EARLY RISK-ASSESSMENT METHODS FOR PREDICTION OF PREECLAMPSIA DEVELOPMENT AND SAFER PREGNANCY OUTCOMES

By

BREANNA LYNN HORN

A Thesis Submitted to The W.A. Franke Honors College

In Partial Fulfillment of the Bachelor's Degree

With Honors in

Nursing

THE UNIVERSITY OF ARIZONA

D E C E M B E R 2 0 2 4

Approved by:

Dr. Melissa Goldsmith
Department of Nursing

Abstract

Preeclampsia is a multi-system obstetrical syndrome which is responsible for up to six percent of pregnancy complications worldwide. The purpose of this thesis is to explore early-risk assessment methods for preeclampsia development utilizing combined scientific evidence about clinical risk factors and biochemical index markers, and to provide evidence-based recommendations for implementation into nursing practice. Preeclampsia and other hypertensive disorders account for 16% of maternal deaths in the United States (ACOG, 2020).

There is emerging research which reveals that blood-based biomarkers, early risk-assessment model implementation and early routine blood pressure readings may predict preeclampsia development before the 20th week gestation. The most relevant and statistically significant clinical risk factors are shown to be history of preeclampsia and chronic hypertension. Several biochemical markers, such as Placental Growth Factor, TNF-alpha and Plasma Protein-A are shown to have relevance in predicting and diagnosing preeclampsia development. Patients who are identified as high-risk in early gestation can begin prophylactic Aspirin therapy starting at 11 weeks gestation. This is shown to reduce the incidence of preeclamptic preterm deliveries (Rolnik, et al., 2017). The last chapter includes an implementation proposal for nursing practice, and evaluation of practice recommendations utilizing the Plan-Do-Act-Study model.

Chapter One

The purpose of this thesis is to explore antepartum risk-assessment methods, specifically blood-based biomarkers and early risk-assessment models, for preeclampsia in pregnant women prior to the twentieth week of gestation. This paper also aims to provide evidence-based recommendations based on emerging research for implementation of early risk assessment strategies into nursing practice.

Background

Preeclampsia complicates 2-6 percent of pregnancies worldwide annually, and is a major cause of maternal and fetal mortality. Preeclampsia is known to be one of the "greatest obstetrical syndromes" which comprises several overlapping pathological processes (Jung, et al., 2022, p. 844). Additionally, 16% of maternal deaths can be attributed to hypertensive disorders, and the rate of preeclampsia in the United States has increased by over 25% since the 1980s (ACOG, 2020). Preeclampsia is a major cause of maternal and fetal mortality worldwide. Preeclampsia usually occurs after twenty weeks of pregnancy, and symptoms can appear up to twelve weeks postpartum. Several social demographic factors are associated with preeclampsia. These include lower educational status, lack of access to prenatal care, advanced maternal age, and African-American ethnicity (Khan et al., 2022). The risk factors for pregnancy-induced hypertension include: first pregnancy, sperm from a man who has fathered another pregnancy affected by preeclampsia, anemia, family history of preeclampsia, chronic hypertension, chronic renal disease, obesity, preexisting diabetes, multifetal pregnancy, antiphospholipid syndrome and pregnancy resulting from assisted reproductive technology. The cause of preeclampsia is unknown but research supports etiologic factors linked with preeclampsia and eclampsia, such as sleep disorders, maternal obesity, periodontal disease, uteroplacental ischemia, fetal diseases,

autoimmune disorders, placental aging, breakdown of maternal-fetal immune tolerance, and endocrine disorders (Jung et al., 2022).

There are several classifications of hypertension during pregnancy. The first category is gestational hypertension, which is defined as a systolic blood pressure equal to or higher than 140 mmHg or a diastolic blood pressure equal to or higher than 90 mmHg which develops after the 20th week gestation but resolves within six weeks postpartum. Gestational hypertension does not include proteinuria. Preeclampsia has the same criteria as gestational hypertension with the addition of proteinuria of 0.3 gram or higher in a 24-hour urine collection. Recently, some professional organizations have suggested that preeclampsia diagnoses can be made in the absence of proteinuria if there is multi-system involvement, and the patient is exhibiting other clinical symptoms of the syndrome without an alternative attributive cause (Jung et al., 2022).

Eclampsia is defined as the development of preeclampsia leading to generalized seizures which are not attributable to other causes. There is also chronic hypertension, which exists before pregnancy or develops before the 20th week gestation. Chronic hypertension also exists when blood pressure does not resolve in the postpartum period. Finally, a woman can experience preeclampsia superimposed on chronic hypertension. This occurs in women who have chronic hypertension and develop new-onset proteinuria. Preeclampsia development should be suspected if the patient has proteinuria that develops, a sudden increase in blood pressure which was previously controlled, thrombocytopenia development or abnormal AST or ALT elevation which reflects involvement of the liver (Decaj, et al., 2016).

The pathophysiology of preeclampsia is essentially rooted in generalized vasospasm. A normal response to pregnancy is an increase in vascular volume, and a consequential increase in cardiac output. However, most pregnant women develop resistance to vasoconstrictors such as

angiotensin II, so their blood pressure does not increase. Certain vasodilators, such as prostacyclin, prostaglandin E2 and endothelium-derived relaxing factor (EDRF) act to decrease peripheral vascular resistance as well (Decaj, et al., 2016).

In a preeclamptic pregnancy, the sensitivity to Angiotensin II and the decrease of other vasoconstrictors leads to increased peripheral vascular resistance. Vasospasm also decreases the diameter of blood vessels, and consequently results in endothelial damage and decreased EDRF. Vasospasm is also responsible for the increase in blood pressure, as well as an impeded blood flow. The result of this is that perfusion of the organs decreases. Endothelial dysfunction reduces blood flow to the organs which causes venous congestion. In the kidneys, one of the significant resulting changes is reduced glomerular filtration rate (GFR), which manifests as elevated BUN and Creatinine labs. Secondary to the reduced renal blood flow, damaged glomeruli allow for proteins to leak across the membrane. The loss of protein in the kidneys reduces colloid osmotic pressure to allow interstitial fluid shift. The fluid shift may cause relative hypovolemia, which manifests as a rise in hematocrit and generalized edema. In the presence of hypovolemia, Angiotensin II and aldosterone are secreted more in order to retain sodium and water. The additional Angiotensin II release furthers the vasospastic and hypertensive effects (Sharma, et al., 2024).

There is decreased blood perfusion to the liver, which leads to impaired function. This is followed by hepatic edema and subcapsular hemorrhage, which can cause necrosis. Preeclamptic patients will often have elevated liver enzymes present in the maternal serum. The woman may also experience epigastric pain (beneath the right breast) as a result of hepatic dysfunction (Tassi, et al., 2023).

Cerebral vasoconstriction can cause pressure-induced ruptures of capillaries, which leads to small cerebral hemorrhage. Arterial vasospasm can manifest as headache, blurred vision and hyperreflexia. The decrease in colloid oncotic pressure can cause leaking from the pulmonary capillary membrane which results in pulmonary edema, producing dyspnea. Finally, the decrease in placental circulation can increase the risk of HELLP syndrome or abruptio placentae. Preeclamptic pregnancies also have a higher association with fetal intrauterine growth restriction and fetal hypoxemia.

Usually, the first indication of preeclampsia development is new or worsening hypertension. Blood pressure should be taken with the woman in the sitting position, and women may need to be hospitalized for serial blood pressures in order to exclude elevation from anxiety. Another distinguishing factor is proteinuria, which should be measured using a clean-catch 24 hour specimen (PE proteinuria is defined as over 300 mg in a 24 hour specimen). Women may also present with narrowed arteries in the retina, brisk deep tendon reflexes, pitting edema and pulmonary edema, nausea and vomiting and headache (Sharma, et al., 2024).

Preeclampsia is a condition which progresses rapidly and can often go unnoticed in the beginning because the symptoms are attributable to other causes. Many women already have advanced preeclampsia when it is diagnosed. It is classified as mild, severe, or eclampsia, which is assessed by blood pressure, creatinine serum levels, proteinuria, platelet count, liver enzymes, urine output, and the presence or absence of other symptoms. HELLP syndrome represents a complication of severe pre-eclampsia and has a mortality rate of 0-24% in women and up to 37% perinatally. The goal of preeclamptic management is to prevent maternal seizures and ensure safe delivery of the fetus (Khalid, et al., 2023).

The American College of Obstetricians and Gynecologists published two updated

guidelines sets related to preeclampsia in 2024. As new research emerges, these practice guidelines will continue to evolve and change. The first set of guidelines is an algorithm for acute hypertension in pregnancy and postpartum. The algorithm begins with asking the patient, “are you pregnant or have you been pregnant in the past six weeks?”. If the patient answers yes, and has a systolic blood pressure of ≥140, or a diastolic pressure of ≥90, the algorithm should be utilized. First, the blood pressure should be monitored every fifteen minutes for up to four hours. If at any time the patient has a systolic pressure more than 160 or a diastolic pressure more than 110, confirm in the next fifteen minutes and proceed to the ‘preeclampsia with severe features’ box. The patient should be assessed for potential signs and symptoms of preeclampsia, such as a new-onset headache or visual disturbances. Lastly, labs should be considered, such as urine protein, complete blood count, serum creatinine and AST/ALT. These labs can indicate level of function in organs affected by preeclampsia, including the liver and kidneys. A patient with normal labs and no symptoms, who does not have high enough pressures to be considered severe, is treated as having gestational hypertension. A patient who has the addition of proteinuria is treated as preeclamptic, and should have an OB consultation. A patient who has any additional abnormal labs or symptoms qualifies as being preeclamptic with severe features. Treatment recommendations for sustained hypertension can include a primary antihypertensive such as IV Labetalol or Hydralazine, or PO Nifedipine. Simultaneously to antihypertensive treatment, magnesium sulfate should be administered (ACOG, 2024). The most current ACOG clinical practice update is from April 2024, and corresponds to the practice bulletin on preeclampsia and gestational hypertension. This update provides guidance on the utilization of biomarker immunoassay to aid in risk assessment for preeclampsia (ACOG Clinical Practice

Update, 2024). These risk assessment methods will be expanded upon in the literature reviewed in chapter two.

Long-Term Health Effects

Women who experience a hypertensive pregnancy have a higher risk of later developing chronic hypertension, cardiovascular disease, diabetes, renal dysfunction, dyslipidemia and thromboembolism. The prevalence of cardiovascular risk factors is dependent on the severity of hypertension disorder during pregnancy, and the existence of other complicating risk factors. It is believed that this is because the endothelial dysfunction and pro-inflammatory state persists after pregnancy for several years. Postpartum follow-up and education is essential for these patients in preventing adverse health events in the future. The ACOG suggests a postpartum check-up within 7-10 days for women who experienced hypertensive disorders in pregnancy, and within 72 hours postpartum for those who had severe hypertension. Postpartum visits should prioritize an individual assessment of cardiovascular disease risk, and patient education for lifestyle modifications which can lower their risk, especially if women plan to have any future pregnancies (Tassi, et al., 2023).

Significance to Nursing

Early detection of risk for preeclampsia development is important for proactive management and reducing maternal and fetal mortality. Preeclampsia is known to occur more often in women with type one and two diabetes mellitus or chronic hypertension, and so these patients should be monitored closely (Quan, et al., 2017). Nurses should pay close attention to blood pressure, deep tendon reflexes, urine output and edema. They should also try to ask targeted questions to assess presence of persistent headache which is not attributed to another cause, vision changes and persistent right upper quadrant pain, which are some common signs

indicating preeclampsia. Nurses are also responsible for initiating preventive and safety measures such as bed rail padding, floor mattresses and suction at the bedside for possible seizures in patients who are known to be preeclamptic. Nurses should be aware that seizures may occur in preeclamptic patients without severe features or an elevated blood pressure (Magley, et al., 2024).

Summary

Preeclampsia is a life-threatening pregnancy complication which impacts thousands of women each year. There is emerging evidence that blood-based biomarkers, early risk-assessment model implementation and early routine blood pressure readings may identify the development of preeclampsia before the 20th week gestation which is when symptoms present and the condition advances. Implementation of early gestation risk-assessment would allow healthcare providers to have crucial additional treatment time in order to prevent maternal and fetal mortality, and reduce the incidence of preterm delivery. In the future, evidence-based practice guidelines based on this research will help to streamline higher quality care for complicated pregnancies.

Chapter Two

Chapter two summarizes the current literature related to early risk-assessment of preeclampsia. The search of research based literature was guided by the following PICOT question: In pregnant women (P), how does the utilization of early risk-assessment methods (I) differ from current practice (C) and impact of health outcomes for the maternal and fetal patient (O), during the antepartum period (T)? Primarily, research for early-screening methods was conducted based on the recommendations of the American College of Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE).

The databases used for research included Pubmed Central from the National Library of Medicine and CINAHL Plus with Full Text. The search only included articles published in the last ten years (2014-2024), to ensure that the evidence presented was current. A variety of search filters were used to guide research, such as to include only articles of level I, II and III evidence. The search terms and phrases included the following: “preeclampsia”, “early risk-assessment”, “screening”, “placental ischemia”, “first trimester” and “hypertensive disorders”. The search terms, filters and databases used ultimately guided research to provide articles which were relevant to the proposed PICOT question.

Literature Review Results

The following sections include studies and systematic reviews which met the criteria for this review and address current practices for risk-assessment of preeclampsia development as well as emerging research about potentially more effective assessment methods and interventions based on early-prediction.

Maternal History Risk Factors for Preeclampsia Development

This study is a systematic review and meta analysis of 92 studies which included a total of over 25 million pregnancies (Chaemsaithong et al., 2022). These studies were reviewed to analyze clinical risk factors of preeclampsia development which could be identified before 16 weeks gestation. The two most relevant and statistically significant risk factors were determined to be: history of preeclampsia and chronic hypertension. Other clinical risk factors identified include: nulliparity, maternal age over 35 years old, chronic kidney disease, conception using assisted reproductive technology, a pre-pregnancy body mass index (BMI) over 30kg/m2, and diabetes mellitus (excluding gestational). This study also outlines high-risk factors identified by several different organizations such as ACOG and NICE. ACOG additionally identifies systemic lupus erythematosus, multifetal gestation and antiphospholipid syndrome as high-risk factors. NICE additionally identifies autoimmune disease as a high-risk factor. Moderate-risk factors, according to ACOG, include interpregnancy intervals longer than 10 years, family history of preeclampsia (specifically, the maternal mother or sister), history of a small for gestational age (SGA) or adverse outcome pregnancy and some sociodemographic characteristics such as low socioeconomic status or African-American descent (Chaemsaithong et al., 2022).

In accordance with these risk factors, several organizations have developed guidelines for indications of low-dose Aspirin as a prophylactic therapy in the first trimester for preeclampsia. The most recent guideline from the United States Preventive Services Task Force (USPSTF) is endorsed by ACOG, the Society of Maternal-Fetal Medicine and the American Diabetes Association. This guideline recommends the use of daily Aspirin at 81 mg/d starting at the 12th week gestation until the 28th week for women with one or more high-risk factors or more than one moderate-risk factors, which were outlined in the previous paragraph (Chaemsaithong et al., 2022).

This meta analysis has several strengths, such as a large sample size, which ensures that the research can be generalized to several populations. Additionally, the study took into the account the current recommendations and guidelines of leading organizations in fetal and maternal health, such as ACOG. The authors attempted to minimize bias by critically appraising several screening methods for preeclampsia development in current practice (Chaemsaithong et al., 2022).

Risk Assessment Models

This study is a model-based impact study. The study aimed to compare three risk assessment models for determining the benefits, cost-effectiveness and overall effectiveness in prediction of each (Strijbos et al., 2023). Each model was used to identify women for use of prophylactic Aspirin, and then studied for financial yield and number of preeclampsia cases. The study was conducted through the development of an analytical model which was used to calculate the number of preeclampsia cases using each model compared to no risk assessment. Data used for calculating the model was gathered from published literature and available government reports. All data was based on nulliparous pregnancies. The three models tested were those from the Fetal Medicine Foundation (FMF), National Institute for Care and Excellence (NICE) and the EXPECT model, which is currently being used in the Southern Netherlands. The study predicted that the EXPECT model would yield the highest financial benefit and a higher number of women identified for Aspirin use. Nulliparous women were assessed using one of the three models, and then either tested positive or negative for preeclampsia (PE) risk. Of the positive tests, Aspirin therapy use was set at 50% and then variance rate was set between 30-80%. In comparison with no risk assessment, the NICE method decreased PE cases by 445, FMF decreased cases by 1105 and EXPECT decreased cases by

1019. The total financial benefit relative to no risk assessment was found to be highest for the EXPECT model (Strijbos et al., 2023).

Based on the sensitivity analysis, the FMF and EXPECT models were determined to be comparable, with the NICE model having lower screening effectiveness. The study also addresses the use of a treat-all method with Aspirin, since use during pregnancy is considered safe. However, it is expected that without risk assessment, there will be a generally lower adherence rate due to lower risk awareness. Using the EXPECT model, there was a strong association found between higher absolute risk and higher adherence to Aspirin therapy (Strijbos et al., 2023).

Some of the strengths of this study include a large hypothetical cohort (100,000), an analytical model and data input based on actual government reports. Some of the limitations include the specificity to nulliparous pregnancies, which may mean the findings are not valid for the pregnant population which is multiparous. Additionally, the study does not consider the implementation costs of the three methods, for example, FMF requires the use of a doppler. Lastly, the study utilizes an estimated adherence rate, which may not be entirely accurate in reality (Strijbos et al., 2023).

Preeclampsia Prediction Based off Logistic Regression Analysis

This is a logistic regression study which aimed to investigate the predictive value of a combination of high risk factors in the clinical setting as well as biochemical markers of preeclampsia in pregnant patients. The study sample included 558 pregnant patients within one Obstetric Hospital from June 2015-June 2016. All patients had to meet the diagnostic criteria for preeclampsia. The control group comprised 435 pregnant women from the same time period who had no obstetrical complications. Basic data was collected from each patient with informed

consent which aided to identify high risk clinical factors. This data included: age, body weight, history of hypertension, diabetes, preeclampsia family history, smoking and drinking history, hyperlipidemia, other systemic organ diseases, pregnancy complications and recorded vitals at the time of care (Quan, et al., 2017). Additionally, each patient had a 2ml peripheral blood draw at gestational age of 10-14 weeks. Biochemical detection was done using enzyme linked immunosorbent assay (ELISA) which detects levels of pregnancy associated plasma protein-A, placental growth factor, fetal hemoglobin, D-dimer, CRP, IL-6 and TNF-alpha (Quan, et al., 2017).

Thirteen variable risk factors were analyzed through multivariate logistic regression which ultimately revealed five high-risk factors related to preeclampsia development. These factors are as follows: advanced maternal age, history of hypertension, high blood lipids, history of diabetes mellitus and BMI. The predictive value of measured biochemical index levels was analyzed utilizing the receiver operating characteristic (ROC) curve. Results revealed that TNF-alpha, plasma protein-A and fetal hemoglobin indeed have predictive values for preeclampsia. Then the ROC curve analysis was used to investigate which combination of risk factors and biochemical indexes could most improve the predictive power of preeclampsia. The highest specificity (90.70%) and sensitivity (78.54%) combination was BMI combined with history of hypertension, TNF-alpha and plasma protein-A (Quan, et al., 2017).

A particular strength of this study is the investigation of combined clinical factors and laboratory markers, rather than only looking at predictive measures of biochemical factors as previous studies have done. The study also had an adequately sized sample (558 participants) and a control group being analyzed during the same period. One weakness of the study is that all

participants were enrolled from one hospital, which could imply that certain demographics that particular hospital does not serve as frequently were not fully represented.

Use of Blood Biomarkers for Prediction of Preeclampsia Onset

This systematic review and meta-analysis aims to determine blood biomarkers which are associated with preeclampsia development, particularly those which could predict the syndrome during early pregnancy. Prospective studies included measured blood biomarkers to predict or diagnose preeclampsia utilizing 1000 or more participants. Blood biomarker data was considered from first to third trimester, but excluded during labor. Identifying a blood biomarker which could predict the onset of preeclampsia in early pregnancy and is reliable, inexpensive and non-invasive could widely reduce maternal and fetal complications associated with the disease. In current practice, no biomarker has been identified. Two biomarkers which are utilized according to NICE guidelines, Placental Growth Factor (P1GF) and sFlt-1, are used in combination during the third trimester (but before 37 weeks) to rule out preeclampsia diagnosis when suspected. P1GF specifically was measured for predictive value utilizing random effect meta-analysis models (Danielli, et al., 2022).

A total of 18,170 pregnant women were considered within this review, and 7295 of them had gestational hypertension or preeclampsia. Seven of the 43 studies were considered international. Serum was the component of blood most frequently analyzed across studies. Most of the studies analyzed blood which was drawn between 10-14 weeks gestation, during the first antenatal visit. A total of 62 biomarkers were included in this review (Danielli, et al., 2022).

Placental Growth Factor (P1GF) was utilized in nineteen studies as a measured biomarker in both healthy and preeclamptic pregnancies. P1GF measurements, when provided, trended higher in the healthy pregnancies compared to the pre-eclamptic ones. The mean differences

between P1GF in comparing healthy and preeclamptic pregnancies appears to increase as gestational time goes on (11.01 in early pregnancy, up to 361.30 after 26 weeks gestation). While results among studies also highlight consistency among biomarkers such as PAPP-A, leptin, sEng and hemoglobin, outcomes most strongly suggest P1GF as a diagnostic tool for pre-eclampsia development in the third trimester. However, the predictive value of P1GF in early pregnancy is not high enough for making an early diagnosis. P1GF is a proangiogenic molecule which plays a large role during 26-20 weeks gestation. P1GF induces systemic vasodilation within the placental bed which transforms placental vessels from being high-resistance to low-resistance. Therefore, low levels of this molecule in late pregnancy would result in placental hypoperfusion, which would predispose the patient to preeclampsia development. Further studies will be necessary to understand the role of P1GF as a predictor during early pregnancy (Danielli, et al., 2022).

The main strength of this review is that researchers utilized multiple databases and comprehensive search strategy for selection of published studies. Publication bias and study quality was assessed as well to ensure that included studies were high quality. While meta-analysis was performed for P1GF, it was not performed for the other various biomarkers since there was not enough homogeneous data available. The review also does not include biomarkers from saliva, urinary or ultrasound molecules. This review also includes a large variety of study methods and designs, so the effect of confounding factors could not be fully analyzed.

Low-Dose Aspirin During Pregnancy

This study published in the New England Journal of Medicine aims to test the hypothesis that aspirin at a dose of 150mg per day would result in decreased incidence of preterm

preeclampsia compared to a placebo control group. Preterm preeclampsia specifically describes when the preeclamptic condition leads to unexpected preterm delivery (before 37 weeks gestation). This is a double-blind, placebo-controlled trial where singleton pregnancy women who were at a high risk for preeclampsia took either a daily placebo or 150 mg of aspirin from the 11th-14th week of gestation until the 36th week gestation. The trial was conducted among thirteen maternity hospitals. Each patient received a screening for preeclampsia which included maternal factors, mean arterial pressure, placental growth factor and pregnancy associated plasma protein A. These screenings occurred at prenatal visits between 11 weeks 0 days and 13 weeks 6 days gestation. Inclusion criteria for the study included the following: 18 years or older, singleton pregnancy, live fetus at the time of preeclampsia screening, and high risk (>1 in 100) for preterm preeclampsia (Rolnik, et al., 2017).

The primary outcome being measured within this study was delivery with preeclampsia before 37 weeks gestation. The hypothesis was that the low-dose aspirin group would have rates of preterm preeclampsia development 50% lower than the placebo group. The sample included 1776 women in the trial after the screening was completed and inclusion criteria were assessed, and then 152 of those women withdrew consent and four participants did not follow-up throughout the trial. Preterm preeclampsia occurred in 1.6% of the aspirin group and 4.3% of the placebo group. At least one serious adverse event occurred in 1.6% of the aspirin group and in 25.9% of the placebo group. Seventy-nine percent of participants had good rated adherence to treatment, and 14.9% had moderately rated adherence. These results demonstrate a significantly lower incidence of preterm preeclampsia in women who take low-dose aspirin compared to a placebo control (Rolnik, et al., 2017).

Some of the strengths of this study are that it has a large sample size, was double-blind, and identified participants using a combined screening of maternal characteristics and biomarkers. Some potential weaknesses are that some participants had a low adherence rate to their medication regimen, and that the group receiving aspirin each took 150mg, which could potentially be too low or too high of a dose for achieving maximum efficacy.

Summary

The presented literature review and analysis highlights current knowledge related to risk factors associated with preeclampsia development as well as potential interventions for earlier detection and treatment of the condition. Research has identified that specific clinical risk factors exist which may predispose pregnant women to the development of preeclampsia. These include history of preeclampsia and chronic hypertension, nulliparity, advanced maternal age, chronic kidney disease, conception using assisted reproductive technology, a pre-pregnancy body mass index (BMI) over 30kg/m2, and diabetes mellitus (excluding gestational). Women who possess these risk factors are monitored more closely for clinical changes which indicate preeclamptic symptoms or manifestations. The review also addresses some of the early risk-assessment models being utilized in practice, which identify women who are at a higher risk for developing preeclampsia so that they can be started on Aspirin prophylaxis. It is important to highlight that while Aspirin can be used as a ‘treat-all’ method, adherence to the therapy is stronger among patients who know they have been identified as high-risk. The logistic regression analysis study highlights combined factors women may possess which predispose them to preeclamptic development. P1GF is a promising blood biomarker for diagnosing preeclampsia in the third trimester, but further research is necessary to identify its role in early pregnancy. Continued research on blood biomarkers could pave the way for eventually having the tools to predict

preeclampsia in early pregnancy. This would allow providers to intervene earlier during gestation, and prophylactic measures such as aspirin therapy could reduce the incidence of serious adverse outcomes associated with preeclampsia.

Since this research is relevant to one of the most severe obstetrical syndromes, there are various clinical implications. Nurses who work with this population should continue to follow emerging research about characteristics of patients which alert them to being at a higher-risk for preeclampsia. Additionally, nurses are responsible for helping promote adherence to early prenatal care, screenings, and prophylactic therapies a patient may be prescribed. All pregnant patients, regardless of their risk level, should be educated about preeclampsia and the clinical symptoms they may experience which they should seek medical attention for.

Chapter Three

This chapter provides evidence-based practice recommendations (Table 1) for early-risk assessment methods and nursing management of preeclampsia in pregnant patients. Preeclampsia is a multi-system disease which leaves patients and their newborns susceptible to fatal adverse outcomes. Nurses are involved in the screening and assessment process of patients which may reveal a woman's risk for developing preeclampsia. Furthermore, preeclamptic or high risk pregnancies require specific nursing management, and staying current with evidenced-based practice will enable nurses to ensure the safest possible care for these patients.

Table 1

Best Practice Recommendations for Early-Risk Assessment and Management of Preeclampsia

Recommendation	*Rationale*	*Reference*	*Level of Evidence*
Assess for the following clinical risk factors during first prenatal care appointment (4 weeks gestation) to identify patients at moderate to high risk for developing preeclampsia: history of preeclampsia, chronic hypertension, African American ethnicity, advanced maternal age, diabetes mellitus, chronic kidney disease, conception using assisted reproductive technology, and/or pre-pregnancy body mass index (BMI) over 30kg/m2.	History of preeclampsia and chronic hypertension are the most statistically prevalent risk factors for preeclampsia. Several existing clinical and demographic factors can increase a patient's risk for developing preeclampsia in pregnancy. These clinical risk factors are the earliest identifiable measures of a patient's risk level.	Chaemsaithong, P., Sahota, D. S., & Poon, L. C. (2022). First trimester preeclampsia screening and prediction. *American journal of obstetrics and gynecology*, *226*(2S), S1071–S1097.e2. https://doi.org/10.1016/j.ajog.2020.07.020	Level I
Utilize the EXPECT risk assessment tool	The EXPECT model has high sensitivity, low	Strijbos, L. T. M., Hendrix, M. L. E., Al-Nasiry, S., Smits, L. J. M., & Scheepers, H. C. J. (2023). Which	Level III

for identifying women who need to be treated with Aspirin according to PE risk. EXPECT is a web-based predictive model based on maternal characteristics.	implementation costs, does not require doppler technology, and was found to identify a higher number of women eligible to be treated with Aspirin.	first-trimester risk assessment method for preeclampsia is most suitable? A model based impact study. *American Journal of Obstetrics & Gynecology MFM*, *5*(7). https://doi.org/10.1016/j.ajogmf.2023.100974	
Combine analysis of clinical risk factors such as hypertension and high BMI with biochemical index levels (TNF-alpha and plasma protein-A) for early-prediction assessment of PE between 10-14 weeks gestation.	BMI combined with history of hypertension, TNF-alpha and plasma protein-A is shown to have high specificity and sensitivity levels for PE prediction.	Quan, L.-M., Xu, Q.-L., Zhang, G.-Q., Wu, L.-L. and Xu, H. (2018). An analysis of the risk factors of preeclampsia and prediction based on combined biochemical indexes. The Kaohsiung Journal of Medical Sciences, 34: 109-112. https://doi.org/10.1016/j.kjms.2017.10.001	Level III
Anticipate measurement of Placental Growth Factor blood marker levels in the third trimester of gestation (after 28 weeks gestation) with the aim of ruling out a diagnosis of preeclampsia.	Low levels of the Placental Growth Factor molecule in late pregnancy predisposes women to development of PE.	Danielli, M., Thomas, R. C., Gillies, C. L., Hu, J., Khunti, K., & Tan, B. K. (2022). Blood biomarkers to predict the onset of pre-eclampsia: A systematic review and meta-analysis. *Heliyon*, *8*(11), e11226. https://doi.org/10.1016/j.heliyon.2022.e11226	Level I

Anticipate the prescription of low-dose Aspirin during the 11th-36th week gestation for women at high-risk for PE development and provide patient education.	There is a significantly lower incidence of preterm preeclampsia in women who take low-dose Aspirin during gestation. Nurses are responsible for ensuring patients have proper education on their medication.	Rolnik, D. L., Wright, D., Poon, L. C., O'Gorman, N., Syngelaki, A., de Paco Matallana, C., Akolekar, R., Cicero, S., Janga, D., Singh, M., Molina, F. S., Persico, N., Jani, J. C., Plasencia, W., Papaioannou, G., Tenenbaum-Gavish, K., Meiri, H., Gizurarson, S., Maclagan, K., & Nicolaides, K. H. (2017). Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *The New England journal of medicine*, *377*(7), 613–622. https://doi.org/10.1056/NEJMoa1704559	Level II

Summary

The first key to preventing maternal and neonatal morbidity and mortality associated with combating preeclampsia is to be able to identify a woman's susceptibility to the condition before she displays syndrome, and intervene to prevent it. Current evidence provides indications of existing clinical risk factors pregnant patients may present with in their early prenatal care appointments. A priority within these early appointments should be screening women for these factors in order to assess their risk level for preeclampsia development. Women who have a history of preeclampsia or are diagnosed with chronic hypertension are at a statistically significant risk of developing preeclampsia during or after their pregnancy (Chaemsaithong, et al., 2022). This identification of high-risk patients allows for providers to plan for more frequent prenatal care visits, blood pressure monitoring and potential prophylactic interventions such as low-dose aspirin therapy.

Several models exist for calculating the relative risk of a patient's susceptibility for preeclampsia development. The FMF and EXPECT models have comparable risk-assessment accuracy. However, choosing risk-assessment methods which are financially feasible is important in ensuring that patients have equal access to reliable healthcare regardless of their economic status. For this reason, the EXPECT model is the superior choice for preeclampsia risk assessment, since it has the highest total financial benefit relative to no risk assessment (Strijbos, et al, 2023). The benefit of using a standardized risk-assessment model across the entire population is that over time, it can help reveal more correlations between patients who develop the condition, and that data is valuable for developing and updating standard guidelines for identification and treatment of the condition.

The future of preeclampsia research lies within the study of biochemical index markers which are altered in the development of preeclampsia. In addition to the known clinical risk factors of BMI and history of hypertension, TNF-alpha and plasma protein-A show high sensitivity and specificity for early risk factors (Quan, et al., 2018). Existing evidence of the role of Placental Growth Factor molecule aids in excluding preeclampsia diagnosis in the third trimester. There is potential that this molecule could also play a beneficial role in early-risk assessment of preeclampsia, before symptoms begin to develop. Further research is also needed to investigate the specifics of other molecules believed to play a role in preeclampsia (Danielli, et al., 2022).

Emerging tools for early-risk assessment of preeclampsia calls for implementation of prophylaxis measures for patients identified to be high risk. One of the most prevalent interventions identified among the studies of the literature review is low-dose Aspirin therapy. Recent studies have utilized aspirin for women at high risk at a dosage of 81 mg or 150 mg. As soon as women can be identified as high-risk after the 11th week of gestation, they should begin taking aspirin daily until the 36th week of pregnancy. Women who adhere to aspirin therapy are shown to have a lower incidence of preterm preeclampsia compared to those who do not (Rolnik, et al., 2017).

Chapter Four

The recommendations proposed in chapter three were synthesized from evidence presented in the research literature which was reviewed. Chapter four will address a proposed implementation and evaluation of these recommendations within clinical practice. The model used for implementation and evaluation is the Plan-Do-Study-Act (PDSA) cycle recommended by the Institute of Healthcare Improvement. PDSA is referred to as a cycle because several cycles of the four-step model will likely be necessary to result in real change (Institute for Healthcare Improvement, 2017).

The PDSA cycle consists of four steps. The first step is Plan, which includes planning the test or observation to be implemented and a plan for collecting the data for evaluation. Next, execution of the plan, or 'Do', should carry out the test, document outcomes and observations and begin the analysis of data. Step three is 'Study' which includes completing data analysis, and discussion of the result. Finally, the 'Act' step is about refining the change based on what was learned, and planning for the next cycle. Ultimately, the PDSA cycle is useful for implementing a change into an environment through action-oriented learning (Institute for Healthcare Improvement, 2017).

Plan

The objective of this PDSA cycle is to test the implementation of evidence-based practice recommendations for early-risk assessment of preeclampsia. Additionally, recommendations address utilization of Aspirin prophylactic therapy starting at the 11th week gestation. The plan is to implement and evaluate an algorithm within the Electronic Health Record system at an obstetrics clinic or antepartum unit. This algorithm would be based on the EXPECT model, since research shows that model to be effective and cost realistic.

This tool would be developed in collaboration with staff from the IT department. The algorithm would be introduced to providers and nurses through clinical in-services. Then, an in-depth training would be required of every staff member that would be involved in collecting, entering and analyzing the data. These trainings would be taught by a clinical nurse educator who is an expert in this area, alongside a member of IT who helped in creating the algorithm.

The EHR risk assessment algorithm for preeclampsia would be paired with a protocol for risk assessments in the first prenatal care appointment. The nurse would collect data for the electronic health record by asking the patients questions such as “do you have a history of preeclampsia or chronic hypertension?” and objective findings, such as their current blood pressure. The nurse would then input these findings in the patient’s EHR, and the algorithm would automatically trigger to assess the patient’s risk level for pre-eclampsia. In subsequent prenatal appointments, if the patient were to have no risk of preeclampsia prior, but develops an elevated blood pressure, proteinuria, weight gain and/or edema, or additional symptoms, the machine-learning algorithm would be activated. The algorithm activation will prompt the primary nurse to notify the provider and subsequently begin established preeclampsia protocol pathways for the facility. This may include additional lab testings, more frequent prenatal visits, initiating daily blood pressure checks at home, and having patients record their daily weight.

Predictions for the implementation of this algorithm would include the following for the patient population of the specific clinic or unit: decreased preeclampsia rates, decreased incidence of preterm deliveries in pregnancies complicated by preeclampsia, decreased maternal and fetal mortality associated with preeclampsia, decreased incidence of eclamptic seizures, improved workflow for nurses in assessing for and recognizing signs and symptoms of preeclampsia, and increased utilization of Aspirin prophylactic therapy.

Do

The next phase of the implementation cycle would involve the introduction of the algorithm into the clinical setting. A date for technology to go live should be provided to all of the staff, and training should be completed prior to the release. As the staff asks questions and provides feedback during the training, the algorithm may be modified to become more user friendly, and a guide should be uploaded to the hospital educational resource database. A nurse who acted in teaching in-services and training would act as a lead for questions about collecting and inputting the data. Once the patient's risk level is determined by the algorithm, there will be a flag that appears within the chart if the patient has moderate or severe risk for developing pre-eclampsia. This flag in the chart would be initiated if patient data indicate risk for or current development of preeclampsia throughout pregnancy. The patient's risk level would prompt a series of recommendations for labs to be drawn, patient education, prophylactic interventions and follow-up appointments. The primary nurse would also be responsible for notifying the physician of risk level alerts.

Study

The third phase of the PDSA cycle involves data analysis of the implementation. This data collection will be completed through a thorough audit of the electronic health record and interviewing nurses on their experience using the algorithm. The analysis should go on to describe how many people were identified as being 'at risk' by the algorithm and how often the algorithm is being utilized and completed during a first prenatal visit. Additionally, accuracy can be studied by comparing how many of the identified patients at risk ended up developing preeclampsia. Additionally, electronic health record data can be analyzed for patient outcomes, frequency of follow-up visits, and demographic factors among patients with risk for or

established preeclampsia. Furthermore, comparison of the patients who were identified to benefit from Aspirin therapy, and those who actually started it should be completed, as well as how many of the patients who underwent Aspirin therapy developed preeclampsia, or experienced severe preeclampsia.

Act

The final stage of the PDSA cycle has emphasis on the evaluation of the intervention which has been tested. The data collected from the EHR audit and nurse interviews would determine if the algorithm is effective in predicting the development of preeclampsia and initiating further testing and assessment. Evaluation should also measure how effectively the EHR algorithm identified patients for Aspirin therapy and closer monitoring and follow-up. Additionally, this data would go on to produce results about the ease of using the algorithm as well as the adherence of nurses and providers to following the algorithm. The benefit of testing the algorithm in an obstetrics clinic is that they will be able to collect data from those same patients later on in pregnancy and determine specific outcomes based on the incidence of pregnancy complications such as delivering before 37 weeks gestation. Ultimately, this evaluation will determine if the algorithm should continue to be implemented into practice and expanded for usage in multiple obstetrics clinics and is beneficial for leading to better pregnancy outcomes.

Summary

The recognition of risk factors for preeclampsia at the earliest prenatal appointments could have profound effects on the outcomes of certain high-risk pregnancies. The PDSA cycle is highly effective for implementation and evaluation of this evidenced-based intervention. Although the proposed algorithm will provide streamlined electronic reminders for further

evaluation of a patient's condition, it is still important that nurses stay educated on the updated guidelines for preeclamptic assessment and management. Overall, comprehensive and early assessments of pregnant patients can ensure that more patients are identified for preeclampsia risk before symptoms develop, and thus can be evaluated and managed more closely with the aim of preventing adverse pregnancy outcomes. Ultimately, nurses should utilize emerging tools for providing more effective care, but must also be knowledgeable about the pathophysiology, risk factors, symptoms and management of preeclampsia.

References

ACOG Clinical Practice Update: Biomarker Prediction of Preeclampsia With Severe Features. (2024). *Obstetrics & Gynecology*, *143*(6), e153-e154. https://doi.org/10.1097/aog.0000000000005576

ACOG (2024) Acute hypertension in pregnancy & postpartum algorithm. *The American College of Obstetricians and Gynecologists.* https://www.acog.org/-/media/project/acog/acogorg/files/pdfs/programs/ob-emergencies/hypertension_algorithm.pdf

ACOG (n.d.) Gestational hypertension and preeclampsia. *The American College of Obstetricians and Gynecologists.* https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2020/06/gestational-hypertension-and-preeclampsia

Chaemsaithong, P., Sahota, D. S., & Poon, L. C. (2022). First trimester preeclampsia screening and prediction. *American Journal of Obstetrics and Gynecology*, *226*(2S), S1071–S1097.e2. https://doi.org/10.1016/j.ajog.2020.07.020

Decaj, R., Izetbegovic, S., Stojkanovic, G., & Dreshaj, S. (2016). Elevated liver enzymes in cases of Preeclampsia and intrauterine growth restriction. *Medical Archives (Sarajevo, Bosnia and Herzegovina)*, *70*(1), 44–47. https://doi.org/10.5455/medarh.2016.70.44-47

Danielli, M., Thomas, R. C., Gillies, C. L., Hu, J., Khunti, K., & Tan, B. K. (2022). Blood biomarkers to predict the onset of pre-eclampsia: A systematic review and meta-analysis. *Heliyon*, *8*(11), e11226. https://doi.org/10.1016/j.heliyon.2022.e11226

Institute for Healthcare Improvement (2017). *PDSA Worksheet.*

http://www.ihi.org/resources/Pages/Tools/PlanDoStudyActWorksheet.aspx?PostAuthRed=/resources/_layouts/download.aspx?SourceURL=/resources/Knowledge%20Center%20Assets/Tools%20-%20Plan-Do-Study-ActPDSAWorksheet_2f9145ee-2203-49c6-be19-7dcda98b31c5/QIToolkit_PDSAWorksheet.pdf

Jung, E., Romero, R., Yeo, L., Gomez-Lopez, N., Chaemsaithong, P., Jaovisidha, A., Gotsch, F., & Erez, O. (2022). The etiology of preeclampsia. *American Journal of Obstetrics and Gynecology*, *226* (2, Supplement), S844-S866. https://doi.org/https://doi.org/10.1016/j.ajog.2021.11.1356

Khalid F, Mahendraker N, Tonismae T. (Updated 2023) HELLP syndrome. *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing*; https://www.ncbi.nlm.nih.gov/books/NBK560615/

Khan, B., Allah Yar, R., Khakwani, A. K., Karim, S., & Arslan Ali, H. (2022). Preeclampsia incidence and its maternal and neonatal outcomes with associated risk factors. *Cureus*, *14*(11), e31143. https://doi.org/10.7759/cureus.31143

Magley M, Hinson M, Haddad L (Updated 2024). Eclampsia (nursing). *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.* https://www.ncbi.nlm.nih.gov/books/NBK570548/

Quan, L.-M., Xu, Q.-L., Zhang, G.-Q., Wu, L.-L. and Xu, H. (2018). An analysis of the risk factors of preeclampsia and prediction based on combined biochemical indexes. The Kaohsiung Journal of Medical Sciences, 34: 109-112. https://doi.org/10.1016/j.kjms.2017.10.001

Rezk, M. , Grasegger, L. , Brandstetter, N. , Pol-Edern, L. , Stelzl, P. , Oppelt, P. & Arbeithuber, B. (2022). Biomarker screening in preeclampsia: an RNA-sequencing approach based on data from multiple studies. *Journal of Hypertension, 40* (10), 2022-2036. doi: 10.1097/HJH.0000000000003226.

Rolnik, D. L., Wright, D., Poon, L. C., O'Gorman, N., Syngelaki, A., de Paco Matallana, C., Akolekar, R., Cicero, S., Janga, D., Singh, M., Molina, F. S., Persico, N., Jani, J. C., Plasencia, W., Papaioannou, G., Tenenbaum-Gavish, K., Meiri, H., Gizurarson, S., Maclagan, K., & Nicolaides, K. H. (2017). Aspirin versus placebo in pregnancies at high risk for preterm Preeclampsia. *The New England Journal of Medicine*, *377*(7), 613–622. https://doi.org/10.1056/NEJMoa1704559

Sharma, D. D., Chandresh, N. R., Javed, A., Girgis, P., Zeeshan, M., Fatima, S. S., Arab, T. T., Gopidasan, S., Daddala, V. C., Vaghasiya, K. V., Soofia, A., & Mylavarapu, M. (2024). The management of Preeclampsia: A comprehensive review of current practices and future directions. *Cureus*, *16*(1), e51512. https://doi.org/10.7759/cureus.51512

Strijbos, L. T. M., Hendrix, M. L. E., Al-Nasiry, S., Smits, L. J. M., & Scheepers, H. C. J. (2023). Which first-trimester risk assessment method for preeclampsia is most suitable? A model based impact study. *American Journal of Obstetrics & Gynecology MFM*, *5*(7). https://doi.org/10.1016/j.ajogmf.2023.100974

Tassi, A., Sala, A., Mazzera, I., Restaino, S., Vizzielli, G., Driul, L. (2023) Long-term outcomes of patients with preeclampsia, a review of the literature. *Hypertension in Pregnancy,* 42:1, DOI: 10.1080/10641955.2023.2217448