THE RISKS OF ADVERSE OUTCOMES (MATERNAL AND FOETAL) IN HYPERTENSIVE DISORDERS OF PREGNANCY

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CONTENT PAGE

ACRONYMS

Hypertensive Disorders of Pregnancy (HDP)

Intrauterine growth restriction (IUGR)

Low and Middle-Income Countries (LMICs)

HELLP syndrome (Haemolysis, elevated liver enzymes and low platelet count)

Pre-eclampsia Integrated Estimate of Risk Study (PIERS)

Lactate dehydrogenase (LDH)

ASpartate Transaminase- (AST)

Placental Growth Factor (PlGF)

Soluble tyrosine kinase-1 (sflt-1)

I. **Abstract**

The hypertensive disorders of pregnancy are some of the major contributors to maternal and neonatal/perinatal morbidity and deaths resulting from them. There have been studies conducted to investigate the incidence of these hypertensive disorders of pregnancy (HDP) especially pre-eclampsia but the studies investigating the occurrence of adverse outcomes from the HDP are very limited in number. The outcomes from HDP can be severe and lethal and therefore deserve to be focused on as well. This term paper discusses the hypertensive disorders of pregnancy and the most common predictive factors being used and describes few studies that have examined the use some of these factors in predicting adverse maternal and foetal complications. Predicting the adverse outcomes resulting from HDP with timely, non-invasive and effective methods will not only contribute to the management of hypertension in pregnancy, thereby reducing maternal and foetal morbidity and mortality but will also aid in the best use of limited resources in healthcare.

1.0 INTRODUCTION

1.1 Background

Hypertension is one of the most commonly encountered problems in pregnancy, thereby complicating the natural cause of pregnancy and delivery[1,2]. Hypertension in pregnancy is generally defined as having a systolic blood pressure of 140mmHg or above, or a diastolic pressure of 90mmHg or above and this elevated BP must occur at least twice when taken 4 hours apart[1;3]. The hypertensive disorders of pregnancy (HDP) which include chronic hypertension, gestational hypertension, pre-eclampsia, and preeclampsia superimposed on chronic hypertension, account for about 5-10% of complications in pregnancies worldwide[4,5]. The effects of these complications range from being mild to really severe and life-endangering and contribute significantly to maternal, foetal and neonatal morbidity and mortality[3;6].

The severe adverse maternal complications from HDP include eclampsia, stroke, acute respiratory distress syndrome, cerebral haemorrhage and infarction, pulmonary oedema, renal dysfunction, haematoma and placental abruption and the severe adverse neonatal outcomes include intrauterine growth restriction (IUGR) or low birth weight and neonatal death[7,8]. The majority of these morbidity and deaths occurring in Low and Middle-Income Countries (LMICs) due to poor health practices and limited resources for proper health care[9,10]. Although there are relatively lower cases of maternal mortality resulting from the HDP in high-income countries, there are still associated poor outcomes of pregnancy and severe morbidity reported in high-income countries and it is reported to be the cause of 16.1 % of maternal deaths in developed countries [1;10-12]. In fact, the HDP are among the top three major causes of maternal mortality worldwide accounting for the leading cause of maternal deaths in Latin America, the Caribbean and Canada[2;12]. The attempt to meet the Millennium Development Goal 5 of improving maternal

health and reducing maternal mortality thus remains a challenge, even in some of the high-income countries[13].

The management of HDP includes treatment of symptoms using antihypertensive and anticonvulsant therapies (expectant management) but delivery is the ultimate cure[14,15]. When HDP occurs in earlier gestation (<32-34 weeks), the decision to induce labour or carry out expectant management is usually dependent on the diagnosis, severity and mainly on the personal experience and expertise of the clinician[6]. This is due to lack of sufficient clinical evidence as to the clear effect of expectant management versus interventionist approaches as to the benefits of the mother's health or the disadvantage to foetus, if delivered at preterm[14;16]. Therefore, the HDP are of great health concern and constitute a burden not only to clinicians but also to women, families and societies globally[17,18].
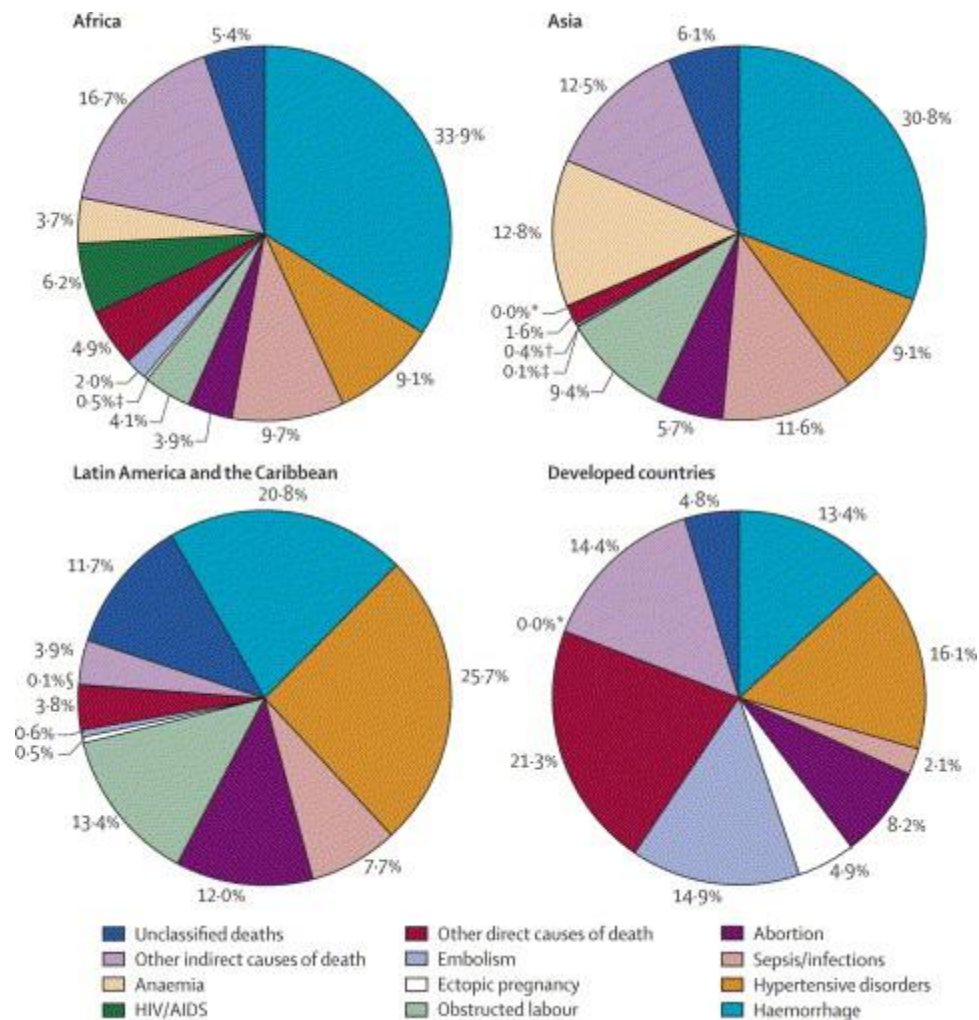
Figure 1: Geographical variation in distribution of causes of maternal deaths.
Adapted from WHO analysis of causes of maternal death: a systematic review by Khan et al.[12]

1.2 Classification of hypertensive disorders of pregnancy

There are several classifications of hypertension in pregnancy by different academic societies but these are mainly divided into 4 broad types - chronic hypertension, gestational hypertension, Pre-eclampsia and super-imposed pre-eclampsia which are described briefly below[3;6;19].

I. Chronic hypertension

Chronic hypertension is defined as having elevated blood pressure (systolic blood pressure of ≥140 mmHg or diastolic of ≥90 mmHg that is diagnosed before 20 weeks of gestation or before pregnancy (pre-existing hypertension). If the hypertension continues after pregnancy, it is still considered as chronic hypertension even if it was first diagnosed after 20 weeks of gestation. Chronic hypertension is reported to approximately 1 – 3 % of pregnancies and increasing maternal age (35 years or greater) is a risk factor for its development[5;20].

II. Gestational hypertension

Gestational hypertension is defined as hypertension that occurs during pregnancy after 20 weeks gestation and the blood pressure normalizes within 12 weeks after delivery. Population-based data suggest that gestational hypertension affects about 5-6% of pregnancies. There are usually no severe adverse outcomes for both mother and foetus if gestational hypertension remains mild and is not complicated by pre-eclampsia or other health morbidities[5;19].

III. Pre-eclampsia

The classical definition for pre-eclampsia is the onset of hypertension (BP ≥140/90 mmHg in 24 h) and proteinuria (≥300 mg in 24 h by urinary protein: creatinine ratio) after 20 weeks gestation[1, 15]. However, this definition alone does not entirely reflect the variable multi-systemic and heterogenic nature of the disease presentation in clinical practice[12;14]. Pre-eclampsia may occur atypically as hypertension without proteinuria, but associated with systemic symptoms and HELLP syndrome (Haemolysis, elevated liver enzymes and low platelet count)[5].

Pre-eclampsia can be sub-divided into mild (occurring after 36 weeks gestation) associated with more favourable maternal and perinatal outcomes, and severe (occurring before 33 weeks gestation or/and with a systolic pressure of ≥160 mmHg or diastolic of ≥110 mmHg) associated with higher maternal and perinatal morbidity and mortality[1, 4]. The risk factors for pre-eclampsia include primiparity, obesity, pre-gestational diabetes mellitus, low sperm exposure, multiple gestation, extreme maternal age (≤19 or ≥35 years) and family or previous history of pre-eclampsia[1;5]. Pre-eclampsia complicates 2-3% of pregnancy and overall, is responsible for about 50,000 maternal deaths annually[1].

IV. Super-imposed pre-eclampsia

This is diagnosed when there is a new-onset of proteinuria or any other systemic features of pre-eclampsia in a pregnant woman with already existing chronic hypertension. Thus, it is usually called pre-eclampsia superimposed on chronic hypertension[1;5].

These classes of the hypertensive disorders of pregnancy are associated with each other. Studies have shown that about 17- 30 % of the women initially suffering from gestational hypertension but without proteinuria and also, about 20-25 % of women initially presented with chronic hypertension only, develop pre-eclampsia subsequently[21-22]. In rare cases, some women who did not present with hypertension or proteinuria may also develop postpartum hypertension or pre-eclampsia and can also contribute to serious damage of maternal organs if not managed efficiently[23]. Studies have also shown that women who suffered from the HDP also have higher risks of developing cardiovascular diseases such as ischemic heart disease and venous

thromboembolic disease in the future[1;24]. It is therefore ultimately necessary to pay proper attention and care in treating and following the progression of any signs of the HDP[25].

2.0. RISKS OF DEVELOPING ADVERSE OUTCOMES FROM THE HYPERTENSIVE DISORDERS OF PREGNANCY

2.1 The need to identify risks of developing adverse maternal or foetal outcomes

Reports from research studies and clinical surveys have shown that not all cases of the HDP develop adverse outcomes and some pregnant women (about 40 %) that did not present hypertension or proteinuria develop eclampsia or other severe outcomes within a week[23;26]. There is therefore a need to understand and predict the development of these adverse outcomes.

There have been several studies on predicting the incidence of the hypertensive disorders of pregnancy especially pre-eclampsia but only a few studies have been carried out to identify the risks of developing complications or adverse outcomes from the HDP[27-29]. Predicting the risk of incidence of the HDP only and taking supplements and medication may just reduce the symptoms and protect the woman from certain damage but it also does not change the progression of the disease nor prevent the impending poor outcomes[19;30]. There are also reports of negative effects on placental perfusion when the maternal BP is reduced and the use of antihypertensive drugs especially ACE inhibitors and ARBs are associated with increased risk of IUGR and congenital anomalies[1;19]. The use of corticosteroids for lung maturation of the fetus in preterm delivery is very common but there is also ongoing debate about its true benefits due to

concerns about the negative effect of corticosteroid on cerebral and neuronal growth of the baby in the long-run[31].

The ability to determine disease prognosis and predict adverse outcomes of the HDP is therefore important to aid in clinical decision making and management of HDP so as to identify women and foetuses at high risk and give timely and appropriate care[11;13;32].

2.2 Prediction/prognostic factors and tests

The Pre-eclampsia Integrated Estimate of Risk Study (PIERS) group and other studies have reported relevant tests and factors that may be predictive of adverse outcomes of pre-eclampsia and other hypertensive disorders of pregnancy[20-22; 32]. The predictive factors most commonly used are as follows:

I. Blood Pressure

High blood pressure is the abnormality usually observed earliest in the hypertensive disorders of pregnancy and its associated outcomes. Systolic pressure greater than 160 mmHg was reported in a case study to be a risk factor for stroke independently while diastolic pressure greater than 90 mmHg has also been reported in a study to be a better predictor of adverse perinatal outcomes[23;32].

II. Proteinuria

Proteinuria can be measured using dipstick method or by laboratory tests ($\geq$30mg/mmol by urinary protein:creatinine ratio, or of $\geq$2+ by dipstick, $\geq$0.3g/d by 24 hour collection) and is one of the factors used for prediction, especially in pre-eclampsia cases. The presence of proteinuria

in pregnancy has been shown to be more associated with adverse perinatal outcomes than maternal risks[32].

III. Plasma Uric Acid

Some studies including a meta-analysis conducted by Koopmans et al have reported uric acid plasma concentration to be a useful predictor of outcomes for both mother and foetus in women suffering from the HDP[6;33]. Hyperuricaemia (uric acid greater than local upper limit of local non-pregnancy normal range) is thought to be highly associated with poor outcomes of pregnancy[34].

IV. HELLP syndrome factors

HELLP syndrome is reported to be associated with poor maternal outcomes such as eclampsia, abruptio placentae and intravascular coagulopathy[35]. The components of the HELLP syndrome which are platelet count less than 100×10^9 /L, serum albumin less than 20 g/L, elevated liver enzymes (lactate dehydrogenase (LDH) or aspartate transaminase- (AST)) and elevated creatinine have been shown to have predictive value for adverse maternal outcomes in pre-eclampsia by the PIERS[34].

V. Biomarkers

Recent studies have been consistent in suggesting that certain pro- and anti-angiogenic factors especially the placental growth factor (PlGF) and soluble tyrosine kinase-1 (sflt-1) as well as their ratio (sFlt-1: PlGF developed by Roche diagnostics) are useful in predicting the incidence of early onset pre-eclampsia and may also have value in predicting adverse foetal outcomes[3;23;36].

Higher than normal values measured when measured in the second trimester, may serve as a predictor of adverse outcomes but more research is required to prove this. Other biomarkers suspected to have predictive values of adverse outcomes of the hypertensive disorders of pregnancy include VEGF, sEng and placental protein 13 but high-quality research studies are yet to confirm this[3;23;36].

VI. Doppler Ultrasonography

Doppler ultrasound can be used to study blood flow through the uteroplacental circulation[37]. A few studies have reported that an abnormal uterine Doppler test result (high pulsatility index and/or presence of an early diastolic notch) especially during the second trimester has a predictive ability of foetal growth restriction in pregnancy and even better ability when combined with serum markers such as the placental growth factor, placenta protein 13, VEGF and soluble tyrosine kinase-1 (sflt-1)[3;23;37].

VIII. HDP Symptoms

The symptoms of the hypertensive disorders of pregnancy such as vomiting and nausea, dyspnoea or chest pain, headache, visual disturbances and epigastric pain have all been reported to be associated with adverse maternal outcomes, having a better predictive value especially when combined with the occurrence of low platelet count, hyperuricaemia, and elevated creatinine and liver enzymes[32;34].

IX. Oxygen saturation

The PIERS reported that SpO_2, which is usually used to predict respiratory complications risks, may have good predictive values for the prediction of combination of poor outcomes in pre-eclampsia. More research is needed to investigate the value of oxygen saturation in prediction of outcomes of the HDP[34].

These factors have been employed in some studies described in the paper.

2.3 Studies reporting risks identification of adverse outcomes in the HDP

As mentioned earlier, there have been limited studies carried out to predict or identify the risks of adverse outcomes in women with HDP. More studies have been carried out on investigating the recurrence of hypertensive disorders in pregnancy and have reported about a 50 % risk of recurrence of hypertension in new pregnancies with pre-eclampsia having a recurrence of about 25%. These studies also stated that the recurrence rate was higher in women with chronic hypertension and that these pregnancies were prone to having greater risks of adverse outcomes. However, the studies did not investigate the risk of developing the adverse outcomes using predictor factors nor report the exact adverse risks in those pregnancies[38,39].

Below are summaries of few studies that have tried to identify and predict the risks of developing adverse outcomes in women with hypertensive disorders in pregnancies.

I. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia.

An observational study by Rana et al tested the association between the sFlt1/PlGF ratio and adverse outcomes within 2 weeks in women at less than 34 weeks gestation, with suspected pre-eclampsia[40]. Samples were collected within an hour of arrival and the sFlt1/PlGF ratio was measured using the Elecsys platform assays developed by Roche Diagnostics. Other predictors used were available demographic information, laboratory results and blood pressure at the time of evaluation. The adverse foetal outcomes of interest were small for gestational age (≤10th percentile for gestational age, abnormal umbilical artery Doppler (absent or reverse diastolic flow), iatrogenic delivery and death (foetal/neonatal); the adverse maternal outcomes included hypertension, elevated AST or ALT, pulmonary oedema, acute renal failure, cerebral haemorrhage, de novo seizure, abruption (clinical and/or pathological), disseminated intravascular coagulation and maternal death.

Adverse outcomes occurred in 87 % of the women and the authors reported that sFlt1/PlGF ratio of 85 as a cut-off point gave a sensitivity of 72.9% and a specificity of 94.0% in identifying women with or without these adverse outcomes significantly, using the receiver operating curve (ROC) analysis. They also reported that systolic blood pressure, uric acid, proteinuria, creatinine, low platelet count and greater sFlt1/PlGF ratio (with sFlt1/PlGF ratio having the most predictive

accuracy) remained significant predictors of adverse outcomes in women at ≤34 weeks gestation, using both single-variable and multivariable logistic regression models while factors such as body mass index (BMI), smoking, history of chronic hypertension, and maternal or gestational age were not associated with the adverse outcomes. They therefore concluded that sFlt1/PlGF ratio predicts adverse outcomes within 2 weeks in women with suspected pre-eclampsia presented at ≤34 weeks' gestation.

II. The role of uterine artery doppler in predicting adverse pregnancy outcome.

A review by Papageorghiou *et. al.* summarized findings from twenty studies on the use of uterine artery Doppler in studying the uterine artery flow impedance for the prediction of adverse foetal pregnancy outcomes[37]. These outcomes include foetal growth restriction (FGR), pre-term delivery (before 35 weeks gestation) and death in women with pre-eclampsia observed in the first and second trimesters. This review reported that uterine artery Doppler had higher sensitivity in predicting more severe diseases such as foetal/neonatal death and pre-eclampsia with FGR or/and requiring delivery rather than predicting the occurrence of preeclampsia alone and the sensitivity was higher in the second trimester studies compared to women studied in the first trimester.

The review reported abnormal Doppler results had a pooled likelihood ratios for FGR of 4 and perinatal death of 2.4 compared to 0.8 for both, for women with normal Doppler results. It also reported sensitivities of 80 %, 60 % and 19 % for predicting delivery before 34 weeks gestation, FGR and perinatal death respectively for women studied in their second trimester. The

sensitivities reported for identifying adverse outcomes in women during the first trimester were lower, being 50 % and 24 % for pre-term delivery before 34 weeks and FGR respectively. The review therefore concluded that uterine artery Doppler was more useful in identifying the risk of developing adverse outcomes in pre-eclampsia during the first trimester of pregnancy.

III. Comparison of placental growth factor and foetal flow Doppler ultrasonography to identify foetal adverse outcomes in women with hypertensive disorders of pregnancy: an observational study.

An observational study by Molvarec *et al.* compared the use of foetal flow Doppler ultrasonography and PlGF in identifying adverse foetal outcomes in 89 Caucasian women with HDP in singleton pregnancy, between the 22nd and 34th weeks gestation[40]. The HDP included were pre-eclampsia, chronic and gestational hypertension, superimposed pre-eclampsia and HELLP syndrome and the adverse foetal outcomes observed were pre-term birth, IUGR and oligohydramnios. PlGF levels were measured using the Alere Triage® assay and classified as very low (PlGF≤12 pg/ml), low (12 pg/ml<PlGF<100 pg/ml) or normal (PlGF≥100 pg/ml), while foetal flow was observed using Doppler ultrasonography and classified as normal flow or abnormal foetal flow (presence of diastolic block, reverse flow or increased resistance in the umbilical artery or descending aorta, with decreased resistance in the middle cerebral artery).

A total of 61 women had pre-term delivery and there were 22 cases of IUGR out of the 89 women with HDP included in the study. Of the women who delivered preterm, 56 had low or very low PlGF while 20 of them had abnormal foetal flow and 41 had normal foetal flow. There

was however a high concordance between PlGF and foetal flow as all 20 women with abnormal foetal flow also had low or very low PlGF and there was no occurrence of IUGR amongst the women with both normal foetal flow and normal PlGF. Amongst the 22 IUGR neonates, all had low or very low maternal PlGF and 10 out of 22 had abnormal foetal flow. In the 27 cases of oligohydramnios that occurred, 20 of the women had low or very low PlGF. The study thus reported that a positive PlGF test result had a significant association with adverse foetal outcomes in HDP and had more prognostic efficiency in identifying these outcomes in <35 weeks gestation than foetal flow Doppler ultrasonography.

IV. Plasma uric acid remains a marker of poor outcome in hypertensive pregnancy: a retrospective cohort study.

A retrospective cohort study by Hawkins *et al.* was carried out to investigate the association between hyperuricaemia and haemoconcentration (measured as haematocrit or haemoglobin concentrations indirectly) and adverse maternal and foetal outcomes in 1578 women with HDP, using data from databases of hypertensive pregnant women. The HDP included were gestational hypertension and pre-eclampsia; the adverse maternal outcomes included were severe hypertension, liver disease (AST >40 U/l), thrombocytopenia (low platelet count), renal insufficiency, and cerebral irritation (severe headaches with hyper-reflexia or sustained clonus ≥3 beats, repeated visual scotomata, or requiring magnesium sulphate). The adverse foetal outcomes of interest were small-for-gestational-age infant, admission to special-care nursery prematurity (<37 weeks of gestation) and perinatal death. Using logistic regression analysis, hyperuricaemia was found to be associated with an increased risk of small-for-gestational-age

infant and prematurity, but not associated with adverse maternal outcomes in women with gestational hypertension. However, hyperuricaemia was found to be associated with increased risk of both adverse foetal and maternal outcomes in the whole cohort of combined gestational hypertension and pre-eclampsia in pregnant women but haemoconcentrations did not have any associations with the adverse outcomes. This study led to the conclusions by the researchers that uric acid was an important predictor of adverse maternal outcomes and even better predictor of adverse foetal outcomes in women with gestational hypertension and pre-eclampsia.

V. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model.

This is a multicentre study carried out by von Dadelszen *et al.* to develop and validate a model, fullPIERS (Pre-eclampsia Integrated Estimate of Risk Study) for high-resource settings[34]. The fullPIERS model is a symptom-, sign-, and laboratory test-based multivariate model that was developed and validated in a prospective observational cohort of women with pre-eclampsia in tertiary hospital settings to predict the adverse maternal outcomes occurring within 48hrs of diagnosis with pre-eclampsia[20]. The fullPIERS model included women that had hypertension and either proteinuria or hyperuricaemia; HELLP syndrome even in the absence of hypertension or proteinuria; superimposed pre-eclampsia excluding women admitted in spontaneous labour or having any maternal outcome before fulfilling the eligibility criteria or collection of predictor data.[20].

The predictor factors included in the model were creatinine, platelet count, AST, chest pain or dyspnoea, SpO_2 and gestational age at onset of disease or delivery and the maternal outcomes of interest included disseminated intravascular coagulation, cerebrovascular bleeding, liver

haematoma, retinal detachment, pulmonary oedema, acute renal failure, stroke, abruptio placentae and eclampsia. The model was successful in predicting adverse outcomes in a cohort of 2023 women admitted to tertiary units across the UK, Canada, New Zealand and Australia within 48 hours (AUC ROC 0.88, 95% CI 0.84-0.92) and up to 7 days of eligibility (AUC ROC 0.76, 95% CI 0.72-0.80). fullPIERS also performed well when reassessed using predictor variables within 6 and 24 hours of admission with a likelihood ratio of 14.8 (95% CI 9.1-24.1) or 17.5 (95% CI 11.7-26.3) respectively, as an accurate rule-in test for adverse maternal outcome[23]. The authors therefore concluded that the fullPIERS model significantly identifies the increased risk of adverse maternal outcomes in women with pre-eclampsia up to 7 days before the outcomes occur.

In addition to the studies summarized above, there is an ongoing prospective cohort study PREP which aims to develop and validate a model for the prediction of adverse foetal and neonatal outcomes in women with early pre-eclampsia. The authors also stated plans in their protocol to validate the model externally when completed using the PIERS cohort and the Pre-eclampsia Eclampsia TRial Amsterdam (PETRA, Netherlands) study. The study is expected to be concluded in 42 months.

There are also some studies examining the severity of adverse outcomes in recurrence of HDP in subsequent pregnancies compared to nulliparous pregnancies or in pregnant women with HDP that have not suffered any HDP in subsequent pregnancies. These studies reported higher rates of adverse outcomes such as pre-term deliveries, abruptio placenta and foetal death in women with recurrent HDP compared to those without[39; 42].

3.0 DISCUSSION

Overall, five main studies (one of which was a review) investigating the risks of adverse outcomes of HDP were described in detail in this paper. These studies employed the use of different factors to predict the adverse outcomes in HDPs, which included angiogenic factors, uterine artery Doppler ultrasonography, uric acid and combination of two or more factors. However, the various studies had their individual strengths and weaknesses.

Although all the included studies stated prediction of identification of adverse outcomes as their aims, it is important to note that the definitions of these outcomes and the outcomes of interest varied amongst the different studies. The studies by Papageorghiou *et al.* and Molvarec *et al.* examined the risks of adverse foetal outcomes, the study by von Dadelszen examined risks for adverse maternal outcomes while the studies by Rana *et al.* and Hawkins *et al.* examined the risks of both maternal and foetal outcomes[33-34; 37; 40-41]. Except for the studies by Hawkins *et al.* (which investigated outcomes from all HDP) and Molvarec *et al.* (investigated outcomes from both gestational hypertension and pre-eclampsia), the other studies focused solely on the adverse outcomes resulting from pre-eclampsia. The definition of pre-eclampsia differed in the studies with the major difference being the time interval between the occurrence of hypertension (ranging from 2 to 4 hours apart in the studies) and also, the inclusion of the HELLP syndrome in the fullPIERS as a form of pre-eclampsia[34]. Addition of the HELLP syndrome may be useful in identifying more women at risks of outcomes since the classical definition of pre-eclampsia alone has been reported not to fully capture the multivariable nature of the disease. Nonetheless, this inclusion of the HELLP syndrome may have affected the results of the study and the ability

to compare results across other studies on pre-eclampsia except the same inclusion criteria is being used.

The inclusion criteria, the weeks of gestation of interest and the study design and data analysis in these studies were also different. These differences were especially seen in the studies included in the review by Papageorghiou *et al.* such as the differences in the definition of abnormal flow making it difficult for the authors to draw out very strong conclusions based on the findings of the different studies[37]. The population also varied and so did the settings; therefore, the findings of these studies may not be applicable to a different setting or population. For example, the study by Molvarec *et al.* examined only Caucasian women and so, the results of the study may not be reproducible if the same study was conducted in a Latino population[41]. The time of prediction for the occurrence of these outcomes were only stated in the studies by von Dadelszen *et al.* (investigated outcomes occurring within 48 hours of eligibility up to 7 days) and by Rana *et al.* (outcomes occurring within 2 weeks)[34; 40]. Stating the time of observation is important as this gives a clearer understanding of when these outcomes may occur and might be useful to the clinician in planning and for better management of the pregnancy such as in steroid administration, induction of labour or transfer of the patient to a higher care unit[40].

The study by Rana *et al.* used the Roche diagnostics to identify adverse outcomes and reported a sensitivity of 72.9 % while the study by Molvarec *et al.* reported 100 % sensitivity in identifying IUGR using the Alere Triage assay (which was similar to the 100 % sensitivity report for diagnosing early pre-eclampsia in the study by Benton *et al.*), although the sensitivity for identifying pre-term delivery was lower (91.8 %)[36-37; 40]. The performance of both diagnostics have been compared in a study by Benton *et al.* and the Alere Triage assay was reported to have

a higher sensitivity and better diagnostic accuracy than the Elecsys sFlt/PlGF Ratio assay by Roche diagnostics. This study had some limitations as it was based on a small sample size (44 patients) and was aimed at identifying the women at risks of pre-eclampsia in earlier pregnancy rather than the risks of adverse outcomes[36]. However, the type of diagnostic test used may affect the results as these two methods have different designs; the Alere measures only the PlGF using the fluorescence immunoassay technique while the Roche diagnostic measures the sFlt/PlGF Ratio using the electrochemiluminescence method. Setting an appropriate cut-off point for the optimum performance of these tests is also important as different cut-off marks give different sensitivities and specificities[36].

There were also contradictions in the results of the studies with other studies. The study by Hawkins reported that hyperuricaemia was useful in predicting foetal outcomes such as small-for-gestational age and pre-term delivery in both gestational hypertension and pre-eclampsia cases but it did not predict any adverse maternal outcome in only gestational hypertension except when combined with pre-eclampsia[33]. The fullPIERS also reported that blood pressure did not predict maternal complications independently and the study by Rana *et al.* reported that history of previous chronic hypertension was not predictive of adverse outcomes[34; 40]. However, these studies reported improved prediction of adverse outcomes when these factors were combined with other factors; platelet count AST or proteinuria. This correlates with the findings from certain studies that many of the factors do not predict outcomes independently or have lower prediction values when used alone[43]. From these findings, the ability of these factors to predict an adverse outcome may also depend on the type of HDP being studied[33].

The study by von Dadelszen was the only study that developed a multivariate model to identify the risks of adverse outcomes[34]. The use of prognostic models is becoming more common in healthcare and clinical practice and has some advantages over individual study methods because it is not affected by confounding factors[45] (Steyerberg). The fullPIERS model therefore seems to be a promising tool for the prediction of adverse outcomes in pre-eclampsia and related HDP. However, in order to implement it into routine clinical practice, the model has to be validated externally and assessed for generalisability, that is, the model has to be applied to a different setting/population other than the original setting of development[45]. Another advantage of the use of prognostic model is that it can be recalibrated and updated using newer predictor factors if identified [45].

Almost all the studies included reported fairly small sample size as part of the study limitations especially as the occurrence of adverse outcomes in the studies was relatively small. The importance of adequate sample size in research cannot be overemphasized as the quality sample is necessary to investigate factors in details and make more valid conclusions[45].

Based on the studies reviewed, there is still room for more research in identifying more predictor factors and the risks of developing the adverse outcomes from HDP. Recommendations to improve prediction of adverse outcomes include:

I. Conducting more research using univariable and multivariable logistic regressions to identify and combine the most effective prediction factors. This will be helpful in avoiding carrying out many tests which may not be necessary in prediction of these outcomes[31].

II. Using a bigger sample size and wider population so as to produce more generalisable findings[41].

III. External validation of the fullPIERS model using other data sets and also, updating using new predicting factors such as the PlGF to investigate its predictive effects[45].

IV. Conducting more studies to examine prediction of adverse outcomes within specified time limits for better management[34].

V. Conduction of systematic reviews to draw out the overall effects of these factors. This will help in better understanding of these factors and may lead to setting of standard cut-off points and definitions which may better reflect the adverse outcomes.

4.0 CONCLUSION

The neonatal, perinatal and maternal morbidity and mortality from the hypertensive disorders of pregnancy continue to pose a serious health problem globally[1; 45]. It is therefore important to identify the risks of developing these adverse outcomes for both the mother and foetus as this will aid in clinical decisions and management[30]. The nature of some of these hypertensive disorders especially pre-eclampsia remains complex[3]. Identifying the factors that might be predictive of adverse outcomes will not only help to control and manage these outcomes but can contribute to better understanding of these disorders[30;45].

As seen in the discussed studies, not every case of HDPs result in adverse outcomes; some are uneventful. With the transition in healthcare directed more towards patient-involvement, the ability to predict adverse outcomes will help to inform the patient of whatever risks might be

involved. Predicting adverse outcomes will contribute to the identification of women with the greatest or lowest risk of complications and aid in clinical decision as to the best way to manage the cases (whether expectant management or interventionist) especially when remote from term for the maximum benefits of both mother and foetus[30; 45].

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