [1]n (%)	Midline [1]n (%)
Smoking		
Yes	1 (0.2)	
No	402 (98.0)	382(100.0)
Alcohol intake		
Yes	14 (3.5)	
No	389 (96.5)	382(100.0)
Usual hours of sleep in the night	**8 (7, 9)[a]**	**8 (7, 9)[a]**
< 8	155 (38.5)	127 (33.2)
≥ 8	248 (61.5)	255 (66.8)
Pica practice		
Yes	40 (9.9)	21 (5.8)
No	363 (90.1)	361 (94.2)
Main means of transportation		
Public transport	332 (82.4)	328 (85.9)
Private transport	71 (17.6)	54 (14.1)
Exposure to sunlight	**6 (5,7)[a]**	**6 (5, 7)[a]**
> 1-4	75 (18.6)	64 (16.8)
≥ 5	328 (81.4)	318 (83.2)

[a]value in median (IQR) [1]n = 403 at baseline [1]n = 382 midline

4.6 Gynaecological Factors of Pregnant Women

As indicated in table 4.5, majority 197 (48.8%) of the women had their first ante natal visit after 14 weeks of gestational age. A total of 257 (63.8%) women had their first birth within the age range of 20 – 35. Majority 229 (56.8%) of them had 1 – 2 children with a median parity of 1 (1, 4). A total of 187 (46.4%) and 30 (7.4%) had ever had miscarriage and had ever had still births respectively with a few of them 85 (21.1%) who have used contraceptives before their current pregnancy.

Table 4.5 Gynaecological Factors of the Pregnant Women

Variable	[1]n (%)
Gestational age at first ante natal booking (weeks)	**14 (12, 17)[a]**
≤ 12	49 (12.2)
13-14	157 (39.0)
> 14	197 (48.8)
Age at first birth	**24 (22, 28)[a]**
15 – 19	13 (3.2)
20 – 35	257 (63.8)
36 – 3	6 (1.5)
Nulliparous	127 (31.5)
Parity	**1(1, 4)[a]**
0	144 (35.7)
1-2	229 (56.8)
3-4	30 (7.4)
Had ever Miscarried	
No	216 (53.6)
Yes	187 (46.4)
Had ever had Still birth (s)	
No	373 (92.6)
Yes	30 (7.4)
Birth interval (years)	
< 2	60 (14.9)
2 – 4	132 (32.8)
>4	84 (20.8)
N/A	127 (31.5)
Contraceptive use before current pregnancy	
No	318 (78.9)
Yes	85 (21.1)

[a]value in median (IQR) [1]n = 403

4.7 Maternal Other Health Condition and Family Medical History at Baseline and Midline

From table 4.6, prevalence of family history of gestational diabetes and pregnancy induced hypertension were 23% and 29% respectively.

Table 4.6 Maternal Other Health Condition and Family Medical History at Baseline and Midline

Health condition	n1 (%)	n2 (%)
Diarrhoea		
No	371 (92.1)	372 (97.4)
Yes	32 (7.9)	10 (2.6)
Fever/Malaria		
No	364 (90.3)	374 (97.9)
Yes	39 (9.7)	8 (2.1)
Coughing		
No	347 (86.0)	369 (96.6)
Yes	56 (14.0)	13 (3.4)
Sore throat		
No	383 (95.0)	379 (99.2)
Yes	20 (5.0)	3 (0.8)
Nasal discharge		
No	354 (87.8)	375 (98.2)
Yes	49 (12.2)	7 (1.8)
Abdominal pains		
No	273 (67.7)	362 (94.8)
Yes	130 (32.3)	20 (5.2)
Bleeding		
No	390 (96.8)	382 (100.0)
Yes	13 (3.2)	
Vaginal discharge		
No	341 (84.6)	382 (100.0)
Yes	62 (15.4)	
Headaches		
No	378 (93.8)	375 (98.2)
Yes	25 (6.2)	7 (1.8)

[1]n = 403 at baseline [1]n = 382 at midline

Table 4.6 Maternal Other Health Condition and Family Medical History at Baseline and Midline continued

Health condition	n1 (%)	n2 (%)
Headaches		
No	378 (93.8)	375 (98.2)
Yes	25 (6.2)	7 (1.8)
Hospital admission		
No	372 (92.3)	377 (98.7)
Yes	31 (7.7)	5 (1.3)
Family history of gestational diabetes		
No	380 (94.3)	
Yes	23 (5.7)	
Family history of pregnancy induced hypertension		
No	374 (92.8)	
Yes	29 (7.2)	

[1]n = 403 baseline [1] n = 382 at midline

4.8 Biochemical Measurements of Pregnant Women at Baseline, Midline and Endline

Majority had high serum vitamin D and magnesium respectively with majority 108 (53.2%) been deficient in serum calcium. At midline, prevalence of proteinuria was 20 (5.2 %). Prevalence of anaemia decreased from ≤ 20 weeks gestation through to 6 weeks postpartum.

Table 4.7 Biochemical Measurement of Pregnant Women

Measurement	[1]n (%)
Serum vitamin D (ng/ml) ([1]n = 203)	**41 (19 , 43)[a]**
< 20	98 (48.3)
≥ 20	105 (51.7)
Serum Calcium (mmol/L) ([1]n =203)	**2.2 (1.9 , 2.4)[a]**
< 2.2	108 (53.2)
≥ 2.2	95 (46.8)
Serum Magnesium (mmol/L) ([1]n=203)	**0.8 (0.7,1.0)[a]**
< 0.66	25 (12.3)
≥ 0.66	178 (87.7)
Haemoglobin (g/dl)	
Baseline ([1]n = 403)	**11.2 (10.1, 12.0)[a]**
< 11.0	160 (39.7)
≥ 11.0	243 (60.3)
Midline ([1]n = 382)	**11.7 (10.8 , 12.2)[a]**
< 11.0	85 (22.3)
≥ 11.0	297 (77.7)
Endline ([1]n =358)	**11.8 (10.9, 12.3)[a]**
< 11.0	30 (8.4%)
≥ 11.0	328 (91.6)
Proteinuria (Trace)	20 (5.2)
Sickle Disease ([1]n = 403)	
No	391 (97.0)
Yes	12 (3.0)

[a]values in median (IQR) [1]n = 203 for calcium, magnesium and 25 hydroxyvitamin D analysis [1]n = 403 for haemoglobin analysis at baseline; [1]n = 382 for haemoglobin analysis at midline; [1]n = 358 for haemoglobin analysis at endline

4.9 Correlation between Independent Binary Variables and Dependent Variable

A significant positive correlation was observed between estimated pre-pregnancy body mass index ≥ 30, estimated pre-pregnancy weight > 71 and potentially high risk for preeclampsia (high systolic or diastolic blood pressure or oedema or proteinuria) at $r_s = 0.541$ and $p < 0.001$, $r_s = 0.539$ and $p < 0.001$, respectively (Table 4.8).

Table 4.8 Correlation between Independent Variables and Dependent Variable (Potentially High Risk for PE)

Variables	r_s	[1]Pvalue
Maternal Age	0.052	0.292
Maternal Highest educational level attained	0.045	0.377
Maternal occupation	-0.057	0.264
Maternal monthly income	0.063	0.290
Maternal ethnicity	0.034	0.510
Marital status	0.053	0.304
Monthly income of partner	-0.010	0.849
Age at first birth	0.075	0.146
Use of tobacco	0.030	0.559
Alcohol intake	-0.042	0.418
Hours of sleep in the night ≤ 20 weeks	-0.033	0.526
Regular exposure to sunlight ≤ 20 weeks	-0.022	0.674
Pica practice ≤ 20 weeks	0.093	0.069
Number of times of eating in a day ≤ 20 weeks	-0.041	0.422
Time of eaten last meal ≤ 20 weeks	0.005	0.928
Cups of water drank in a day ≤ 20 weeks	-0.040	0.432
Eaten of dark green vegetables at once in a week at ≤ 20 weeks	0.048	0.373
Eaten of vitamin A rich fruits and vegetables at least once in a week at ≤ 20 weeks	-0.004	0.954
Eaten of fruits at least once a week ≤ 20 weeks	-0.023	0.657
Eaten of other vegetables at once a week at ≤ 20 weeks	0.028	0.440
Eaten of beans and nuts at least once a week at ≤ 20 weeks	-0.023	0.656
Use of artificial spices at least once a week at ≤ 20 weeks	0.005	0.950
Eaten of sweets ≤ 20 weeks	-0.03	0.569

Table 4.8 Correlation between Independent Variables and Dependent Variable (Potentially High Risk for PE) continued

Variables	r_s	[1]Pvalue
Gestational age at first time antenatal booking	0.071	0.168
Parity	0.100	0.051
History of miscarriage	-0.046	0.370
History of still birth	0.065	0.202
Chronic Lower abdominal	-0.061	0.236
Vaginal/Urethra discharge at ≤ 20 weeks	0.055	0.288
Contraceptive use	0.064	0.213
Sickle cell disease	-0.055	0.285
Diarrhea at ≤ 20 weeks	0.019	0.716
Fever/malaria at ≤ 20 weeks	0.008	0.875
Abdominal pains at ≤ 20 weeks	-0.063	0.224
Family history of pregnancy induced hypertension	0.082	0.111
Family history of gestational diabetes	0.033	0.518
Estimated pre - pregnancy weight	0.539	**<0.001****
Estimated pre – pregnancy body mass index	0.541	**<0.001****
Height	0.420	0.413
Haemoglobin level at ≤ 20 weeks	0.023	0.650
Serum hydroxyvitamin D at ≤ 20 weeks	0.316	0.821
Serum calcium level ≤ 20 weeks	0.365	0.364
Serum magnesium level ≤ 20 weeks	0.056	0.430
Main means of transportation ≤ 20 weeks	-0.051	0.320

Dependant variable was potentially high risk for PE (having at least a high systolic blood pressure or high diastolic blood pressure or oedema or proteinuria) [1]p-value associated with Spearman correlation. Statistical significance tested at < 0.05

4.10 Predictors of Potentially High Risk for Preeclampsia

From the table 4.9, pregnant women with estimated pre-pregnancy BMI ≥ 30 kg/m^2 and estimated pre-pregnancy weight > 71 kg were at a significantly high risk and had a greater potential for PE; AOR = 3.6 (95% CI = 1.09 – 11.75) p-value of 0.040 and AOR = 3.4 (95% CI = 1.250 – 12.703) p-value 0.019 respectively.

Table 4.9 Logistic Regression to show Factors Associated with Potentially High Risk for Preeclampsia

Variable	AOR (95% CI)	Pvalue
Maternal age		
≤35	0.9 (0.298 - 2.645)	0.831
≥ 36	1	
Serum vitamin D		
Deficiency	1.1 (0.096 – 12.856)	0.934
Non deficiency	1	
Estimated pre - pregnancy BMI		
≥ 30	3.6 (1.09 – 11.75)	**0.040***
< 30	1	
Estimated pre-pregnancy weight		
> 71	3.4 (1.250 - 12.703)	**0.019***
≤ 71	1	
Primiparity		
Yes	1.2 (0.410 - 3.413)	0.755
No	1	
Serum calcium		
Deficiency	4.8 (0.458 – 49.835)	0.191
Non deficiency	1	
Age at first birth		
≤ 35	0.4 (0.042 - 4.532)	0.488
> 35	1	

Hosmer-Lemeshow Statistic: P = 0.731; Nagelkerke R^2 = 0.419 *denotes associations that were significant at p value of < 0.05

4.11 Path Analysis of Factors Influencing Potentially High Risk for PE

From table 4.10, potentially high risk for PE, few items under family medical history, sociodemographic factor, dietary factors, lifestyle practices, biochemical data, maternal medical and gynaecological factors and anthropometric indices were retained. Upon modification of the initial measurement model, potentially high risk for PE, socio-demographic characteristics, anthropometric indices and maternal medical and gynaecological factors were retained.as seen in Table 4.11.

Table 4.10 Initial Confirmatory Factor Analysis (CFA) Results of Initial Measurement Model

Construct	Items	Standardized Loadings	S.E.	t-values	p-values	R-Square	Decision
Potentially High Risk for Preeclampsia	PE1	0.911	0.118	10.487	< 0.001	0.830	Retain
	PE2	0.854	0.076	10.573	< 0.001	0.730	Retain
	PE3	0.325	0.038	4.384	< 0.001	0.105	Retain
	PE4	0.449	0.026	6.158	< 0.001	0.202	Retain
Family History of Medical Conditions	FH1	0.222	0.266	1.591	0.112	0.049	Drop
	FH2	0.727	3.914	1.005	0.315	0.528	Retain
Socio-Demographic Characteristics	SD1	0.183	0.890	0.838	0.402	0.033	Drop
	SD2	0.046	0.426	0.558	0.577	0.022	Drop
	SD3	0.683	2.456	2.269	0.023	0.466	Retain
	SD4	0.784	4.957	2.283	0.022	0.615	Retain
	SD5	-0.126	0.775	-1.308	0.191	0.016	Drop
	SD6	0.029	0.243	0.365	0.715	0.001	Drop
	SD7	0.695	6.046	2.272	0.023	0.484	Retain
Dietary Characteristics	DF1	0.074	10.383	0.580	0.562	0.006	Drop
	DF2	-0.039	0.897	-0.339	0.734	0.002	Drop
	DF3	-0.023	2.005	-0.211	0.833	0.001	Drop
	DF4	0.597	13.054	0.702	0.483	0.357	Retain
	DF5	0.108	2.666	0.596	0.551	0.012	Drop
	DF6	0.263	5.726	0.695	0.487	0.069	Drop
	DF7	0.184	3.742	0.670	0.503	0.034	Drop
	DF8	0.048	2.485	0.395	0.693	0.002	Drop
	DF9	0.144	3.359	0.643	0.520	0.021	Drop

Table 4.10 Initial Confirmatory Factor Analysis (CFA) Results of Initial Measurement Model Continued

Construct	Items	Standardized Loadings	S.E.	t-values	p-values	R-Square	Decision
Lifestyle Characteristics	LP1	-0.102	0.549	-0.799	0.424	0.010	Drop
	LP2	-0.068	2.524	-0.716	0.474	0.005	Drop
	LP3	0.872	13.125	1.284	0.199	0.761	Retain
	LP4	-0.005	0.991	-0.057	0.955	0.000	Drop
	LP5	0.588	19.800	1.285	0.199	0.346	Retain
	LP6	0.014	9.401	0.177	0.859	0.000	Drop
	LP7	0.492	6.428	1.277	0.202	0.242	Drop
Biochemical Data	BD1	0.069	0.477	-0.990	0.322	0.005	Drop
	BD2	-0.385	2.026	-1.018	0.309	0.148	Drop
	BD3	-1.055	4.885	-0.911	0.362	1.112	Retain
	BD4	0.050	0.237	0.607	0.544	0.003	Drop
Anthropometric Indices	ANTH1	-0.287	0.510	-5.435	< 0.001	0.082	Retain
	ANTH2	-0.161	0.066	-5.282	< 0.001	0.026	Retain
	ANTH3	2.557	10.063	0.773	0.439	6.536	Retain
Maternal Medical and Gynecological Factors	MMGF1	0.039	0.249	0.642	0.521	0.002	Drop
	MMGF2	-0.020	5.641	-0.327	0.744	0.000	Drop
	MMGF3	0.350	60.724	0.729	0.466	0.122	Drop
	MMGF4	0.066	9.812	0.629	0.529	0.004	Drop
	MMGF5	1.218	200.153	0.726	0.468	1.484	Retain
	MMGF6	-0.225	18.823	-0.722	0.470	0.051	Drop
	MMGF7	0.021	1.958	0.347	0.728	0.000	Drop
	MMGF8	0.074	4.961	0.647	0.518	0.005	Drop

Table 4.10 Initial Confirmatory Factor Analysis (CFA) Results of Initial Measurement Model Continued

Construct	Items	Standardized Loadings	S.E.	t-values	p-values	R-Square	Decision
Maternal Medical and Gynecological Factors	MMGF9	-0.023	2.719	-0.375	0.708	0.001	Drop
	MMGF10	0.233	16.058	0.723	0.470	0.054	Drop
	MMGF11	0.546	75.674	0.731	0.465	0.299	Retain

GFI = 0.771; NFI = 0.423; CFI = 0.673; $\chi 2/df = 1.495$; RMSEA = 0.050; RMR = 0.105; TLI = 0.649; PClose = 0.496 *** p value < 0.001; ** p value < 0.01; * p value < 0.05

Items Dropped: FH1, FH2,† SD1, SD2, SD5, SD6, DF1, DF2, DF3, DF4†, DF5, DF6, DF7, DF8, DF9, LP1, LP2, LP4, LP6, LP7, BD1, BD2, BD3†, BD4, MMGF1, MMGF2, MMGF3, MMGF4, MMGF6, MMGF7, MMGF8, MMGF9, MMGF10.

† Items must be dropped because one-item measurement is not allowed in SPSS AMOS.

PE1: systolic blood pressure of ≥ 130 mmHg, PE2: diastolic blood pressure of ≥ 80 mmHg, PE3: Proteinuria , PE4 : Oedema SD1- maternal age, SD2 – maternal employment status, SD3 – maternal highest level of education, SD4- maternal income, SD5 – ethnicity, SD6 – marital status, SD7 – partner's income, MMGF1: sickle cell disease, MMGF2: abdominal pains, MMGF3: age at first birth, MMGF4: gestational age at first ante natal booking, MMGF5: parity MMGF6: history of miscarriage, MMGF7: history of still birth, MMGF8: lower abdominal pains, MMGF9: vaginal/urethra discharge, MMGF10: contraceptive use, MMGF11: gravidity, ANTHRO1: weight, ANTHRO2: height, ANTHRO3: BMI, FH: family history of pregnancy induced hypertension, BD1: serum vitamin D, BD2: serum calcium BD3: serum magnesium BD4: haemoglobin, LP1: alcohol intake, LP2: hours of sleep in the night, LP4: smoking, LP3: pica practice, LP5: means of transportation LP6: stress level LP 7: exposure to sunlight, DF1: number of times of eating in a day, DF2: time of eating supper, DF3: number of cups of water drunk in a day, DF4: eating of dark green vegetables at least once in a week DF5: eaten of vitamin A- rich veges and fruits at least once in a week, DF6: eaten of other fruits at least once in week, DF7: eaten of beans and nuts at least once a week, DF8: usage of artificial spices in meals DF9: Eaten of other vegetables at least once in a week.

Table 4.11 Final CFA Results of Measurement Model

Construct	Items	Standardized Loadings	S.E.	t-values	Construct Reliability	Average Variance Extracted	Cronbach's α
Potentially High Risk for Preeclampsia	PE1	0.903	0.102	10.237	0.759	0.472	0.717
	PE2	0.862	0.080	10.206			
	PE3	0.327	0.039	4.403			
	PE4	0.450	0.026	6.138			
Socio-Demographic Characteristics	SD3	0.706	0.069	7.779	0.761	0.515	0.704
	SD4	0.746	0.240	7.777			
	SD7	0.701	0.314	7.641			
Lifestyle Characteristics	LP3	0.844	0.628	0.162	0.693	0.537	0.674
	LP5	0.601	0.411	3.878			
Anthropometric Indices†	ANTH1	0.863	0.138	8.887	0.827	0.706	0.821
	ANTH3	0.817	0.092	8.887			
Maternal Medical and Gynaecological Factors	MMGF5	0.970	0.443	3.755	0.827	0.710	0.796
	MMGF11	0.692	0.160	3.755			

Notes: GFI = 0.907; NFI = 0.863; CFI = 0.915; $\chi 2/df = 2.313$; RMSEA = 0.081; RMR = 0.090; TLI = 0.880; PClose = 0.004; †The Reliability Test suggested further deletion of: ANTH2

Table 4.11 shows the final results of the confirmatory factor analysis after several items were dropped. Out of the total of 47 items measuring 9 constructs, 33 items were dropped because they failed to meet the minimum threshold of standard loadings of 0.5. Further, the acceptable fit indices of CFI, GFI and NFI were below the minimum threshold.

Validity and Reliability

Convergent validity of the items was assessed by Average Variance Extracted (AVE). As displayed in Table 4.12, with the exclusion of AVE value of 0.472 for potentially high risk for Preeclampsia, the AVE values of 0.515 to 0.710 are above the minimum required assessment of 0.50, as proposed by Fornell and Larcker (1981), confirming the coalescent or convergent validity for all the constructs measured. The Cronbach's Alpha (Cα) and Combined Reliability (CR) were calculated to assess the consistency of each item. Table 4.12 shows that, the reliability measures for the modified measurement model are above the acceptable standards (Cα > .60, AVE > .50, and CR > .60) as established by (Nunnally and Bernstein, 1994). Further on, Fornell-Lacker criterion and cross loadings remained engaged to establish the discriminant legitimacy of the construct. Hence Fornell-Larcker (1981) indicated that the square base of the AVE ought to be more prominent than the connection amongst the construct and the other constructs. The square root of the AVE and the correlations among the constructs has been displayed diagonally (Table 4.12).

Table 4.12 Pearson Correlation Matrix

	1	2	3	4	5
1 – High Risk for Preeclampsia	**0.687**				
2 – Socio-Demographic Characteristics	0.101	**0.717**			
3 – Lifestyle Practices	-0.070	-0.461**	**0.732**		
4 – Anthropometric Indices	0.553**	0.265**	-0.071	**0.840**	
5 – Maternal Medical and Gynaecological Factors	0.126	-0.199	0.064	0.201**	**0.843**
Mean	2.074	4.002	2.550	4.535	1.294
SD	0.583	2.083	0.622	1.174	0.840
Cα	0.717	0.704	0.674	0.821	0.796
CR	0.759	0.761	0.693	0.827	0.827
AVE	0.472	0.515	0.537	0.706	0.710

Notes: **. Correlation is significant at the 0.01 level (2-tailed); Since the square of the AVEs (bold values on the diagonal) are greater than the corresponding inter-construct square correlations (values off the diagonal), discriminant validity is achieved.

Table 4.13 Structural Model Assessment

del	Path Relationship	β Estimate	S.E.	t-value	p-value
2.0	Socio-Demographic Characteristics ---> Potentially High Risk for PE	-0.008	0.017	-0.125	0.901
2.1	Socio-Demographic Characteristics ---> Gynaecological Factors	-0.134	0.028	-1.904	0.057
2.3	Socio-Demographic Characteristics ---> Lifestyle Practices	-0.298	0.020	-4.400	< 0.001
4.0	Lifestyle Practices ---> Anthropometric Indices	-0.046	0.134	-0.644	0.520
6.0	Anthropometric Indices ---> Potentially High Risk for PE	0.519	0.030	8.545	< 0.001
7.0	Gynaecological Factors ---> Potentially High Risk for PE	0.016	0.043	0.261	0.794

Notes: R^2 for Preeclampsia = 0.270; R^2 for Lifestyle = 0.089; R^2 for Anthropometric = 0.002; R^2 for Gynaecological = 0.018; *** p < 0.001

Table 4.13 displays the results of the regression analysis of the path relationships. The path relationship of socio-demographic characteristics and potentially high risk for preeclampsia has a negative relationship that is not substantial (β = -0.008; t-value = -0.125; p value = 0.901). Also, the correlation between socio-demographic characteristics and gynaecological factors is negative and insignificant (β = -0.134; t-value = -1.904; p value = 0.057). However, socio-demographic characteristics depicts a negative substantial linkage with lifestyle practices (β = -0.298; t-value = -4.400; p-value = 0.001). Lifestyle practices and anthropometric indices exhibit an insignificant inverse relationship (β = -0.046; t-value = -0.644; p-value = 0.520). Nonetheless, the path relationship for anthropometric indices and potentially high risk for preeclampsia shows a progressive significant interactions (β = 0.519; t-value = 8.545; p-value < 0.001). Finally, the path relationship for gynaecological factors and potentially high risk for preeclampsia has a constructive, yet insignificant relatedness (β = 0.016; t-value = 0.264; p-value = 0.794). Figure 4.2 diagrammatically displays the results of the path relationships as presented above, where each path relationship shows the path coefficient and t-value (in parenthesis).

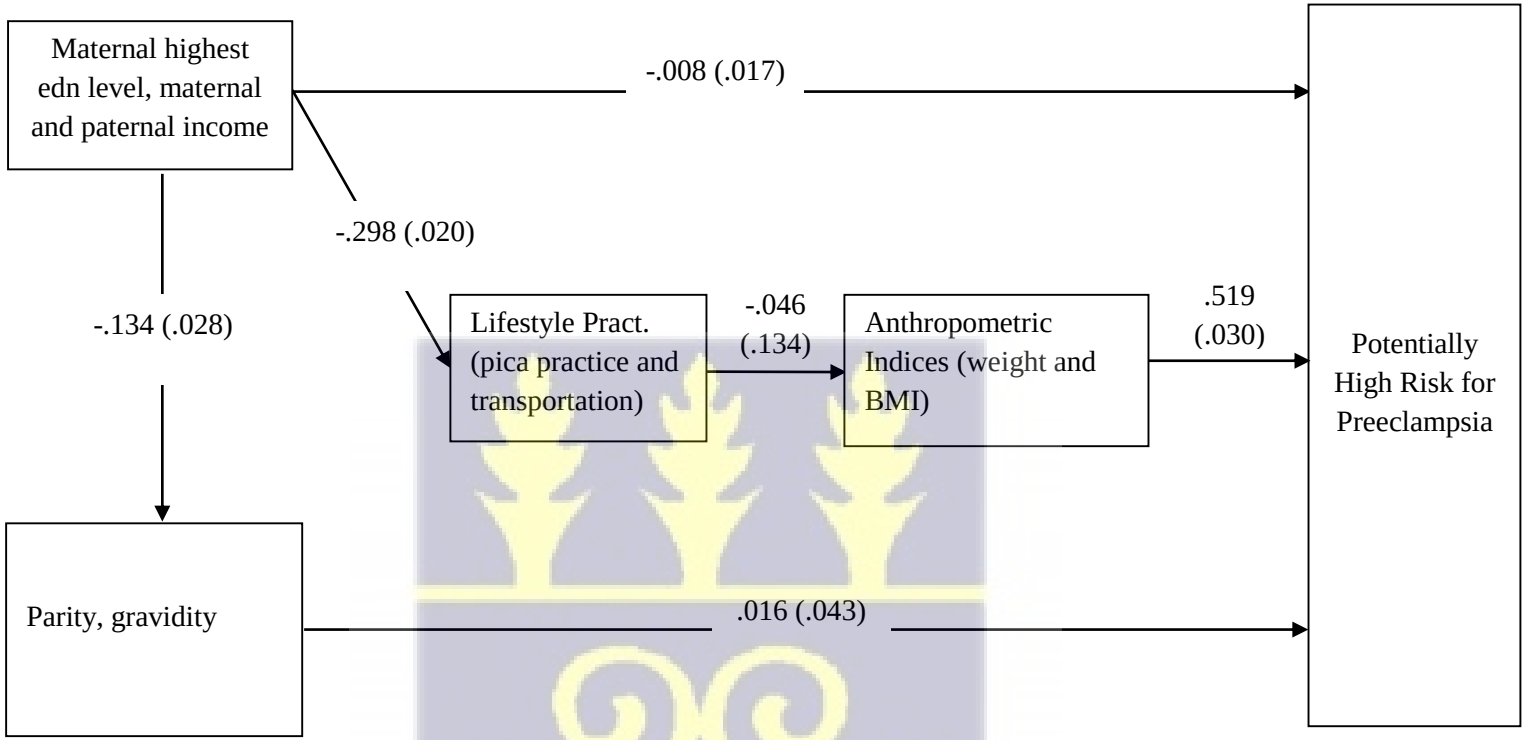

Figure 4.2: Post-Study Framework

CHAPTER FIVE

5.0 DISCUSSIONS

5.1 Background Information

This was a prospective study of expectant mothers attending antenatal clinics at some University of Ghana and Ghana Police Hospitals in Accra. We determined the predictors of potentially high risk for preeclampsia and the pathway through which these predictors operate. The independent variables examined were maternal age, estimated pregnancy body mass index, estimated pre-pregnancy weight, serum vitamin D, serum calcium, parity and age at first birth.

In urban Ghana, the mean age of childbearing has been reported to be 32.4 years with the Greater Accra region recording 33 years (Ghana Statistical Service, 2010). However, this current study recorded a mean age of 31 ± 5 years which is similar to 31 ± 5 years reported by Amoakoh-Coleman et al. (2017) at Korle Bu Teaching Hospital, Accra and 30 ± 6 years by Dassah and colleagues in Komfo Anokye Teaching Hospital, Kumasi (Dassah *et al.*, 2019). This mean age (31 ± 5 years) of the participants is protective against PE (Morikawa *et al.*, 2013). In contrast, Ordinioha and Brisibe in a study at the Teaching Hospital of University of Port Harcourt, South-South, Nigeria reported a mean age of participants of 29.5 ± 4.6 years (Ordinioha and Brisibe, 2015) which is lower than that recorded for this study. The lower mean age recorded for the participants in the Nigerian study may be due to the culture of marrying at a tender age in Muslim-dominated countries of which Nigeria is one compared to women in this study who spent longer years in school before marrying.

The evaluation of the educational background of participants revealed that 48.1% of the pregnant women had attained tertiary education. This is expected since University Hospital, Legon, Accra and Ghana Police Hospital is mostly patronized by staff and relatives as well as elites in the nearby communities. This is higher compared to the 40.2% reported by Amoako-Coleman and colleagues in the Korle Bu Teaching Hospital study (Amoakoh-Coleman *et al.,* 2017). As indicated by Sole et al. (2018), having an advanced education lessens ones vulnerability to developing PE.

With regard to employment, 41.2% pregnant women involved in this research were self-employed. This value is lower than 56.2% and 49.0% reported by van Middendorp and colleagues for urban and rural women respectively in Kumasi, Ghana (van Middendorp *et al.,* 2013). Most of the Ashantis, as a result of their traditional/cultural practices, train in one particular trade or another to be self-employed at an early age of life instead of gaining higher formal learning; hence, a situation like this is expected. Although the prevalence of self-employment for this study is lower than that of Kumasi, this value is still high (41.2%) and can be as a result of the shift of attention from government-dependent jobs to entrepreneurship.

5.1.1 Lifestyle Characteristics of Pregnant Women

Lifestyle characteristics investigated among the pregnant women included alcohol intake, pica practice and smoking. According to Tampaah-Naah and Amoah, Ghana has a national average prevalence of 17.5% for alcohol consumption among Ghanaian women aged 15 to 49 years (Tampaah-Naah and Amoah, 2015). In this study, a prevalence of 3.5% was reported for drinking alcohol in the past among the participants. This prevalence is lower, compared to the prevalence of 78.0% alcohol

intake reported among pregnant women in Jamestown, Accra (Lekettey *et al.*, 2017).This higher prevalence recorded in Jamestown may be as a result of majority of the participants included in this study having attained higher level of formal education compared to participants in the Jamestown study.

Pica practice is associated with anaemia (Khoushabi *et al.*, 2014) and anaemia is also associated with PE (OR = 3.6, 95% CI: 1.4 – 9.1, p = 0.007) (Ali *et al.*, 2011). The finding of pica practice among the pregnant women was 9.9% at ≤ 20 weeks and decreased to 5.5% between 28 and 32 weeks in this study. This decrease in the prevalence of pica practice across trimesters has also been reported by Khoushabi et al. (2014). This prevalence was lower compared to the prevalence of 47.0% recorded among pregnant women in Kumasi (Mensah *et al.*, 2010), 48.4% among pregnant women in Ho (Kortei *et al.*, 2019), 57.3% reported in Korle Bu Teaching hospital and Osu maternity home (Koryo-Dabrah *et al.*, 2012) and 30.25% reported in Bibiani-Anhwiaso Bekwai district (Boadu *et al.*, 2015).

5.1.2 Body Mass Index and Blood Pressure Levels of the Pregnant Women

Obesity has been found to influence the increased danger of developing PE (Roberts *et al.*, 2011). Estimated pre-pregnancy BMI for the participants in this study indicated that 46.2% and 27.3% of the participants were overweight and obese respectively. Overweight prevalence was higher for the women in this current study compared to 40.4% prevalence of overweight recorded among pregnant women at Korle Bu Teaching Hospital (Amoakoh-Coleman *et al.*, 2017), 31.3% among pregnant women at Maamobi General Hospital and the Out Patient Department section of the Greater Accra Regional Hospital (Van Der Linden *et al.*, 2016) and 42.2% (overweight) at the

Kwame Nkrumah University of Science and Technology Hospital, Kumasi (van Middendorp *et al.,* 2013).

The majority of the participants were married and according to Benkeser et al. (2012) this might have resulted in financial stability hence they are able to afford and eat as much as they want to eat and attain body sizes, which signifies prosperity but are associated with excess body weight. Also the cultures of a people relate good marriages to weight gained. Furthermore, these observations may be attributed mostly to peoples' preference for body sizes/images which often is associated with a BMI above normal (Appiah *et al.,* 2016), westernization of diet and low physical activity levels (Ofori-Asenso and Gracia 2016). Comparing the current study to other African countries, the prevalence of overweight in this present study was higher compared to 38.4% recorded in Katsina Nigeria (Azubuike and Danjuma, 2017) but lower than a prevalence of 49.8% recorded in Africa as a whole (Noubiap *et al.,* 2019).

Regarding obesity, this present study recorded a lower prevalence compared with the prevalence of 33.3% recorded in Korle Bu Teaching Hospital among pregnant women by Amoakoh-Coleman et al. (2017). This may be due to the high patronage of the Korle Bu Teaching Hospital by people of varying backgrounds and also because it is a referral hospital. van Middendorp et al. (2013) reported an obesity incidence of 28.6% for pregnant women attending antenatal clinic at KNUST Hospital, Kumasi, a value higher than the prevalence recorded in this present study. This again can be due to peoples' preference for body image which is associated with a BMI above normal (Appiah *et al.,* 2016) among others that were not investigated in this present study.

The systolic and diastolic blood pressures in this study at every stage were higher than 105/66 mmHg recorded among pregnant women who were over 20 weeks gestational age at Kumasi (van Middendorp *et al.*, 2013).

The high blood pressure recorded in this current study may be due to the high levels of overweight recorded and notable stressful lifestyle in Accra compared to that of Kumasi. However, the prevalence of gestational hypertension of 9 (2.4%) and 3(0.8) preeclampsia (PE) in this study were very low compared to the 32.4% of gestational hypertension and 48.8% PE recorded at Komfo Anokye Teaching Hospital (Dassah *et al.*, 2019). This low prevalence in the current study could be the result of intake of calcium additives by the expectant mothers who were at risk for PE as recommended by WHO (World Health Organization, 2018).

5.1.3 Biomakers Profiles of the Pregnant Women

Biochemical parameters examined were 25 hydroxyvitamin D, calcium, magnesium in blood serum and haemoglobin of the participants. In this study, the prevalence of serum 25 (OH) vitamin D deficiency and non-deficiency were 48.3% and 51.7% respectively. This relatively high prevalence of low vitamin D measurements among participants may be related with the wrong time of exposure to the sunlight as well as the type of clothing style and cosmetics used since the majority of the participants reported to have exposed themselves to the sunlight for 5 days or more in a week. This observation might also be as a result low consumption of vitamin D rich foods such as, oily fish, fortified foods and milk as reported by the pregnant women. Milk; however is not a primary food resource for Ghanaians compared to the western

countries Sarkodie-Addo (2017) Ghana lags behind in milk production and consumption | 3NEWS.com).

Fondjo and colleagues in a study in Kumasi among 58 - 59 years type II diabetics and non-diabetics, recorded a high prevalence of serum 25 (OH) vitamin D deficiencies of 92.4% and 60.2% for the diabetics and non-diabetics respectively (Fondjo *et al.*, 2017). This prevalence is higher than the current prevalence, which may be as a result of they being older and spend often more time indoors hence the frequency at which their skin is exposed to the sunlight is lower than the average. High deficiency of vitamin D is expected among the diabetics because Vitamin D decreases the insulin resistance in the encompassing tissues and in this manner diminishes the inordinate insulin discharge in light of expanded blood sugar because of insulin obstruction. Therefore, it increases the insulin affectability. In this manner, Vitamin D inadequacy is a danger factor for metabolic condition and type 2 diabetes mellitus (Chiu *et al.*, 2004).

In Ethiopia however, a prevalence of 15.8% non-deficiency was reported by (Gebreegziabher and Stoecker, 2013). This observation could be as a result of the fact that Ethiopians are mainly Muslims and hence they dress to cover their entire body limiting the effect of sunshine on their skin. Furthermore, Mogire and partners in some analysis involving studies carried out in African countries recorded prevalence of low 25(OH) vitamin D estimates of 18.46% with a median of 67.78 nmol/L (Mogire *et al.*, 2020) .

The median serum calcium concentrations of the pregnant women in this study was 2.2 (1.9, 2.4) mmol/L with 53.2% having a low level. This prevalence of high calcium

deficiency amongst the expectant mothers in this current study can be as a result of deficient amount of 25 hydroxyvitamin D since it is needed for the metabolism of calcium (Fujita *et al.,* 2008; Kutuzova and Deluca, 2004). Also it may be due to poor intake of diets rich in calcium before and during pregnancy, severe hypomagnesemia and others (Almaghamsi *et al.,* 2018). The poor intake of calcium rich foods which are mainly dairy products is not a surprise since it is a common practice among the Ghanaian populace. The finding in this current study is similar to a mean of 2.13 ± 0.44 mmol/L recorded in Korle Bu Teaching Hospital (Djagbletey *et al.,* 2018). Ephraim and colleagues in a case control study recorded a prevalence of 100% low calcium among preeclamptics (Ephraim *et al.,* 2014). This is higher than the prevalence recorded in this current study. It may be as a result of very poor intake of meals rich in calcium as well as poor serum vitamin D level.

Majority of the participants 87.7% had healthy levels of serum magnesium. This is not surprising as Ghanaian meals are high in whole grains, spinach, okro, nuts among others. This is protective against PE and this was confirmed in Ephraim and colleagues' case control study in which all preeclamptics (100%) were deficient in magnesium. Findings of a study in a rural community in India indicated that 43.6% of the pregnant women were deficient in magnesium (Pathak *et al.,* 2003). This prevalence of magnesium deficiency is higher than the prevalence of deficiency recorded (12.3%) in this present study and may be partly due to poor intake of magnesium rich foods. In a study among Sudanese pregnant women, prevalence of magnesium deficiency was 57.2% (Eltayeb *et al.,* 2019) which is higher than the prevalence recorded (12.3%) in this present study. This is expected because of the food insecurity issues in Sudan hence poor dietary intake among the population.

Prevalence of anaemia (haemoglobin level < 11g/dl) at ≤ 20 weeks, 28 – 32 weeks and 6 weeks postpartum was 39.7%, 22.3% and 8.4% respectively. These prevalence's of anaemia might be somewhat due to insufficient dietary iron consumption or absorption, increased needs for iron during pregnancy as well as worm infestation and infections (Camargo *et al.*, 2013). The decrease in the prevalence of anaemia as the trimester go by in this current study can be attributed to the nutrition education given them on regular basis and their compliance with the intake of iron-folate supplement. The prevalence of anaemia (39.7%) at ≤ 20 weeks gestation was very close to the Ghana National prevalence of 42% among women in their reproductive age (Ghana Statistical Service and Ghana Health Service, 2015).

In a study conducted by Wemakor among pregnant women in Tamale, prevalence of anaemia was 50.8% and on the contrary the prevalence of anaemia kept on increasing from trimester to trimester (Wemakor, 2019). The differences observed in Tamale and present study may be due to the fact that the northern regions of Ghana are faced with poor standard of living as well as food insecurity. Additionally, Wemakor reported that usage of insecticide nets was low, prevalence of malaria infection was high, high intake of plant based meals high in non-haem iron as well as high intake of pica. Also Tamale Teaching Hospital receives referral cases and may have contributed to the high prevalence. The increasing prevalence as the trimester go by may be partly due to low or non–compliance with the iron-folic supplement compared to the women in this current study who complied with the intake of iron-folic supplement as well as the nutrition education given them. Mockenhaupt et al. (2000) also in a study in Ghana found that prevalence of anaemia among expectant mothers was 54%, which is

much higher compared to the prevalence recorded in this present study. This high prevalence was attributed to high prevalence of malaria infections and inflammations.

5.2 Summary of the Main Findings

Among pregnant women with an average age of 31 ± 5 years attending ante natal clinics at University of Ghana and the Ghana Police hospitals in Accra, the prevalence of potentially high risk for Preeclampsia was 34.0%. The statistically significant predictors of potentially high risk for Preeclampsia were estimated pre-pregnancy body weight > 71 kg (60^{th} percentile of the sample pre-pregnancy weight distribution) and estimated pre pregnancy BMI ≥ 30 kg/m^2. From the path analysis, anthropometric indices construct (estimated pre-pregnancy body mass index (obesity) and pre-pregnancy weight combined) was significantly, positively and directly linked with a potential that is high towards developing PE along with a magnitude of influence on the outcome of 0.519. This implies that as anthropometric indices increases by one unit, potentially high risk for PE would be expected to increase by 0.519 while holding all other relevant regional connections constant.

5.3 Prevalence of Potentially High Risk for Preeclampsia (PE)

From the current study, 34.0% of the participants had either a high systolic or diastolic blood pressure of greater than 130 mmHg and 80 mmHg, respectively or oedema or proteinuria or a combination of two or more. PE is characterized by high blood pressure (high systolic and high diastolic blood pressure), proteinuria with or without oedema (Lorquet *et al.*, 2010; Mayo Foundation for Medical Education and Research, 1998 – 2017) hence having any of the above mentioned parameters cause one to have a status of being at a potentially high risk of preeclampsia. This

prevalence of 34.0% of the participants have the status of being potentially high risk for preeclampsia may be due to the obesity status (27.3% of the pregnant women were obese with 91.8% of them being at a potentially high risk of PE). In obesity, calcium ions responsible for appropriate vasodilation and contraction become impaired and hence causing buildup of high blood pressure. Also in obese people, Tprv4 gene and protein which is present on endothelial cells which allow calcium entry into the cells to help maintain normal blood pressure stops working causing the calcium entry points to become pathological microdomain (Sonkusarea *et al.*, 2006).

Prevalence of obesity (27.3%) in this current study can be partly due to high academic attainment of the participants (48.0%) (Hsieh *et al.*, 2020), the fact that majority are married (86.0%) (Benkeser *et al.*, 2012), preference for body shape associated with excess weight gain, (OR = 5.197, p 0.032) (Appiah *et al.*, 2014) and westernization of diet and low physical activity level lifestyles (Kearney, 2010; Ng and Popkin, 2012).

Regarding obesity, this present study recorded a lower prevalence (27.3%) compared with the prevalence of 33.3% recorded in Korle Bu Teaching Hospital (KBTH) among pregnant women by Amoakoh-Coleman et al. (2017). This observation can partly be as result of the fact that this current study was carried out in institutionalized hospitals which were mostly patronized by highly educated people (48.1% had attained tertiary education) who knows the dangers associated with excess weight gain and vice versa compared to people of different academic levels who patronized KBTH and can be partly be due to the fact that KBTH is a tertiary and a referral hospital and hence receives complicated cases.

In a study in Tapei, Taiwan, prevalence of obesity among women with years of education 6 years or less and those with ≥ 16 years was 24.1% and 12.1% respectively (Hsieh *et al.,* 2020). Similarly, in the USA, a lower prevalence of obesity was recorded among the higher educated women compare to their counterparts who were less educated; 29.7% and 45.2% (Ogden, *et al.,* 2017). Obesity prevalence found currently in this study can partly be as a result of most women in the study been married. Benkeser and colleagues in a Women's Health Study in Accra recorded prevalence of obesity among the married and unmarried to be 42.40% and 30.70% respectively (Benkeser *et al.,* 2012). Being married may result in emotional and financial stability translating into increased body weight or being overweight as well as the culture appeal on body weight.

Appiah et al. (2014) in the study of obesity in Kumasi involving women randomly recruited from seven churches in Kumasi found prevalence of obesity to be 37.1%. This observation can be partly attributed to the culture and tradition of the people in the Ashanti region especially those in Kumasi with preference for body images which is associated with a higher BMI compare to the participants in this current study. Also it can partly be as result of the fact participants were recruited from the general populace compared with the participants of this current study in which majority of the participants had similarities.

The prevalence of overweight recorded for this study is lower compared to what was recorded in Katsina Nigeria (Azubuike and Danjuma, 2017). The higher prevalence recorded in Azubuike and Danjuma study may be due to the fact that estimated pre-pregnancy BMI was determined using modified weight after 20 weeks instead of the

first antenatal weight recorded used in this current study and different cutoffs. Furthermore, 47.2% of the women in their study were housewives compared to 11.7% women who were unemployed in this current study which could make them less physically active hence gaining excess weight. The higher prevalence of high academic level attained by the participants of this study compared to their study could also be a contributory factor.

In a study in Tanzania, prevalence of obesity was reported to be 7.3% (Mrema *et al.*, 2018). This prevalence was lower than the prevalence recorded in this current study. This lower prevalence in the Tanzania study may due to the fact that, the study was limited to pregnant women who have never or one previous pregnancy but this current study included pregnant women with more previous pregnancies hence causing the higher prevalence in this current study since pregnancies mostly comes with weight again.

Prevalence of high systolic blood pressure measured at any time during pregnancy was 18.8% which implies that this percentage of the expectant mothers were potentially at an increased risk of developing PE so far as high systolic blood pressure was concern with a median (Q1, Q3) of 120 (88, 141) mmHg. This prevalence is higher compare to a prevalence of 6.10% recorded by Amoakoh-Coleman et al. (2017). This indicates that more participants in this current study were at a potentially high risk for PE. This high prevalence of high systolic blood pressure may be as a result of high prevalence of serum vitamin D deficiency (48.3%) recorded among the pregnant women in this current study. Vitamin D metabolites in the serum are inversely associated with circulating renin (Tomaschitz *et al.*, 2010) and according to

Jorde et al. (2010) and Kota et al. (2011), systolic blood pressure increased among individuals with inadequate vitamin D.

Furthermore, the high prevalence of systolic blood pressure recorded for this study may be the consequences of high prevalence of calcium deficiency (53.2%) among the pregnant women causing the release of renin and synthesis of angiotensin II and aldosterone a known vasoconstrictor and hence the build of high systolic blood pressure (Villa-Etchegoyen *et al.*, 2019).

In a situation control investigation conducted in Brong Ahafo regional hospital, 7.1% of the pregnant women had a high systolic blood pressure (Gyasi *et al.*, 2016). This prevalence is lower than the prevalence recorded in this current study. This can be partly due to the high prevalence of vitamin D and calcium deficiencies. Also urbanization and nutritional transition which are factors related to high systolic blood pressure is on a lower side in the Brong Ahafo region areas compare to that in Accra.

Prevalence of oedema at any time after 20 weeks during pregnancy in this current study was 40 (10.5%). This prevalence was higher than the prevalence (8.5%) recorded by Nkwo in Nigeria (Nkwo, 2009). This prevalence of oedema can be a consequence of the high prevalence of calcium deficiency among pregnant women. Low calcium intake diminished the plasmatic calcium fixation invigorating parathyroid chemical (PTH) and the renin-angiotensin-aldosterone framework (RAAS). Both angiotensin II and PTH were expanded in aldosterone emission because of the adrenal organ. Aldosterone regulates epithelial sodium channels (ENaC) in the main cells of the gathering pipe in the kidney, expanding apical layer

penetrability for sodium particles, consequently sodium and water reabsorption which prompts increase of extracellular fluid volume (Villa-Etchegoyen *et al.,* 2019).

The prevalence of oedema (10.5%) recorded in this present study was lower than 33.7% recorded by Agyare et al. (2018). The higher prevalence recorded in Agyare et al. (2018) can partly be due to the fact that one the facilities used in the study was a referral hospital.

Prevalence of proteinuria at any time after 20 weeks during pregnancy in this current study was 20 (5.2%). This prevalence may be partly due to low Vitamin D. Preservation of podocytes health is also influenced by Vitamin D preventing epithetlial-to-mesenchymal change smothering renin gene expression and inflammation of the kidney. Vitamin D has being known to cause reduction in albuminuria in the presence of angiotensin-converting enzyme inhibition for patients with protracted kidney ailment (CKD) (Agarwal, 2009). About 38.0% level of occurrence of proteinuria was recorded at Korle Bu Teaching Hospital (Adu-Bonsaffoh *et al.,* 2017a) and was also higher than the prevalence (5.2%) recorded in this study and can be as result of KBTH receiving referrals and regular cases.

Again the prevalence of proteinuria (5.2%) in this current study is much lower than 451 (48.8%) recorded in Komfo Anokye Teaching Hospital (Dassah *et al.,* 2019). This high prevalence reported by Dassah and colleagues may be partly due to the fact that 80% of the participants were referrals and as such had one complication or the other which can lead to the development of proteinuria or associated with proteinuria. A prevalence of 36% of proteinuria was also recorded in a case control study carried

out in Brong Ahafo Regional hospital (Gyasi *et al.*, 2016). Similarly, this prevalence value is higher than that recorded for this present study and can partly be as a result of the referral status the hospital bears.

5.4 Predictors of Potentially high Risk for Preeclampsia

Pregnant women with estimated pre-pregnancy bodyweight of > 71 kg were at a potentially high risk for PE as compared with those with weight ≤ 71 kg. Similarly pregnant women of estimated pre-pregnancy BMI ≥ 30 kg/m^2 were at potentially high risk for preeclampsia compared with those with BMI < 30 kg/m^2. This high weight and body mass index recorded may be due to the Ghanaian women preference for certain body shapes which is associated with high body weight/body mass index (Appiah *et al.*, 2016). Excessive weight gain can lead to atherosclerosis and hence build-up of high blood pressure (World Heart Federation, 2017). Furthermore, reverse relationship exist for serum vitamin D level and obesity as a result of volumetric dilution (Walsh *et al.*, 2017) and thus vitamin D to influencing the parameter of blood pressure as a consequence of regulating the Renin-Angiotensin System (RAS)(Li *et al.*, 2002; Li *et al.*, 2004).

Similarly, the findings of Mrema among pregnant women in Tanzania indicated that women classified as obese are at a much higher risk of emergent preeclampsia in comparison to those within the normal BMI range (Mrema *et al.*, 2018). Canto-Cetina and colleagues in a study in Mexico found preeclamptics to have a higher pre-pregnancy body mass index compared with non-preeclamptics (Canto-Cetina *et al.*, 2018). A meta-analysis by Poorolajal and Jenabi indicated that obesity was associated with a high risk of developing PE (Poorolajal and Jenabi, 2016). Furthermore, Bej

and colleagues in a study in India, found increased BMI to be proportional to the risk of PE development (Bej *et al.*, 2013). In Columbia, Northern South America, similar observation on BMI to risk of PE condition has been established (Ayala-Ramírez *et al.*, 2020).

5.5 Pathway of Predictors of Potentially High Risk for PE

Anthropometric indices had a direct, positive significant association with potentially high risk for PE. This implies that as the anthropometric indices increase ones risk of being at a potentially high risk for PE increase. High body weight and high body mass index are known to lead to build–up of blood pressure through downward regulation of nitric oxide secondary to upward regulation of asymmetric dimethylarginine (ADMA) and oxidative stress or through increased expression of sympathetic tone and angiotensinogen by adipose tissue (Dandona *et al.*, 2005).

5.6 Strengths and Weaknesses

This study has added onto the knowledge previously known about PE; prevalence of potentially high risk for PE, its predictors and the path ways through which these predictors operate. However, there are limitations to this study. First and foremost, percentage body fat should have been measured instead of BMI to really know that the excess weight is due to fat and not muscles. Secondly, biochemical analysis for 25 hydroxyvitamin D, calcium and magnesium were only carried out with samples at the baseline hence the influence on PE should their concentration change in the cause of the study will be missed out because of financial challenge. Thirdly, serum vitamin D, calcium, haemoglobin and magnesium were the only biochemical data determined even though there are other biochemical data which may be of importance due to

financial constraint. Fourthly, the study was limited to public hospitals hence the findings cannot be generalized since public and private hospitals may have different practices which may/not influence the development of PE or place one at any potentially risk of developing PE. Finally, out of the 403 participant recruited, only 203 gave us their blood samples and this can go a long way to affect the analysis and their reasons for refusing to give their blood samples were they were anaemic and also they are afraid their blood will be used for ritual. The findings from this research will serve as a base for future research on PE and work as a reference for policy planners in their quest towards curbing this menace.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

This chapter presents the main conclusions for the study based on objective set and proposes recommendations for interventions, future studies and policies**.**

6.1 Conclusions

Prevalence of potentially high risk for PE was 34.0%. This study identified significant correlation between estimated anthropometric indices before pregnancy such as weight (> 71 kg), BMI (≥ 30 kg/m^2) and potentially high risk for PE. These correlates; estimated pre-pregnancy weight, estimated pre–pregnancy BMI were significantly associated with potentially high risk for PE. In contrast to the literature, in this cohort of study participants, vitamin D and calcium deficiencies were not associated with PE.

From the path analysis, anthropometric indices had a significant, positive and direct association causing potentially high risk to the developing PE with a magnitude of influence on the outcome of 0.519.

6.2 Recommendation

6.2.1 Recommendations for Future Studies

Extensive studies should be carried out on dietary, socio-demographics characteristics and lifestyle practices in relation to the development of preeclampsia or to be at a potentially high risk for preeclampsia. Also prospective studies should be carried out on biomarkers and preeclampsia risk from as early as 14 weeks of gestation to 6 weeks postpartum at different stages of pregnancy to be able to monitor the effect of

any change in the biomarker's level on PE risk. As early as 14 weeks because after 14 weeks some changes occur in the pregnant women such as weight gain, hormonal changes, fluid retention and other factors hence the pre-pregnancy data will be lost.

6.2.2 Recommendations for Policy Makers

High prevalence of 25-hydroxyvitamin D and serum calcium deficiencies were recorded in this current study and these are known to be major risk factors for preeclampsia. Therefore there is the need to have policies to organise regular evaluation of 25-hydroxy vitamin D and calcium among females in the reproductive age range nationwide as well as provide supplements and nutrition education on how they can enrich their stores through their diets. In addition, there should be policies to enforce routine testing of serum calcium, magnesium and vitamin D status of the pregnant women at the antenatal clinics. Also obesity was determined in this study to be a predictor of preeclampsia and hence policies will be needed to drive regular nutrition education campaign on the need to have the right weight (normal BMI) on the media in order to curb the menace.

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APPENDICES

Appendix 1. Ethical

UNIVERSITY OF GHANA

ETHICS COMMITTEE FOR BASIC AND APPLIED SCIENCES (ECBAS)

P. O. Box LG 1195, Legon-Accra

Ref. No: ECBAS 025/17-18

17th August, 2020.

Mrs. Heckel Amoabeng Abban
Department of Nutrition and
Food Science
University of Ghana
Legon, Accra

Dear Mrs. Abban,

ECBAS 025/17-17: DETERMINANTS OF PREECLAMPSIA AMONG PREGNANT WOMEN ATTENDING ANTE NATAL CLINICS IN SELECTED HOSPITALS IN ACCRA

This is to inform you that the above reference study has been presented to the Ethics Committee for Basic and Applied Sciences for a full board review and the following actions taken subject to the conditions and explanation provided below:

Expiry Date:	01/07/2021
On Agenda for:	Initial Submission
Date of Submission:	02/03/2020
ECBAS Action:	Approved
Reporting:	Annually

Please accept my congratulations.

Yours sincerely,

Professor Daniel Bruce Sarpong
ECBAS Chairperson

ETHICS COMMITTEE FOR BASIC AND APPLIED SCIENCES APPROVED 17 AUG 2020 UNIVERSITY OF GHANA

UNIVERSITY OF GHANA
SCHOOL OF BIOLOGICAL SCIENCES

Ref. No.: SBS1/7

Monday, June 4, 2018

The Medical Director
University Hospital
Legon, Accra

Dear Sir/Madam,

INTRODUCTION: HECKEL AMOABENG ABBAN

I write to introduce to you and your hospital Mrs Heckel Amoabeng Abban, a PhD Nutrition Part II candidate, of the Department of Nutrition and Food Science, School of Biological Sciences, University of Ghana. As part of the requirements for graduation, PhD candidates are supposed to do an independent research that are of national importance. In view of this, Heckel has chosen the field of maternal nutrition and health which is a global as well as national challenge. Specifically, her research topic is

"DETERMINANTS OF PREECLAMPSIA AMONG PREGNANT WOMEN ATTENDING ANTE NATAL CLINIC AT SELECTED HOSPITALS IN ACCRA".

Director, your well – known hospital which is servicing a greater number of women from University Campus, Madina, Adenta and its environs has been selected to be used as one of the study sites. As per ethics regulations, we write to seek your kind permission to allow us entry into your facility to recruit and work with patients. All data collected as well as participants who volunteer to participate will be treated with all confidentiality as required by ethics protocol. Please find attached the necessary documents.

Thanks for understanding and looking forward to hearing from you.

Yours faithfully,

Prof. Matilda Steiner- Asiedu
Dean and Principal Supervisor

ADMINISTRATOR
UNIVERSITY HOSPITAL
LEGON

INTEGRI PROCEDAMUS

COLLEGE OF BASIC AND APPLIED SCIENCES
P. O. Box LG 1256, Legon, Accra, Ghana.
• Telephone: +233 (0) 303 964 988 • Email: deansbs@ug.edu.gh • Website: www.ug.edu.gh

Appendix 2. Consent Form

UNIVERSITY OF GHANA

COLLEGE OF BASIC AND APPLIED SCIENCES

Official Use only
Protocol number

Ethics Committee for Basic and Applied Sciences (ECBAS)

PROTOCOL CONSENTFORM

Section A- BACKGROUND INFORMATION

Title of Study:	Determinants of Preeclampsia among pregnant women attending antenatal clinics at selected hospitals in Accra
Principal Investigator:	Heckel Amoabeng Abban (Mrs)
Certified Protocol Number	

Section B–CONSENT TO PARTICIPATE IN RESEARCH

General Information about Research

The purpose of this study is to determine the possible risk factors that can cause pregnancy - induced hypertension. This research is very critical because hypertension in pregnancy is known to be one of the major causes of maternal and neonatal deaths in Ghana and the world as a whole. The outcome of this study to will contribute to the achievement of the Sustainable Development goal 5 (improve maternal health)

Duration of study

You will be expected to be in the study till eight weeks after delivery of your baby.

Procedure/Methodology

About 3 – 5 ml of blood will be taken from you by a qualified Phlebotomist (a person who has been trained to take blood from patients in the hospital) at the clinic/hospital at the beginning and end of the study. Questionnaires will also be given to obtain your background, lifestyle, dietary, health and other relevant information.

Benefits/of the study

Tel: +233-277493259 Email: ekacquaah@ug.edu.gh/ ethicscbas@ug.edu.gh

Contact for Additional Information

In case of answers to pertinent questions about the research or research-related injury kindly contact the project supervisors, Prof. Matilda Steiner – Asiedu (0541260704), Dr Seth Adu – Afarwuah (0249149385), Dr Timothy Senuyeme (Senior Gynaecologist) (0204600056), Dr Frederick Vuvor or Mrs. Heckel Amoabeng Abban (student/principal investigator) (0244450327).

- If you have any issues on your rights as a participant you can contact the address below:

  Administrator, Ethics Committee for Basic and Applied Sciences
  College of Basic and Applied Sciences
  University of Ghana
  P. O. Box LG 68
  Legon – Accra
  Tel: + 233 277493259
  Email: ekacquaah@ug.edu.gh

Section C-VOLUNTEER AGREEMENT

"I have read or have had someone read all of the above, asked questions, received answersregarding participation in this study, and I am willing to give consent for me, mychild/ward to participate in this study. I have not waived any of my rights by signingthis consent form. Upon signing this consent form, I will receive a copy for my personal records."

_____

Name of Volunteer

_____ _____

Signature or mark of volunteer Date

If volunteers cannot read the form themselves, a witness must sign here:

I was present while the benefits, risks and procedures were read to the volunteer. All questions were answered and the volunteer has agreed to take part in the research.

_____

Name of witness

_____ _____

Signature of witness Date

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this research have been explained to the above individual.

_____

Name of Person who obtained Consent

_____ _____

Signature of Person who obtained Consent Date

Tel: +233-277493259 Email: ekacquaah@ug.edu.gh/ ethicscbas@ug.edu.gh

Appendix 3. Questionnaire Baseline

DEPARTMENT OF NUTRITION AND FOOD SCIENCE
UNIVERSITY OF GHANA, LEGON, ACCRA

QUESTIONNAIRE
DETERMINANTS OF PREECLAMPSIA AMONG PREGNANT WOMEN ATTENDING ANTE NATAL CLINICS IN SELECTED HOSPITALS IN ACCRA
Baseline

Interviewer's name:…….. **Date: ……..**

Subject ID:…… **Hospital:……**

Contact of participant:……..

KINDLY TICK TO INDICATE YOUR CHOICE WHERE A BOX IS PROVIDED OR ANSWER IN THE GIVEN SPACE AS APPLICABLE.

A. BACKGROUND CHARACTERISTICS	
1. What is your age (completed years)? _____	1.____
2. What is your highest academic level attained? 1 = None; 2 = Primary; 3 = Junior Secondary/Middle School 4 = Secondary 5 = Vocational or Commercial 6 =Tertiary	2.____
3. Where do you live? _____	3.____
4. What is your major occupation? 1= Home Keeping 2=Farming 3=Trader 4= Cleaner 5= Teacher 6= Nurse 7= Banker 8.Lecturer 9. Caterer 10. Medical doctor/Pharmacist 11. Other (specify)	4.____
5. On average what is your monthly income? 1= <200 GHC 2= 200 – 400 GHC 3= 401-600 GHC 4= 601-800 GHC 5= 801– 1000 GHC 6= 1001 – 1200 GHC 7 = 1200 – 1400 8 = >1400 GHC	5.____
6. What is your ethnicity? 1=Krobo 2=Akan 3=Ga/Adangbe 4 = Ewe 5 =Northern ethnicity 6 = Ga 7= Other	6.____
7. What is your marital status? 1= Single, never been married 2 = Single, married before 3 = Married 4=Co-habiting 5 = Divorced 6 =Widowed	7.____
8. If married or cohabiting, what is the highest level of education of your partner? 1 = None; 2 = Primary; 3 = Junior Secondary/Middle School 4 = Secondary 5 = Technical or Commercial 6 = Tertiary 7= Don't know 999 = NA	8.____
9. On average what is his monthly income? 1= <200 GHC 2= 200 – 400 GHC 3= 401-600 GHC 4= 601-800GHC 5= 801– 1000 GHC 6= 1001 – 1200 GHC 7 =1200 – 1400 8 = >1400 GHC	

Interviewer's name: …….. **Date:……..**

ID: …… **Place of interview:……..**

Contact of participant: ……..

B. MATERNAL FACTORS	
10. How old were you when you had your first child? N/A = 999	10. ___
11. Is your current partner the father of your other children? 0 = No 1 = Yes N/A = 999	11. ___
C. LIFESTYLE PRACTICES	
12. Have you ever smoked 0 = No 1 = Yes	12. ___
13. Do you consider yourself an alcohol drinker? 0 = No 1= Yes	13. ___
14. How many hours do you usually sleep in a day?	14. ___
15. What is your main means of movement? 1= walking 2 = driving in car	15. ___
16. Do you have regular exposure to the early morning sunlight? 0 = No 1 = Yes	16. ___
17. If YES to qn 16 how many times in a week?	17. ___
18. Do you eat any pica (non – dietary substance)? 0 = No 1 = Yes	18. ___
19. If Yes to qn 18 state it.	19. ___
20. When (month(s)) did you start taken pica?	20. ___
21. How often do you take pica in a week?	21. ___
Physical activities	
22. Does your work usually involve vigorous-intensity activity that causes large increases in breathing or heart rate like (carrying or lifting heavy loads, hawking of wares) for at least 10 minutes continuously? 0 = No 1 = Yes	22. ___
23. In a typical week, on how many days do you do vigorous intensity activities as part of your work?	23. ___
24. How much time do you spend doing vigorous- intensity activities at work on a typical day?	24.____
25. Do you usually do any moderate intensity sports, fitness or recreational (leisure) activities that causes a small increase in breathing or heart rate such as brisk walking,(cycling, joking, volleyball,) for at least 10minutes continuously? 0 = No 1= Yes	25._____
26. In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (leisure) activities?	26. ___
27. Do you usually do laundry by hands? 0 = No 1 = Yes	27. ___
28. Do you usually wash dishes? 0 = No 1 = Yes	28. ___
29. Do you usually do cooking? 0 = No 1 = Yes	29. ___
30. Do you usually have a child/children you take care of? 0 = No 1 = Yes	30. ___
31. Do you usually do cleaning? 0 = No 1 = Yes	31. ___

Interviewer's name: …… **Date:……..**

ID:…… **Hospital:……**

Contact of participants:.....

32. Do you get stressed up at the end of the day? 0 = No 1 = Yes	32. ——
33. If Yes, how stressed are you on a scale of 1 to 10?	33. ____
C. DIETARY PATTERN AND FOOD SECURITY	
34. How many times do you usually eat in a day?	34. ——
35. When do you usually eat your first meal?	35. ——
36. When do you usually eat your last meal?	36. ——
37. How many sachets/glasses of water do you usually drink in a day?	37. ——
38. Please write the number of times you eat food prepared from the following foodstuffs on a weekly or monthly basis	

Food substance	**Weekly**
Fermented cereals	
Dark green leafy vegetables	
Other vegetables	
Other Vitamin A rich foods	
Fruits and fruit juices	
Organ meat	
Flesh meat	
Eggs	
Beans and nuts	
Sea foods	
Smoked river fish	
Probiotic foods	
Milk and other milk products	
Artificial spices, condiments	
Sweets	
Tea	
Coffee	

DATA TO BE ABSTRACTED FROM HOSPITAL RECORDS	
Gynaecological data	
39. Date of first visit	39._____
40. Gestational age	40. ——
41. Expected date of delivery	41. ——
42. Gravidity (number of times you have been pregnant)	42. ___
43. How many children (dead or alive) have you ever had?	43. ——
44. How many do you have alive?	44. ——
45. How old is your last child?	45.
46. Miscarriage (losing pregnancy before 20 weeks) 0=No 1=Y es	46. ——
47. Still birth 0 = No 1= Yes	47. ——
48. Mode (s) of delivery of your last child. 1= Caesaerean section 2 = Vaginal delivery 999 = N/A	48. ——

Interviewer's name:…….. **Date:**……

ID:…….. **Hospital:**……

41. Expected date of delivery	41. ___
42. Gravidity (number of times you have been pregnant)	42. ___
43. How many children (dead or alive) have you ever had?	43. ___
44. How many do you have alive?	44. ___
45. How old is your last child?	45. ___
46. Miscarriage (losing pregnancy before 20 weeks) 0 = No 1= Yes	46. ___
47. Still birth 0 = No 1= Yes	47. ___
48. Mode (s) of delivery of your last child. 1= Caesaerean section 2 = Vaginal delivery 999 = N/A	48. ___
49. Chronic lower abdominal pain 0 = No 1 = Yes 88 = missing 99 = Don't know	49. ___
50. Vaginal / urethral discharge 0 = No 1 = Yes 88 = missing 99 = Don't know	50. ___
51. Genital sores 0 = No 1 = Yes 88 = missing 99 = Don't know	51. ___
52. Genital lumps/warts 0 = No 1 = Yes 88 = missing 99 = Don't know	52. ___
53. Painful urination 0 = No 1 = Yes 88 = missing 99 = Don't know	53. ___
54. Contraceptives use prior to this pregnancy 0 = No 1 = Yes	54. ___
55. If yes to qn 51, please state it.	55. ___
Medical history	
56. Diabetes 0 = No 1 = Yes 88 = missing 99 = Don't know	56. ___
57. Sickle cell disease 0 = No 1 = Yes 88 = missing 99 = Don't know	57. ___
58. Jaundice 0 = No 1 = Yes 88 = missing 99 = Don't know	58. ___
59. Mental illness 0 = No 1 = Yes 88 = missing 99 = Don't know	59. ___
Family History	
60. Hypertension disorders in pregnancy 0 = No 1 = Yes 88 = missing 99 = Don't know	60. ___
61. Gestational Diabetes 0 = No 1 = Yes 88 = missing 99 = Don't know	61. ___
62. Sickle cell disease 0 = No 1 = Yes 88 = missing 99 = Don't know	62. ___
63. Multiple pregnancies 0 = No 1 = Yes 88 = missing 99 = Don't know	63. ___
64. Mental illness 0 = No 1 = Yes 88 = missing 99 = Don't know	64. ___

Interviewer's name:…….. **Date:……**

ID:…… **Hospital:……**

Morbidity

Now I would like to ask you about some illnesses you may have had in the last two weeks. [Note: Each time the woman responds "yes" for last two weeks, ask her how many days she had that symptom, and then ask her if she had the symptom yesterday.]

	Since last visit/ Last two weeks		Yesterday
In last two weeks:	0] No 1]Yes 9] DK 7] NA	Number of days 99] DK 77] NA	0] No 1]Yes 9] DK 7] NA
65. Were there any days when your appetite was poor and you did not feel like eating?	|___|	|__|__|	|___|
66. Did you have nausea?	|___|	|__|__|	|___|
67. Have you had any days when you were vomiting?	|___|	|__|__|	|___|
68. Have you had any diarrhea?	|___|	|__|__|	|___|
69. [If yes to diarrhea] Did you have bloody stools on any of those days?	|___|	|__|__|	|___|
70. [If yes to diarrhea] Was there mucus in your stools on any of those days?	|___|	|__|__|	|___|
71. Have you had any fever?	|___|	|__|__|	|___|
72. Have you had any days when you were coughing?	|___|	|__|__|	|___|
73. Have you had a sore throat?	|___|	|__|__|	|___|
74. Have you any nasal discharge?	|___|		|___|
1 [If yes to nasal discharge] Was the discharge ever thick and yellowish?	|___|	|__|__|	|___|
76. Have you had any abdominal pains	|___|	|__|__|	|___|
77. Have you had any pregnancy-related bleeding	|___|	|__|__|	|___|
78. Any other illness? (sp): _____	|___|	|__|__|	|___|
79. If yes to qn 75, state it.			

DK: Don't Know

Interviewer's name:…….. **Date:**……

ID:…….. **Hospital:**……

80. Since you got pregnant have you gone to the hospital or clinic because you were sick? 0 = No 1= Yes 99 = Don't know	80.___
81. [If yes] How many times have you gone to the hospital or clinic because you were sick?	81.___
82. Since you got pregnant, have you been admitted to the hospital? 0 = No 1 = Yes 99 = Don't know	82.___
83. [If yes] For what reason were you admitted? 1 = Fever 2= shortness of breath 3 = vomiting 4 = Diarrhea 5 = Abdominal pain 6 = Cough 7 = Dizziness 8 = Injury 9 = Pregnancy related bleeding 10 = Other	83._____
Supplements use	
84. In last two weeks, did you use any supplement(s) 0 = No 1 = Yes 99 = Don't know	84.___
85. [If yes] Please tell me the name of the supplement?	85._____
86. In the last two weeks, did you take any herbal preparation? 0 = No 1 = Yes 99 = Don't know	86._____
87. [If yes] Please tell me the name of the preparation? [Name of preparation]**:**	87._____
Anthropometric data	
88. Weight (kg)	88._____
89. Height (m)	89._____
Clinical	
90. Systolic blood pressure (mmHg)	90._____
91. Diastolic blood pressure (mmHg)	91._____
Biochemical data	
92. Haemoglobin (Hb) (g/dl)	92._____
93. Sickling test 1= Negative 2 = Positive	**93.**_____
94. Hb electrophoresis 1= Normal 2 = Carrier 3 = Abnormal	94._____
95. Blood group 1 = O 2 = A 3 = AB 4 = B	95._____
96. Rhesus factor 1 = positive 2 = Negative	96._____
97. Fasting blood sugar	97. _____
98. G6PD 1 = Normal 2 = positive 3. Partial	98._____
99. Stool RE 1 = Negative 2 = positive	99._____
100. Urine RE 1 = Negative 2 = Positive	100._____
101. Urine protein 1 = Negative 2 = Trace 3 = Positive	101_____

Appendix 3. Questionnaire Midline/Endline

DEPARTMENT OF NUTRITION AND FOOD SCIENCE
UNIVERSITY OF GHANA, LEGON, ACCRA
QUESTIONNAIRE

DETERMINANTS OF PREECLAMPSIA AMONG PREGNANT WOMEN ATTENDING ANTE NATAL CLINICS IN SELECTED HOSPITALS IN ACCRA

Midline / Endline

Interviewer's name:…… **Date: ……..**

Subject ID:…… **Hospital:……**

A. LIFESTYLE PRACTICES	
1. Do you consider yourself an alcohol drinker? 0 = No 1= Yes	1. ___
2. How many hours do you usually sleep in a day?	2. ___
3. What is your main means of movement? 1= walking 2 = driving in car	3. ___
4. Do you get regular exposure to the early morning sunlight? 0 =No 1=Yes	4. ___
5. If YES to qn 4 how many times in a week?	5. ___
6. Do you eat any pica (non – dietary substance)? 0 = No 1 = Yes	6. ___
7. If Yes to qn 6 state it.	7. ___
8. When (month) did you start taken pica?	8. ___
9. How often do you take pica?	9. ___
Physical Activities	
10. Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate like (carrying or lifting heavy loads, hawking of wares) for at least 10 minutes continuously? 0 = No 1 = Yes	10. ___
11. In a typical week, on how many days do you do vigorous intensity activities as part of your work?	11. ___
12. How much time do you spend doing vigorous- intensity activities at work on a typical day?	12. ___
13. Do you do any moderate intensity sports, fitness or recreational (leisure) activities that causes a small increase in breathing or heart rate such as brisk walking,(cycling, joking, volleyball,) for at least 10minutes continuously?	13. ___
14. In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (leisure) activities?	14. ___
15. Do you do laundry by hands?	15. ___
16. Do you wash dishes?	16. ___
17. Do you do cooking?	17. ___
18. Do you have a child/children you take care of?	18. ___
19. Do you do cleaning?	19. ___
20. Do you get stressed up at the end of the day? 0 = No 1 = Yes	20. ___
21. If Yes, how stressed are you on a scale of 1 to 10? _____	21. ___

Interviewer's name: …… **Date:……..**

ID:…… **Hospital:……**

B. DIETARY PATTERN AND FOOD SECURITY	
22. How many times do you usually eat in a day?	22. ___
23. When do you usually eat your first meal?	23. ___
24. When do you usually eat your last meal?	24. ___
25. How many sachets of water do you usually drink in a day?	25. ___

26. Please write the number of times you eat the following foods on a weekly or monthly basis

Food substance	**Weekly**
Fermented cereals	
Dark green leafy vegetables	
Other vegetables	
Other Vitamin A rich foods	
Fruits and fruit juices	
Organ meat	
Flesh meat	
Eggs	
Beans and nuts	
Sea foods	
Rivers fish	
Probiotic foods	
Milk and other milk products	
Artificial spices, condiments	
Sweets	
Tea	
Coffee	

DATA TO BE ABSTRACTED FROM PARTICIPANTS RECORDS

Parameter	**Values**
27. Haemoglobin	
26. Fasting blood sugar	
27. Urine protein	
28. Systolic blood pressure	
29. Diastolic blood pressure	
30. Change in weight	

Interviewer's name: …… **Date:……..**

ID:…… **Hospital:……**

Morbidity

Now I would like to ask you about some illnesses you may have had in the last two weeks. [Note: Each time the woman responds "yes" for last two weeks, ask her how many days she had that symptom, and then ask her if she had the symptom yesterday.]

	Since last visit/ Last two weeks		Yesterday
In last two weeks:	0] No 1]Yes 9] DK 7] NA	Number of days 99] DK 77] NA	0] No 1]Yes 9] DK 7] NA
31. Were there any days when your appetite was poor and you did not feel like eating?	|___|	|___|___|	|___|
32. Did you have nausea?	|___|	|___|___|	|___|
33. Have you had any days when you were vomiting?	|___|	|___|___|	|___|
34. Have you had any diarrhea?	|___|	|___|___|	|___|
35. [If yes to diarrhea] Did you have bloody stools on any of those days?	|___|	|___|___|	|___|
36. [If yes to diarrhea] Was there mucus in your stools on any of those days?	|___|	|___|___|	|___|
37. Have you had any fever?	|___|	|___|___|	|___|
38. Have you had any days when you were coughing?	|___|	|___|___|	|___|
39. Have you had a sore throat?	|___|	|___|___|	|___|
40. Have you any nasal discharge?	|___|		|___|
2 [If yes to nasal discharge] Was the discharge ever thick and yellowish?	|___|	|___|___|	|___|
42. Have you had any abdominal pains	|___|	|___|___|	|___|
43. Have you had any pregnancy-related bleeding	|___|	|___|___|	|___|
44. Any other illness? (sp): _____	|___|	|___|___|	|___|
45. If yes to qn 44, state it.	45		

DK: Don't Know

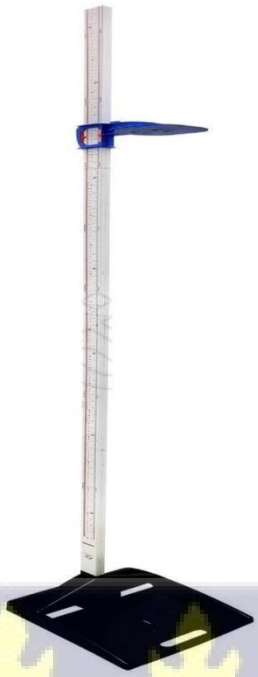
Interviewer's name:…….. **Date:……**

ID:…… **Hospital:……**

46. Since you got pregnant have you gone to the hospital or clinic because you were sick? 0 = No 1= Yes 99 = Don't know	46.___
47. [If yes] How many times have you gone to the hospital or clinic because you were sick?	47.___
48. Since you got pregnant, have you been admitted to the hospital? 0 = No 1 = Yes 99 = Don't know	48.___
49. [If yes] For what reason were you admitted? 1 = Fever 2= shortness of breath 3 = vomiting 4 = Diarrhea 5 = Abdominal pain 6 = Cough 7 = Dizziness 8 = Injury 9 = Pregnancy related bleeding 10 = Other	49.____
Supplements use	
50. In last two weeks, did you use any supplement(s) 0 = No 1 = Yes 99 = Don't know	50.___
51. [If yes] Please tell me the name of the supplement?	51.____
52. In the last two weeks, did you take any herbal preparation? 0 = No 1 = Yes	52.____
53. [If yes] Please tell me the name of the preparation? [Name of preparation]:	53.____

Appendix 4. Weighing Scale

Appendix 5. Stadiometer



Appendix 6. BMI Classification

BMI	
Underweight	< 18.5 kg/m^2
Normal weight	18.5 – 24.9 kg/m^2
Overweight	25.0 – 29.9 kg/m^2
Obesity	≥ 30.0 kg/m^2

Appendix 7. Standard Reference for Biochemical samples

Serum Vitamin D

Deficiency - < 20 ng/ml

Non – deficient - ≥ 20 ng/ml

Agilent High Performance Liquid Chromatography

Appendix 8

Selectra Pro S

Serum Calcium

Deficiency - < 2.2 mmol

Non – deficient - ≥ 2.2 mmol

Serum Magnesium

Deficient – 0.66 mmol

Non – deficient - ≥ 0.66 mmol

Haemoglobin

Anaemia - < 11.0g/dl

Non – anaemic - ≥ 11.0g/dl

Appendix 9. American Heart Association Standard and ACOG (2002) Reference

Systolic Blood Pressure

Non – hypertensive - < 130 mmHg

Hypertensive - ≥ 130 mmHg

Diastolic Blood Pressure

Non – hypertensive - < 80 mmHg

Hypertensive - ≥ 80 mmHg