2013

Prediction, prevention and management of preeclampsia

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

PREDICTION, PREVENTION AND MANAGEMENT OF PREECLAMPSIA

by

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Submitted in partial fulfillment of the

requirements for the degree of

Master of Arts

2013

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DEDICATION

This work is dedicated to my mother Ghostly Brutus Laguerre who is a Registered Nurse in the Labor and Delivery Unit at Boston Medical Center. Her tirelessness in caring for her patients, her family, and her Sunday School students is such a great inspiration for me. Sharing stories about her days on the floor sparked my interest in obstetrics and gynecology, leading to the focus of this work. Thanks for your support throughout the years, and even throughout this work. I love you, Mommy.

PREDICTION, PREVENTION AND MANAGEMENT OF PREECLAMPSIA

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ABSTRACT

Background: Pregnancy-related health complications can pose imminent threats to the health of both mother and fetus. Gestational hypertension accompanied by proteinuria after 20 weeks' gestation characterize the condition known as preeclampsia, which puts mothers and their fetuses at risk for a number of adverse outcomes.

Significance: From 1987 to 2004, the incidence of preeclampsia rose by 25%. Adverse outcomes in the mother-to-be include preterm delivery, acute renal failure and maternal death. As a result of preeclampsia, the fetus can suffer intrauterine growth restriction, preterm birth and low birth weight.

Aim: Researchers have explored a number of strategies to predict, prevent and manage preeclampsia. This work will explore the various strategies employed and documented in the literature.

Conclusion: Treatments that may be beneficial for the mother (delivering the infant), may not necessarily be beneficial for the fetus (may have a young gestational age) and vice versa. Therefore, determining the appropriate method of handling each case of preeclampsia is critical to the work of the obstetrician, and should be decided from evidence-based treatments and management.

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LIST OF ABBREVIATIONS

BP	blood pressure
GA	gestational age
GH	gestational hypertension
HT	hypertension
IUGR	intrauterine growth restriction
LDA	low-dose aspirin
LVDD	left ventricular diastolic dysfunction
$MgSO_4^{2-}$	magnesium sulfate
NICU	neonatal intensive care unit
PE	preeclampsia
PIH	pregnancy-induced hypertension
PlGF	placental growth factor
S/D ratio	ratio of systolic blood pressure over diastolic blood pressure
SGA	small for gestational age
sFlt-1	soluble Fms-like tyrosine kinase-1
UAPI	uterine artery pulsatility index
vitCE	combined vitamin C and E supplementation

GLOSSARY

Active management of labor – the constant monitoring and technical control of labor to limit its duration.

Amniotic fluid – the fluid surrounding the fetus in the uterus.

Angiogenesis – the production of blood vessels.

Birth weight – weight of neonate at birth in grams.

Chronic hypertension – elevated blood pressure (greater than 140/90mmHg) before week 20 of pregnancy that can persist beyond 6 weeks after the birth of the neonate.

Eclampsia – seizures occurring in pregnancy, accompanied by symptoms of preeclampsia, i.e. hypertension and proteinuria.

Embryo – from conception to 8 weeks' gestation.

Fetus – the developing child in the uterus from the end of the embryonic state at about the twelfth week of pregnancy, until birth.

Gestation – the length of time between conception and delivery.

Gestational age – age of developing fetus counting from conception (usually measured in weeks).

Gestational hypertension – systolic BP of 140 mmHg or higher or diastolic BP of 90 mmHg or higher (or both) occurring de novo after 20 weeks' gestation, and disappearing soon after birth.

Induction – the process of artificially starting labor and keeping it going; also referred to as hormone-accelerated labor.

Intrauterine growth restriction (IUGR) – birthweight less than the 10th percentile.

Low birthweight baby – a baby who weighs below 5 ½ lbs (2500g) immediately after birth.

Neonatal – of or relating to the first 28 days of life (first 4 weeks after birth).

Oligohydramnios – low urine output.

Perinatal – the period from the 24th week of gestation to one week following delivery.

Preeclampsia – gestational hypertension combined with proteinuria detected after 20 weeks of gestation; pregnancy-induced hypertension and proteinuria.

Placental abruption – (i.e. abruption placentae) premature separation of the placenta (the organ that nourishes the fetus) from the uterine wall prior to delivery that can lead to IUGR and hemorrhage.

Prenatal – before delivery.

Preterm birth – birth before 37 wk of gestation.

Prophylaxis – a measure taken to prevent disease by specified means or against a specified disease.

Proteinuria – 300 mg of protein or more in a 24-h urine specimen or a positive reaction (1) on a midstream urine specimen; or 30mg/mmol spot urine protein/creatinine ratio.

Soluble fms-like tyrosine kinase-1 – a tyrosine kinase protein that disables proteins that cause blood vessel growth.

Term – completing a full-length pregnancy; about 38 to 42 weeks from the last menstrual period, i.e. 37 completed weeks of gestation.

I. INTRODUCTION

A. Significance

Hypertension is the 3rd leading cause of pregnancy-related deaths in the United States, after hemorrhage and embolism (Koonin et al., 1997; MacKay et al., 2001). Of the 500,000 maternal deaths that occur worldwide each year, it is estimated that between 10-15% are caused by hypertensive disorders of pregnancy (Khan el al., 2006; Leslie et al., 2011). Approximately 5-10% of all pregnant women will develop some form of hypertension (MacKay et al., 2001). Essential hypertension, which develops without apparent cause, accounts for about 90% of these cases, while secondary causes, such as kidney diseases and endocrine and connective tissue disorders, are responsible for the rest (Koren, 2004). Pregnancy complications related to hypertension account for 15% of antenatal hospitalizations (MacKay et al., 2001).

Mothers who develop hypertension for the first time during their pregnancy are at greater risk for acute renal failure and cardiovascular complications among other problems. This de novo gestational hypertension (GH), when accompanied by proteinuria, is referred to as preeclampsia (PE). Preeclampsia is a complex clinical syndrome characterized by elevated blood pressure, proteinuria and occasionally pathologic edema all that appear after 20 weeks' gestation, which is during the 2nd trimester. Preeclampsia develops in 6-8% of pregnancies, 70% of which are first-time pregnancies (Thepregnancyzone.com, 2012). Preeclampsia

can be either mild or severe, or can develop into full-blown eclampsia for which seizures are a common symptom (Langenveld et al., 2011).

Preeclampsia can lead to adverse outcomes in the fetus including low birthweight, premature birth, and still birth. In a population-level study of the secular trends of preeclampsia, eclampsia and gestational hypertension, it was found that from 1987 to 2004, the rate of preeclampsia rose by 25% (**FIGURE 1**) (Wallis et al., 2008). This could partly be due to the rise in the number of older mothers and the number of multiple births in which preeclampsia occurs more frequently (Sutton, 2009). However, the overall proportion of pregnancies with GHduring the study period increased significantly (184%), though this can be partly attributed to the change in definition over the years (Wallis et al., 2008). Rates of eclampsia showed a non-significant decrease of 22%.

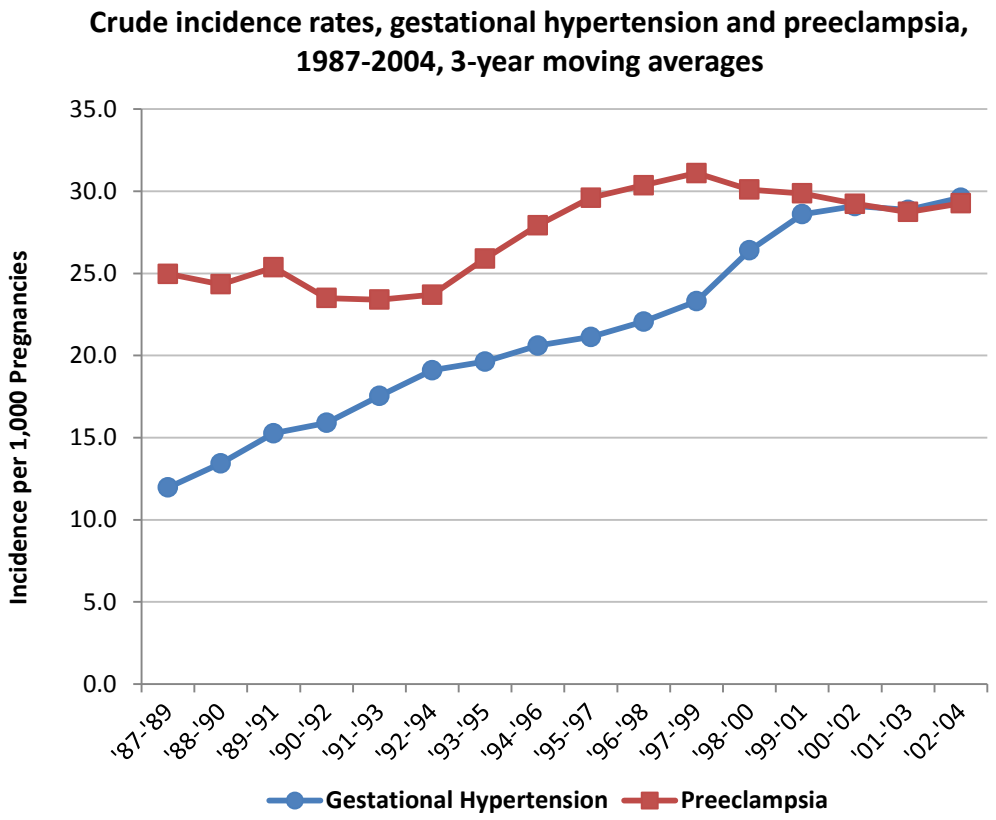

FIGURE 1 | Age-adjusted incidence per 1,000 deliveries for women with gestational hypertension ($P < 0.0001$) or preeclampsia ($P = 0.009$) with 3-year moving averages, 1987–2004. Refer to Appendix A for a table with the weighted number of cases and crude incidence rates accompanying this figure. Figure amended from Wallis et al., 2008.

B. Diagnosis

In order for a diagnosis of preeclampsia to be made, both hypertension and proteinuria must be present. Edema was once included in the criteria for diagnosing PE; however, due to the difficulty in objectively quantifying edema, it is no longer a required element for diagnosis of PE. Occurring at or after 20 weeks' gestation, preeclampsia is defined as a systolic pressure of greater than or equal to 140mmHg or diastolic pressure of greater than or equal to 90mmHg, or both, accompanied by proteinuria in previously normotensive women (**TABLE 1**). Regular urine and blood pressure readings are necessary to diagnose and treat this problem in its early stages. During monthly prenatal visits, taking urine samples is a routine procedure (North et al., 2011). Three approaches are currently used in the clinic to determine excessive excretion of protein: the qualitative dipstick, the quantitative 24h urine collection, and the protein/creatinine or albumin/creatinine ratios on a single voided urine (Lindheimer and Kanter, 2010).

TABLE 1. Essentials of Diagnosis of Moderate to Severe Preeclampsia.

		Measurements	
Feature	**Normal**	**Preeclampsia**	**Severe PE**
SBP	110-120mmHg	≥140mmHg*	≥160mmHg*
DBP	70-80mmHg	≥90mmHg*	≥110mmHg*
Proteinuria			
24h Urine*	<300mg	≥ 0.3-5g	≥5g
Dipstick*	1+	2+	4+

*On at least two occasions 4h to 6h apart, developing in previously normotensive women with proteinuria of 300 mg or more in 24 h, or two readings of at least 2+ on dipstick analysis of midstream or catheter urine specimens if 24-h urine collection was not available.

Sources: McPhee and Papadakis, 2011; Yu et al., 2011; North et al., 1999.

1. Timing of Onset of Disease

The timing in which a pregnant woman presents with preeclampsia is influenced by the various biochemical and clinical features that contribute to the development of the disease (Meler et al., 2010). Early-onset PE (occurring between 20^{+0} and 33^{+6*} weeks' gestation) is associated with placental insufficiency due to defective trophoblastic invasion. The late-onset form (occurring at or after 34^{+0} weeks) is more prevalent. Greater than seventy percent (70%) of preterm infants are born between 34^{+0} and 37^{+0} weeks gestation, thus late preterm infants account for the vast majority of preterm births

* Base number refers to the number of weeks' gestation, whereas superscript refers to the number of days' gestation. For example: 21^{+2} refers to 21 weeks' and 2 days' gestation.

(Langenveld et al., 2011). Mothers can also develop preeclampsia late postpartum, anywhere between 48 hours and 6 weeks after delivery (McPhee and Papadakis, 2011).

C. Etiology

Preeclampsia is a multisystem disorder with multiple factors contributing to its development. Although there are several postulations for what causes preeclampsia, there is still controversy on what actually causes it. The pathophysiology of preeclampsia involves defective trophoblastic invasion of the maternal spiral arteries during early gestation (Yu et al., 2011). The proteinuria reflects kidney malfunction and damage. The middle panel of **FIGURE 2** illustrates the inadequate penetration into the myometrium; although this can also be showing what could be the initial stages of normal invasion. These events affect the uterine environment and thus have effects on fetal development and outcome.

Immunological and inflammatory processes are suspected to be involved in the development of PE, specifically as a result of defective trophoblastic invasion of the myometrium (Hofmeyr et al., 2011). In normal receptive endometrium, the maternal immune marker pentraxin-3 is known to be present; however, expression is abnormally high in as early as the first trimester in women who develop preeclampsia. This supports the hypothesis that there is an

excessive maternal inflammatory response to pregnancy in the cause of pre-eclampsia (Hofmeyr et al., 2011).

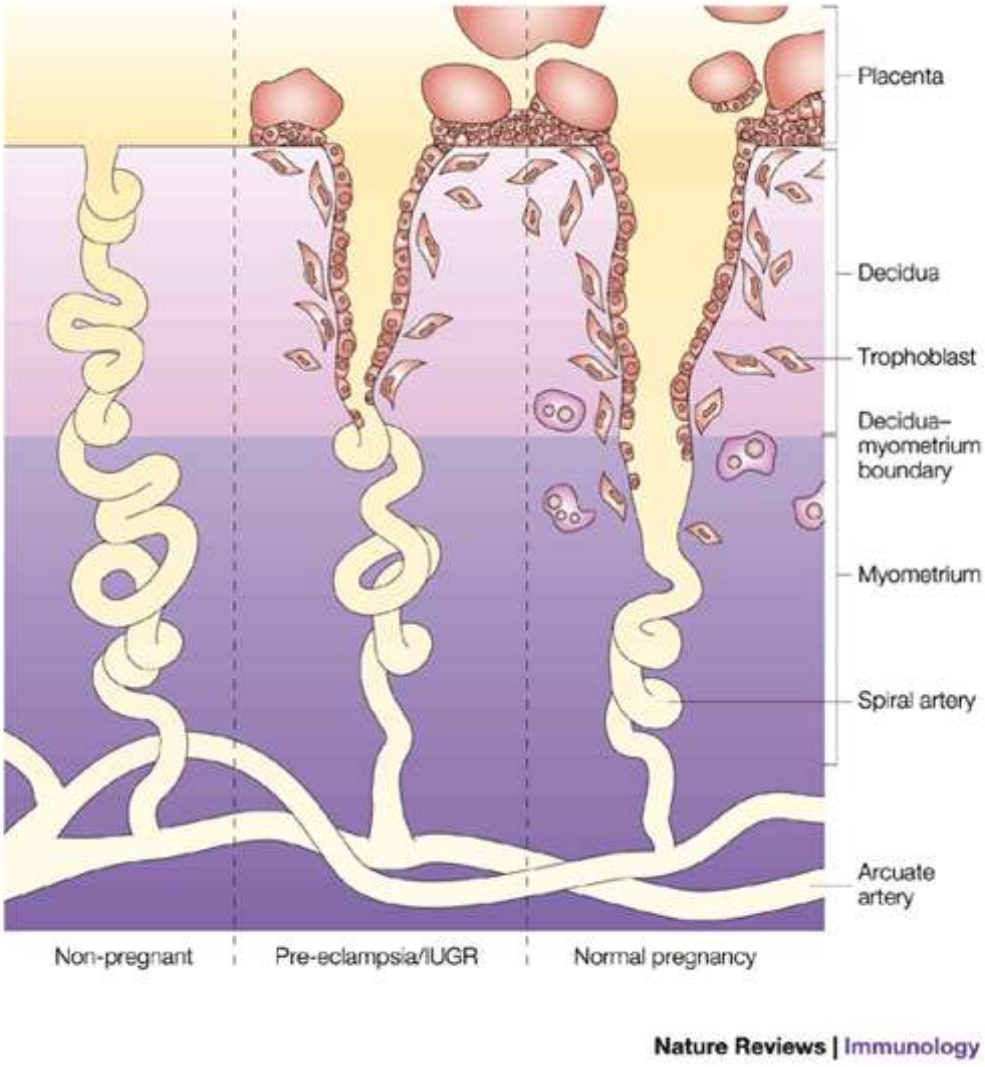

FIGURE 2 | **Inadequate vs. Adequate Trophoblastic Invasion of the Myometrium during Pregnancy.** Trophoblastic invasion is instrumental in increasing blood flow through the maternal uterine arteries during pregnancy. The left panel shows the uninvaded spiral arteries of a non-pregnant woman. The middle panel shows inadequate invasion of the media by trophoblasts characteristic of pathologic conditions of pregnancy such as preeclampsia and IUGR. This will lead to decreased blood flow that can lead to ischemic placenta, systemic endothelial dysfunction in the mother and ultimately preeclampsia. The right panel shows adequate invasion of the trophoblastic cells into the myometrium, characteristic of a normal pregnancy. (Bell, 2004)

D. Differential Diagnosis

Preeclampsia and eclampsia can mimic and be confused with many other diseases, particularly when preexisting conditions are present. In addition, there are several other disorders that can also lead to symptoms that are often associated with preeclampsia. Chronic hypertension, chronic kidney disease, and immune thrombocytopenia are among the diseases that can be mistaken for PE in pregnancy (**TABLE 2**).

TABLE 2. Other diseases that are easily confused with preeclampsia.

Chronic hypertension
Chronic kidney disease
Primary seizure disorders
Gallbladder and pancreatic disease
Immune thrombocytopenia
Hemolytic-uremic syndrome

Source: McPhee and Papadakis, 2011.

Meanwhile, arterial embolism or thrombosis, seizure disorder, and metastatic gestational trophoblastic disease can be mistaken for eclampsia (**TABLE 3**). Nevertheless, preeclampsia should be considered a possibility in any women beyond 20 weeks of gestation who is presenting with preeclamptic signs and symptoms (McPhee and Papadakis, 2011). In such cases where diagnosis is uncertain, it may be helpful to determine uric acid values because hyperuricemia

in pregnancy is typically only common in gout, kidney disease or preeclampsia (McPhee and Papadakis, 2011).

TABLE 3. Differential diagnosis of eclampsia.

Cerebrovascular accidents	Previously undiagnosed brain tumors
Hemorrhage	Metastatic gestational trophoblastic disease
Ruptured aneurysm	Metabolic diseases
Arterial embolism or thrombosis	Reversible posterior leukoencephalopathy syndrome
Cerebral venous thrombosis	Catastrophic antiphospholipid syndrome
Seizure disorder	Thrombotic thrombocytopenic purpura
Angiomas	Postdural puncture syndrome
Hypertensive encephalopathy	Cerebral vasculitis
Hypoxic ischemic encephalopathy	

Source: Sibai, 2009.

E. Risk Factors

Understanding the underlying mechanisms and conditions that might lead to preeclampsia and associated conditions is critical to identifying mothers who are at risk for developing PE. Currently, the strongest predictor of a mother developing preeclampsia in a current pregnancy is having had developed it in a previous pregnancy. History of preeclampsia in primary relatives, i.e. mothers and sisters, also puts women at greater risk of developing PE themselves

(Koren, 2004). Incidence of preeclampsia is increased with multiple pregnancies, chronic hypertension, diabetes, kidney disease, collagen-vascular and autoimmune disorders, and gestational trophoblastic disease (McPhee and Papadakis, 2011). First-time mothers are more frequently affected (McPhee and Papadakis, 2011). One study found having a BMI over 30, hypertension during the incident pregnancy, and having a previous cesarean section are all predictive factors of developing preeclampsia in the late postpartum period (Koren, 2004). Women of African American descent are also at greater risk than their white counterparts. Although their sample was quite small, the researchers postulate that their findings were still significant (Larsen et al., 2012).**TABLE 4** indicates other factors associated with higher risk of developing PE.

High-risk nulliparous women represent the largest proportion of pregnant women at risk for PE (Bujold, 2011). Rates of preeclampsia and eclampsia increase with maternal age, and are also higher during the teenage years (MacKay et al., 2001). Mothers considered at-risk are those who bear the risk factors listed in **TABLE 4**, have positive Doppler ultrasonography or, other predictive test (these tests will be described in the “Prediction” section). Low-risk mothers are considered to be those without any risk factor or positive predictive tests (Trivedi, 2011). A Finnish study found that the stress of daily living was not associated with increased risk of PE, whereas depression, anxiety, and stress from strenuous work were (Koren, 2004).

TABLE 4. Risk factors for preeclampsia.

- High blood pressure before becoming pregnant
- Previous with high blood pressure or preeclampsia
- Obesity (BMI of 30 kg/m^2 or greater)
- Younger than age 20 or older than age 40
- Pregnant with more than one baby
- Certain health conditions, such as
  - Diabetes (pre-gestational or gestational)
  - Preexisting kidney disease
  - Rheumatoid arthritis
  - Lupus (autoimmune)
  - Scleraderma
  - Underlying blood clotting disorders
  - Cardiovascular disease
- Primiparity (first-time mother)
- Maternal primary history (i.e. sister or mother with PE)
- Smoked prior to pregnancy
- Being Black or African American

Sources: Sutton, 2009; Bohn et al., 2011; ACOG, 2000; England et al., 2002.

F. Adverse Outcomes

Gestational hypertension accompanied by proteinuria presents a number of risks to both mother and infant (**TABLE 5**). Compared with normotensive mothers, mothers with preeclampsia are at greater risk for placental abruption, acute renal failure, and maternal mortality, among a number of other serious complications. Women with moderate to severe PE can develop serious life-threatening complications rapidly without warning. Thus, they and their fetuses should be closely and continuously monitored.

TABLE 5. Adverse Outcomes Related to Severe Preeclampsia.	
Maternal Complications	***Fetal Complications***
Acute renal failure	Premature birth
HELLP syndrome	Low birthweight
Preterm delivery	Intrauterine growth restriction
Placental abruption (cause of hemorrhage)	Placental abruption (i.e. deprive fetus of oxygen and nutrients)
Caesarean section	Small for gestational age
Proteinuria	Respiratory distress syndrome
Edema (i.e. pulmonary)	Admission to NICU> 7 days
Central nervous system dysfunction	Metabolic morbidities (i.e. hypoglycemia)
Hepatocellular injury	Gastrointestinal morbidities (i.e. hyperbilirubinemia)
Thrombocytopenia (low platelet count <150x10^9/L)	Necrotizing enterocolitis – any stage
Oliguria (low urine output)	Stillbirth or death before discharge from hospital
Cardiovascular complications	SBP> 95th percentile during childhood
Intensive care unit admission	DBP> 95th percentile during childhood
Eclampsia	
Admission to ICU > 7 days	
Seizures	
Coma	
Maternal death	
Bleed through orafices	

Sources: Langenveld et al., 2011; Hofmeyr et al., 2010; Barton et al., 2008; MacKay et al., 2001.
Abbreviations: ICU, intensive care unit; NICU, neonatal intensive care unit; SBP, systolic blood pressure; DBP, diastolic blood pressure.

1. Signs and Symptoms

Variables that are reliable indicators of severity of preeclampsia include status of blood pressure control, evidence of increasing organ damage in the liver and hematological systems, evidence of falling glomerular filtration rate, and signs of neurological involvement (Lindheimer and Kanter, 2010).

TABLE 6. Signs and symptoms consistent with preeclampsia.

Right upper quadrant pain
Epigastric pain
Retrosternal chest pain
Nausea and vomiting
Shortness of breath/congestive heart failure
Headaches (not responsive to analgesics)
Visual changes
Altered mental status
Bleeding from mucosal membranes
Overactive reflexes (hyperreflexia)
Jaundice
Edema (swelling in the face or hands)
Sudden weight gain (3 pound/week or more)

Source: McPhee and Papadakis, 2011.

Preeclampsia exerts its effects on six major sites of the body: the central nervous system, kidney, liver, hematologic, vascular, and fetal-placental unit (McPhee and Papadakis, 2011). **TABLE 7** describes the indicators of mild versus severe preeclampsia-eclampsia in each of these sites.

TABLE 7. Indicators of mild versus severe preeclampsia-eclampsia.

Site	***Indicator***	***Mild to Moderate***	***Severe***
Central nervous system	Symptoms and signs	Hyperreflexia	Seizures Blurred vision Scotomas Headache Clonus Irritability
Kidney	Proteinuria Uric acid Urinary output	0.3-5g/24h or catheterized urine with 2+ protein ↑>4.5mg/dL >30mL/h	>5g/24h or catheterized urine with 4+ protein ↑↑>4.5mg/dL <30mL/h
Liver	Liver enzymes: AST, ALT, LDH	Normal	Elevated LFTs Epigastric pain Ruptured liver
Hematologic	Platelets Hemoglobin	> 100,000/mcL Normal range	< 100,000/mcL Elevated
Vascular	Blood pressure Retina	< 160/110mmHg Arteriolar spasm	> 160/110mmHg Retinal hemorrhages
Fetal-placental unit	Growth restriction Oligohydramnios Fetal distress	Absent Absent Absent	Present Present Present

Source: McPhee and Papadakis, 2011.
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; LFTs, liver function tests.

In severe PE, symptoms are more dramatic and persistent than in mild to moderate PE. Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a form of severe preeclampsia named for the resulting complications (Ciantar and Walker, 2011). HELLP syndrome occurs in 10-20% of cases of severe preeclampsia, and in 0.5-0.9% of all pregnancies (Haram et al., 2009). Thrombocytopenia, which is low platelet count, if present, can progress to disseminated intravascular coagulation in which coagulation and fibrinolysis are inappropriately begun resulting in systemic generation of thrombin. This excess thrombin will then cause thrombosis throughout the body leading to depletion of antithrombotic agents and eventually to hemorrhage (McPhee and Papadakis 2011; AHDC). Furthermore, women may experience severe epigastric pain resulting from hepatic subcapsular hemorrhage with significant stretch or rupture of the liver capsule (McPhee and Papadakis, 2011).

Preeclampsia can lead to a number of metabolic and gastrointestinal alterations in the fetus, including hypoglycemia and hyperbilirubinemia, respectively (Barton and Sibai, 2008). This syndrome can also lead to inadequate blood flow through the blood vessels in the uterus, potentially depriving the fetus of oxygen and nutrients causing intrauterine growth restriction. Many of the morbidities seen in fetuses are driven mainly by the gestational age (GA) of the fetus as well as the mode of delivery,[†] i.e. vaginal vs. cesarean (Langenveld et al., 2011). Pregnant women suffering from

[†]More about the effects of the mode of delivery in the ***Management*** section.

preeclampsia who complain of headaches and blurred vision have approached the severe end of the disease. On the extreme level of severe preeclampsia, mothers can experience a graver range of symptoms including dysfunction of the central nervous system leading to seizures and hepatocellular injury. **TABLE 7** provides a detailed list of signs and symptoms known to be present in mothers who have developed severe preeclampsia. Specific causes of death among women who died from preeclampsia or eclampsia range from cerebrovascular hemorrhage to renal or hepatic failure to HELLP syndrome (**TABLE 8**).

TABLE 8. Specific Causes of Death Among Women Who Died of Preeclampsia or Eclampsia.

Cause of death	Percent of Deaths		
	PE	**Eclampsia**	**Total**
Cerebrovascular events	17.3	21.4	38.7
Cerebrovascular hemorrhage	15.8	18.8	34.7
Cerebral edema	1.1	1.8	2.9
Cerebral embolus	0.4	0.8	1.1
Renal or hepatic failure	7.2	5.4	12.5
HELLP syndrome	4.8	2.3	7.1
Other complications of Hypertension	13.9	11.8	25.7
Not specified hypertension	7.6	8.3	15.9
Preeclampsia and eclampsia	50.8	49.2	100.0

Source: MacKay et al., 2001.

2. Postpartum Complications

Preeclampsia in pregnancy may reveal a woman's risk for chronic disease and other negative conditions later in life (Rich-Edwards, 2012). Women who developed preeclampsia during pregnancy have a greater risk of having cardiac arrest in the 10 to 20 years following the incident pregnancy, compared to women who did not have PE (Koren, 2004). That there is a chance a woman can still develop preeclampsia may up to 6 weeks following her delivery (McPhee and Papadakis, 2011) calls for continuous monitoring of at-risk women even after delivery.

II. AIM

This work will discuss predictive measures, describe prevention measures, explore methods of treating and managing preeclampsia, and recommend approaches to treat cases of preeclampsia.

III. LITERATURE REVIEW

A. Prediction

Many models have been explored and proposed to attempt to accurately predict which pregnant women will develop preeclampsia. The more comprehensive models that incorporate both biochemical and biophysical tests along with maternal characteristics are more promising. Although the scientific community has yet to come to discover a wide-ranging predictive model, there are several methods that have demonstrated promise for successfully predicting preeclampsia development. **TABLE 9** lists the World Health Organization's suggestion for prediction and screening tests.

TABLE 9. Suggested criteria for a prediction test: World Health Organization systematic review 2004.

Simple
Rapid
Non-invasive
Inexpensive
Easy to carry out early in gestation
Imposes minimal discomfort or risk
Widely available technology
Valid
Reliable
Reproducible
High likelihood ratio for a positive result (>10)
Low likelihood ratio for a negative result (<0.1)

Source: WHO Report, 2004.

1. Biomarkers

The use of pregnancy-related biomarkers has gained much popularity by researchers in predicting preeclampsia. A number of promising biomarkers for development of the disease have been identified and are currently being explored for the prediction of preeclampsia and associated hypertensive conditions during pregnancy (Papageorghiou and Roberts, 2005; Madazli et al., 2005). The biomarkers listed in **TABLE 10** that are used in predicting preeclampsia are gathered from maternal peripheral venous blood samples to measure mid-trimester[‡] serum levels. Women who went on to develop preeclamsia tended to have significantly higher second-trimester levels of serum activin A and fibronectin and S/D ratios as well as significantly lower levels of PlGF than mothers who did not develop PE, i.e. remained normotensive (Madazliet al., 2005).

[‡] Mid-trimester is the same as second-semester.

TABLE 10. Predicting preeclampsia in mothers between 21^{+0} to 25^{+6} weeks'gestation.	
Higher in Preeclampsia	**Lower in Preeclampsia**
Soluble endoglin	Placental growth factor (PlGF)
Serum Activin A	Transforming growth factor beta 1 (TGF-β1)
Fibronectin	
Vascular endothelial growth factor (VEGF)	
Soluble Fms-like tyrosine kinase 1 (sFlt-1)	

Source: Madazliet al., 2005.

Lim et al. discovered that preeclampsia may be effectively predicted by calculating the ratio of four select angiogenesis-related factors: sFlt-1, solubleendoglin, PIGF, and TGF-β1 (Lim et al., 2008). Similar to Madazli et al., the levels of these factors were collected in the second trimester from both women who subsequently developed PE and those who did not. The researchers found that sFlt-1 and solubleendoglin levels are higher in preeclamptic women than in normotensive women where as PlGF and TGF-β1 levels are lower.

2. Uterine Artery Doppler

Leslie et al. conducted an exhaustive review of the literature on predicting pre-eclampsia in appendix (Leslie el al., 2011). Their findings on screening tests that have been proposed for identifying mothers who will develop preeclampsia are summarized in **APPENDICES B1 and B2**. The uterine artery pulsatility index

(UAPI) is a measure of blood flow through the uterine arteries and can be assessed by performing a Doppler ultrasound. In patients who subsequently developed preeclampsia, the UAPI was increased in the late second trimester likely as a result of the defective trophoblastic invasion (Yu et al., 2011). Improvements in technology over the past several decades allow for greater assessment of the flow of blood through the uterine artery. Abnormal uterine artery Doppler waveform uterine artery Doppler evaluation has been studied extensively for the prediction of preeclampsia and intrauterine growth restriction that reflects the involvement of a defective trophoblastic invasion. Uterine artery Doppler allows for the prediction of preeclampsia based on the involvement of a defective trophoblastic invasion (Meler et al., 2010). Combining UAPI and serum biomarkers provides the greatest predictive value for preeclampsia.

B. Prevention

As preeclampsia can develop at any time around 20 weeks' gestation, appropriate measures such as blood pressure readings and urine samples should be taken regularly and begin as soon as possible to detect signs of PE (Leslie et al., 2011). Careful monitoring of patients will not necessarily prevent preeclampsia, however it will allow for early diagnosis when it does occur. Preventing preeclampsia would reduce a great deal of stress on the potentially affected mother and the health care system which cares for her. This section will

discuss preventive measures that have been explored and the rationale for their use.

1. Combined Vitamin C and E Supplementation

In pregnant women with preeclampsia, levels of free radicals are increased and levels of antioxidants, which scavenge free radicals, are decreased. These imbalanced alterations are a result of impaired placental development in early pregnancy (Basaran et al., 2010) and contribute to oxidative stress which in turn likely contributes to the development of preeclampsia. This presents the rationale for use of the antioxidant preventive measure of the combined vitamin supplements. Randomized control studies have been published that studied the preventive qualities of combined vitamin C and E supplements (vitCE) during pregnancy (Polyzos et al., 2007). Timing, dosage and location of injection were investigated to determine the effectiveness of this preventive measure. Results from the majority of these studies show that there are no significant differences between vitCE and placebo groups (Rumbold et al., 2006; Polyzos et al., 2007; Basaran et al., 2010; Conde-Agudelo et al., 2011). Thus, there is no reduction in risk for preeclampsia using this combined antioxidant regimen during pregnancy. Furthermore, an association has been found in which it may slightly increase the risk of preterm birth in the neonate

(Poston et al., 2006). Thus, combined vitamin C and E supplements during pregnancy are not recommended for the prevention of preeclampsia.

2. Dietary and Lifestyle Measures

Research has shown that there are no benefits in preventing preeclampsia by taking particular dietary measures—such as salt restriction, reduced protein or energy intake, garlic or fish oils (Leslie et al., 2011). In morbidly obese women (BMI > 35), losing weight before getting pregnant may reduce their risk of developing PE; their odds ratio of developing the disease is 7.2 over women who are not obese (Leslie et al., 2011). Weight loss can also help women who are obese or overweight. On the other hand, exercise in moderation can also modify the risk of developing PE, possibly by boosting immune functions and reducing chronic inflammation (Lu, 2009).

3. Calcium Supplementation

Calcium (Ca^{2+}) supplements have shown to be successful in reducing the incidence of preeclampsia in high-risk women without a history of the syndrome and women in countries where there is low calcium intake (Hofmeyr et al., 2011). Supplementation of Ca^{2+} would need to begin at 34^{+0} weeks' gestation or less (specifically in the first half of pregnancy). When supplementation begins in the first trimester, it may be able to prevent endothelial dysfunction associated with

PE; whereas, if Ca^{2+} supplementation is begun in the second half of pregnancy, its effect might be reducing blood pressure directly. Calcium supplementation affects uteroplacental blood flow by lowering the resistance index (RI) in uterine and umbilical arteries (Sanchez-Ramos et al., 1995).

4. Low-Dose Aspirin Therapy

There is currently no consensus on the efficiency of low dosage of aspirin (LDA) being administered to women at risk of developing preeclampsia. Factors that should be contemplated when trying to explain the heterogeneity between results in studies include: 1. the dosage and time of day for LDA administration, 2. the population investigated, and 3. the intervention time during pregnancy.

A meta-analysis of low-dose aspirin for the prevention of preeclampsia that included results from over 28,000 women found that LDA has a small but significant effect (RR=0.79, 95% CI 0.65-0.97) on preventing PE among women considered to be at high risk for developing PE (Trivedi, 2011). The dosage of aspirin administered in a daily regime to prevent preeclampsia ranged from 50 to 150 mg. Thus, the use of LDA in high-risk women is associated with the modest benefit of a 21% reduction in the prevalence of PE. On the contrary, LDA preventive effects were insignificant in low-risk women (RR=0.86, 95% CI 0.64-1.17).

A recent meta-analysis indicated that starting LDA administration before 16^{+0} weeks of gestation is associated with a statistically significant 53% reduction in the risk of preeclampsia (Bujold et al., 2010). **TABLE 11** highlights the differences in results depending on whether the timing of administration before or after 16^{+0} weeks' gestation. Bujold et al. concluded that aspirin therapy in low doses begun in the first trimester of pregnancy, more specifically started at 16^{+0} weeks' gestation or earlier, is efficient in reducing the incidence of preeclampsia, among women identified to be at moderate or high risk for PE (Bujold et al., 2012). LDA started that early also is associated with a reduction in the incidence of IUGR, preterm labor and gestational hypertension (Bujold et al., 2010).

TABLE 11. Relative Risk of Outcomes Associated with the Use of Low-Dose Aspirin According to Gestational Age at Initiation of Intervention.

Effects of low-dose aspirin started *at or before* 16 weeks gestation.						
Adverse Outcome	**RR**	**95% CI**	**No. of Trials**	**No. of Participants**	**Prevalence**	
					Treated	**Control**
Preeclampsia	0.47	*0.34-0.65	9	764	9.3%	21.3%
Severe PE	0.09	*0.02-0.37	3	278	0.7%	15.0%
Gestational hypertension	0.62	†0.45-0.84	7	548	16.7%	29.7%
Preterm birth	0.22	*0.10-0.49	4	387	3.5%	16.9%
IUGR	0.44	†0.30-0.65	5	414	7.0%	16.3%
Placental abruption	0.62	0.08-5.03	4	360	1.1%	3.3%
Effects of low-dose aspirin started *after* 16 weeks.						
Adverse Outcome	**RR**	**95% CI**	**No. of Trials**	**No. of Participants**	**Prevalence**	
					Treated	**Control**
Preeclampsia	0.81	0.63-1.03	18	10,584	7.3%	8.1%
Severe PE	0.26	0.05-1.26	2	669	0.6%	2.4%
Gestational hypertension	0.63	†0.47-0.85	14	4,303	11.6%	15.0%
Preterm birth	0.90	†0.83-0.97	16	10,398	18.6%	20.8%
IUGR	0.92	0.78-1.10	10	1,381	13.4%	16.0%
Placental abruption	1.56	0.96-2.55	6	3,583	2.3%	1.4%

Source: Bujold et al., 2010. *$P<0.001$ †$P<0.05$

Abbreviations: RR, relative risk; CI, confidence interval; IUGR, intrauterine growth restriction.

C. Management

The chief requirements for successful management of preeclampsia are early diagnosis, close follow-up, and timely delivery (Koren, 2004). When the severity of preeclampsia dramatically increases, rapid measures are required to attain a positive and healthy outcome for both mother and fetus. The only sure way to cure a mother of her preeclampsia is to deliver the fetus and placenta, and this should be done at a time as favorable as possible for the survival of the infant (McPhee and Papadakis, 2011). The younger the GA the greater the risk of fetal morbidities and mortality, and cesarean section also presents a higher risk of fetal morbidities and mortality than does vaginal delivery. Vaginal delivery is preferred essentially because it involves less blood loss and requires fewer coagulation factors than a cesarean section (McPhee and Papadakis, 2011). Symptoms usually resolve within a few days and the mother is cured, but may require temporary use of blood pressure medications if elevated BP persists.

1. Labor Induction

Depending on the gestational age of the fetus and condition of the mother, providers have to make educated decisions on whether to use temporizing management that will prolong the gestation of the fetus, or to deliver right away in order to minimize danger to the mother. The objectives of treatment are to prolong pregnancy in order to allow fetal lung maturity, all the while preventing

progression to severe disease and eclampsia (McPhee and Papadakis, 2011). On average, labor induction in aggressive management is no longer than 48 hours after detection of eclampsia. Strong indications for delivery of the fetus include epigastric pain, severe range blood pressures, thrombocytopenia, and visual disturbances (McPhee and Papadakis, 2011), thus, typically severe preeclampsia will require delivery.

2. Expectant Management

Expectant management, i.e. temporizing management, involves providing the expecting mother with antihypertensive treatments that may be harmful to the fetus, although this management will also prolong the gestational age of the fetus (Brichant et al., 2010). A major benefit of expectant management is prolonging the gestational age of the fetus allowing for fetal lung maturation (Brichantet al., 2010). This is done while trying to lower the woman's blood pressure into a safe range. Practitioners must weigh the risks and benefits of staying in the uterus versus being born preterm. Particularly when used for early onset preeclampsia, i.e. before 32 weeks' gestation, temporizing management requires close monitoring of mother and fetus (Langenveld et al., 2011).

In patients with early-onset preeclampsia, expectant management improves neonatal outcome in selected cases and decreases neonatal care intensive unit admittance and neonatal respiratory distress (Meler, 2010).Based

on a review of studies involving 1677 women between 24^{+0} and 33^{+6} weeks' gestation and 115 women under 24 weeks gestation, Sibai and Barton suggest that expectant management is safe for those women who develop severe preeclampsia beyond 24 weeks if conducted in a suitable hospital. This is likely due to the viability of the fetus beginning at 24^{+0} weeks GA. EM among this select group of women is also associated with improved neonatal outcome. However, for those with a GA below 24 weeks, prolonging the pregnancy was not only associated with little benefit for the fetus, but also with high risk of maternal morbidity. These two researchers propose selecting appropriate candidates for expectant management based on maternal condition and fetal gestational age (Sibai and Barton, 2007).

3. Seizure Prophylaxis with Magnesium sulfate

Seizures in preeclampsia typically occur at the extreme end of the disease. More than 70 years after research has documented the safety and efficacy of magnesium sulfate ($MgSO_4^{2-}$), it continues to be the anticonvulsant of choice to prevent or treat seizures caused by preeclampsia (Brichant et al., 2010; Mozlemizadeet al., 2011). It is a muscle relaxant that relaxes the uterine and cardiac muscles so it keeps the blood pressure down and prevents the occurrence of the seizure… it is also a diuretic making them pee. . For seizure prophylaxis in patients with severe preeclampsia, the recommended dosage is 4-

6g load followed by 2-3g/h maintenance. When administered at the recommended levels, there are very few side effects when using $MgSO_4^{2-}$. (**TABLE 10**). However, adverse effects of $MgSO_4^{2-}$ can include complete neuromuscular blockade and respiratory depression. Therefore, close monitoring after careful administration is imperative. Magnesium sulfate is usually used in combination with corticosteroids to help the fetal respiratory system mature. Or else the infant may have trouble breathing due to lungs that are not fully formed. Once the eclamptic patient is stabilized, the child should be delivered.

TABLE 12. Recommended Magnesium Sulfate Dosing Guidelines.

	Loading Dose:	**Loading Dose:**	**Maintenance:**	**Maintenance:**
Clinical Indications	**IM Protocol[a]**	**IV Protocol**	**Periodic IM Injections**	**Continuous IV Infusion**
Seizure prophylaxis: eclampsia[b] or severe preeclampsia	4 g (20%)[c] IV at 1 g/min, then follow immediately with IM dosing	4-6 g (20%) in 100 mL over 15-20 min	10 g (50%)[d] 5 g deep IM each buttock. Repeat every 4 h	2-3 g/h (20%) continued until 24 h after birth

Source: McPhee and Papadakis, 2011; Hunter and Gibbins, 2011.
Abbreviations: IM, intramuscular; IV, intravenous.
[a] Initial dose is given via slow IV push.
[b] A second bolus of 2 g can be given IV over 3-5 min for acute seizure management.
[c] All IV doses should be diluted to 20% solution.
[d] IM doses can be given undiluted (50% solution).

4. Other Medications of Choice

Methyldopa (e.g. Aldomet) and hydralazine (e.g. Apresoline) are the antihypertensive medications of choice during pregnancy (Koren, 2004); although there are conflicting results in studies whether these drugs have benefits for proteinuria, progression to serious disease, and neonatal respiratory syndrome (Koren, 2004). Diuretic therapy is particularly indicated for chronically hypertensive pregnant women with salt-sensitive hypertension or with evidence of left ventricular diastolic dysfunction (LVDD). Nine randomized clinical trials concluded that diuretic use protected the specific subset of women with hypertension and LVDD from developing preeclampsia (Koren, 2004). Angiotensin-converting enzyme (ACE) inhibitors in the 2nd and 3rd trimesters are contraindicated because they cause kidney failure in the fetus and other fetal complications.

IV. DISCUSSION and CONCLUSION

The World Health Organization recommendations call for a screening prediction test that is rapid, non-invasive, widely available, and easy to carry out early in gestation. Being able to predict cases of preeclampsia will allow for closer surveillance and earlier intervention to improve outcomes, inform methods of treatment, and increase evidence-based spending. With all the complexities of preeclampsia and all the organ systems it affects and all the complications if causes, it may be appropriate to describe preeclampsia as a syndrome rather than a single disease or disorder. Standardizing criteria to treat patients with PE is problematic due to the widely variable spectrum in how preeclampsia develops. While it is unlikely that a single preventive measure or treatment will be adequate for all the possible presentations of PE, there are measures that can be taken to lessen the degree of severity that is achieved by the disease. Due to recent indications that maternal factors combined with biochemical markers and/or ultrasound markers could identify women at high-risk as early as the first trimester, a randomized trial studying low-dose aspirin at bedtime should be considered soon (Bujold, 2011). Despite improvements in the diagnosis and management of preeclampsia, severe complications can still occur in both the mother and the fetus. Evidently, preeclampsia encompasses a wide spectrum of symptoms with unpredictable and sometimes uncontrollable disease progression

(Hunter and Gibbins, 2011).Upon researching the topic of preeclampsia, the challenges obstetricians face when dealing with a preeclamptic mother-to-be became clear rather quickly. Providers across disciplines must work together to best treat and care for mothers with preeclampsia.

APPENDIX

APPENDIX A. Weighted number of cases and crude incidence rates, gestational hypertension and preeclampsia, 1987-2004.

Table 1 | Weighted number of cases and crude incidence rates, gestational hypertension and preeclampsia, 1987–2004

Diagnosis	1987	1988	1989	1990	1991	1992
Gestational hypertension (ICD-9-CM 642.3)						
No. of cases	41,249	40,671	57,484	60,005	64,958	64,374
Rate (95% CI)	10.5 (8.2, 12.9)	10.8 (8.0, 13.5)	14.6 (11.3, 17.9)	14.9 (12.0, 17.9)	16.3 (13.1, 19.6)	16.5 (13.3, 19.6)
Preeclampsia (ICD-9-CM 642.4–5)						
No. of cases	98,017	83,046	109,846	93,168	99,446	87,263
Rate (95% CI)	25.1 (21.5, 28.6)	21.9 (18.2, 25.7)	27.9 (23.1, 32.6)	23.2 (19.3, 27.0)	25.0 (20.7, 29.3)	22.3 (18.6, 25.9)
Diagnosis	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**
Gestational hypertension (ICD-9-CM 642.3)						
No. of cases	79,380	81,864	68,184	86,902	85,985	83,698
Rate (95% CI)	19.8 (16.0, 23.5)	21.0 (17.3, 24.7)	18.1 (14.8, 21.4)	22.7 (18.8, 26.6)	22.6 (18.9, 26.3)	20.9 (17.3, 24.5)
Preeclampsia (ICD-9-CM 642.4–5)						
No. of cases	91,931	100,936	108,689	111,551	117,770	125,262
Rate (95% CI)	22.9 (18.7, 27.1)	25.9 (21.9, 29.9)	28.9 (24.4, 33.3)	29.0 (24.6, 33.5)	30.9 (26.4, 35.4)	31.2 (26.0, 36.5)
Diagnosis	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
Gestational hypertension (ICD-9-CM 642.3)						
No. of cases	100,586	119,338	105,522	110,123	125,630	122,667
Rate (95% CI)	26.4 (21.9, 30.9)	31.9 (27.2, 36.6)	27.5 (23.2, 31.7)	27.9 (23.3, 32.4)	31.2 (26.0, 36.5)	29.7 (25.4, 33.9)
Preeclampsia (ICD-9-CM 642.4–5)						
No. of cases	119,221	104,437	117,248	115,924	106,282	132,800
Rate (95% CI)	31.2 (26.6, 35.8)	27.9 (23.8, 32.1)	30.5 (26.1, 35.0)	29.3 (24.8, 33.9)	26.4 (22.3, 30.6)	32.1 (27.6, 36.6)

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Source: Wallis et al., 2008.

APPENDIX B1. Fetoplacental screening test for pre-eclampsia: findings in the published literature.

Fetoplacental Unit	
Placental resistance	Placental products
Uterine artery Doppler	Pregnancy-associated plasma protein A
	Alpha fetoprotein
	Human chorionic gonadotrophin
	Oestriol
	Inhibin A
	Activin A
	Placental growth factor
	Corticotrophin- releasing hormone
	Placental protein 13
	Pro- and anti-angiogenic protein ratios
	Leptin

Source: Leslie et al., 2011.

APPENDIX B2. Maternal screening test for pre-eclampsia: findings in the published literature.

Maternal Factors					
Cardiovascular status	Renal dysfunction	Metabolic status	Endothelial dysfunction	Oxidative stress or hypoxia	Inflam-matory
Mean arterial blood pressure (MAP)	Cystatin C	Insulin resistance	Endothelin	Homo-cysteine	C-reactive protein
Mid- trimester diastolic blood pressure [a]	Serum uric acid [a]	Sex hormone binding globulin	Plasminogen activator inhibitor	Iso-prostanes	Pentraxin-3
Roll over test [a]	Micro-albuminuria [a]		Fibronectin	Ischaemia modified albumen	
Isometric exercise test[a]	Urinary calcium excretion[a]		Vascular cell adhesion molecule 1	Anti-oxidant status	
24- h ambulatory blood pressure monitoring	Urinary kallikrein		P and L selectin		
Intravenous infusion of angiotensin II [a]	Micro-transferrinuria		Platelet count		
	N-acetyl-β glucose-minidase		Throm-boxane		
			Prostacyclin		
			Antithrombin III		
			C-reactive protein		
			Antiphos-pholipid antibodies		
			Serum lipids		
			Neutrophil gelatinase-associated lipocalin		

Source: Leslie et al. 2011.
[a] show to be of low predictive value.

APPENDIX C1. Interventions that are recommended for *prevention* of preeclampsia and eclampsia.

Recommendation	Quality of Evidence	Strength of Recommendation
In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5-2.0 g elemental calcium/day) is recommended for the prevention of preeclampsia in all women, but especially those at high risk of developing preeclampsia.	Moderate	Strong
Low-dose acetylsalicylic acid (aspirin, 75 mg) is recommended for the prevention of preeclampsia in women at high risk of developing the condition.	Moderate	Strong
Low-dose acetylsalicylic acid (aspirin, 75 mg) for the prevention of preeclampsia and its related complications should be initiated before 20 weeks of pregnancy.	Low	Weak
Magnesium sulfate is recommended for the prevention of eclampsia in women with severe preeclampsia in preference to other anticonvulsants.	High	Strong

Source: WHO Report, 2011.

APPENDIX C2. Interventions that are recommended for *treatment* of preeclampsia and eclampsia.

Recommendation	Quality of Evidence	Strength of Recommendation
Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs.	Very low	Strong
The choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician's experience with that particular drug, its cost and local availability.	Very low	Weak
Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants.	Moderate	Strong
The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia.	Moderate	Strong
For settings where it is not possible to administer the full magnesium sulfate regimen, the use of magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended for women with severe preeclampsia and eclampsia.	Very low	Weak
Induction of labor is recommended for women with severe preeclampsia at a gestational age when the fetus is not viable or unlikely to achieve viability within one or two weeks.	Very low	Strong
In women with severe preeclampsia, a viable fetus and before 34 weeks of gestation, a policy of expectant management is recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.	Very low	Weak
In women with severe preeclampsia, a viable fetus and between 34 and 36 (plus 6 days) weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.	Very low	Weak
In women with severe preeclampsia at term, early delivery is recommended.	Low	Strong

In women with mild preeclampsia or mild gestational hypertension at term, induction of labor is recommended.	Moderate	Weak
In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended.	Very low	Strong
Treatment with antihypertensive drugs is recommended for severe postpartum hypertension.	Very low	Strong

Source: WHO Report, 2011.

APPENDIX C3. Interventions that are *not* recommended for prevention or treatment of preeclampsia and eclampsia.

Recommendation	Quality of evidence	Strength of recommendation
Advice to rest at home is not recommended as an intervention for the primary prevention of preeclampsia and hypertensive disorders of pregnancy in women considered to be at risk of developing those conditions.	Low	Weak
Strict bedrest is not recommended for improving pregnancy outcomes in women with hypertension (with or without proteinuria) in pregnancy.	Low	Weak
Restriction in dietary salt intake during pregnancy with the aim of preventing the development of preeclampsia and its complications is not recommended.	Moderate	Weak
Vitamin D supplementation during pregnancy is not recommended to prevent the development of preeclampsia and its complications.	Very Low	Strong
Individual or combined vitamin C and vitamin E supplementation during pregnancy is not recommended to prevent the development of preeclampsia and itscomplications.	High	Strong
Diuretics, particularly thiazides, are not recommended for the prevention of preeclampsia and its complications.	Low	Strong
The use of corticosteroids for the specific purpose of treating women with HELLP syndrome is not recommended.	Very Low	Weak

Source: WHO Report, 2011.

LIST of JOURNAL ABBREVIATIONS

Acta Clin Belg	Acta Clinica Belgica
Am J Obstet Gynecol	American Journal of Obstetrics and Gynecology
Am J Hypertens	American Journal of Hypertension
BMC Pregnancy and Childbirth	Boston Medical Center Pregnancy and Childbirth
Int J Gynaecol Obstet	International Journal of Gynecology and Obstetrics
J Biol Chem	Journal of Biological Chemistry
J Matern Fetal Neonatal Med	Journal of Maternal-Fetal and Neonatal Medicine
J Postgrad Med	Journal of Postgraduate Medicine
J Reprod Med	Journal of Reproductive Medicine
MMWR CDC Surveill Summ	Morbidity and Mortality Weekly Report Center for Disease Control and Prevention Surveillance Summary
N Engl J Med	The New England Journal of Medicine
Obstet Gynecol	Obstetrics and Gynecology
Obstet Gynecol Surv	Obstetrical and Gynecological Survey
Pak J Biol Sci	Pakistan Journal of Biological Sciences
Ultrasound Obstet Gynecol	Ultrasound in Obstetrics & Gynecology

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