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FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

Maternal Outcome by Mode of Delivery Following Severe Preeclampsia in Two Referral Hospitals in Yaoundé

A dissertation submitted in partial fulfilment of the requirements
for the award of a Specialist Diploma in Obstetrics and Gynaecology

by

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Academic Year 2023 - 2024

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DEDICATION

This piece of work is dedicated to all women who suffer from Preeclampsia, including those who lost their lives.

ACKNOWLEDGEMENTS

I will like to express my sincere gratitude to:

- To the Lord God Almighty for life, strength, good health and the necessary means to brave these long years of study.
- To Professor NGO UM MEKA Esther, Dean of the Faculty of Medicine and Biomedical Sciences at the University of Yaoundé I, for her direction and discipline to residents.
- To Professor Dohbit Julius Sama, for agreeing to supervise this thesis. Dear Sir, please allow me to express my deep admiration for your human and professional qualities. My immense gratitude for your supervision, your teachings, your availability, your wise advice. Thank you for believing in me.
- To Dr EBONG Clifford, for agreeing to co-supervise this work. Your expertise allowed us carry out this work successfully. Thank you for your availability and your concern.
- To Professor MBU ENOW Robinson. Dear Sir, we were particularly marked by your fatherly guidance throughout our training, your permanent concern to teach and transmit knowledge despite your tight schedule. Thank you for your support and thank you for believing in us.
- To the members of the jury for agreeing to judge this work in order to contribute to its scientific improvement.
- To all our lecturers in the Department of Obstetrics and Gynaecology for the lessons received during our training.
- To our seniors in the profession: Dr Nzometia Crysantus, Dr Ombaku Kingsly, Dr Mbala Peter for their friendship and support.

- To my dear parents, Dr and Mrs MUKWELE for all the efforts, prayers, encouragements, love and support throughout my training.
- To my dear husband, Dr Choffor Nchinda Emmanuel and to our children Aidric and Riley, your unwavering support, unconditional love and boosting me be the best version of me every day.
- To my siblings Mukwele Henrita, Isaac and Rene of blessed memory, all my aunties home and abroad, my in-laws and cousins for the support and prayers.
- To all my friends: Sakerette MDs, Sakerettes 03, Lorraine Tankou and husband, Dr Glennise Aben, Dr Chuwanga clinic staff, for your friendship and your prayers.
- To all members of the Association of Residents and Interns of Gynaecology and Obstetrics in Cameroon (ARIGOC), particularly to B-lynch MDs, Drs DONGMO, Mbia, Anubodem, Mboutou, Musa, just to name a few, for the great collaboration, support and for the family we have created.
- To all those who directly or indirectly contributed to my training and the completion of this work, especially Bah Felix 5th year medical student, the archive staff, reception staff and majors.

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ABSTRACT

Background: Preeclampsia is a complex pregnancy-related condition that poses significant risks to maternal and foetal health and contributes to a significant proportion of maternal mortality, particularly in Africa. This study aimed to investigating the relationship between mode of delivery and maternal outcomes among women diagnosed with severe preeclampsia.

Methodology: It was a nested retrospective cohort study focused on women with severe preeclampsia who delivered at Yaoundé Gynaeco-Obstetric and Paediatric Hospital and Yaoundé Central Hospital over a 10-year period from 1st June 2014 to 31st May 2024. The study population included women who met specific diagnostic criteria and inclusion parameters, with a calculated minimum sample size of 78 participants. Data were carefully collected from medical records. Statistical analyses used descriptive methods, univariate tests and multivariate logistic regression to assess associations between mode of delivery and maternal outcomes, controlling for potential confounders. The measure of association was reported as relative risk with 95% confidence interval and p-value. The significance level was set at p-value < 0.05.

Results: The study included a total of 349 patients with severe preeclampsia. The caesarean section rate was 53.9%, with the most common indication being a poor Bishop score. A total of 42.9% of vaginal births were induced and 16.9% of induction failed. Apart from eclampsia, there were no other statistically significant differences in complications before caesarean or vaginal delivery. Women who had caesarean deliveries were significantly more likely to have adverse maternal outcome than women who had vaginal deliveries. However, after multivariate logistic regression analyses, only acute pulmonary oedema (aRR = 1.31 [CI: 1.01 - 2.73]) and intensive care unit admission (aRR = 2.22 [CI: 1.98 - 3.45]) were independently associated to mode of delivery.

Conclusion: Caesarean section is more performed in patients with severe preeclampsia, and it's significantly associated with adverse maternal outcomes. However, this study shows that it is possible to achieve timely vaginal delivery in these patients by induction of labour.

Key words: caesarean section; maternal outcomes; mode of delivery; complications; severe preeclampsia; vaginal delivery.

RÉSUMÉ

Contexte : La pré-éclampsie est l'une des principales causes de morbidité et de mortalité maternelles et périnatales dans le monde. L'interruption de grossesse est son seul traitement efficace, mais il existe des controverses sur le choix des modes d'accouchement.

Objectif : Le but de cette étude était d'étudier le devenir des patientes atteintes de pré-éclampsie sévère en ce qui concerne le mode d'accouchement dans deux hôpitaux de référence de Yaoundé.

Méthodes : Il s'agit d'une étude de cohorte rétrospective portant sur des femmes atteintes de prééclampsie sévère ayant accouché à l'hôpital gynéco-obstétrique et pédiatrique de Yaoundé et à l'hôpital central de Yaoundé sur une période de 10 ans allant du 1er juin 2014 au 31 mai 2024. La population étudiée comprenait des femmes qui répondaient à des critères de diagnostic et à des paramètres d'inclusion spécifiques, avec une taille d'échantillon minimale calculée de 138 participants. Les données ont été collectées à partir des dossiers médicaux. Les analyses statistiques ont utilisé des méthodes descriptives, des tests univariés et une régression logistique multivariée pour évaluer les associations entre le mode d'accouchement et les issues maternelles, en contrôlant les facteurs de confusion potentiels. La mesure de l'association a été rapportée sous forme de risque relatif avec un intervalle de confiance à 95 % et une valeur p. Le niveau de signification a été fixé à une valeur $p < 0,05$.

Résultats : Cette étude a inclus un total de 349 patientes atteintes de pré-éclampsie sévère. Le taux de césarienne était de 53,9 %, l'indication la plus courante étant un mauvais score de Bishop. Au total, 42,9 % des femmes ayant accouché par voie basse ont été induites, et 16,9 % des inductions ont échoué. A l'exception de l'éclampsie, il n'y avait pas d'autre différence statistiquement significative dans les complications avant l'accouchement par césarienne ou par voie basse. Les femmes ayant accouché par césarienne étaient significativement plus susceptibles d'avoir un devenir défavorable par rapport à celles qui avaient accouchée par voie basse. Cependant, après des analyses de régression logistique multivariée, seule l'œdème pulmonaire aigu (aRR = 1,31 [IC : 1,01 – 2,73]) et l'admission en unité de soins intensifs (aRR = 2,22 [IC : 1,98 – 3,45]) étaient indépendamment associées au mode d'accouchement.

Conclusion : L'accouchement par césarienne est plus fréquemment pratiqué chez les patientes atteintes de prééclampsie sévère et est significativement associée à un devenir maternel défavorable. Cette étude a cependant montré qu'il est possible de faire un accouchement par voie basse après induction du travail chez ces patientes.

Mots clés : césarienne ; devenir maternel ; mode d'accouchement ; complications ; pré-éclampsie sévère ; accouchement vaginal

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LIST OF ABBREVIATIONS

ACE Angiotensin converting enzyme

ACOG American College of Obstetrics and Gynaecology

AHA American heart association

ARB Angiotensin II receptor blocker

COMT Catechol-O-methyl transferase

DBP Diastolic blood pressure

DV Decidual vasculopathy

EVT Extra-villous trophoblast

HDP Hypertensive disorders of pregnancy

HELLP Haemolysis, elevated liver enzymes, low platelet count

HIP Hypertension in pregnancy

HLA Human leucocyte antigen

HO Heme-oxygenase

ISSPH International Society for the Study of Hypertension in Pregnancy

IV Intravenous

PAPP-A Pregnancy associated protein – A

ROS Reactive oxygen species

RUPP Reduced uterine perfusion pressure

SBP Systolic blood pressure

SGA Small for gestational age

TFs Transcription factors

VEGF Vascular endothelial growth factor

WHO World Health Organization

YCH Yaoundé Central Hospital

YGOPH Yaoundé Gynaeco-Obstetric and Paediatric Hospital

RR Risk ratio

CI Confidense interval

CS Caesarean section

APE Acute pulmonary oedema

AKI Acute kidney in

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Preeclampsia is a multisystem disorder of unknown aetiology unique to pregnancy [1]. It has various complications which individually or in combination can lead to maternal/foetal morbidity and mortality 3]. According to the American College of Obstetrics and Gynaecology (ACOG) 2019, preeclampsia is defined as the presence of a systolic blood pressure (SBP) greater than or equal to 140 mm Hg or a diastolic blood pressure (DBP) greater than or equal to 90 mm Hg, on two occasions at least 4 hours apart in a previously normotensive patient, with proteinuria of greater than or equal to 0.3 grams in a 24-hour urine specimen, a protein (mg/dl)/creatinine (mg/dl) ratio of 0.3 or higher, or a urine dipstick protein of 1+ (if a quantitative measurement is unavailable) [4]. This pathology is classified into; preeclampsia without severe features (mild) and preeclampsia with severe features (severe).According to the World Health Organization, preeclampsia is the third cause of maternal mortality after severe haemorrhages and infections accounting for 14% of deaths worldwide[5]. In Africa, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy [6]. In Cameroon, preeclampsia occurs in 4.9% to 7.7% of pregnancies [7]. In the North West region, a prevalence of severe preeclampsia of 10.8% among women with hypertensive disease in pregnancy was reported in 2020[8]. In one of the major reference hospitals in Yaoundé, preeclampsia and eclampsia were found to be the first cause of maternal death [7].

Delivery is considered the optimum treatment of preeclampsia and generally, Caesarean section is often proven to be the faster mode of delivery when faced with the need for rapid control of blood pressure (especially in the absence of labour) and vaginal births come secondary -10]. In two referral hospitals in Yaoundé, severe preeclampsia was found to be associated with increased post-operative complications [11]. So far, there's limited data available on the effects of mode of delivery on maternal outcomes [12]. Therefore rapid decision on the mode of delivery is absolutely vital in order to reduce maternal and perinatal morbidity and mortality [13]. Implementing optimum care for women during pregnancy and the post-partum period to prevent and treat severe preeclampsia and its complications is a necessary step towards the achievement of the health targets of the Sustainable Development Goals [5].

1.2 JUSTIFICATION

There is scarcity of data concerning the relationship between the outcomes of patients with severe preeclampsia with respect to the mode of delivery. The need to identify a potential relationship, as well as factors that could influence this relationship will enable practitioners to propose the better mode of delivery for these women.

1.3 RESEARCH QUESTION

Was the mode of delivery a determinant of maternal outcome in women diagnosed with severe preeclampsia?

1.4 RESEARCH OBJECTIVES

1.4.1 General Objective

Study maternal outcome in severe preeclampsia patients with respect to mode of delivery.

1.4.2 Specific Objectives

1. To describe the socio-demographic and clinical profile of the study participants.
2. To identify the complications presented by women with severe preeclampsia before delivery by mode of delivery.
3. To compare progress of complications by mode of delivery.
4. To compare maternal outcome by mode of delivery.

CHAPTER TWO: LITERATURE REVIEW

2.1 DEFINITION OF PREECLAMPSIA

Over the years, the definition of preeclampsia has changed. Formerly, it was defined as the appearance of hypertension accompanied by proteinuria after 20 weeks of gestation. Today, the International Society for the Study of Hypertension in Pregnancy (ISSHP) and American College of Obstetrics and Gynaecology (ACOG) have a broader definition, which is the most accepted internationally [14].

Preeclampsia is defined as the presence of systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg at 20 or more weeks of gestation, taken at least 4 hours later in a woman with normal pre-pregnancy blood pressures [15] with presence of proteinuria.

Severe preeclampsia or preeclampsia with severe features is defined as the presence of one of the following symptoms or signs in the presence of preeclampsia [4] :

- SBP of 160 mm Hg or higher or DBP of 110 mm Hg or higher, on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy has previously been initiated)
- Impaired hepatic function as indicated by abnormally elevated blood concentrations of liver enzymes (to double the normal concentration), severe persistent upper quadrant or epigastric pain that does not respond to pharmacotherapy and is not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration >1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease)
- New-onset cerebral manifestations (convulsion)
- New onset visual disturbances
- Persistent headache
- Pulmonary oedema
- Thrombocytopenia (platelet count < 100,000/µl)
- Uterus-placental dysfunction: foetal growth restriction, altered umbilical artery Doppler or death [16].

Table I : clinical definition of preeclampsia [15].

Preeclampsia without severe features
Systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg, on 2 occasions, 4hours apart
AND
Proteinuria ≥ 0.3 g in a 24 hours urine collection
Or protein/creatinine ≥0.3
Or dipstick reading =1+
Preeclampsia with severe features (one or more of the following)
Systolic blood pressure ≥160 mm Hg or diastolic ≥110 mm Hg, 2 occasions, 4 hours apart
Thrombocytopenia (<100 000/µl)
Elevation of blood liver enzyme concentrations by twice the normal or severe persistent right upper quadrant or epigastric pain
Serum creatinine concentration >1.1 mg/dl or doubling of serum creatinine concentration in the absence of other renal disease
Pulmonary oedema
New-onset cerebral or visual symptoms
Eclampsia

2.2 EPIDEMIOLOGY OF PREECLAMPSIA

The World Health Organization (WHO) reported that hypertensive disorders of pregnancy (HDP) account for 14.0 % of global maternal deaths. Maternal mortality is higher in a preeclamptic pregnancy than in a non-preeclamptic pregnancy. In Latin-American and Caribbean countries about 26 % of maternal deaths were due to HDP; in Asia and Africa, it contributed to 9 % of maternal deaths and in fact about 16 % in sub-Saharan Africa [17]. The Health Care America Corporation revealed in a study of several hospitals that preeclampsia and it's complications was the second leading cause of pregnancy-related intensive care unit admissions after obstetric haemorrhage [15].

In Cameroon, hypertension in Pregnancy (HIP) occurs in 7.7 – 8.2 %. In the Far North Region, hypertension in pregnancy was the first cause of maternal death, representing almost 18 % of the 63 maternal deaths recorded between 2003 and 2005 [18]. In the South West Region, Maternal

Mortality from HDP was estimated at 1887/100,000 live birth [19]. In the NWR, Egbe *et al.* [20] showed that 14.5 % of maternal deaths in Mezam Division were due to HDP. In the centre region, Mboudou *et al.* [7] reported a prevalence of 8.2 % with preeclampsia being the most frequent (78 %) and over 10.7 % of the patients developing complications. Preeclampsia complicates 0.52 % of pregnancies in high income countries. In Cameroon, the prevalence of preeclampsia is between 5.9 and 6.4 % [6] and severe preeclampsia 10.8 % [8]. It is worth noting that studies have reported a 7-20 % chance of preeclampsia recurrence in a subsequent pregnancy. This risk is further increased in a woman who has had two prior pregnancies with preeclampsia and is also influenced by gestational age of onset.

The risk of foetal death in preeclamptic pregnancies is higher than that in non-preeclamptic pregnancies [21] as a result of foetal growth restriction and placental abruption. Infant mortality is three times higher in low resource settings compared to high income countries, mainly as a result of less access to neonatal intensive care facilities. High rates of medically indicated preterm birth also result in an increase in neonatal deaths, which are 2.7 times higher than in pregnancies resulting in a term birth [21].

2.3 CLASSIFICATION OF PREECLAMPSIA

Preeclampsia is classified based on severity and time of onset according to the International Society for the Study of Hypertension in Pregnancy.

Table II: classification of preeclampsia [22].

Based on severity **[I] Preeclampsia with severe features (At least one of the following)**: -Blood pressure ≥160/110 mmHg -Haemolysis, -Elevated liver enzymes and low platelet count (HELLP), -Lactate dehydrogenase ≥600 IU/l -Blurry vision, headache, seizures -Epigastric/right upper quadrant tenderness, -Oliguria, Creatinine >1.1mg/dl -Foetal growth restriction <tenth percentile - Plus or minus proteinuria 3+ on urine dipstick. **[II] Preeclampsia without severe features:** -Blood pressure >140/90 mmHg, and at least one other condition including -Proteinuria (urine protein to creatinine ratio ≥0.3 mg/dl, albumin to creatinine ratio≥ 0.3 mg/dl) or 24hour urine collection ≥0.3 g/day.
Based on gestational age at clinical presentation **[I]** Preterm (<37 weeks of gestation) preeclampsia **[II]** Term (≥37 weeks of gestation) preeclampsia **[III]** Postpartum (diagnosed within 6weeks after delivery) preeclampsia

2.4 RECALL

2.4.1 Placentation

The placenta is the main element for the development of preeclampsia as the disease is found only when a placenta is or was recently present. The proper functioning and health of the placenta depends on extensive placental villus branching and vascularization during early pregnancy, with the mature placenta largely formed by the end of the first trimester.

Pregnancy is initiated following implantation of a competent blastocyst into a receptive endometrium. The endometrium is transiently receptive to blastocyst implantation during the mid-luteal phase of the menstrual cycle [19]. Following implantation, the placenta is formed from extra-embryonic lineages in the blastocyst: trophectoderm cells differentiate into villus progenitor cytotrophoblast, which fuse to form the syncytiotrophoblast or differentiate into invasive extra-villous trophoblast, and extra-embryonic mesoderm differentiates into villus core stromal tissue and blood vessels. The placental villus is lined by two layers of trophoblast: the multinucleated syncytiotrophoblast, which covers the entire placenta and is in direct contact with maternal blood, and the cytotrophoblast, which formed the extra-villous trophoblast and anchors the placental villus to the maternal decidua via cell columns [24]. Extra-villous trophoblasts invade from cell columns into the upper third of the myometrium from as early as 14 days after implantation until 18 weeks of gestation, when placentation is largely completed. Factors released by the extra-villous trophoblasts (including progesterone) enhance decidualization, creating the semi-permanent decidual tissue maintained throughout pregnancy [25].

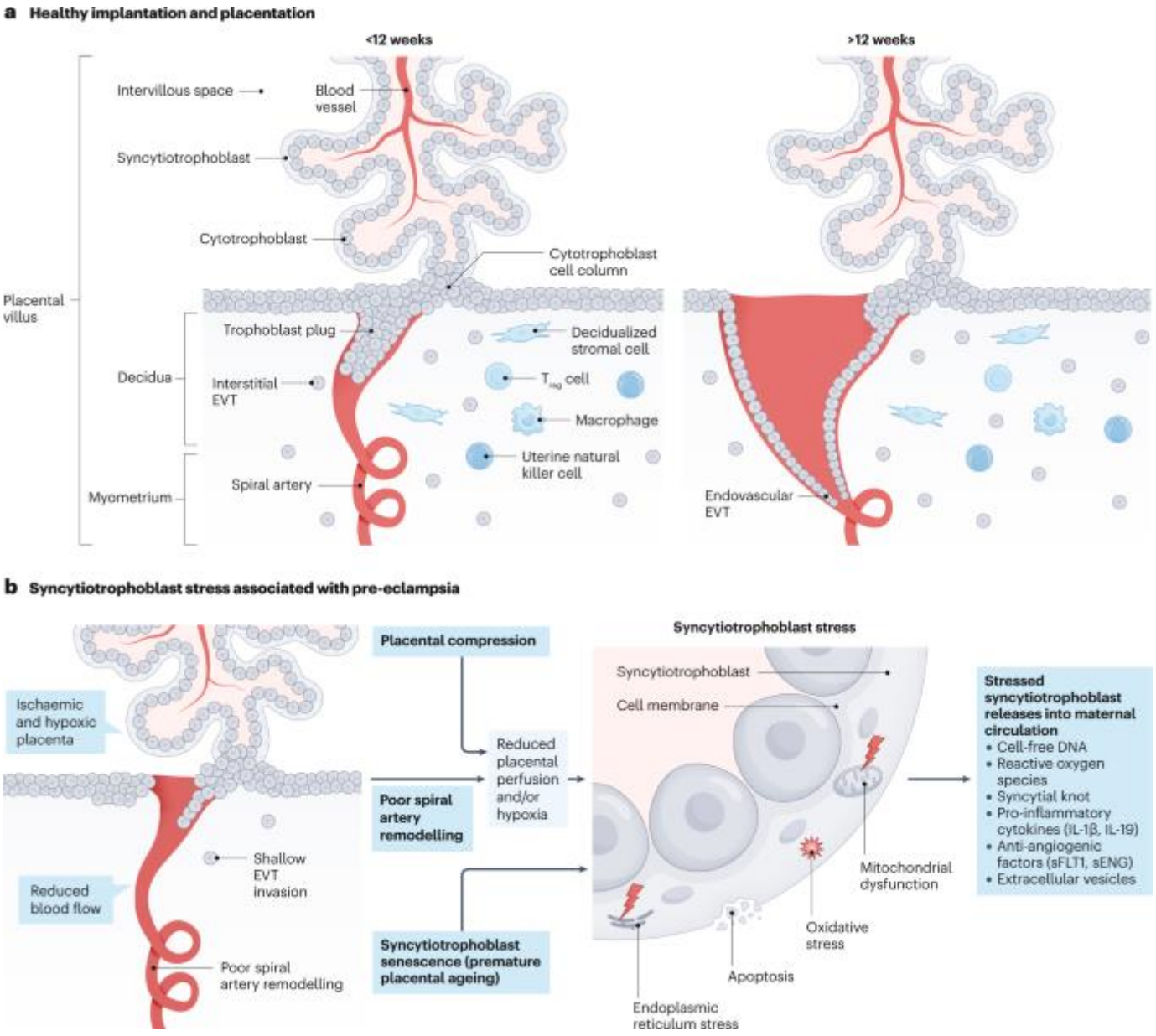

Figure 1: syncytiotrophoblast stress is driven by dysfunctional placental perfusion.[25]

a, each placental villus has a mesodermal core surrounded by an inner layer of progenitor cytotrophoblasts and an outer syncytiotrophoblast layer. Cytotrophoblasts at the villous tip interrupt the syncytiotrophoblast to form a columnar structure, which anchors the placenta to the decidua. Extra-villous trophoblasts (EVTs) differentiate from the columnar cytotrophoblasts and migrate into the decidua into the upper myometrium (interstitial EVTs) or plug maternal spiral arteries (endovascular EVTs), preventing maternal blood flow into the inter-villous space until about 12 weeks of gestation, when the trophoblast plugs are lost. EVTs and uterine-resident

immune cells, including uterine natural killer cells and regulatory T (T_{reg}) cells, actively remodel the maternal spiral arteries into wide-bore, low-flow uterine arteries by removing vascular smooth muscle cells that surround the artery. **b**, there are multiple proposed drivers of syncytiotrophoblast stress associated with pre-eclampsia. Poor spiral artery remodelling, which is associated with shallow EVT invasion, is proposed to drive syncytiotrophoblast stress by causing an ischaemic blood supply to the placenta. Overcrowding and compression of the placental villus are proposed to cause reduced placental perfusion and a hypoxic placenta, driving syncytiotrophoblast stress. Syncytiotrophoblast senescence from premature placental ageing may also lead to syncytiotrophoblast stress. Syncytiotrophoblast stress manifests as endoplasmic reticulum stress, mitochondrial dysfunction, oxidative stress, and apoptosis and leads to abnormal syncytiotrophoblast release of factors, including cell-free DNA, reactive oxygen species, syncytial knots, exosomes/micro-vesicles, pro-inflammatory cytokines and anti-angiogenic factors, into the maternal circulation.

Placental villi bathed in maternal blood facilitate all nutrient and gas exchange required to support the foetus during pregnancy. Blood vessels within the villus core transport nutrients and gases to and from the foetus via the umbilical blood vessels. During the first trimester, uterine spiral arteries are remodelled to create wide-bore, high-flow, low-resistance vessels [26] capable of accommodating increased placental perfusion requirements in the later stages of pregnancy. Remodelling is initiated by uterine-resident innate immune cells, including uterine NK cells and T regulatory (T_{reg}) cells, which cause the loss of vascular smooth muscle cells surrounding the spiral arteries and regulate extra-villous trophoblast invasion through the decidua via the secretion of angiogenic growth factors and cytokines [27]. Endovascular extra-villous trophoblasts invade the arteries, replacing vascular endothelial cells and temporarily plugging the maternal arteries, blocking blood flow to the developing placenta, and leading to embryo development under low oxygen conditions. At around 10–12 weeks of gestation, the trophoblast endovascular plugs dislodge [28], enabling increasing volumes of maternal blood to perfuse the inter-villous space and thus increasing foetal-placental oxygenation.

2.4.2 Vascular adaptations during pregnancy

In a healthy pregnancy, the maternal cardiovascular system undergoes significant expansion, including increased plasma volume and increased cardiac output from as early as 3–4 weeks of

gestation, primarily driven by placental-released factors [29]. Resultant increases in blood pressure are prevented by concomitant decreases in systemic vascular (peripheral) resistance, increased arterial compliance, increased peripheral vasodilation, blunted contractility, enhanced endothelial release of vasodilatory factors and activation of the renal renin–angiotensin–aldosterone system [30]. There is little evidence for autonomic regulation driving changes in the cardiovascular system during pregnancy: the primary adaptations are endothelial and myogenic. The endothelium is the interface between blood and vascular smooth muscle and is highly responsive to humoral factors and physical forces [29].

2.5 RISK FACTORS OF PREECLAMPSIA

Many risk factors have been identified as associated with preeclampsia; however, individually, none of these have a high predictive value of preeclampsia risk and even in combination, their predictive power is weak. Recognized high-risk factors are broadly similar among ISSHP [22] and American College of Obstetricians and Gynaecologists (ACOG) guidelines.

Table III: risk factors of preeclampsia [22].

High risk	Previous preeclampsia
	Genetic
	Chronic renal disease
	Chronic hypertension
	Diabetes mellitus
	Body mass index ≥30 kg/m^2
	Multiple pregnancy
Moderate risk	First pregnancy
	Age ≥40 years
	Inter-pregnancy interval >10 years
	Family history of pre-eclampsia
	Black race
	Low socioeconomic status

2.5 PATHOGENESIS OF PREECLAMPSIA

The underlying aetiology of preeclampsia remains uncertain. It is likely that maternal and placental factors are involved. A two stage model of preeclampsia proposes that it results from placental dysfunction causing syncytiotrophoblast stress (stage 1), which leads to the maternal clinical manifestation of preeclampsia (stage 2). The cause and timing of the placental insult are proposed to differ between disease occurring during the preterm and term/postpartum period.

Syncytiotrophoblast stress (stage 1) manifests as oxidative stress, endoplasmic reticulum stress, mitochondrial damage, dysregulated metabolism and apoptosis. The stressed syncytiotrophoblast abnormally releases pro-inflammatory cytokines, reactive oxygen species, extracellular vesicles, anti-angiogenic agents into the maternal circulation. These factors promote maternal endothelial dysfunction and systemic multi-organ disorder that involves vasoconstriction, systemic inflammation and thrombosis (stage 2). The effects include hypertension, liver and renal impairment, thrombocytopenia, and coagulopathy [16].

a) Stage 1: Abnormal Placentation, Trophoblast Invasion, and the Maternal-Foetal Interface

During normal placental implantation, cytotrophoblasts migrate into the maternal uterine spiral arteries, forming vascular sinuses at the foetal-maternal interface to provide nutrition to the foetus. In normal pregnancy, this invasion progresses deeply into the spiral artery to the level of the myometrium, which leads to extensive remodelling of the maternal spiral arterioles into high capacitance, high flow vessels [31]. In placentas destined to develop preeclampsia, cytotrophoblasts fail to transform from the proliferative epithelial subtype to the invasive endothelial subtype which causes incomplete remodelling of the spiral artery. Inadequate spiral arteriolar remodelling leads to narrow maternal vessels, and relative placental ischemia. The narrow spiral arteries are prone to atherosis, characterized by the presence of lipid-laden macrophages within the lumen, fibrinoid necrosis of the arterial wall, and a mononuclear perivascular infiltrate, leading to further compromise in placental flow. In humans, placental ischemia can be noninvasively identified using uterine artery Doppler studies. During normal pregnancy, uterine artery Doppler studies have confirmed robust systolic and diastolic uterine arterial flows; in contrast, women with preeclampsia have significant impairment of diastolic flow with a characteristic notch in the waveform that antedates clinical signs and symptoms of preeclampsia [32]. These findings suggest that an abnormality in the trophoblasts themselves may result in shallow placentation and inadequate transformation of the spiral arteries, leading to placental ischemia and the maternal syndrome of preeclampsia [33].

Atherosclerotic changes in maternal radial arteries that supply the decidua, as opposed to the spiral arteries are also observed in preeclampsia. Decidual vasculopathy (DV) is a lesion common to disorders of placental insufficiency, including intrauterine growth restriction and preeclampsia, and combines acute atherotic lesions with medial hypertrophy and perivascular lymphocytes. Within preeclampsia phenotypes, the presence of DV is associated with worse clinical outcome, higher diastolic BP, worse renal function, and perinatal foetal death. Histologically, normal third-trimester decidual vessels are characterized by flat endothelium and a loss of medial smooth muscle, while preeclamptic decidua show signs of loose, oedematous endothelium, hypertrophy of the vessel media, and loss of smooth muscle modifications (as seen in atherosclerosis), characterizing DV. Correlated with clinical diagnosis, DV has the highest association with

preeclampsia with small for gestational age (SGA) and a lesser but significant association with SGA with doppler abnormalities, suggesting a pathogenetic similarity between SGA with doppler abnormalities and preeclampsia with SGA at the level of the decidua. Overall, there is significant evidence that decidual vessels demonstrate secondary atherosclerotic changes in preeclampsia. Further studies are needed to determine if these changes are representative of the maternal systemic endothelial damage secondary to pathological changes such as hypertension or if DV contributes to the pathogenesis of stage 1 [34].

In addition to utero-placental insufficiency, epidemiological studies suggest that poor uterine decidualization, the stromal transformation of uterine endometrium to prepare for implantation may affect the development of preeclampsia. Global transcriptional profiling of chorionic villus samples points to insufficient or defective decidualization in pregnancies that were later complicated by severe preeclampsia. Endometrial stromal cells from non-pregnant donors with a history of severe preeclampsia fail to decidualize in vitro and are transcriptionally inert, suggesting baseline genetic abnormalities or genetic modifications. Finally, global transcriptional profiling of decidual tissue from the women with preeclampsia also revealed defects in gene expression. These cells failed to re-decidualize in culture, and their conditioned medium failed to support cytotrophoblast invasion, suggesting that decidual cells may be an important contributor to downregulated cytotrophoblast invasion in preeclampsia. The in vitro studies are confirmed ex vivo in histological studies of preeclampsia showing shallow placentation [35]. Given the mounting evidence of foetal and maternal abnormalities in preeclampsia, defective placentation might be the result of combinations of factors that affect both trophoblast and decidua.

- **Oxidative Stress**

While low oxygen tension followed by maternal blood flow oxygenation results in normal placentation, intermittent hypoxia and re-oxygenation caused by poor spiral artery invasion may cause oxidative stress. At the molecular level, preeclamptic placentas show an imbalance of reactive oxygen species (ROS)-generating enzymes and antioxidants. In the ex vivo preeclamptic trophoblast, ROS-producing enzyme expression and activity are increased [36] and inhibit the Wnt/β-catenin signalling pathway that promotes trophoblast invasiveness. Oxidative stress may also promote the transcription of antiangiogenic factors such as sFLT1 [37]. In humans, placental antioxidant mechanisms are impaired in patients with preeclampsia, as shown by their decreased

expression of superoxide dismutase and glutathione peroxidase compared with women with normal pregnancies. However, treatment with the antioxidants Vitamin E and Vitamin C did not alter disease in women with preeclampsia, suggesting that ROS may be less integral to the pathway of the human syndrome [38].

ROS may derive from mitochondrial stress. Based on evidence that hydrogen sulphide donors inhibit HIF-1α, [34] Covarrubias *et al.* [39] demonstrated that AP39, a mitochondrial-targeting hydrogen sulphide donor, pre-treatment could decrease sFLT1 expression in human syncytiotrophoblasts and increase cytochrome C oxidase activity in a dose-dependent fashion in normal and preeclamptic placentas, preventing the release of ROS and the subsequent stabilization of HIF-1α [40]. Recently published studies with mitochondrial antioxidants in animal models of preeclampsia have also been promising [41].

Another possible source of oxidative stress is endoplasmic reticulum stress caused by ischemia-reperfusion injury [42]. Endoplasmic reticulum stress has been observed in the decidua and placentas of patients with foetal growth restriction and preeclampsia and triggers decidual cell and cytotrophoblast apoptosis through the activation of the UPR (unfolded protein response). PERK (PKR-like endoplasmic reticulum kinase), a transmembrane kinase that decreases the translational burden of the endoplasmic reticulum and upregulates pro-apoptotic TFs, has emerged as the leading signalling pathway implicated in preeclampsia [43]. Interestingly, a recent study suggests that synergy between ATF4 (activating transcription factor 4), a TF downstream of PERK, and ATF6, a TF regulator of misfolded proteins in endoplasmic reticulum homeostasis, [44] negatively regulate the transcription of PlGF (placental growth factor), an proangiogenic factor central to the pathogenesis of preeclampsia [45].

- **Hypoxia and Trophoblast Invasion**

Upregulation of hypoxia-inducible transcription factors (TFs) and hypoxia-related gene signatures in the placenta suggest that hypoxia is central to the pathogenesis of preeclampsia [18]. In the early phases of implantation, the gestational sac exists in a low oxygen tension environment, favouring trophoblast proliferation. Before the invasion, the proliferating trophoblasts anchor the blastocyst to maternal tissues and plug the tips of the spiral arteries within the decidua [46]. Eventually these trophoblastic-spiral artery plugs collapse, forming an inter-villous space. The newly formed sinuses allow for the arrival of maternal blood, increasing oxygen tension,

generating oxidative stress, and promoting trophoblast differentiation from a proliferative to an invasive phenotype that will invade and remodel the spiral arteries. HIF (Hypoxia-inducible factors)-1α and -2α, markers of cellular oxygen deprivation, are expressed at high levels in proliferative trophoblasts and in the placentas of women with preeclampsia. Overexpression of HIF-1α in pregnant mice is associated with hypertension, proteinuria, and foetal growth restriction in mice and may result in failure of trophoblastic differentiation from the proliferative to the invasive phenotype. Furthermore, inhibition of HIF-1α by 2-methoxyestradiol, a metabolite of oestradiol that destabilizes HIF-1α, suppresses the production of sFLT1 (soluble fms-like tyrosine kinase 1), a potent antiangiogenic factor known to contribute to the maternal syndrome[47]. HIF-1α expression is regulated by many factors in addition to hypoxia, therefore, isolating the dysregulated signal upstream is challenging [31]. Magnetic resonance imaging has been used to assess the placental perfusion fraction, an estimate of the fraction of perfused tissue by volume as a marker of uterine flow or placental function [48]. In a Swedish study of 35 women with singleton pregnancies (13 with preeclampsia), Sohlberg *et al.* [49] found a smaller placental perfusion fraction associated with foetal growth restriction, as well as abnormalities in maternal and foetal vessel doppler flow, neonatal weight, and plasma markers, including higher levels of sFLT1. Novel blood oxygen level-dependent magnetic resonance imaging responses promise new, non-invasive, in vivo techniques for assessing maternal-foetal interface oxygen tension and may be useful for mapping areas of placental pathology and insufficiency [50].

- **Hemeoxygenase and other enzyme abnormalities**

There is growing evidence that hemeoxygenase (HO), the heme degradation catalyst, has an important role in the vascular function of the mother and the foetus, as well as in placental development and function. Three isoforms of HO have been characterized, [51] with HO-2 playing a role in spiral artery invasion [52] and HO-1 highly expressed in non-invasive trophoblastic phenotypes [53]. Treatment of the reduced uterine perfusion pressure (RUPP) rodent model with CoPP (cobalt proto-porphyrin), an inducer of HO-1, decreased BP and resulted in a proangiogenic shift in the VEGF (vascular endothelial growth factor)/sFLT1 ratio in the placenta [54]. These preclinical studies have fuelled interest in manipulating the expression of HO-1 as a potential therapeutic intervention for preeclampsia.

Another influence on trophoblastic invasion and spiral artery re-modelling may come from Corin, a transmembrane enzyme that locally activates atrial natriuretic peptide through zymogen modification. Corin acts primarily in heart tissue, however, Cui *et al.* [55] found significantly decreased uterine-localized corin mRNA and protein levels as well as several corin gene mutations in preeclamptic patients. The group then created a knockout corin rodent model as well as transgenic crosses that retained isolated cardiac corin activity. Both phenotypes mimicked the hallmarks of preeclampsia, independently of pre-existing hypertension or cardiac-derived atrial natriuretic peptide. However, in human studies, the evidence is mixed, as systemic levels of corin and its target atrial natriuretic peptide are upregulated during preeclampsia [56] not downregulated as would be expected based on the animal studies.

In earlier studies, women with hypertensive disorders of pregnancy were found to have lower levels of placental Catechol-O-methyl transferase (COMT) enzyme, while women with normal gestations were found to have increasing concentrations of 2-methoxyestradiol, the COMT breakdown product of oestradiol. Based on these observations, Kanasaki *et al.* [47] characterized a COMT knockout rodent model that reproduced the hallmarks of preeclampsia. However, COMT alterations are not a feature of severe early-onset preeclampsia in humans. Given that COMT is decreased in many hypertensive disorders of pregnancy [57], more evidence is required to implicate COMT in the pathogenesis of preeclampsia rather than a risk factor for all gestational hypertensive disorders.

- **NK Cells and Impaired Placentation**

The uterine NK (uNK) is well characterized in decidualization physiology [58] and may play a role in the abnormal placentation observed in preeclampsia. Unlike peripheral NKs, uNK is not cytotoxic [59]. Rather, in the decidua, uNK cells regulate the depth of placentation, spiral artery remodelling, and trophoblastic invasion. As the main immunologic player interacting at the allogenic maternal-foetal cell interface [58] uNKs recognize self-major histocompatibility complexes (MHCs) derived from the maternal contribution and non-self-allogenic MHCs from the paternal genotype. Specifically, uNK express KIR (killer cell Ig-like receptors), [60] while foetal invasive extra-villous trophoblasts express the main KIR ligand, polymorphic HLA-C (human leukocyte antigen-C) MHCs. Because of independent segregation of maternal KIR and HLA loci [60] and the paternal contribution to extra-villous trophoblast HLA-C, every pregnancy results in

a unique combination of KIR (maternal) and HLA-C (foetal) which may affect the success of placentation. Mouse models selected for non-matched maternal uNK and paternal MHC molecules in otherwise genetically identical parents have demonstrated that allogenicity may promote decidual artery dilation, spiral artery remodelling, more efficient placentas, and larger foetal weights. In other words, inhibition of the uNK response by MHC-self recognition may lead to defective artery remodelling. Furthermore, certain maternal KIR haplotypes (uNK) appear protective against preeclampsia while others confer risk [61]. However, the presence of the risk-associated haplotype is insufficient for disease, suggesting an additional environmental or genetic hit.

b) Stage 2: Pathogenesis of the Maternal Syndrome

- **Imbalance in Circulating Angiogenic Factors**

More than a decade ago, several groups identified elevated levels of the antiangiogenic protein sFLT1 in placentas collected from women with a clinical diagnosis of preeclampsia. sFLT1 is a soluble protein that exerts antiangiogenic effects by binding to and inhibiting the biological activity of proangiogenic proteins VEGF and PlGF. VEGF is important for the maintenance of endothelial cell function, especially in fenestrated endothelium, which is found in the brain, liver, and glomeruli, the primary organs affected by preeclampsia. A member of the VEGF family, PlGF is important in angiogenesis and selectively binds to VEGFR1/sFLT1 not VEGFR2. Several findings implicated sFLT1 in the pathogenesis of preeclampsia: sFLT1 protein levels were high in maternal plasma or serum; sFLT1 mRNA expression was high in preeclamptic placentas [62]; and injecting exogenous sFLT1 into rodents led to hypertension, proteinuria, glomerular endotheliosis (a hallmark of preeclampsia seen in renal biopsy), as well as several other preeclamptic features; treatment of cancer patients with anti-VEGF drugs results in hypertension and proteinuria75); depletion of sFLT1 in preeclamptic plasma using antibodies reverses the antiangiogenic phenotype in cell culture studies [64]; lowering sFLT1 or antagonizing sFLT1 in animal models of preeclampsia improves clinical symptoms and, spontaneous resolution of clinical signs and symptoms of preeclampsia, when sFLT1 levels are lowered by 50 % or more by treatment of the underlying placental conditions such as foetal hydrops or removal of diseased placenta in multiple pregnancies. In addition to the elevated sFLT1 levels, circulating levels of free PlGF were reduced

in women with preeclampsia, suggesting an imbalance of antiangiogenic and proangiogenic proteins [65].

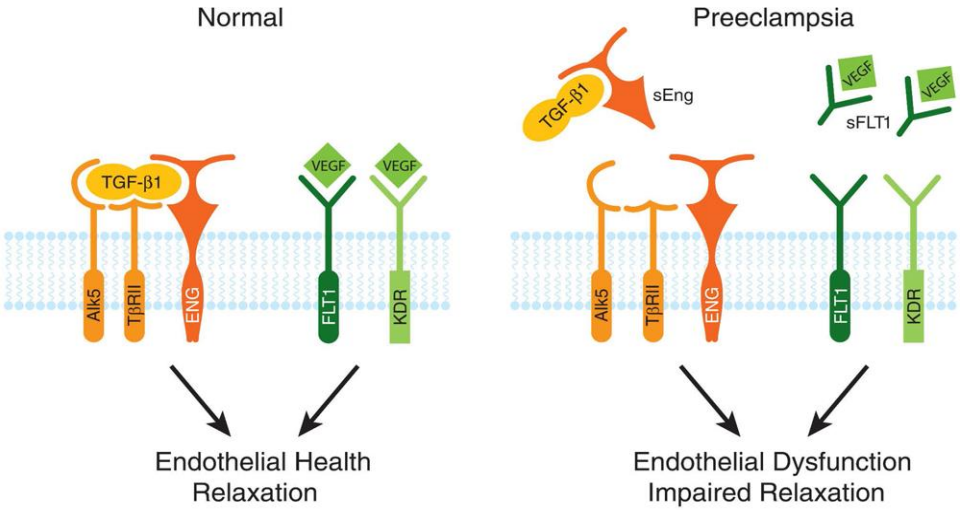

Figure 2: sFLT1 (soluble fms-like tyrosine kinase 1) and sENG (soluble endoglin). [66]

There is mounting evidence that VEGF and TGF-β1 are required to maintain endothelial health in several tissues including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signalling in the vasculature. In preeclampsia, excess placental secretion of sFLT1 and sENG (2 endogenous circulating antiangiogenic proteins) inhibits VEGF and TGF-β1 signalling respectively in the vasculature. This results in endothelial cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of pro-coagulant proteins.

The availability of robust immunoassays for angiogenic factors led to a number of clinical studies measuring the antiangiogenic/proangiogenic markers in large cohorts of human pregnancies showing that sFLT1 levels are high and free PlGF is low at the time of clinical diagnosis of preeclampsia as well as several weeks before the diagnosis. Angiogenic factor abnormalities in the plasma correlated with severity of presentation, predicting disease, and adverse outcomes [66]. Early studies called into question the utility of angiogenic factors in prediction of preeclampsia. However, a recent multisite, blinded randomized trial for the use of aspirin for prevention of preeclampsia used several physiological and biochemical parameters, including PlGF, with detection rate of 90 % at a fixed false positive rate of 5 % for preeclampsia, suggesting that the

markers may be used algorithmically for early diagnosis. Such a strategy for prediction of the syndrome in early pregnancy would identify women who are at risk for developing the disease and who may benefit from preventative interventions such as aspirin. Early diagnosis would also reduce anxiety and unnecessary interventions in women at otherwise low risk of developing preeclampsia [59].

Another antiangiogenic protein that has also been extensively studied in preeclampsia is soluble endoglin (sENG), an endogenous TGF-β1 (transforming growth factor β1) inhibitor. sENG is elevated in the sera of preeclamptic women 2 months before the onset of clinical signs of preeclampsia, correlates with disease severity, and falls after delivery. In pregnant rats, it appears to potentiate the vascular effects of sFLT1 to induce a severe preeclampsia-like state, including the development of thrombocytopenia and foetal growth restriction, and, in combination with sFLT1, appears to induce cerebral oedema resembling the reversible posterior leukoencephalopathy seen in patients with eclampsia [44].

- **Inflammatory Cytokines and Immune Cell Alterations**

It is well-established that preeclampsia is a pro-inflammatory state, but the culpable cells have yet to be fully elucidated. Syncytial knots are allogenic nano to micro-vesicles shed from apoptotic or activated trophoblasts that have been identified in the lungs [67] and plasma of normal pregnancies and in increased amounts in preeclampsia. Rich in sFLT1 and endoglin, syncytiotrophoblast micro vesicles and exosomes may instigate an inflammatory response. In vitro, syncytiotrophoblast micro-vesicles activate cultured peripheral blood mononuclear cells, causing a release of pro-inflammatory cytokines that is even more robust when exposed to peripheral blood mononuclear cells from pregnant patients. However, in vitro data are not consistent, as micro-vesicles induced by an alternative mechanism are not pro-inflammatory [68].

IL (Interleukin)-10, a cytokine that induces the differentiation of the T cell into the Th (T helper type) 2 phenotype—stands out in the literature as an important mitigator of the maternal syndrome by neutralizing pro-inflammatory cytokines, AT1-AA (angiotensin II receptor 1 autoantibodies), placental ROS, and ET-1 (endothelin-1). Many cell types in preeclamptic patients demonstrate a dysregulation in the balance of IL-10 and pro-inflammatory cytokines, including uterine and circulating NKs and peripheral blood mononuclear cells. Studies of peripheral blood mononuclear cells of preeclamptic women had reduced IL-10 secretion, which may lead to failure of T-cell

differentiation. Commonly referred to as Th2 polarization, normal pregnancy is characterized by a shift in T-cell phenotype towards Th2 relative to Th1. Multiple studies have reported an aberrant shift towards the Th1 phenotype in preeclampsia, resulting in insufficient trophoblast invasion. Furthermore, a preeclamptic-like syndrome can be induced in normal pregnant rats with transfer of CD4+ cells obtained from RUPP models [45].

Preeclampsia is also associated with elevated complement levels and with genetic mutations in C3. In animal models, complement inhibition restores spiral artery capacitance and decreases sFLT1 production, and a C1q knockout mouse model mimics preeclamptic features. However, complement dysregulation is most severe in the form of severe preeclampsia called haemolysis elevated liver enzymes low platelets (HELLP) syndrome.

- **Renin-Angiotensin Pathway**

There is evidence for alterations in the renin-angiotensin-aldosterone system in the pathogenesis of preeclampsia. Several studies show enhanced angiotensin II sensitivity during and before the onset of preeclampsia despite reduced circulating renin and angiotensin II during preeclampsia when compared with normal pregnancy. One potential mechanism for the increased angiotensin II sensitivity is the presence of circulating autoantibodies to AT1 in the sera of preeclamptic women. In preclinical studies, autoantibodies to AT1 reproduce many of the hallmark characteristics of preeclampsia: vasoconstriction through activation of ET-1163; endothelial cell necrosis and apoptosis in human umbilical vein endothelial cells; stimulation of tissue factor production contributing to hyper-coagulation; reduction of trophoblast invasion in human cell culture models; and increased production of ROS in culture models. Produced in response to placental ischemia and systemic inflammation, anti-AT1-AA can also stimulate placental production of antiangiogenic factors sFLT1 and sENG. Finally, CD19+CD5+ cells, as well as anti-AT1-AA activity, are elevated in the sera of preeclamptic patients, implicating B lymphocytes as an immune player. These findings suggest that anti-AT1-AA made by a subpopulation of CD19+CD5+ in response to placental ischemia and systemic inflammation may contribute to the hypertension and production of antiangiogenic factors that characterize the maternal syndrome [65], [69].

Recent preclinical studies on the hypersensitivity of the AT1 receptor when complexed with the bradykinin B2 receptor provide compelling evidence for another model for the activation of the

renin-angiotensin-aldosterone system in the setting of downregulated renin. Using a new transgenic mouse model with maternal, systemically upregulated smooth muscle AT1-B2 complexes, the group was able to replicate the preeclampsia syndrome, with pregnant animals developing hypertension, proteinuria, low platelets, increased sFLT1, AT1-AA, and ET-1, smaller litter sizes, intrauterine growth restriction, lower renin levels, and a decreased placental labyrinth layer. Furthermore, when heteromerized with B2, ATI seems independently sensitive to angiotensin II and mechanic stimulation, which, the authors suggest, may evolve with an increase in foetal-placental mass regardless of renin activity. The preeclamptic-like transgenic mice were then rescued with lentiviral administration of an inactivation-resistant variant of Arrb1 (β-arrestin-1), G-protein coupled receptor-associated protein that desensitizes the AT1 receptor leading to signal dampening. In ex vivo studies of human placentas, the group found significantly elevated levels of inactivated (phosphorylated) levels of Arrb1 in preeclamptic placentas compared with normotensive placentas, as well as increased AT1-B2 complex formation on the vessels of the basal plate of a preeclamptic placenta. Though the AT1-B2 model does appear to replicate the maternal syndrome well, only a small number of human placentas were analysed as part of this study. Additional human studies are required to assess applicability of this model to the biology of preeclampsia [70].

Elevated levels of an oxidized form of angiotensinogen that is more readily cleaved by renin have also been implicated in the pathogenesis of the hypertension observed in preeclampsia. However, robust assays to measure this modified form of angiotensinogen in the blood are needed to characterize a role for oxidized angiotensinogen in preeclampsia. Finally, in animal models, elevated levels of circulating sFLT1 were sufficient to induce angiotensin II sensitivity by interfering with endothelial nitric oxide production [53].

- **Sympathetic Nervous System**

While a major emphasis of study in the pathogenesis of preeclampsia has been on the link between placental factors and maternal endothelial dysfunction, several studies have implicated the sympathetic nervous system in the pathogenesis of preeclampsia. Schobel *et al.* observed that muscle sympathetic nerve activity is elevated in women with preeclampsia over normal pregnant and hypertensive, non-pregnant control women. Women with preeclampsia also have reduced baro-reflex sensitivity and greater antihypertensive responses to nonselective adrenergic receptor

blockade. Studies using experimental animal models supports that sympathetic nerve activity is increased in preeclampsia. Placental ischemia-induced hypertension in the RUPP rat model is associated with a hypertensive shift in baroreceptor control on renal sympathetic nerve activity, and a recent study found that adrenergic receptor blockade markedly attenuates placental ischemia-induced hypertension. Collectively, studies from humans and animal models suggest that an intact sympathetic nervous system may be important in eliciting the full hypertensive response to factors released in response to placental ischemia [56].

2.6 DIAGNOSIS AND SCREENING FOR PREECLAMPSIA

The ACOG committee opinion reaffirmed in 2017 does not recommend screening to predict preeclampsia beyond obtaining an appropriate medical history [71]. Because of the lack of adequate screening methods and the severe sequelae of the disease, all women suspected of preeclampsia undergo resource intensive testing, often requiring several-day hospitalizations for further investigation. Other methods of screening have been investigated, including a metabolomic pathways and combined metabolomic-proteomic data approaches. A 2017 head to head comparison of the Foetal Medicine Foundation algorithm-based screening method (a combination of maternal factors, mean arterial pressure, uterine-artery pulsatility index, and PlGF) demonstrated superiority to the screening methods currently recommended by National Institute for Health and Care Excellence and ACOG. Using a similar screening algorithm with the addition of maternal serum PAPP-A (pregnancy-associated plasma protein-A), the ASPRE trial (aspirin for evidence-based preeclampsia prevention) screened women in the first trimester to identify those at high risk for preeclampsia. High-risk women were then randomized to receive 150 mg of aspirin or placebo daily until 36 weeks gestation. Daily low-dose aspirin use in high-risk women was associated with a significantly lower incidence of preterm preeclampsia than placebo, and detection rate of preterm preeclampsia was 76.7 % (138/180), 43.1 % for term preeclampsia with a false positive rate of 9.1 %. These results suggest that early screening with plasma biomarkers and imaging studies allows for early intervention and possible prevention of disease [65].

Perhaps most promising among screening methods is the use during the third trimester of combined biomarkers such as sFLT1, sEng, and PlGF with high sensitivity and specificity for early diagnosis and prognosis of preeclampsia. Substantial evidence already demonstrates

encouraging test characteristics of biomarker assays in this population. In a study of over 600 women undergoing initial evaluation of preeclampsia, an sFLT1/PlGF ratio of ≥ 85 correlated with diagnosis of preeclampsia and predicted adverse outcomes and delivery within 2 weeks among women presenting < 34 weeks gestation. Furthermore, the biomarker ratio performed better than all other currently available tests for prediction of preeclampsia. A follow-up study of 402 patients presenting with preterm singleton pregnancies by the same group showed that an sFLT1/PlGF ratio >85 had a PPV of 59 % in all patients and 74 % among patients presenting < 34 weeks for developing preeclampsia with severe features within 2 weeks. Patients with preeclampsia with normal angiogenic profile have fewer adverse outcomes suggesting that the angiogenic form of preeclampsia is clinically more important. Other groups have shown similar results. In a multi-center study of women with suspected preeclampsia, authors showed a reverse association of free PlGF with gestational age at delivery. In a recent multisite study of angiogenic factors, authors concluded that an sFLT1/PlGF ratio of ≤38 had a negative predictive value of 99.9 % for ruling out preeclampsia within 1 week. A follow-up study from the same cohort showed a negative predictive value of 95 % within 4 weeks. Overall, serum or plasma angiogenic factors appear to be a reliable risk-stratification method among women with suspected preeclampsia, especially for preterm preeclampsia, allowing for appropriate management [59].

Recent studies have also suggested that by reducing false positive rates of diagnosis and consequent unnecessary hospitalizations, risk stratification with biomarkers is economical. Assays using these plasma biomarkers are available for clinical use in Europe, Canada, Africa, and Asia, and their clinical success has led to the incorporation of angiogenic factors in the definition of preeclampsia in the British National Institute for Health and Care Excellence and national German guidelines. Finally, a study in Mozambique showed that measurement of PlGF is feasible in resource poor environments. The authors concluded that low PlGF in women with suspected preeclampsia was associated with increased transfers to higher levels of care and increased maternal and perinatal risks. Looking forward, biomarker assays are a cost-effective and reliable screening method that could be lifesaving, even in areas of limited expertise and resources [45].

2.7 MANAGEMENT OF PREECLAMPSIA

2.7.1 Preventive management

The severe short-term and lifelong health risks of being exposed to a preeclamptic pregnancy for both the mother and child emphasize the need for new treatments to prevent preeclampsia. Adequately powered, multi-centre studies are required to identify patient populations who may benefit from the different preventive treatments under development.

2.7.2 Evidence based preventive treatments

The use of aspirin to prevent pre-eclampsia has long been proposed. Despite a randomized trial published in 1985 showing that prophylactic aspirin leads to a large reduction in pre-eclampsia, FGR and stillbirth in women at high risk, further trials were highly heterogeneous regarding aspirin dose, time of initiation and, importantly, the method used to select women at increased risk. An individual-participant data meta-analysis concluded that aspirin provides a statistically significant but clinically modest 10 % reduction in preeclampsia risk. Further meta-analysis suggested that aspirin is highly effective in preventing preterm preeclampsia when given to women at high risk from before 16 weeks of gestation [72]. The Aspirin for Evidence-Based preeclampsia (ASPRE) prevention trial, a multicentre, randomized, double-blind placebo-controlled trial of 1,776 women at high risk identified by means of combined screening with the FMF algorithm, provided further convincing evidence that daily aspirin from the first trimester reduces the risk of preterm preeclampsia by 62 % (95 % CI 20–80 %), with no significant effect on the rate of term disease. A meta-analysis of 30 trials identified that low-dose calcium supplementation halves the risk of preeclampsia (both for early and late onset) in women at high risk of developing preeclampsia and with low dietary calcium intake, and is therefore recommended by ISSHP guidelines. Furthermore, the ISSHP guidelines recommend exercise to reduce the likelihood of gestational hypertension and preeclampsia [22]. A meta-analysis of 27 trials found that exercise of at least 260 metabolic equivalents of task minutes/week reduced the odds of developing pre-eclampsia by 25 % [73]. In a preeclamptic pregnancy, the mother and foetus have competing interests. For the mother, delivery of the placenta will alleviate symptoms; however, this may cause preterm birth and the resulting complications of prematurity for the neonate. Preterm management of preeclampsia (**Figure 3**) requires treatment of maternal high blood pressure with the goal of preventing severe maternal outcomes and prolonging pregnancy

with surveillance of foetal health and timing of delivery to provide the best outcome for both mother and neonate.

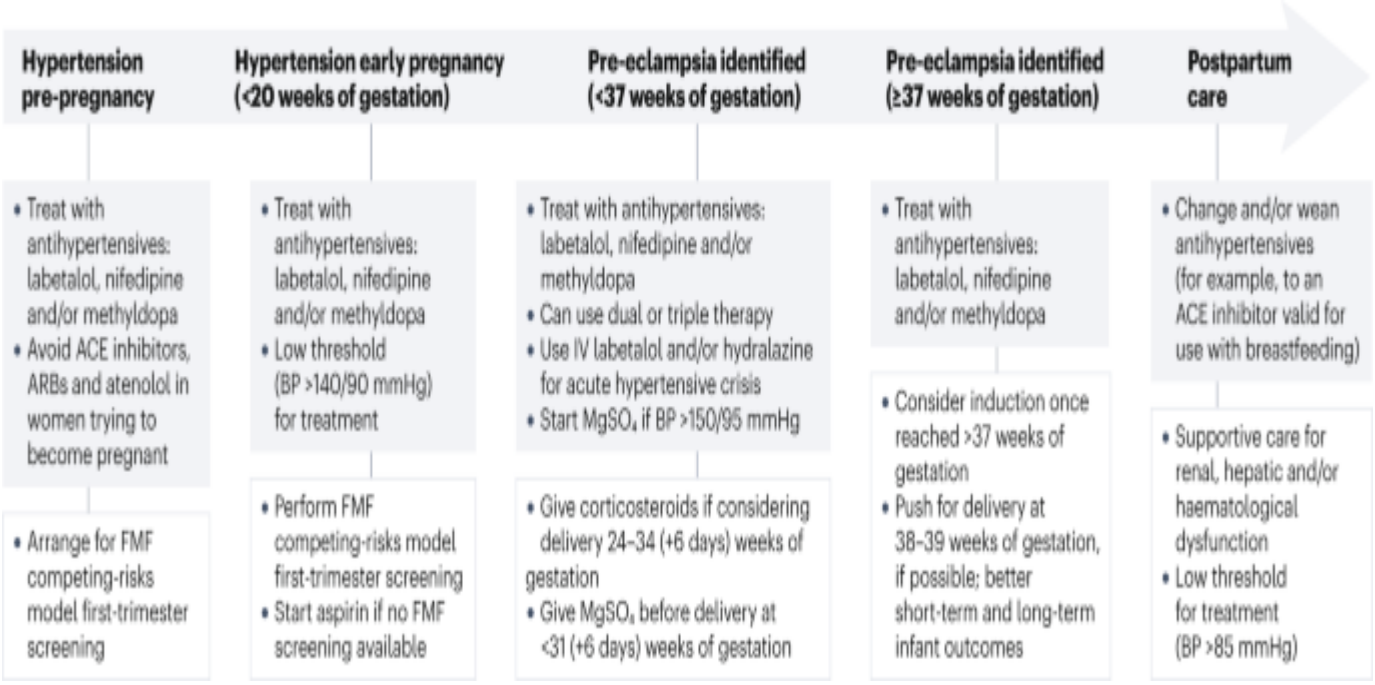

Figure 3: treatment algorithm for pregnancies presenting with hypertension.[73]

Antihypertensive medications should be given to all women with hypertension (blood pressure (BP) >140/90 mmHg) trying to become pregnant or who are pregnant. Labetalol, nifedipine and methyldopa are recommended. Women who have hypertension before pregnancy or during early pregnancy should be screened using the Foetal Medicine Foundation (FMF) competing-risks model [74] in the first trimester. If this screening is unavailable, women with hypertension in early pregnancy should be started on aspirin. When preeclampsia is diagnosed preterm, corticosteroids and $MgSO_4$ should be given to mature foetal lungs and for foetal neuroprotection, respectively. When preeclampsia is diagnosed at ≥37 weeks of gestation, induction should be considered. Women should be weaned from antihypertensive medications at postpartum or they should be changed to antihypertensive medications valid for use while breastfeeding. Support for renal/hepatic/haematological dysfunction should be given [16].

2.7.3 Management of planned delivery in severe preeclamptic pregnancies

a) Triggers for delivery

- Haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome or significant biochemical derangements
- Eclampsia
- Inability to control blood pressure despite maximum dose of antihypertensive medication
- Abnormal foetal wellbeing parameters and/or foetal distress

b) Managing delivery

- Induction of labour or caesarean delivery [18]
- Avoiding maternal morbidity
- Avoiding foetal morbidity

c) Postpartum management and follow-up

- Acute management of hypertension

d) Short-term follow-up: continued regular monitoring of blood pressure postpartum and treatment with antihypertensive medications to prevent postpartum eclamptic fit. Management of any other acute sequelae of preeclampsia such as the development of pulmonary oedema or deranged renal/hepatic function

e) Long-term follow-up and inter-pregnancy advice: ensure blood pressure returns to normal pre-pregnancy levels by about 6 weeks postpartum. Prescribe appropriate antihypertensive medications if there is residual chronic hypertension. Identify other risk factors for maternal cardiovascular disease and encourage risk mitigation

2.7.4 Treatment common to all disease subtypes

Hypertension is the predominant diagnostic feature of preeclampsia and typically becomes progressively worse with advancing gestation. Severe hypertension (≥160/110 mmHg) may lead to intracerebral haemorrhage, eclampsia and placental abruption and should be treated in all circumstances. The aim of treatment is to reduce blood pressure to a target range of 140–155/90–105 mmHg [75].

a) Oral antihypertensive medications

Although intravenous antihypertensive agents may be indicated in an acute situation, oral medications that are commonly used to manage hypertension in pregnancy include methyldopa, labetalol and nifedipine. These agents are typically available even in low-resource settings. A recent multicentre, parallel-group, open-label, randomized controlled trial compared these three agents (hourly doses of either nifedipine or labetalol or a daily dose of methyldopa) and reported that, although as a single drug, nifedipine resulted in a greater frequency of blood pressure control (120–150 mmHg systolic and 70–100 mmHg diastolic blood pressure) within 6 h, all three agents are potentially viable initial options for the treatment of severe hypertension in pregnancy [76].

Nifedipine is a calcium channel antagonist and causes peripheral vasodilatation. It has a rapid onset of action and women may complain of severe headaches (particularly in the first 24 h), dizziness, flushing, palpitations and increasing ankle oedema. Initially, sublingual dosing was supported for rapid correction of severe hypertension in pregnancy but there have been significant adverse outcomes in non-pregnant adults, and this can also cause acute foetal distress due to reduced placental perfusion pressure [76].

Labetalol blocks β1, β2 and α1 adrenergic receptors and reduces peripheral vascular resistance [77]. It is a negative inotrope and may promote pulmonary oedema and cardiac failure. It may cause bronchospasm and should be avoided in women with a history of asthma. Women may report headaches and nausea, particularly within the first 24 h of use. Peak plasma doses are reached within 2 h of oral dosing and the peak effect is reached within 48 h of treatment.

Methyldopa is a centrally acting sympatho-mimetic acting as an α2 adrenergic receptor agonist. Women commonly report feeling lethargic and drowsy, particularly within the first 72 h of use, and methyldopa may worsen depression [78]. Peak plasma doses are reached 6 h after oral dosing with the peak effect reached following 72 h of treatment, potentially making other treatment strategies more useful at acute presentation. Abrupt cessation (following long-term use) may cause rebound hypertension.

b) Planned delivery

The Hypertension and Preeclampsia Intervention Trial At Near Term-I (HYPITAT-I) trial showed a significant decrease in adverse maternal outcomes with active management (induction of labour) than expectant monitoring of women with gestational hypertension or mild preeclampsia at >36 weeks of gestation, and concluded that induction of labour should be advised for these women [10,12]. However, the HYPITAT-II trial showed a significant increase in the risk of neonatal respiratory distress syndrome with immediate delivery (induction of labour or caesarean section within 24 h of randomization into trial groups) than with expectant monitoring (prolonging pregnancy until 37 weeks of gestation) in women with non-severe preeclampsia at 34–37 weeks of gestation, and concluded that it is generally safe and beneficial to prolong pregnancy until 37 weeks of gestation. By contrast, the Planned early delivery or expectant monitoring for late preterm preeclampsia (PHOENIX) [79] study showed a significantly lower incidence of the co-primary maternal outcome, a composite of maternal morbidity or recorded systolic blood pressure of >160 mmHg, and a significantly higher incidence of the co-primary perinatal outcome (composite of perinatal deaths or neonatal unit admission) in the planned delivery group than in the expectant monitoring group in women with late preterm preeclampsia at 34–37 weeks of gestation. The authors recommended that this trade-off between the maternal and neonatal prognosis should be discussed with patients to enable shared decision-making on the timing of delivery [79].

2.7.5 Treatments for specific patient populations

Some signs and symptoms in pre-eclampsia deserve special attention, including several continuous or recurrent headaches, visual scotomas (blind spots), nausea/vomiting, epigastric pain and severe hypertension as well as changes in laboratory tests, such as increased creatinine or liver

transaminases, thrombocytopenia, and altered foetal growth and foetal wellbeing tests. All of these are signs and symptoms that manifest when special conditions, such as eclampsia and HELLP syndrome, occur in pre-eclampsia. If a woman has had a chronic disease before pregnancy, especially hypertension, problems often occur during pregnancy, requiring close blood pressure control, including drug switching, from early pregnancy [80].

a) Chronic hypertension

Factors such as increasing maternal age and obesity are associated with chronic hypertension, which affects about 2 % of pregnant women [81]. Aspirin prophylaxis against preeclampsia may be less effective in these women, who have a significant risk of a range of adverse maternal and perinatal outcomes, including a higher prevalence of 'superimposed' preeclampsia (preeclampsia complicating hypertension of another cause), FGR and placental abruption.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are commonly used to manage hypertension in a non-pregnant population but have been associated with adverse outcomes, including FGR, oligohydramnios, foetal renal failure and stillbirth. Angiotensin-converting enzyme inhibitors may also be teratogenic, with increased rates of cardiac anomalies, although it is not clear whether this is independent of other risk factors (such as diabetes). Ideally, women taking these medications should be transferred to oral antihypertensive medications that have a recognized safety profile, such as methyldopa, labetalol and nifedipine, before pregnancy or by 12 weeks of gestation [22].

b) Eclampsia

The initial management in patients with eclampsia should be the use of measures for clinical stabilization of critically ill patients (fasting, oxygenation, tongue protection with Guedel cannula, venous access, bed with raised guardrails and in a semi-sitting position). The patient should preferably be kept in a calm environment but under intense monitoring. $MgSO_4$ is used worldwide as an anticonvulsant to stop and prevent seizures. However, due to its increased risk of caesarean delivery and maternal adverse effects, intense clinical monitoring is required. It is

reasonable therefore to restrict the use of $MgSO_4$ to patients who have presented with eclampsia or 'severe' pre-eclampsia as defined by the Magpie trial (160/110 mmHg, 3 + proteinuria) or a slightly lower threshold (150/100 mmHg, 2 + proteinuria) if accompanied by two or more signs of imminent eclampsia (headache, visual symptoms, clonus) [22]. Medication administration schedules and clinical signs of magnesium intoxication should be monitored. Delivery is generally indicated when eclampsia is present, especially if the gestational age is above viability in the given clinical care setting.

c) HELLP syndrome

HELLP syndrome cases are very serious and delivery is usually indicated. In patients with uncontrolled blood pressure and without prior treatment, treatment optimization can be attempted; early reassessment of laboratory tests (within a maximum of 6 h after admission) and if there is laboratory and clinical improvement, expectant monitoring is possible [82].

d) Postpartum management

The American Heart Association (AHA) considers pre-eclampsia as a significant risk factor for future cardiovascular disease. The Health after Preeclampsia Patient and Provider Engagement Network (HAPPEN) makes recommendations for awareness campaigns (for patients and primary care physicians) and yearly physical exams and laboratory evaluations for all women with prior preeclampsia, including blood pressure monitoring, BMI calculation, and fasting glucose or haemoglobin A1C to assess the risk of glucose intolerance/diabetes. These recommendations are broadly in line with the AHA and ACOG recommendations [4]. A randomized control trial of women with gestational hypertension or preeclampsia showed that self-measurement of blood pressure for 6 months postpartum significantly reduced 24-h diastolic blood pressure at 6 months (–4.5 mmHg, 95 % CI –8.1 to –0.8) and 3.6 years postpartum (–7.4 mmHg, 95 % CI –10.7 to –4.2) [83].

2.8 QUALITY OF LIFE

2.8.1 Long-term health outcomes

a) Effect on the child of a preeclamptic pregnancy

The long-term effect of preeclampsia on the child's health is mainly caused by FGR and medically indicated preterm birth; therefore, these effects are most often associated with preterm preeclampsia. It has been shown that children with foetal exposure to early-onset preeclampsia are more susceptible to cardiovascular dysfunction and hypertension. In addition, children born from severe early-onset pre-eclamptic pregnancies are at higher risk of impaired cognitive ability and neuro-developmental outcomes [84].

b) Psychosocial effects

Preeclampsia has severe negative effects on the psychosocial profile of women. Such effects are associated with the severity of preeclampsia, timing of diagnosis and pregnancy outcomes. Independent observational studies report that a diagnosis of severe preeclampsia has a worse impact on mental health and quality of life than a diagnosis of mild preeclampsia. In this case, within the preterm group, diagnosis of severe preeclampsia before 30 weeks has worse psychosocial consequences than diagnosis at 30–34 weeks of gestation. Three independent time-course studies have investigated psychological effects, including depression and post-traumatic stress disorder, between 6 and 12 weeks postpartum, and recorded an overall decline of effect over time; however, the psychosocial impact of preeclampsia can be long lasting. For women with early-onset preeclampsia with preterm birth, post-traumatic stress symptoms have been recorded 7 years post pregnancy. The psychosocial impact of preeclampsia is also highly associated with pregnancy outcomes. Adverse outcomes, such as perinatal death and admission to the neonatal intensive care unit, have a significant impact on the psychological wellbeing of mothers [85].

c) Outlook

There are still many outstanding questions and opportunities to improve the prevention and treatment of preeclampsia, particularly term preeclampsia. A major obstacle in the field is how to detect placental dysfunction well before diagnosis so that preventive strategies to reverse placental dysfunction can be developed. Predictive biomarkers and causative pathways caused by abnormal placental development/function likely precede diagnosis and, to date, have been difficult to define even though some inroads have been made to predict and prevent preterm preeclampsia. One major consideration is that subtypes of preeclampsia, particularly preterm versus term preeclampsia, most likely have a different pathophysiology, yet much research does not

distinguish between the two subtypes. Indeed, whether abnormal placental development and function drive term preeclampsia is yet to be experimentally proven. Examining placental-specific products directly through CVS or indirectly via liquid biopsies, such as micro-particles, extracellular non-coding RNA and cell-free DNA, in maternal blood can provide a clue of the placental dysfunction that may occur in term preeclampsia [16].

2.9 OUTCOMES/COMPLICATIONS OF PREECLAMPSIA

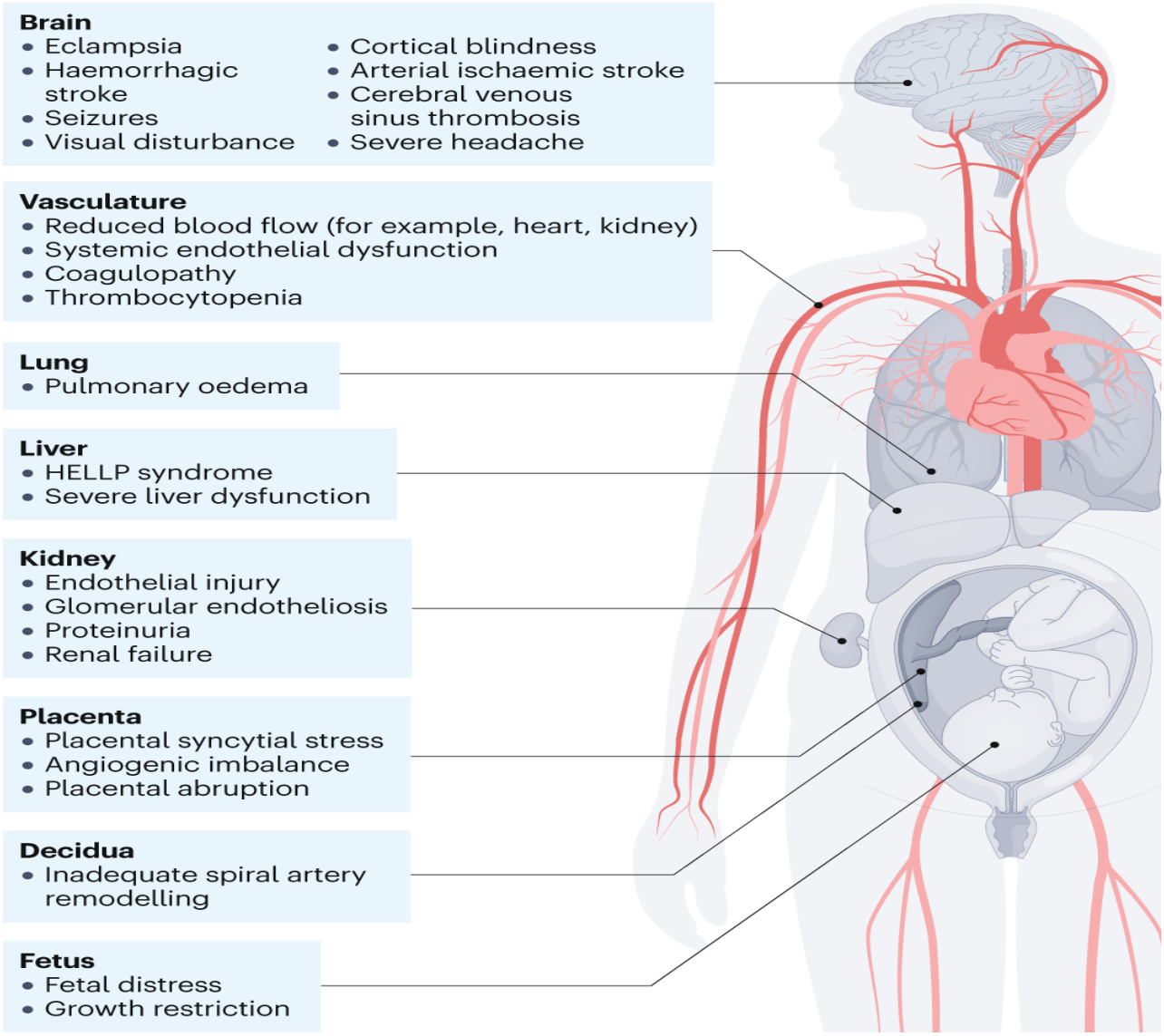

Figure 4: outcomes/complications of preeclampsia. [80]

Preeclampsia is a multisystem pathology with complications involving every system. Several studies in our context have shown that caesarean section is associated with more maternal complications. Figure 4 outlines the various systems affected by preeclampsia.

In our context, studies have been carried out that revealed the following most common complications:

Maternal: Eclampsia, Coma, HELLP syndrome, Maternal death, Ocular pathologies, AKI, PPH, DIC, APE, CVA, ICU Admission, >7 days hospitalisation, Hypertensive crisis or grade 3 hypertenstion (**Table IV**), Severe ascites and severe maternal morbidity (**Table V**).

Foetal: Intra-uterine foetal demise, early neonatal death, Transfer to NICU [3, 9, 12, 89, 90].

Table IV: classification of blood pressure. [88]

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

BP = blood pressure; SBP = systolic blood pressure.
[a]BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
[b]Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
The same classification is used for all ages from 16 years.

Table V: ACOG severe maternal morbidity criteria 2021.

Table 1. Example List of Diagnoses and Complications Constituting Severe Maternal Morbidity*

Severe Maternal Morbidity	Not Severe Morbidity (insufficient evidence if this is the only criteria)
Hemorrhage	
Obstetric hemorrhage with ≥4 units of red blood cells transfused	Obstetric hemorrhage with 2–3 units of red blood cells transfused ALONE
Obstetric hemorrhage with 2 units of red blood cells and 2 units of fresh frozen plasma transfused (without other procedures or complications) if not judged to be overexuberant transfusion	Obstetric hemorrhage with 2 units of red blood cells and 2 units of fresh frozen plasma transfused AND judged to be "overexuberant"
Obstetric hemorrhage with <4 units of blood products transfused and evidence of pulmonary congestion that requires >1 dose of furosemide	Obstetric hemorrhage with <4 units of blood products transfused and evidence of pulmonary edema requiring only 1 dose of furosemide
Obstetric hemorrhage with return to operating room for any major procedure (excludes dilation)	
Any emergency/unplanned peripartum hysterectomy, regardless of number of units transfused (includes all placenta accretas)	Planned peripartum hysterectomy for cancer/neoplasia
Obstetric hemorrhage with uterine artery embolization, regardless of number of units transfused	
Obstetric hemorrhage with uterine balloon or uterine compression suture placed and 2–3 units of blood products transfused	Obstetric hemorrhage with uterine balloon or uterine compression suture placed and ≤1 unit of blood products transfused
Obstetric hemorrhage admitted to intensive care unit for invasive monitoring or treatment (either medication or procedure; not just observed overnight)	Any obstetric hemorrhage that went to the intensive care unit for observation only without further treatment
Hypertension/Neurologic	
Eclamptic seizure(s) or epileptic seizures that were "status"	
Continuous infusion (intravenous drip) of an antihypertensive medication	
Nonresponsiveness or loss of vision, permanent or temporary (but not momentary), documented in physician's progress notes	
Stroke, coma, intracranial hemorrhage	
Preeclampsia with difficult-to-control severe hypertension (>160 systolic blood pressure or >110 diastolic blood pressure) that requires multiple intravenous doses, persistent ≥48 hours after delivery, or both	Chronic hypertension that drifts up to severe range and needs postoperative medication dose alteration: preeclampsia blood pressure control with oral medications ≥48 hours after delivery
Liver or subcapsular hematoma or severe liver injury admitted to the intensive care unit (bilirubin >6 or liver enzymes >600)	Abnormal liver function requiring extra prolonged postpartum length of stay but not in the intensive care unit
Multiple coagulation abnormalities or severe hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome	Severe thrombocytopenia (<50,000) alone that does not require a transfusion or intensive care unit admission
Renal	
Diagnosis of acute tubular necrosis or treatment with renal dialysis	Oliguria treated with intravenous fluids (no intensive care unit admission)
Oliguria treated with multiple doses of Lasix	Oliguria treated with 1 dose of intravenous fluids (no intensive care unit admission)
Creatinine ≥2.0 in a woman without preexisting renal disease OR a doubling of the baseline creatinine in a woman with preexisting renal disease	
Sepsis	
Infection with hypotension with multiple liters of intravenous fluid or pressors used (septic shock)	Fever >38.5°C with elevated lactate alone without hypotension
Infection with pulmonary complications such as pulmonary edema or acute respiratory distress syndrome	Fever >38.5°C with presumed choriometritis/endometritis with elevated pulse but no other cardiovascular signs and normal lactate
	Positive blood culture without other evidence of significant systemic illness
Pulmonary	
Diagnosis of acute respiratory distress syndrome, pulmonary edema, or postoperative pneumonia	Administration of oxygen without a pulmonary diagnosis
Use of a ventilator (with either intubation or noninvasive technique)	
Deep vein thrombosis or pulmonary embolism	
Cardiac	
Preexisting cardiac disease (congenital or acquired) with intensive care unit admission for treatment	Preexisting cardiac disease (congenital or acquired) with intensive care unit admission for observation only
Peripartum cardiomyopathy	Preexisting cardiac disease (congenital or acquired) without intensive care unit admission for observation only
Arrhythmia requiring >1 dose of intravenous medication but not intensive care unit admission	Arrhythmia requiring 1 dose of intravenous medication but no intensive care unit admission
Arrhythmia that requires intensive care unit with further treatments	Arrhythmia that requires intensive care unit observation but no extra treatments
Intensive Care Unit/Invasive Monitoring	
Any intensive care unit admission that includes treatment or diagnostic or therapeutic procedure	Intensive care unit admission for observation of hypertension that does NOT require intravenous medications
Central line or pulmonary catheter used to monitor a complication	Intensive care unit admission for observation after general anesthesia
Surgical, Bladder, and Bowel Complications	
Bowel or bladder injury during surgery beyond minor serosal tear	
Small-bowel obstruction, with or without surgery during pregnancy/ postpartum period	
Prolonged ileus for ≥4 days	Postoperative ileus that resolved without surgery in ≤3 days
Anesthesia Complications	
Total spinal anesthesia	Failed spinal anesthesia that requires general anesthesia
Aspiration pneumonia	Spinal headache treated with a blood patch
Epidural hematoma	

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.

*This list provides a series of examples that may help facilities and health care providers as they evaluate cases to determine if they represent severe maternal morbidity. The College and SMFM have not created or endorsed a single, comprehensive definition of severe maternal morbidity.

Reprinted from Main EK, Abreo A, McNulty J, Gilbert W, McNally C, Poeltler D, et al. Measuring severe maternal morbidity: validation of potential measures. Am J Obstet Gynecol 2016;214:643.e1–10.

2.10 RELATED STUDIES CARRIED OUT ON OUTCOME OF PREECLAMPSIA

Table VI: list of some related studies carried out on outcome of preeclampsia.

Place/Author/Year	Study Title	Study Design	Key Findings
Cameroon /Essiben F, Ngo Um Meka E, Mve Koh V, Gwos L, Ojong S, and Foumane P / 2018	Maternal and foetal outcomes associated with Caesarean deliveries in patients with severe preeclampsia in two Teaching Hospitals, Yaoundé	Case-control study.	The incidence of post-operative complications stood at 26.4%. Maternal and foetal complications were more frequent in preeclamptic women
Cameroon / Fouedjio J, Makengne WM, Ebong EC, Esiene A, Tsague NE, Fouelifack YF, et al. / 2022	Factors associated with maternal and perinatal complications of preeclampsia at the Central Hospital Yaoundé	Cross-sectional study.	There were maternal complications in 44.4% of cases, and factors associated with them were; residing in rural area, nurse-aid as PNC provider, and number of PNC < 4.
Cameroon / Nkwabong E, Djientcheu Deugoue F, and Fouedjio J / 2023	Pre-eclampsia in a Sub-Saharan African country and maternal-perinatal outcome	Retrospective cohort study.	Significant adverse maternal outcomes were eclampsia, HELLP syndrome and placental abruption.
Egypt / Rana ME, Mohamed E, Hesham S, and Mohamed H / 2021	Maternal, foetal and neonatal outcomes of severe preeclampsia in Mansoura University Hospitals: A Prospective study	Prospective cohort study.	Pre-eclampsia tends to threaten maternal health and foetal viability adding to maternal and neonatal mortality and morbidity.
Brazil / Amorim MMR, Katz L, Barros AS, Almeida TSF, Souza ASR, and Faundes A / 2014	Maternal outcomes according to mode of delivery in women with severe preeclampsia: a cohort study	Prospective cohort study.	CS rate was 49.8%. The risk of severe maternal morbidity was greater in patients submitted to CS.
China/ Shao-Wen W and Wei-Yuan Z /2021	Effect of modes and timings of delivery on foeto-maternal outcomes in women with severe preeclampsia: A multi-center survey in mainland China	Retrospective cross-sectional study.	CS rate was 84.9%. The perinatal mortality was lower in the CS groups than vaginal delivery groups

CS = Caesarean section, PNC = Prenatal consultation

CHAPTER THREE: MATERIALS AND METHODS

3.1 STUDY DESIGN

This was a hospital-based retrospective nested cohort study.

3.2 STUDY PERIOD AND DURATION

The study period was 10 years, from the 1st of June 2014 to the 30th of May 2024. The study was conducted for 4 months from the 1st of April 2024 to the 15th of August 2024.

3.3 STUDY SITES

3.3.1 The Yaoundé Gynaeco-Obstetric and Paediatric Hospital.

This is a tertiary hospital, located in Ngousso in Yaoundé, Cameroon. The obstetrics & gynaecology unit has three parts: the maternity ward, the hospitalization wards and the outpatient sub-unit. The maternity is comprised of: an admission room where the parturient are clerked before entering the labour room, a store, a bathroom, two specialist offices, a midwives' post, two post-partum wards with six beds each, a staff and service secretary's desk, a six-bed workroom with two showers, a common delivery room, a special delivery room with an internal toilet, a bathroom and a room of conviviality. As for the hospitalization, the structures are: seven hospital rooms with a capacity of 32 beds, an archives room, a nursing room, a special consultation room with its secretariat, a treatment room, a store, doctors' offices, a residents' room, a unit for monitoring HIV-positive women, outpatient clinics and a family planning sub-unit. Outpatient activities are supervised by a chief nurse who coordinates a team of nurses and has offices and outpatient gynaecology-obstetrics sub-unit. The staff consists of:

- 11 (eleven) obstetrician-gynaecologists including 2 Associate professors (one functioning as the head of the unit) and 1 Professor;
- Residents and interns in obstetrics and gynaecology;
- Nurses supervised by chief nurses;
- Medical and nursing students;
- Paramedical staff.

3.3.2 Central Hospital Yaoundé.

The central hospital Yaoundé was created in 1933, initially as a day hospital. It has undergone several structural changes and is today a second category care establishment. It has a medical and paramedical team specialized in the field of general medicine, and also presents multiple advantages because of its geographical location. The Obstetrics & Gynaecology unit includes: 02 common delivery rooms, common and individual platform, the availability of medical personnel 24 hours a day and the autonomy of services are well in place to cater for patient needs.

The hospitalization wards have a capacity of 95 beds, 04 outpatient consultation boxes, an emergency service integrated merged with the admission department, three ward sections named A, B and reanimation ward, a family planning department, an archives room, a staff room, an operating theatre with 3 rooms, a neonatology department.

Concerning the staff, the Obstetrics & Gynaecology unit has: 07 Obstetrician-Gynaecologists including an Associate Professor, a Professor of Anaesthesia-Intensive care, residents and interns in Obstetrics & Gynaecology, midwives, midwifery nurses, maintenance workers, stretcher bearers.

3.4 STUDY POPULATION

The study population included all women diagnosed with severe preeclampsia who delivered in the two aforementioned hospitals.

3.4.1 Diagnostic criteria

Presence of any one of the following signs or symptoms in women with a high blood pressure diagnosed after 20 weeks of pregnancy:

- Blood pressure of >160mm Hg (systolic) and/or >110 mm Hg (diastolic) taken at least 4hours apart using an electronic blood pressure reader.
- Presence of physical signs of severity: Head ache; blurry vision; convulsion; respiratory distress; epigastric/right upper quadrant pain (in absence of gastritis); oliguria (<500mls in 24hrs); haemolysis.
- Presence of laboratory signs of severity; Elevated ASAT/ALAT; low platelets (<100000/mm3); elevated urea and creatinine.
- Presence of proteinuria of at least 3g/24hrs
- Evidence of microangiopathic haemolytic anaemia

3.4.2 Sampling method

A consecutive and exhaustive sampling was used, for all women who met the inclusion criteria during the study period.

3.4.3 Inclusion criteria

Files of pregnant women diagnosed with severe preeclampsia, admitted and managed in both hospitals.

3.4.4 Exclusion criteria

- Files of women with incomplete information (mode of delivery not found or follow up till at least day 2 partum).
- Women whose labour could not be induced (scarred uterus, twin pregnancy)

3.4.5 Sample size calculation

We used the formula bellow for sample size estimation

$n= [(Z\alpha/2+Z\beta)^2 \cdot (p1 \cdot (1-p1) + p2 \cdot (1-p2))]/(p1-p2)^2$

•Confidence Level: 95% (Zalpha=1.96)

•Power: 90% (Zbeta=1.28)

•Proportion of complications in severe preeclampsia following cesarean section: 55.4% (p1=0.554)

•Proportion of complications in severe preeclampsia following vaginal delivery: 86.7% (p2=0.867)

$n= [(1.96+1.28)^2 \cdot (0.554 \cdot (1-0.554)+0.867 \cdot (1-0.867))]/(0.554-0.867)^2$

$n=38.84$

The required sample size for each group is approximately 39, and the minimum total sample size is 78.

3.5 STUDY PROCEDURE

3.5.1 Collection of data

After the validation of the protocol and ethical clearance obtained from competent authorities, we got into contact with the chief of services of the Obstetrics and Gynaecology units and the Intensive Care units of both hospitals so as to obtain permission to get access to the registers and patient medical records. When the permission was granted, thorough analysis of the registers of the said unit was done, and a list of patients diagnosed with or hospitalised for severe preeclampsia from June 2014 to May 2024 was established. Using this list, medical records were searched for and obtained at the archives of the units.

We retrieved the medical records of patients diagnosed with severe preeclampsia within the aforementioned period, many files were not found and some files found were incomplete. We collected data on sociodemographic and clinical variables (Age, parity gestational age, history of pregnancy, obstetric history, past history, peripartum details, investigations, medical treatment received and mode of delivery), data on complications presentation before delivery, maternal outcome, days of hospital stay and follow up till at least day 2 postpartum from the files. The data collection was facilitated by the use of a structured questionnaire containing all the detailed variables. The independent variables were the mode of delivery, either caesarean section or vaginal delivery. The dependent variables were the maternal complications and outcomes postpartum. Sociodemographic factors included; maternal age, parity, gestational age, marital status, new partner and residence. History of pregnancy included; number of antenatal contacts, baseline blood pressure and preeclampsia prophylaxis. Relevant past history included; history of preeclampsia, and pre-pregnancy hypertension. Clinical data included; seizures, coma, anuria and haemolysis. Mode of delivery included; Vaginal (induction or spontaneous), Caesarean section (indication). Para clinical data included; Full blood count (platelets), ASAT/ALAT, Urea/Creatinine. We also recorded information on management received.

Maternal outcomes and their definitions include:

1) Eclampsia; recordings of tonic clonic seizures in pregnancy (>20weeks) or postpartum or diagnosis recorded in the file.
2) Hypertensive crisis/ grade 3 hypertension; high blood pressure greater than 180 systolic or 110 diastolic (Table IV)

3) Acute kidney injury; Diagnosed and recorded in the files.
4) HELLP syndrome; haemolysis, elevated liver enzymes and low platelets recorded in the file.
5) Acute pulmonary oedema; diagnosed and recorded in the file.
6) Disseminated intravascular coagulopathy; diagnosed and recorded in the file.
7) Stroke diagnosed or suspected and recorded in the file.
8) ICU admission.
9) Coma; any altered state of consciousness with a decrease in Glasgow coma score.
10) Long hospital stay > 7 days; hospitalisation of more than 7days as a result of current illness.
11) Postpartum haemorrhage; diagnosed and recorded in the file.
12) Severe maternal morbidity; ACOG definition 2021 (Table V)
13) Maternal death.

3.5.2 Statistical analysis

Data collected were entered into a data entry form designed on CS Pro version 7.7. The generated data base was exported into IBM SPSS version 26 for statistical analysis.

Descriptive statistics were done for quantitative variables using measures of central tendencies (means or medians) and measures of dispersion (standard deviations-SD or inter quartile ranges-IQR). Qualitative variables were summarised using numbers and their frequencies.

Univariate analyses were done to assess the statistical significance of associations between the mode of delivery and each maternal outcome. A chi square test and fisher's exact test were done to estimate p-values with statistical significance set at 5 %.

A sub-group analysis was done to study the association between mode of delivery and maternal outcomes after delivery in a pseudo-cohort design, with RR (risk ratios) and their 95 % confidence intervals to estimate the magnitude of association. All statistically significant associations from univariate analyses were included into a corresponding multivariate analysis (using multiple logistic regression) to estimate the adjusted RR and adjusted p-values. This is a method used to eliminate the effect of confounders and identify factors that are independently associated with the dependent variable.

3.6 ETHICAL CONSIDERATIONS

- Administrative authorisations were sought from the directors of YCH and YGOPH.
- Ethical clearance was granted by the Institutional Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I.
- Research authorization was granted by the Institutional Committee on Research Ethics for Human Health of YGOPH and YCH.
- Medical confidentiality was respected by ensuring anonymity of data during collection.
- The data and results collected were used for scientific purposes only.

CHAPTER 4: RESULTS

4.1 SAMPLE FLOW CHART

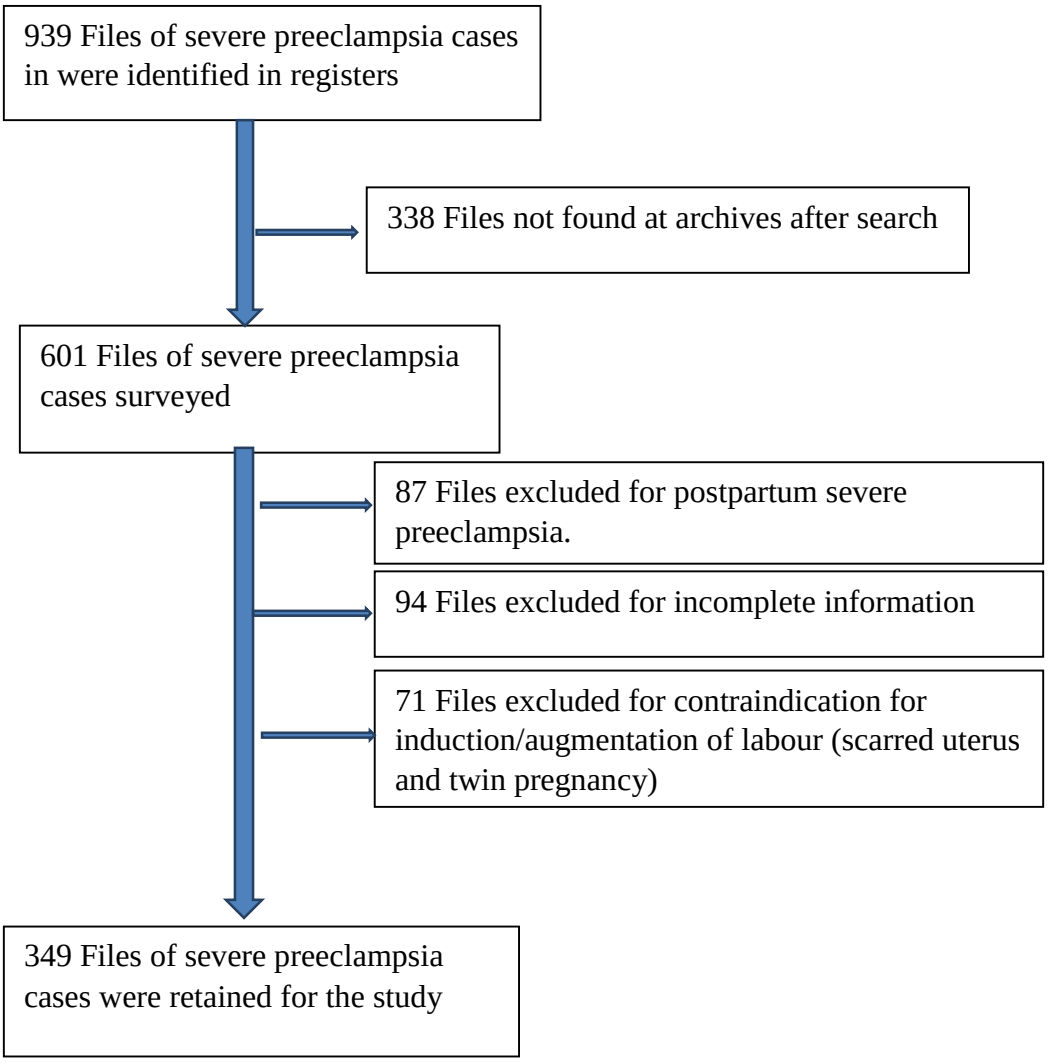

Figure 5 : participant recruitment flow chart.

A total of 947 women were admitted and managed for severe preeclampsia at YGOPH and CHY from 1st June 2014 to 31st May 2024. The medical files of 609 cases were found after search at the archives of both hospitals, among which a total of 260 were excluded for various reasons. Thus, we recruited 349 cases for this study (**Figure 5**).

4.2 SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

4.2.1 Distribution of participants according to age groups

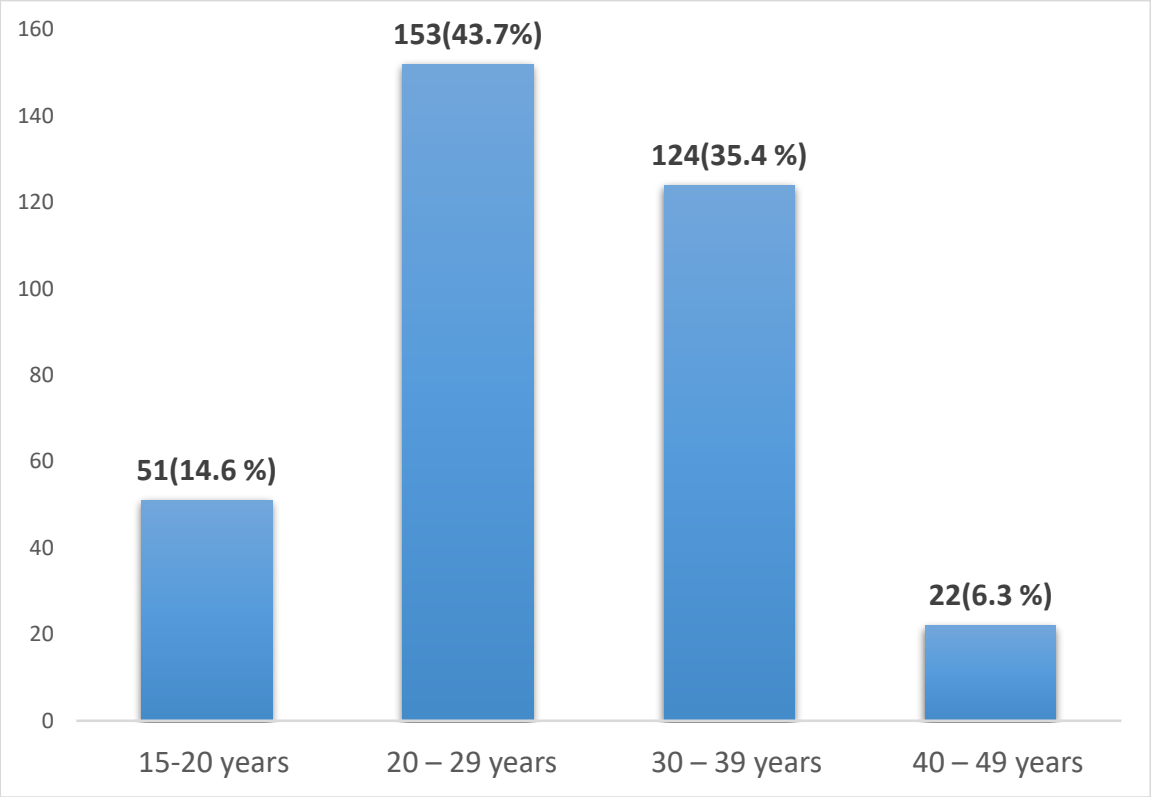

Figure 6 : distribution of participants according to age groups.

Almost half (43 %) of participants were aged between 20 – 29 years. The minimum and maximum age of participants was 15 and 45 years respectively, with a mean age of 28.3 years (±7.1 years).

4.2.2 Socio-demographic description of participants

Most of our participants were single (72.2 %), self-employed (45.8 %), with level of education being at least secondary school (60.5 %). Majority resided in urban areas (95.4 %), were of the Christian faith (79.4 %) and from the Centre region (45.3 %) (**Table VII**).

Table VII : description of study participants according to socio-demographic variables.

Variable and categories	Number, N=349 (n)	Frequency (%)
Marital status		
Married	97	27.8

Single	252	72.2
Profession		
Housewife	47	13.5
Student	99	28.4
Public sector	17	4.9
Private formal	26	7.4
Private informal	160	45.8
Educational level		
None	12	3.6
Primary	78	23.4
Secondary	202	60.5
Higher	42	12.6
Residence		
Urban	333	95.4
Rural	16	4.6
Religion		
Christian	277	79.4
Muslim	58	16.6
Others	14	4.0
Region of Origin		
South	11	3.2
Far North	37	10.6
North	16	4.6
Centre	158	45.3
West	97	27.8
North-west	7	2.0
South-west	7	2.0
Littoral	13	3.7
East	3	0.9

4.2.3 Description of participants according to obstetric data

Almost half of the study population were primiparous (48.4 %) and 46 % were at term on admission. Among those who had antenatal contacts (ANC), 161 (48 %) had less than 4 contacts, (73 %) had their first ANC in the second trimester. Prophylaxis for preeclampsia was recorded in (21 %) of participants (**Table VIII**).

Table VIII : distribution of study participants according to obstetric data.

Variable	Number N=349 (n)	Frequency (%)
Parity		
Nullipara	10	2.9
Primipara	169	48.4
Multipara	115	32.9
Grand-multipara	55	15.8
Gestational Age on Admission		
<28 weeks	15	4.3
[28 – 34[weeks	81	23.2
[34 – 37[weeks	92	26.4
≥37 weeks	161	46.1
Antenatal Contact (ANC)	295	84.5
Number of ANCs [N=295]		
<4	141	47.8
4-7	134	45.4
≥8	20	6.8
GA at first ANC		
<13 weeks	59	22.3
[14-27[weeks	193	72.8
≥28 weeks	13	4.9
PE Prophylaxis received	61	20.7
Calcium	49	16.6
Aspirin (Low dose)	12	4.1
Past History	103	34.9
Preeclampsia	58	19.7
Hypertension	8	2.7
New Partner	37	12.5

ANC = Antenatal Contact, GA=Gestational Age, PE=Preeclampsia

4.2.4 Description of study participants according to physical findings and management.

A) Description of study participants according to blood pressure

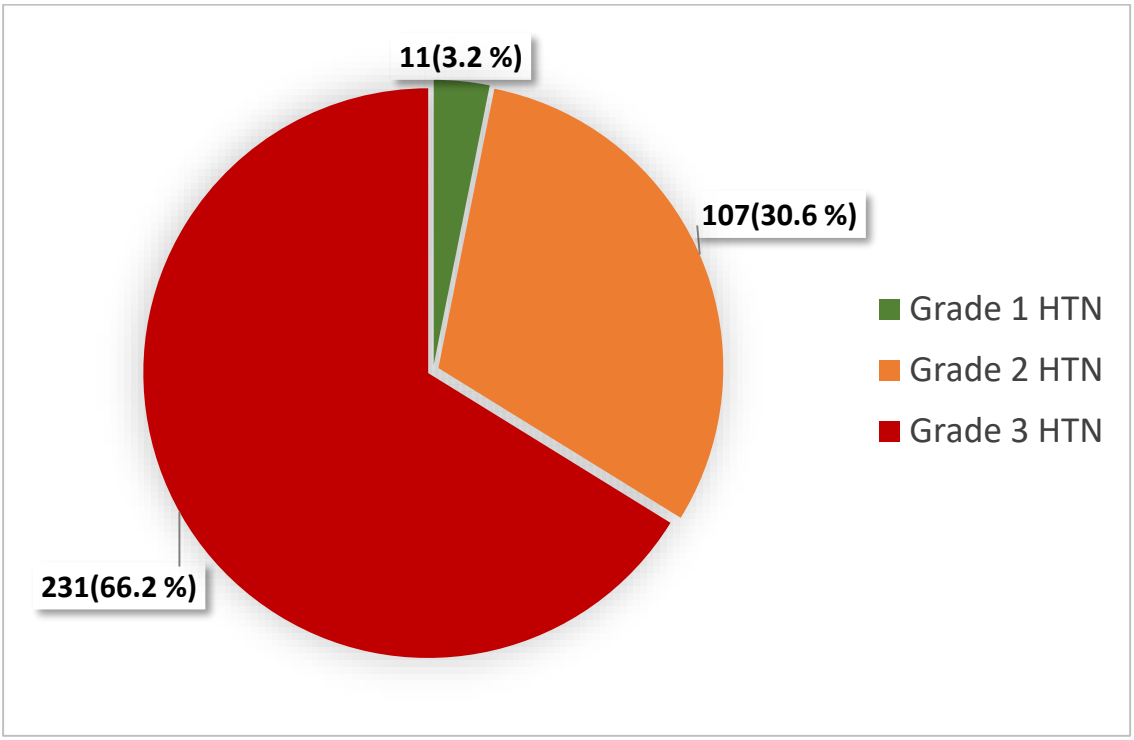

Figure 7 : distribution of study participants according to blood pressure on admission.

More than half of our participants (66.2 %) had grade 3 hypertension on admission (**Figure 7**).

B) Description of participants according to medical management

Most patients received nursing care, anticonvulsants, anti-hypertensive medication, and normo-hydration before delivery (**Table IX**).

Table IX : distribution of study participants according to medical management on admission.

Treatment on admission	Number, N=349 (n)	Frequency (%)
Nursing care	325	93..1
Antihypertensive	341	97.7
Anticonvulsants	339	97.1
Normo-hydration	325	93.1

C) Distribution of study participants according to mode of delivery

The more frequent mode of delivery of severe preeclampsia patients was Caesarean section (N = 188, 53.9 %), with main indication being poor BISHOP score (N = 149, 79.2 %). Among those who delivered vaginally, labour was spontaneous in 57.1 % and induced in 42.9 % (**Table X**).

Table X : distribution of study participants according to mode of delivery.

Variable	Number N=349 (n)	Frequency (%)
Mode of Delivery		
Vaginal delivery	161	46.1
Caesarean section	188	53.9
Vaginal delivery, labour onset [N=161]		
Spontaneous	92	57.1
Induction of labour	69	42.9
Indication of Caesarean section [188]		
Poor Bishop score	149	79.2
NRFS	17	9.1
Failed labour induction	11	5.9
Placenta Abruptio	06	3.2
CPD	05	2.6

CPD = Cephalo-pelvic disproportion, NRFS = Non-reassuring foetal status

4.3 MATERNAL COMPLICATIONS OF SEVERE PREECLAMPSIA BEFORE DELIVERY BY MODE OF DELIVERY

Except for eclampsia, there was no other statistically significant difference in complications before delivery for those who had caesarean or vaginal delivery (**Table XI**).

Table XI : distribution of participants according to complications before delivery by mode of delivery.

Complication	Caesarean, N=188 n(%),	Vaginal, N=161 n(%),	Total. N=349 N(%)	p-value
Eclampsia	**63(33.5)**	**34(21.1)**	**97(27.8)**	**0.014**
Coma	49(26.1)	28(17.4)	77(22.1)	0.051
HELLP syndrome	38(20.2)	20(12.4)	58(16.6)	0.071
Maternal death	0(0.0)	0(0.0)	0(0.0)	---
AKI	15(8.0)	8(5.0)	23(6.6)	0.259
DIC	4(2.1)	4(2.5)	8(2.3)	0.824
APE	5(2.7)	0(0.0)	5(1.4)	0.103
ICU Admission	5(2.7)	5(3.1)	10(2.9)	0.803
Haemorrhagic CVA	0(0.0)	2(1.2)	2(0.6)	0.125
Hypertensive crisis	129(68.6)	102(63.4)	231(66.2)	0.300

CVA=Cerebrovascular accident, APE=Acute pulmonary oedema, DIC=Disseminated intravascular coagulation, PPH=Postpartum haemorrhage, AKI= Acute Kidney Injury,

4.4 PROGRESS OF MATERNAL COMPLICATIONS OF SEVERE PREECLAMPSIA ACCORDING TO MODE OF DELIVERY

The presence of coma, eclampsia, HELLP syndrome, maternal death, acute pulmonary oedema and Intensive care unit admission is significantly increased after delivery in those who had a caesarean compared to those who had vaginal delivery. There was no significant difference in the progress of Hypertensive crisis, AKI, DIC and haemorrhagic CVA.

Table XII : distribution of study participants according to progress of complications by mode of delivery.

Complication	Before (B) /After (A) Delivery	Caesarean N=188 n(%)	Vaginal N=161 n(%)	Total N=349 n(%)	p-value
Eclampsia	B	63(33.5)	34(21.1)	97(27.8)	**0.014**
	A	**24(12.8)**	**10(6.2)**	**34(9.7)**	**0.040**
Coma	B	49(26.1)	28(17.4)	77(22.1)	0.051
	A	**48(25.5)**	**17(10.6)**	**65(18.6)**	**<0.001**
HELLP syndrome	B	38(20.2)	20(12.4)	58(16.6)	0.071
	A	**37(19.7)**	**12(7.5)**	**49(14.0)**	**0.001**
Maternal death	B	0(0.0)	0(0.0)	0(0.0)	---
	A	**40 (21.3)**	**14(8.7)**	**54(15.5)**	**0.002**
AKI	B	15(8.0)	8(5.0)	23(6.6)	0.259
	A	22(11.7)	11(6.8)	33(9.5)	0.121
PPH	B	---	---	---	---
	A	19(10.1)	13(8.1)	32(9.2)	0.512
DIC	B	4(2.1)	4(2.5)	8(2.3)	0.824
	A	11(5.9)	8(5.0)	19(5.4)	0.717
APE	B	5(2.7)	0(0.0)	5(1.4)	0.103
	A	**15(8.0)**	**2(1.2)**	**17(4.9)**	**0.004**
ICU Admission	B	5(2.7)	5(3.1)	10(2.9)	0.803
	A	**128(68.1)**	**32(19.9)**	**160(45.8)**	**<0.001**
CVA	B	0(0.0)	2(1.2)	2(0.6)	0.125
	A	3(1.6)	0(0.0)	3(0.9)	0.107
Hypertensive crisis	B	129(68.6)	102(63.4)	231(66.2)	0.300
	A	14(7.4)	8(5.0)	22(6.3)	0.342

APE=Acute Pulmonary oedema, HELLP=Haemolysis Elevated Liver enzymes Low Platelet count, CVA=Cerebrovascular accident, DIC=Disseminated intravascular coagulation, PPH=Postpartum haemorrhage, AKI= Acute Kidney Injury, ICU=Intensive Care Unit

4.5 MATERNAL OUTCOME BY MODE DELIVERY

After univariate analyses, women who delivered by Caesarean Section were significantly more likely to experience eclampsia (RR = 1.36 [CI; 1.07-1.73], p = 0.034), coma (RR = 1.50 [CI; 1.24-

1.81], p < 0.001), HELLP Syndrome (RR = 1.50 [CI; 1.23-1.82] , p = 0.001), maternal death (RR=1.48 [CI; 1.22-1.79], p = 0.001), APE (RR = 1.58 [CI; 1.20-2.07], p = 0.022), admission to ICU (RR = 2.5 [CI; 2.03-3.11], p <0.001) and more than 7days hospitalisation (RR = 1.76 [CI; 1.47-2.10], p <0.001) (**Table XIII**)

Table XIII : univariate analysis of maternal outcome by mode of delivery.

Outcome	Caesarean N=148 n(%)	Vaginal N=140 n(%)	Total N=288 n (%)	RR [95%CI]	p-value
Eclampsia	**24(12.8)**	**10(6.2)**	**34(9.7)**	**1.36[1.07-1.73]**	**0.034**
Coma	**48(25.5)**	**17(10.6)**	**65(18.6)**	**1.50[1.24-1.81]**	**<0.001**
HELLP syndrome	**37(19.7)**	**12(7.5)**	**49(14.0)**	**1.50[1.23-1.82]**	**0.001**
Maternal death	**40 (21.3)**	**14(8.7)**	**54(15.5)**	**1.48[1.22-1.79]**	**0.001**
AKI	7(3.7)	3(1.9)	10(2.9)	1.31[0.86-1.99]	0.352
PPH	19(10.1)	13(8.1)	32(9.2)	1.11[0.82-1.51]	0.579
DIC	7(3.7)	4(2.5)	11(5.4)	1.18[0.75-1.88]	0.717
APE	**10(5.3)**	**2(1.2)**	**12(3.4)**	**1.58[1.20-2.07]**	**0.022**
ICU Admission	**123(65.4)**	**27(16.8)**	**150(45.8)**	**2.51[2.03-3.11]**	**<0.001**
CVA	3(1.6)	0(0.0)	3(0.9)	1.87[1.70-2.06]	0.107
Hypertensive crisis	8(4.3)	5(3.1)	13(3.7)	1.15[0.74-1.79]	0.572
>7days hospitalization	**84(50.6)**	**26(17.0)**	**110(34.5)**	**1.76[1.47-2.10]**	**<0.001**

APE=Acute Pulmonary Oedema, HELLP=Haemolysis Elevated Liver enzymes Low Platelet count, CVA=Cerebrovascular accident, DIC=Disseminated intravascular coagulation, PPH=Postpartum haemorrhage, AKI= Acute Kidney Injury, ICU=Intensive Care Unit, p= p-value,RR=risk ratio,CI=confidence intervaL

After multivariate logistic regression analyses, acute pulmonary oedema (aRR = 1.31 [CI: 1.01-2.73], p = 0.048), and admission to intensive care unit (aRR = 2.22 [CI: 1.98-3.45], p < 0.001), were showed to be independently associated with mode of delivery (**Table XIV**).

Table XIV : multivariate analysis of maternal outcomes by mode of delivery.

Outcomes	RR [95%CI]	p-value	aRR [95%CI]	ap-value
Eclampsia	1.36[1.07-1.73]	0.034	1.11[0.87-3.46]	0.132
Coma	1.50[1.24-1.81]	<0.001	1.08[0.64-3.92]	0.183
HELLP syndrome	1.50[1.23-1.82]	0.001	1.47[0.93-2.87]	0.088
Maternal death	1.48[1.22-1.79]	0.001	1.29[0.89-2.66]	0.101
APE	**1.58[1.20-2.07]**	**0.022**	**1.31[1.01-2.73]**	**0.048**
ICU Admission	**2.51[2.03-3.11]**	**<0.001**	**2.22[1.98-3.45]**	**<0.001**
>7 days hospitalisation	1.76[1.47-2.10]	<0.001	1.09[0.97-2.92]	0.081

APE=Acute Pulmonary Oedema, HELLP=Haemolysis Elevated Liver enzymes Low Platelet count, ICU=Intensive Care Unit, aRR=adjusted risk ratio, ap-value=adjusted p-value

CHAPTER 5: DISCUSSION

5.1 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

5.1.1 Socio-demographic Characteristics

The mean age of participants was 28.3 ± 7.1 years, which is similar to that reported by Fouedjio *et al.* in 2022 who found a mean age of 28 ±7 years [86] and Essiben *et al.* in 2018 [11], who found 28.16 years in Yaoundé. This similarity could be as a result of the studies being carried out in the same setting. Participants aged between 20 to 29 years were the most affected by severe preeclampsia (43%). This is comparable to findings of Tailanne *et al.* in Brazil [9], and could be explained by the fact that this age group represents the peak period of female reproductive activity, therefore many more pregnancies and hence increased risk of preeclampsia.

The majority of participants were single (72.2 %), had private informal occupation (45.8 %), and were students (28.4 %), which is similar to findings of Kemfang *et al.* [2]. The most frequent level of education was secondary (60.5 %). This was similar to the findings of Fouedjio *et al.* in 2022 in Yaoundé [86] and Diallo et al 2020 in Guinea [89], which is in line with the high risk of severe preeclampsia in women with low socioeconomic status as shown by previous authors [90]. The most represented region was the centre region (45.3 %) followed by the West (27.8 %). This finding was different from that of Nzometia *et al.* who showed that the most represented region to be the West (37.5 %) [91]. Our larger sample size could explain this disparity.

5.1.2 Clinical Characteristics

Primiparous women were the most represented amongst participants (48.4 %), with a gestational age >37weeks (46.1 %) in most women. This result is similar to findings by Kemfang *et al.* and Fouedjio *et al.* and is concurrent with literature, as primiparity is a risk factor for preeclampsia [18]. Majority of our participants started ANC in the second trimester and had <8 ANCs which is less than the normal recommendation by the WHO. Furthermore, 47.8 % of women in our study attended <4 ANCs, which is similar to findings by Fouedjio *et al.* in 2022 but higher than what Nkwabong *et al.* found (29.1 %) in 2020. The difference can be explained by their relatively small sample size. Amongst our study participants, only 20.7 % received prophylaxis for preeclampsia, 16.6% received calcium and 4.1 % received low dose Aspirin. A proportion of 34.9 % had a past history of preeclampsia. This is higher than 15 % found by Kemfang *et al.* in 2015 [2], which could be as a result of our longer study period and larger sample size.

Most women had severe or grade 3 hypertension on admission (66.2 %) which is similar to findings of Nkwabong *et al.* in 3 teaching hospitals in Yaoundé [87] and Amorim *et al.* in Brazil [12]. Treatment of almost all women involved the five steps of management of severe preeclampsia with the fifth being timely delivery. Over half (53.9 %) of the participants were delivered by caesarean section with the most frequent indication being poor bishop score (79.2 %). Our caesarean section (CS) rate is higher than rates found by Kemfang *et al.* in 2015 (42.6 %). This could be explained by our larger sample size. Coupled with the fact that most of those who had a CS had a poor bishop score and the primiparous majority amongst our participants, a CS might have been thought to be a faster mode of delivery. Among those who delivered vaginally (161, 46.1 %), 42.9 % were induced and only 16.9 % of induction failed. This proportion is lower than that of Tailanne *et al.* who found a successful induction rate of 59 %. This difference could be explained by the fact that our study involved only women with severe preeclampsia, while they induced all cases of preeclampsia [9].

5.2 MATERNAL COMPLICATIONS OF SEVERE PREECLAMPSIA BEFORE DELIVERY BY MODE OF DELIVERY

Several maternal complications were observed amongst our study participants, which was similar to studies done in our setting by Kemfang et al and Fouedjio *et al.* [2] [86]. However, none of these studies brought out maternal complications before delivery by mode of delivery. Almost all the complications had no statistically significant difference before delivery in both groups but for eclampsia which had a statistically significant difference before delivery in both groups. This difference could be explained by the fact that most of our participants who eventually had a caesarean delivery (CD) had a poor Bishop score, this could incite health care providers to decide to perform an immediate CD.

5.3 PROGRESS OF SEVERE PREECLAMPSIA COMPLICATIONS BY MODE OF DELIVERY

With regards to progress of complications of severe preeclampsia by mode of delivery, very little has been studied in and out of our setting. Nonetheless, we found that the presence of Eclampsia (p-value < 0.04), coma (p-value < 0.001), HELLP syndrome (p-value = 0.001), maternal death (p-value = 0.002), acute pulmonary oedema (p-value = 0.004), and intensive care unit admission (p-value < 0.001) significantly increase in patients delivered by caesarean section (CS) compared to

those delivered vaginally. Hence, progress of complications was worse in those who had a CS. Essiben *et al.* in 2018 revealed that emergency caesarean delivery is associated with more complications, and complications of severe preeclampsia worsen the condition of the patient [11]. They also revealed that the complications were related to the worsening of preeclampsia rather than complications of the surgical procedure [11].

5.4 MATERNAL OUTCOME BY MODE OF DELIVERY

There was a statistically significant increase in the risk of various postpartum outcome in patients submitted to Caesarean section. The risk of eclampsia was 1.32 times, coma was 1.50 times; HELLP Syndrome 1.50 times; maternal death was 1.48 times; acute pulmonary oedema 1.58 times; admission to intensive care unit was 2.51 times; and hospital stay of > 7 days was 1.76 times found in patients who had a caesarean compared to those who had a vaginal delivery. These findings are similar to that of Amorim *et al.* in Brazil who found SMM (RR= 1.65) and hospitalisation more than 7 days (RR= 2.33) significantly higher in the caesarean group [12]. We note many more adverse outcomes in our study compared to Amorim et al, probably because they carried out a one-year prospective study, which permitted more rigid diagnostic criteria for maternal outcomes and their smaller sample size. Since our study was a ten-year retrospective nested cohort study, the decision for patients to undergo a caesarean or vaginal delivery was not randomized, it was rather the decision of the attending physician or due to hospital protocol. Also, the decision of maybe performing a CS could be influenced by a prepartal maternal complication like eclampsia or HELLP syndrome which could be a high risk of postpartum severe maternal morbidity. This possible bias was controlled using a multivariate logistic regression analysis. After multivariate analysis, severe maternal morbidity, acute pulmonary oedema, and admission to intensive care unit remained independently associated to mode of delivery after controlling for potential confounders with an aRR of 1.4, 1.3 and 2.2 respectively. Our findings solidify the recommendation of an attempt to induce labour in women having severe preeclampsia because it is often successful and may reduce the risks of adverse maternal outcome[12].

5.5 LIMITATIONS

In a bid to achieve our objectives, we were faced with several difficulties.

- We could not exercise control over the accuracy with which patients' information were collected and recorded due to the retrospective nature of our study. As a result, a good number of medical records were incomplete.
- Some cases were recorded in the registers but their medical records were not identified. This led to our sample size being smaller than expected.
- The limited data on this subject also made it difficult to compare our study in our setting.

5.6 CONCLUSION

We were able to come to the following conclusions after our results:

- Severe preeclampsia is mostly common in single young primiparous women of low socioeconomic status and caesarean section (CS) is more commonly performed in these patients, with the most frequent indication being poor bishop score. Only 16.9 % of those who were induced ended up having a caesarean delivery.
- Most complications of severe preeclampsia before delivery are not significantly different amongst those who eventually have a caesarean or vaginal delivery.
- The progress of most complications in severe preeclampsia patients is significantly higher in the caesarean group.
- Severe maternal morbidity, acute pulmonary oedema, and admission to intensive care unit are independently associated to mode of delivery.

5.7 RECOMMENDATIONS

In view of the above findings, we humbly propose the following recommendations:

a) To the Ministry of Public Health

- Organize national health campaigns to sensitize the population on early antenatal contacts, preeclampsia symptoms and complications to encourage early diagnosis and hence timely management.
- To organise trainings for health care providers on the principles of management of preeclampsia.
- Subsidize the management of preeclamptic patients by at least ensuring the presence of Magnesium sulphate at all times in all the maternity units.

- To equip the intensive care units of YGOPH and the CHY with many more equipment to ease management of complications.

b) To Hospital Administrators

- In addition to permitting labour to progress or augmenting when spontaneous contractions are present, labour should be induced in cases of severe preeclampsia with an indication for interrupting the pregnancy, in women with no contraindications to vaginal delivery. Indicating caesarean section only on the basis of a diagnosis of severe preeclampsia should be avoided in patients with no associated maternal or foetal risks, hence preventing the increased risk of adverse maternal outcomes associated with caesarean sections among women whom induction of labour could be considered.
- Digitalise the archive system of the hospitals to allow easy and effective data storage for research purposes in the future.

c) To Researchers

- To conduct a randomized controlled trial, this would provide strong evidence and clarify doubts regarding the optimal mode of delivery for women with severe preeclampsia in our setting.
- To also carry out a prospective study on the foetal outcomes in women with severe preeclampsia by mode of delivery.

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APPENDICES

APPENDIX I: QUESTIONNAIRE

Hospital: YGOPH YCH

Year of admission: 2024 2023 2022 2021 2020 2019 2018 2017 2016 2015 2014

A. SOCIO-DERMOGRAPHIC DATA

Age…… G…...P……. GA on admission…….

Profession: HW, student, public sector, private formal, private informal

Educational level: none prim sec high

Residence: Ur Ru Religion: Mus Chris others

Region of Origin: Far North□ North□ North West□ Centre□ South□ South West□ Littoral□ East □ Adamaoua □ West□ Foreigner □

B. HISTORY OF PREGNANCY

Antenatal Consultation

Any ANC? Yes□ No□

How many done? _____

Initial BP___S/D_____ Initial weight _____

C. PAST HISTORY

Gynaecological History

New partner? Yes □ No □

D. MATERNAL COMPLICATIONS BEFORE DELIVERY

Eclampsia	**Yes□ No □**	*Acute pulmonary oedema*	**Yes□ No □**
Coma (Absent)	**GCS Mild(13-14)**	**Mod(9-12)**	**Severe(3-8)**
Abruptio placentae	**Yes□ No□**	*ICU admission*	**Yes□ No□**
HELLP syndrome	**Yes□ No□**	*Acute kidney injury*	**Yes□ No□**
DIC	**Yes□ No□**	*Intrauterine growth R*	**Yes□ No□**
Severe maternal morbidity	**Yes□ No □**	*Stroke*	**Yes □ No□**

Intra uterine foetal demise **Yes□ No □** *Maternal Death* **Yes□ No□**

If yes, cause of death _____

F. LABORATORY INVESTIGATIONS BEFORE DELIVERY.

Urine proteins +□++□+++□ ++++□

24H Proteinuria

Bedside clotting time Prolonged **Yes □ No □**

G. MANGEMENT ON ADMISION

Antihypertensive **Yes □ No □**

Anticonvulsants **Yes □ No □**

Normo-hydration **Yes □ No □**

Monitoring **Yes □ No □**

H. MODE OF DELIVERY

1. Vaginal? Spontaneous **Yes □ No □**
Induction **Yes □ No □**
Instrumental **Y/N**

If yes, Successful **Yes □ No □**

2. Caesarean Section? Yes □ No □

If yes, Elective□ Emergency□ Failed induction□

I. OUTCOMES AFTER DELIVERY

1. MATERNAL

Eclampsia	**Yes□ No □**	*Acute pulmonary oedema*	**Yes□ No□**
Coma (Absent)	**GCS Mild(13-14) Mod(9-12)**		**Severe(3-8)**
HELLP syndrome	**Yes□ No □**	*ICU admission*	**Yes□ No□**
DIC	**Yes□ No□**	*Acute kidney injury*	**Yes□ No□**
Stroke	**Yes□ No□**		**Yes□ No□**

Postpartum Haemorrhage	**Yes□ No □**	*Severe maternal morbidity*	**Yes□ No□**
Hospital stay >7days	**Yes□ No □**	*Maternal Death*	**Yes□ No□**

If yes, cause of death _____

APPENDIX II: ETHICAL CLEARANCE

UNIVERSITÉ DE YAOUNDÉ I

FACULTÉ DE MÉDECINE ET DES SCIENCES BIOMÉDICALES

COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE
Tel/ fax : 22 31-05-86 22 311224
Email: decanatfmsb@hotmail.com

THE UNIVERSITY OF YAOUNDE I

FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES

INSTITUTIONAL ETHICAL REVIEW BOARD

Ref. : N° 1235 /UY1/FMSB/VDRC/DAASR/CSD

CLAIRANCE ÉTHIQUE 10 SEPT 2024

Le COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE (CIER) de la FMSB a examiné

La demande de la clairance éthique soumise par :

M.Mme : MUKWELE BOKENG EMILIA

Travaillant sous la direction de :

- **Pr DOHBIT Julius SAMA**
- **Dr EBONG Clifird**

Concernant le projet de recherche intitulé : **Maternal outcomes of severe pre-eclampsia by mode of delivery in two referral hospitals in Yaoouné**

Les principales observations sont les suivantes

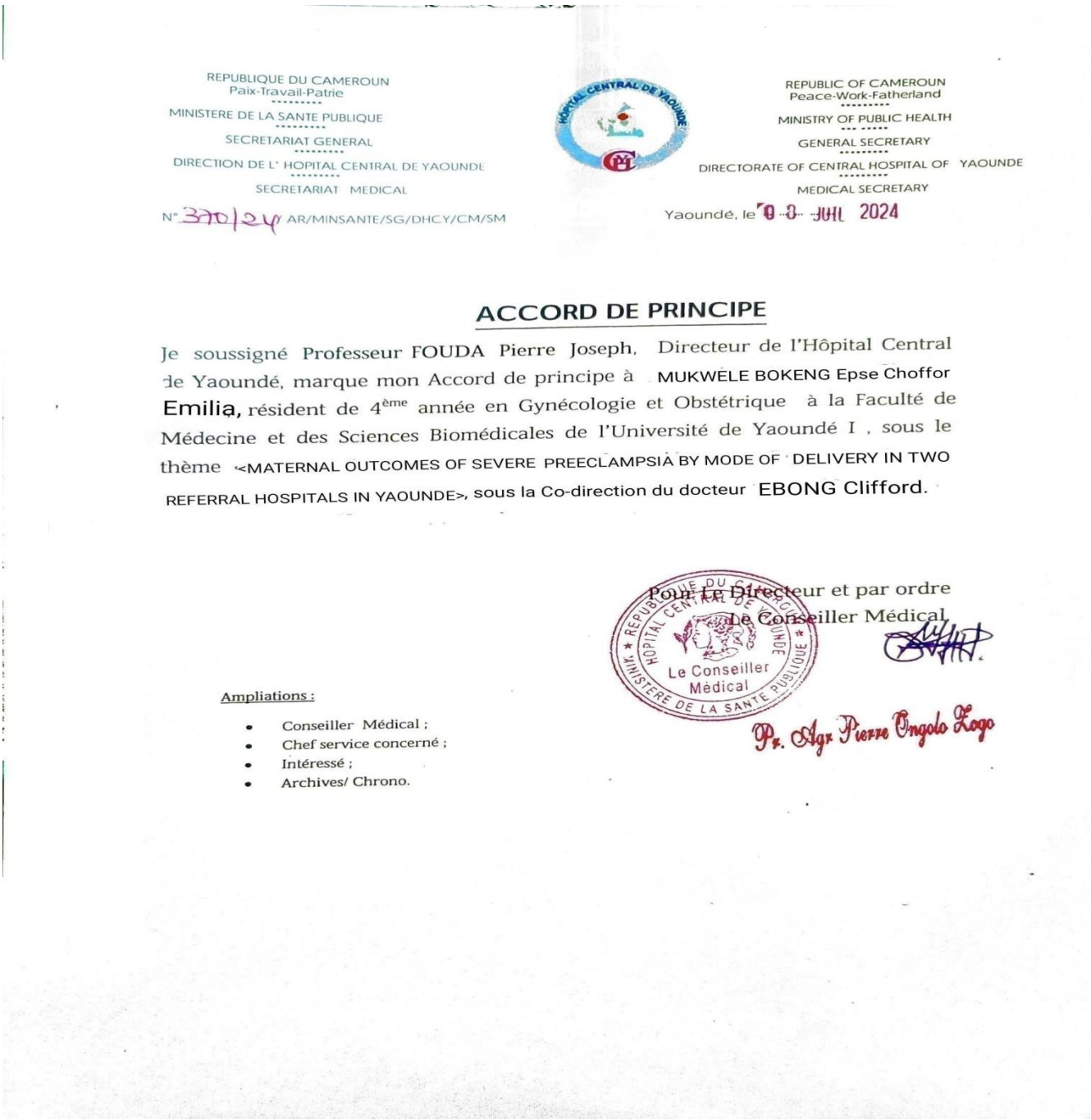
Evaluation scientifique	
Evaluation de la convenance institutionnelle/valeur sociale	
Equilibre des risques et des bénéfices	
Respect du consentement libre et éclairé	
Respect de la vie privée et des renseignements personnels (confidentialité) :	
Respect de la justice dans le choix des sujets	
Respect des personnes vulnérables :	
Réduction des inconvénients/optimalisation des avantages	
Gestion des compensations financières des sujets	
Gestion des conflits d'intérêt impliquant le chercheur	

Pour toutes ces raisons, le **CIER** émet un avis **favorable** sous réserve des modifications recommandées dans la grille d'évaluation scientifique.
L'équipe de recherche est responsable du respect du protocole approuvé et ne devra pas y apporter d'amendement sans avis favorable du **CIER**. Elle devra collaborer avec le **CIER** lorsque nécessaire, pour le suivi de la mise en œuvre dudit protocole.
La clairance éthique peut être retirée en cas de non – respect de la réglementation ou des recommandations sus évoquées.
En foi de quoi la présente clairance éthique est délivrée pour servir et valoir ce que de droit

LE PRESIDENT DU COMITE ETHIQUE

Mme Alena Ondoa
née Obama Marie Thérèse

APPENDIX III: ETHICAL CLEARANCE



REPUBLIQUE DU CAMEROUN
Paix-Travail-Patrie
MINISTERE DE LA SANTE PUBLIQUE
SECRETARIAT GENERAL
DIRECTION DE L' HOPITAL CENTRAL DE YAOUNDE
SECRETARIAT MEDICAL
N° 370/24 AR/MINSANTE/SG/DHCY/CM/SM

REPUBLIC OF CAMEROUN
Peace-Work-Fatherland
MINISTRY OF PUBLIC HEALTH
GENERAL SECRETARY
DIRECTORATE OF CENTRAL HOSPITAL OF YAOUNDE
MEDICAL SECRETARY

Yaoundé, le 08 JUIL 2024

ACCORD DE PRINCIPE

Je soussigné Professeur FOUDA Pierre Joseph, Directeur de l'Hôpital Central de Yaoundé, marque mon Accord de principe à MUKWELE BOKENG Epse Choffor Emilia, résident de 4ème année en Gynécologie et Obstétrique à la Faculté de Médecine et des Sciences Biomédicales de l'Université de Yaoundé I , sous le thème «MATERNAL OUTCOMES OF SEVERE PREECLAMPSIA BY MODE OF DELIVERY IN TWO REFERRAL HOSPITALS IN YAOUNDE», sous la Co-direction du docteur EBONG Clifford.

Pour Le Directeur et par ordre
Le Conseiller Médical

Le Conseiller Médical

Pr. Agr Pierre Ongolo Zogo

Ampliations :

- Conseiller Médical ;
- Chef service concerné ;
- Intéressé ;
- Archives/ Chrono.

APPENDIX IV: ETHICAL CLEARANCE

REPUBLIQUE DU CAMEROUN
Paix-Travail-Patrie
MINISTERE DE LA SANTE PUBLIQUE
HOPITAL GYNECO-OBSTETRIQUE ET PEDIATRIQUE DE YAOUNDE
HUMILITE – INTEGRITE – VERITE - SERVICE

HGOPY YGORH

REPUBLIC OF CAMEROON
Peace-Work-Fatherland
MINISTRY OF PUBLIC HEALTH
YAOUNDE GYNAECO-OBSTETRIC AND PEDIATRIC HOSPITAL
HUMILITY – INTEGRITY – TRUTH - SERVICE

COMITE INSTITUTIONNEL D'ETHIQUE DE LA RECHERCHE POUR LA SANTE HUMAINE (CIERSH)

Arrêté n° 0977 du MINSANTE du 18 avril 2012 portant création et organisation des Comités d'Ethiques de la Recherche pour la santé Humaines. (CIERSH).

AUTORISATION N° 671 /CIERSH/DM/2024

CLAIRANCE ETHIQUE

Le Comité Institutionnel d'Ethique de la Recherche pour la Santé Humaine (CIERSH) a examiné le 26 Mars 2024, la demande d'autorisation et le Protocole de recherche intitulé « **Maternal outcomes of severe preeclampsia by mode of delivery at two referral hospitals in Yaoundé** » soumis par l'étudiant MUKWELE BOKENG épse CHOFFOR NCHINDA EMILIA.

Le sujet est digne d'intérêt. Les objectifs sont bien définis. La procédure de recherche proposée ne comporte aucune méthode invasive préjudiciable aux participants. Le formulaire de consentement éclairé est présent et la confidentialité des données est préservée. Pour les raisons qui précèdent, le CIERSH de HGOPY donne son accord pour la mise en œuvre de la présente recherche.

MUKWELE BOKENG épse CHOFFOR NCHINDA EMILIA, devra se conformer au règlement en vigueur à HGOPY et déposer obligatoirement une copie de ses travaux à la Direction Médicale de ladite formation sanitaire./-

Yaoundé, le 08 AVR 2024

LE PRESIDENT

Prof MBU Robinson
Directeur Général
HGOPY

N°1827 ; Rue 1564 ; Ngousso ; Yaoundé 5ème
BP : 4362 Tél. : 242 05 92 94 / 222 21 24 33 / 222 21 24 31 Fax : 222 21 24 30