NEWSLETTER

Obstetric Medicine

SOMI

NEWSLETTER

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From the Editor's Desk

Dear SOMI Members,

Greetings from Hyderabad. I am glad to share this edition of newsletter on Hypertensive Disorders in Pregnancy with you. This is the most common medical problem one encounters in pregnancy. Pre eclampsia is a multisystem disorder with unpredictable course and protean manifestations.

With a History dating back to 2500 years, the disease is rightly named the "disease of theories" in view of the multiple proposed hypotheses. Despite all the ongoing research, the disease continues to be complex in it's presentation and clinical course.

From the time Hippocrates first described some of its symptoms in 400BCE, constant progress has been made in understanding the pathophysiology, identifying symptoms /signs and classifying the disorder. But it was with the introduction of the mercury manometer in 1896 by Scipione Riva-Rocci that the disease came to be recognized as a Hypertensive disorder.

Initially thought to be a disease of the Central Nervous System our current understanding has established it as a vascular disease.

We owe most of our current knowledge on the disease to Leon Chesley who extensively researched and prospectively followed up mothers with this order. Despite recent advances in the ability to predict, evaluate and manage this disease and its risks, there are still many grey areas.

WE have covered in this edition clinically relevant aspects of the problem. We hope you find our newsletter useful for your practice.

I thank all those who contributed to this volume and also my colleagues at Fernandez Hospital who helped me with editing the articles

Regards,
Usha

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CONTENTS

Citations on history of Pre eclampsia, eclampsia are from

- Leon C chesley, History and Epidemiology of Pre eclampsia-Eclampsia, Clinical Obstetrics and Gynecology, Vol 27, No.4, December 1984.
- Dr Marshall Lindheimer; 2400 years of Pre eclampsia History; Pre eclampsia Foundation
- Offer Erez, Roberto Romero, Eujung Jung, Manaphat Suksai, Dahiana M.Gallo, FranescaG-otsch etal; Pre eclampsia and eclampsia; the conceptual evolution of a syndrome; AJOG; Volume 266, Issue 2, supplement S786-S803; February 2022

Bossier de Sauvages was the one who differentiated Eclampsia from Epilepsy, noting the former was acute in nature and would resolve once the precipitating event was removed.

Gabelchoverus in 1596 specified four kinds of epilepsy: they arose in the head, the stomach, in chilled extremities or in the pregnant uterus. In uterine epilepsy, the mother had the feeling of a rat gnawing at her heart which was probably the epigastric pain which Chaussier described 228 years later.

Hypertensive Disorders in Pregnancy

Classification and Clinical Features

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Dr T Sahithi

Dr G Rekha

Introduction:

Hypertension is the most common medical disorder, complicating 10% of all pregnancies and it is significantly higher in low and middle income countries. The incidence increased by 10.29% from 1990 to 2019 globally. Hypertensive disorders in pregnancy(HDP) is the second leading cause of maternal mortality. Accurate BP measurement and classification of the disorder is necessary for appropriate management

Definition:

Hypertension in pregnancy is defined as systolic BP of ≥140mmHg and or Diastolic BP of ≥90 mmHg on 2 occasions measured at four-hours interval after 20 weeks of gestation in a previously normotensive woman. BP of >160/110mm Hg persistent over fifteen minutes is considered severe hypertension.. If the difference between two readings is more than 10 mm, a third reading should be recorded and the second and third reading should be considered. [1]Chronic hypertension is defined as BP of ≥140/90 diagnosed before pregnancy or on at least two occasions measured at 4 hours interval before 20 weeks of gestation.

Classification:

Though classification of Hypertensive disorders in pregnancy (HDP) may be of help in grouping the women for monitoring, prognosticating and deciding management plan, the final diagnosis with certainty could be made in some instances only in postpartum period. HDP is classified as presented in Table 1

Table 1: Classification
International Society for the Study of Hypertension in Pregnancy 2021:

Types of hypertensive disorders	Definitions
Pre-Pregnancy or at < 20weeks Chronic hypertension	Hypertension detected pre-pregnancy or before 20 weeks gestation
Essential	Hypertension without a known secondary cause
Secondary	Hypertension with a known secondary cause (e.g. Renal disease)
White-coat hypertension	HP >140 and / or dBP >90mmHg when measured in the office or clinic and BP < 135/85 mmHg using HBPM or ABPM reading
Masked hypertension	sBP that is <140/90mmHg at a clinic /office visit but > 135/85mmHg at other times outside the clinic/office
>20 weeks	
Gestation hypertension	Hypertension arising de novo at >20weeks' gestation In the absence of proteinuria or others finding suggestive of pre-eclampsia
Transient gestational hypertension	Hypertension arising at >20 weeks gestation in the clinic, which resolves with repeated BP reading
Pre-eclampsia De Novo	Pre-eclampsia (de novo) is gestational hypertension accompanied by one or more of the following new onset conditions at >20 weeks gestation proteinuria **Other maternal end organ dysfunction, including:** • Neurological complication (e,g eclampsia, altered mental status, blindness, stroke, clonus , severe headache, or persistent visual scotomata) • Pulmonary oedema • Hematological complications (e.g platelet count < 150,000/, DIC, hemolysis) • AKI (such as creatinine > 90 /L or 1 mg/dL) • Liver involvement (e.g elevated transaminases such as ALT or AST > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain) • Uteroplacental dysfunction (e.g, placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine, fetal death).
Superimposed on chronic hypertension	Among women with chronic hypertension, development of new proteinuria, another maternal organ dysfunction(s) or evidence of uteroplacental dysfunction (as above)

According to the ACOG guidelines HDP is classified as Chronic hypertension, Gestational Hypertension,Pre eclampsia and Pre eclampsia superimposed on Chronic Hypertension.[2,3] There is consensus on the definition of the types of HDP in the earlier and current classification except certain criteria like proteinuria not being a diagnostic feature for PE in the presence of maternal end organ dysfunction.[3,4]

Incidence of Chronic Hypertension is 1% ,25% of them go on to develop Pre eclampsia,Gestational Hypertension is 3% and Pre eclampsia is 2-6%,with variability among countries depending on their development status.

In chronic hypertension to diagnose super imposed pre eclampsia only elevated BP cannot be used as a criteria. New onset proteinuria, end organ dysfunction or uteroplacental insufficiency in Chronic hypertension suggests superimposed Pre eclampsia.[1] Home BP monitoring(HBPM) helps in excluding white-coat hypertension. This is important because antihypertensives can be withheld if the diagnosis is white-coat hypertension. But continuous surveillance is indicated in these women in view of increased risk of pre eclampsia[5].Unexplained target organ damage should suggest the possibility of masked hypertension and is an indication for HBPM.[1] (Home BP Monitoring)

Outcome in gestational hypertension depends on the gestational age at which it develops. 25%women who develop it at <34 weeks develop preeclampsia.

Whether there is an association between lowering BP thresholds to prehypertensive category as per the American College of Cardiology guidelines to define HDP and pregnancy outcomes is also being studied.[6]

Clinical presentation of HDP:

Chronic Hypertension:

In women diagnosed with Hypertension prior to pregnancy ,examination may reveal clues to an underlying secondary cause.[7] This should include

- Diminished peripheral pulses in Takayasu's arteritis
- Radio femoral delay in Coarctation of aorta
- Renal Bruit in Renal artery stenosis

Pre eclampsia

Symptoms	Signs
Rapid weight gain Nausea/vomiting Epigastric /Right upper quadrant pain Headache Visual disturbances	Pedal edema/Anasarca Increased BP readings Right hypochondrial tenderness Brisk tendon reflexes Convulsions Placental abruption FGR/IUFD

Conclusion

It is important that all women have access to regular BP measurements and monitoring through the antenatal period and dipstick proteinuria assessment as priority with a thorough clinical examination so that there is early diagnosis and correct classification of HDP for appropriate care and better outcome.

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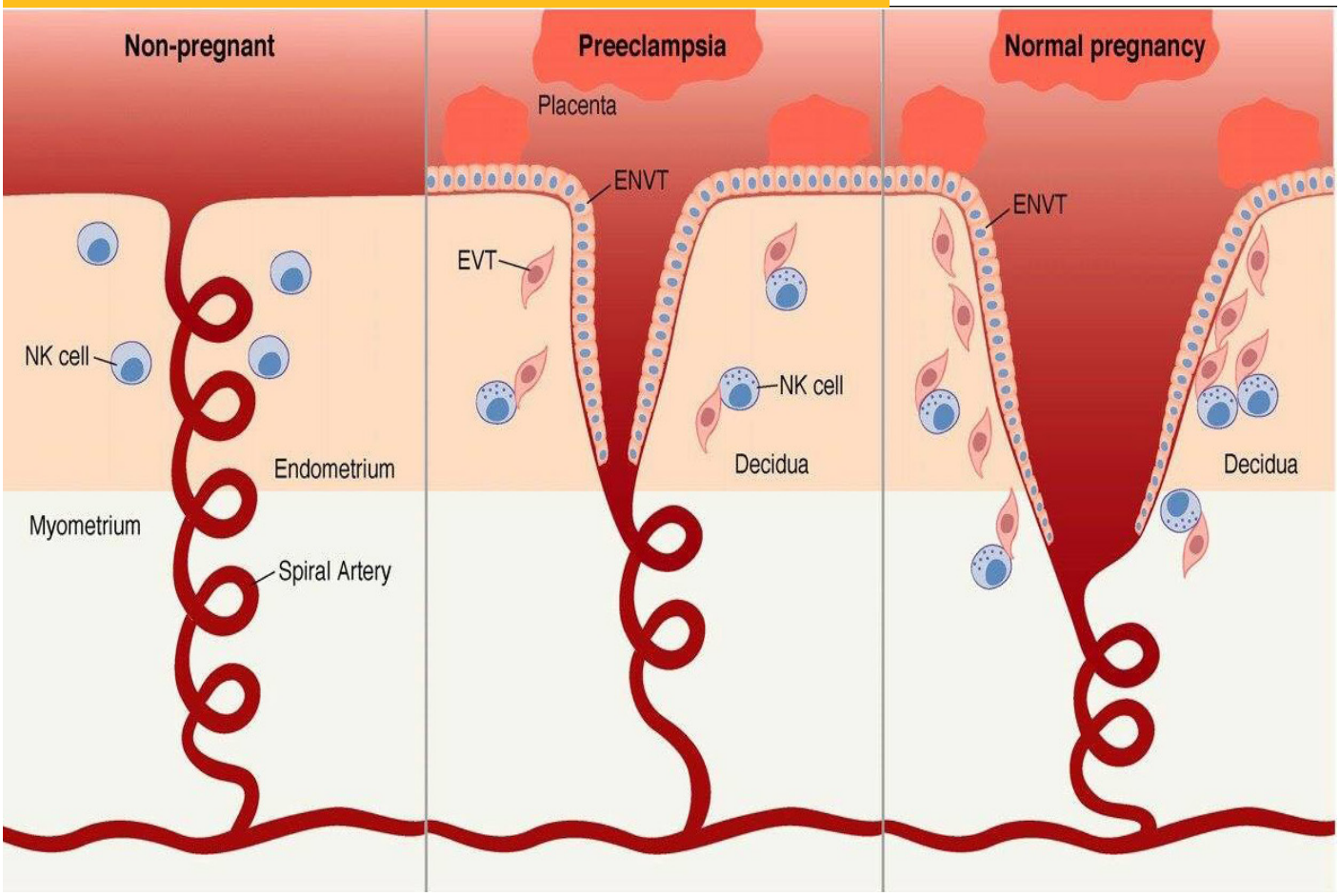
Fishberg,in the fourth edition of his monumental Hypertension and Nephritis denied the specificity of Pre eclampsia, Eclampsia and regarded it as manifestation of essential hypertension, brought to light and peculiarly colored by pregnancy.



Etiopathogenesis and Risk Factors of Preeclampsia

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Dr Shruthi Belide

Introduction:

Preeclampsia (PE) is a multifactorial and multisystem disease. The multiple predisposing risk factors associated with pre eclampsia have provided insights into pathogenesis though the exact cause is still unknown.

Etiopathogenesis:

The pathophysiology of preeclampsia involves both maternal and fetal/placental factors. Abnormalities in the development of placental vasculature in early pregnancy leads to placental hypoperfusion, hypoxia, and ischemia, which releases antiangiogenic factors into maternal circulation. These factors alter maternal systemic endothelial function, causing hypertension and other manifestations of the disease. It is more likely to develop in women with:

1. Exposure to chorionic villi for the first time
2. Exposure to a superabundance of chorionic villi, as with multiple pregnancies or hydatidiform mole
3. Pre-existing conditions associated with endothelial cell activation or inflammation
4. Genetic predisposition
5. Complete molar pregnancy, even in the absence of a fetus

Aetiology

The various mechanisms by which preeclampsia occurs include:

1. Abnormal trophoblastic invasion of uterine vessels
2. Dysfunctional immunological tolerance between maternal, paternal, and fetal tissues
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
4. Genetic factors, including predisposing genes and epigenetic influences

Irrespective of the etiology, the cascade leads to systemic vascular endothelial damage, vasospasm, plasma transudation, and ischemic and thrombotic sequelae.

This can be explained by the two-stage disorder theory based on the degree of remodelling of uterine spiral arterioles by endovascular trophoblasts. Stage I is the placental syndrome, where there is faulty endovascular trophoblastic remodelling, which in turn causes Stage II (the maternal syndrome). This stage manifests as chronic hypertension, renal disease, obesity, immunological or connective tissue disorders, and diabetes. [1]

Stage I - Placental Syndrome

In a normal pregnancy, the cytotrophoblast cells of the developing placenta migrate through the decidua and part of the myometrium to invade both the endothelium and the highly muscular tunica media of the maternal spiral arteries, which are the terminal branches of the uterine artery that supply blood to the developing fetus/placenta. This results in the transformation of small muscular arterioles into high-capacitance vessels of low resistance, facilitating blood flow to the placenta. This remodelling of spiral arteries begins in the late first trimester and is completed by 18-20 weeks of gestation. Veins are invaded superficially only.

In women prone to develop preeclampsia, the cytotrophoblastic cells infiltrate the decidual portion of the spiral arteries, and there is a deficient invasion of the myometrial arterioles, resulting in narrow and rigid spiral arterioles. This impairs placental blood flow, reduces perfusion, and causes hypoxia. This defect in deep penetration is associated with the development of multiple adverse pregnancy outcomes, including preeclampsia, intrauterine fetal growth restriction, second and third-trimester fetal death, abruptio placentae, preterm labour, and prelabour rupture of membranes.

It is exactly not known why the normal sequence of events in the development of the uteroplacental circulation does not occur in some pregnancies. Immunological, vascular, environmental, and genetic factors all appear to play a role. These changes are also associated with necrosis and atherosis of the vessels. Such women are at high risk of atherosclerosis and cardiovascular disease in later life. These changes lead to a systemic inflammatory response, i.e., stage II or maternal syndrome.

Defective Trophoblastic Differentiation

This is one of the possible mechanisms responsible for defective trophoblast invasion of the spiral arteries. During normal differentiation, invading trophoblasts alter their adhesion molecule expression from those that are characteristic of epithelial cells (integrin alpha6/beta1, alphav/beta5, E-cadherin) to those of endothelial cells (integrin alpha1/beta1, alphav/beta3, and VE-cadherin). This process is called pseudo-vasculogenesis, which does not occur in women destined to have preeclampsia.

Placental Hypoperfusion, Hypoxia, and Ischemia

Hypoperfusion appears to be both a cause and a consequence of abnormal placental development. A causal relationship between poor placental perfusion, abnormal placental development, and preeclampsia is evidenced by:

- Maternal conditions associated with vascular insufficiency, such as hypertension, diabetes, systemic lupus erythematosus, renal disease, and acquired and inherited thrombophilias. This vascular insufficiency increases the risk of abnormal placentation and preeclampsia.
- Obstetric conditions that increase placental mass without correspondingly increasing the placental blood flow (e.g., hydatidiform mole, hydrops fetalis, diabetes mellitus, multiple gestation), resulting in relative ischemia and preeclampsia.
- Preeclampsia is more common in women living at high altitudes (>3100 meters).

Hypoperfusion, hypoxia, and ischemia are critical components in the pathogenesis of preeclampsia. As pregnancy advances, these conditions are likely to lead to the secretion of antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng). These factors bind to vascular

endothelial growth factor (VEGF) and placental growth factor (PlGF), resulting in widespread maternal vascular inflammation, endothelial dysfunction, and vascular injury. This leads to hypertension, proteinuria, and other manifestations of preeclampsia. sFlt-1 and sEng levels increase in maternal serum months before the occurrence of preeclampsia.

sFlt-1 and PlGF are non-invasive markers of placental health and their ratio has a correlation with the onset and severity of preeclampsia and eclampsia. sFlt1/PlGF ratio has a very high negative predictive value in ruling out the development of preeclampsia within 7 days, adverse maternal outcomes within 14 days or delivery with preeclampsia within 14 days. An sFlt-1/PlGF ratio cut- off of ≤ 38 ruled out preeclampsia within 1 week (negative predictive value [NPV] 99.3%) or 4 weeks (NPV 94.3%), while ratio values above 38 ruled in preeclampsia within 4 weeks (positive predictive value [PPV] > 36%). A gestational-age-adapted cut-offs have also been defined in a study of 1149 patients which showed that the ratios of > 85 (20–33 + 6 weeks) and > 110 (34 weeks to delivery) are strongly associated with the development of preeclampsia. It can also be used to exclude conditions which mimic preeclampsia, including non-HELLP thrombocytopenia, chronic hypertension, chronic kidney disease and covid-19 disease in pregnancy. [2]

Immunological Factors

The loss of maternal immune tolerance to paternally derived placental and fetal antigens can lead to acute graft rejection. This theory also explains the increased risk of early-onset PE in complete molar pregnancies with abundant paternal antigens. Women previously exposed to paternal antigens with the same partner may be immunized against PE. Multiparous women with a new partner are at higher risk of PE. Paternal antigen-specific regulatory T (PAS-Treg) cells remain in the body after delivery but decrease after 10 years. Therefore, multiparous women with a birth interval of 10 years are at risk of preeclampsia.

In vitro fertilization with a sperm donor, intracytoplasmic sperm injection, and pregnancies conceived by oocyte or embryo donation are associated with an increased risk of preeclampsia, supporting the role of immunological intolerance between the mother and fetus in the pathogenesis of preeclampsia.

Black women are at high risk of PE due to a decrease in the immunosuppressive human leukocyte antigen G (HLA-G) expression. Dysregulation of T-helper cell activity and increased NK cell activity also contribute to PE, where excess Th1 activity leads to increased cytokine secretion. Increased dendritic cell infiltration of the placenta is associated with abnormal implantation, altered maternal immunologic response to fetal antigens, and preeclampsia.

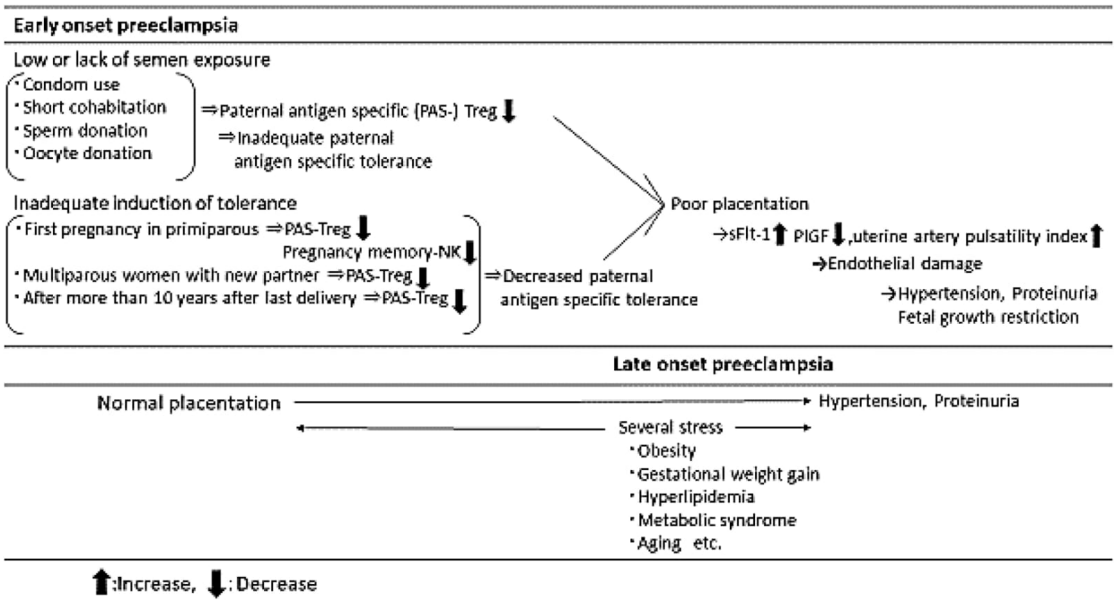

Figure 1 : Pathogenesis of early and late onset preeclampsia.[3]

Increased Pressor Response

There is a decrease in endothelial prostacyclin (PGI2) and an increase in thromboxane A2 (TXA2), leading to increased sensitivity to angiotensin II and vasoconstriction. These changes occur as early as 22 weeks of gestation in women destined to develop PE.
Nitric oxide (NO) is a potent vasodilator. PE is associated with a decrease in nitric oxide synthase expression in the endothelial cells, leading to a decrease in NO synthesis.

Endothelin (ET) is a potent vasoconstrictor. ET-1 levels are high in PE and mediate renal injury. Magnesium sulfate and sildenafil are known to reduce ET-1 concentration.

Genetic Factors

Although most cases of PE are sporadic, genetic factors also play a role in the susceptibility to PE. Women with a family history of preeclampsia (mothers and sisters with PE) have a two to five-fold increased risk of PE compared to primigravid women with no such history. This can be partially explained by imprinted genes—maternal STOX1 missense mutation on 10q22. The risk of preeclampsia is increased more than sevenfold in women who had preeclampsia in their previous pregnancy. Ethnicity also has a predisposition, as seen in African women.

The genes for sFlt-1 and Flt-1 are carried on chromosome 13, and hence fetuses with an extra copy of chromosome 13 have an increased risk of preeclampsia. Alteration in the locus on chromosome 12 (12q23) is associated with the occurrence of HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets).

MicroRNAs (miRNAs), are small single-stranded molecules of 22 nucleotides among non-coding RNAs. These are not involved in protein translation and transcription but are considered as a post-transcriptional regulatory molecule with the ability to degrade mRNA and suppress translation. Some studies have shown a subtle difference in the expression of miRNA in PE. This pattern of miRNA is detected in the placenta, peripheral blood, mesenchymal stem cells. 109 distinct dysregulated miRNAs were identified in comparison to healthy controls. 10 of them (mir-518b, mirR-155, mirR-155-5p, miR-122-5p, miR-517-5p, miR-520a-5p, miR-525-5p, miR-320a, miR-210, and miR-210-3p) have been identified in pathogenesis of PE. More studies are essential in future research to establish their applicability in pathogenesis of PE. [4]

Stage II – Maternal Syndrome

Endothelial Cell Activation and Vasospasm

In response to ischemia, the excess release of antiangiogenic factors and inflammatory leukocyte mediators occurs, leading to endothelial cell dysfunction and vasospasm. Cytokines like TNF-alpha and interleukins cause systemic oxidative stress, leading to a decrease in nitric oxide production and prostaglandin imbalance. This also leads to the production of lipid-laden macrophage foam cells, which cause atherosis and activate systemic microvascular coagulation manifested by thrombocytopenia and increased capillary permeability, as reflected by edema and proteinuria. Vasospasm and interstitial leakage lead to necrosis, haemorrhage, and end organ damage.

Environmental and Maternal Susceptibility Factors

Various dietary and lifestyle factors have been associated with an increased risk of preeclampsia. A possible role of low dietary intake of calcium as a risk factor for preeclampsia is suggested by studies showing the prevention of preeclampsia with calcium supplementation in high-risk women.

High body mass index has a linear relationship with preeclampsia. Obesity increases susceptibility to preeclampsia by inducing chronic inflammation and endothelial dysfunction. [5]

Inflammation

Signs of maternal inflammation are exaggerated in preeclampsia compared to normal pregnancy. Placental hypoxia increases placental necrosis and apoptosis, which releases cell-free fetal DNA (cffDNA) into the maternal circulation, leading to the systemic inflammatory response of preeclampsia. Higher levels of trophoblast cell-free DNA, with a sharp rise three weeks before the clinical signs of preeclampsia become apparent, can occur as early as 17 weeks of gestation. cffDNA concentration of 22.54 Genome Equivalents/ml (GE/ml) in maternal blood at 11–14 weeks of pregnancy has the greatest predictive value for PE with 85.0% sensitivity and 81.8% specificity.[6]

Maternal infection (urinary tract infection and periodontal disease) is also associated with a systemic inflammatory response and preeclampsia.

Conclusion:

Understanding the etiopathogenesis aid clinicians to use biomarkers for diagnosis and prognosis of Pre eclampsia which help in management decisions and improve pregnancy outcome. Also a better understanding of the disease mechanism will improve screening for identification and prevention of cardiovascular disease in these high risk women.

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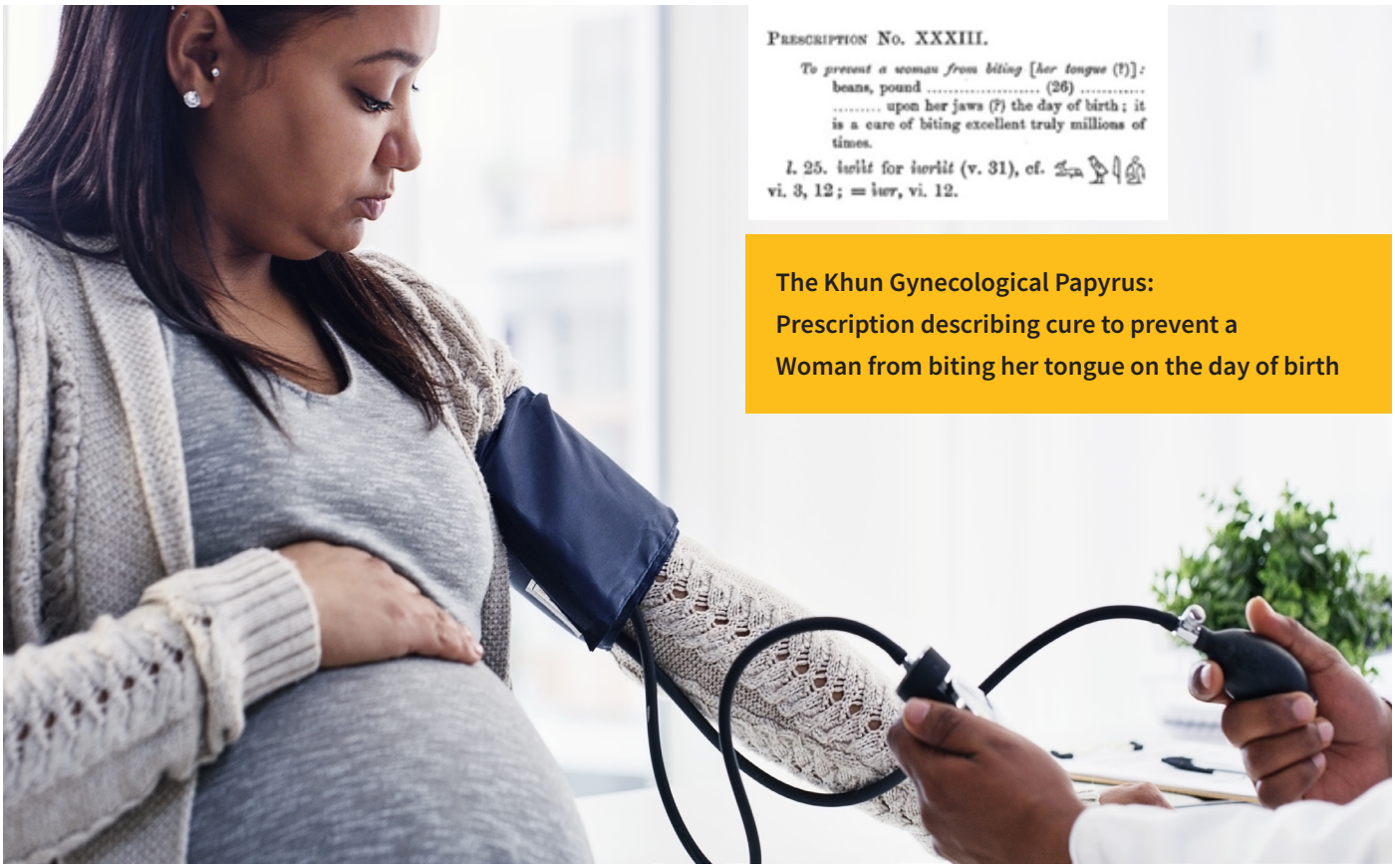

The Khun Gynecological Papyrus:
Prescription describing cure to prevent a
Woman from biting her tongue on the day of birth

Prediction and Prophylaxis of Hypertensive Disorders in Pregnancy

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Introduction

Hypertensive disorder is the most common medical disorder in pregnancy that attributes to 10% of complication in pregnancies.

The more severe form of this hypertension during pregnancy, preeclampsia (PE), affects 4-10% of all pregnant women. This is when hypertension is accompanied with proteinuria, evidence of other maternal organ dysfunction, or uteroplacental dysfunction.

Delay in delivery of patients with PE increases the risk of severe hypertension, resulting in complications such as eclampsia, HELLP syndrome, pulmonary oedema, stroke, renal impairment in the mother. PE accounts for almost 9-26% of maternal deaths in low -income countries and 16% in high- income countries.[1] The fetus may encounter complications such as fetal growth restriction, prematurity and related complications or, in severe cases, fetal demise. Preeclampsia is classified into:[1] early PE (delivery < 34+0 weeks' gestation);[2] preterm PE (delivery < 37+0 weeks' gestation);[3] late-onset PE (delivery ≥ 34+0 weeks' gestation);[4] term PE (delivery ≥ 37+0 weeks' gestation)

Prediction of preeclampsia (PE) in first trimester

A major challenge is to identify the pregnancies at high-risk of early onset PE to enable prevention. The screening strategies for PE involve several parameters in combination[3] which include maternal factors, mean arterial pressure, mean uterine artery pulsatility index, maternal serum pregnancy-associated plasma protein A (PAPP-A) or placental growth factor (PlGF) at 11-14 weeks' gestation

Maternal characteristics

Demographic factors, previous medical history (Chronic hypertension, diabetes mellitus, autoimmune diseases, etc), obstetric history are some risk factors for the development of PE. Demographic factors that require consideration include the maternal age, weight, height, ethnicity, interpregnancy interval, method of conception, smoking or family history of PE.[2] Table 1 shows the maternal risk factors for development of preeclampsia

Table -1 Maternal factors for prediction of PE

	ISSHP 2021	ACOG 2018	NICE 2019	WHO 2011
High- risk	• Prior PE • Chronic hypertension • Pregestational diabetes • Chronic kidney disease • APLA/SLE • ART • Pre-pregnancy BMI >30 kg/m^2	• History of PE • Multifetal gestation • Chronic hypertension • Type 1& type 2 diabetes • Renal disease • APLA/SLE	• Previous hypertensive disease • Chronic kidney disease • APS/SLE • Type 1& type 2 diabetes • Chronic hypertension	• Previous PE • Diabetes • Chronic hypertension • Renal disease • Autoimmune disease • Multiple pregnancy
Moderate risk	• Advance maternal age(>40yrs) • Nulliparity • Multifetal pregnancy • Prior placental abruption • Prior stillbirth • Prior fetal growth restriction	• Family history of PE • Age ≥ 35 years • African American race • Low Socioeconomic status • >10years pregnancy interval • Previous adverse pregnancy outcome • Low birthweight or small for gestational age	• Pregnancy interval of ≥10 years • BMI ≥ 35kg/m^2 • Multifetal pregnancy	

APS- Antiphospholipid antibody Syndrome; SLE: Systemic Lupus Erythematosus; ART: Assisted Reproductive Therapy

Biomarkers

A wide range of potential biomarkers for PE has been identified i.e. maternal blood pressure, uterine artery Doppler PI, and serum biochemical markers. However, none are sufficient to be used as an individual predictor. They are to be used in combination to predict the risk for preeclampsia.

Maternal blood pressure

Mean arterial pressure (MAP) is calculated by dividing the sum of systolic blood pressure with twice the diastolic blood pressure divided by three - (dBP + 1/3 [sBP–dBP]). In a prospective cohort study of 4,749 women, MAP in the first trimester was found to predict 34% of term PE cases, 48% of preterm PE cases, and 60% of early-onset PE cases, with a 10% false-positive rate.[3] Only validated automated blood pressure machines, calibrated at regular intervals are to be used. Average of two measurements in each arm is to be taken after the woman is rested for 5 minutes. Appropriate selection of cuff size and proper patient positioning is essential for accurate blood pressure measurement [4].

Table 2: Errors in blood pressure monitoring

Causes	Effect on blood pressure reading
Improper cuff size	Too large: Decreased by 2-10mmHg Too small: Increased by 2-10mmHg
Improper cuff placement	Increases by 5-50mmHg
Talking during measurement	Increases by up to 10mmHg
Position: -Unsupported back -Improperly or unsupported arm -Feet not resting on floor	Increased by 10mmHg
Full bladder	Increased by 10mmHg

Uterine artery Doppler pulsatility index

It is postulated that the pathogenesis of PE is due to impaired trophoblastic invasion into the maternal spiral arteries leading to inadequate placentation, oxidative stress due to release of inflammatory cytokines and antiangiogenic factors leading to widespread endothelial dysfunction. The uterine artery pulsatility index (PI) is used in the prediction of PE. [5] Measurements can be obtained transabdominally or transvaginally. Adequate training and adherence to a standard ultrasound technique is required to ensure accurate reading.

According to a meta-analysis of 38,611 women, abnormal uterine artery PI in the first trimester was detected in 47.8% of women who developed early PE.[5] Some studies have suggested uterine artery PI are more predictive of PE when done in the first trimester than later in the second trimester. However, this approach may delay the initiation of PE prophylaxis posing a hurdle in PE prevention.[6]
Biochemical markers

Several biochemical markers have been described in the prediction of PE - Placental Growth Factor (PlGF), Pregnancy-associated plasma protein 1 (PAPP-A), soluble Fms-Like Tyrosine Kinase-1 (sFlt1), beta human chorionic gonadotropin (β-hCG), sFlt-1/PlGF ratio, leptin, soluble endoglin (sEng), alpha-fetoprotein (AFP), and Uric Acid (UA). However only two, ie placental growth factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A) have shown significance.

Placental growth factor (PlGF) is a vascular endothelial growth factor (VEGF) in the placenta involved in promoting the improvement and maturation of the placental vascular system. Low PlGF concentrations in early pregnancy are associated with an increased risk of developing early -onset PE. A systematic review and meta-analysis demonstrated that PlGF concentrations can detect 56% of early-onset PE cases with a 9% false-positive rate.[7]

PAPP-A is an insulin-like growth factor-binding protein-4 protease.[8] Low PAPP-A levels are related to insufficient trophoblastic invasion during the first trimester, which is involved in the development of PE.[8] Low PAPP-A levels, i.e., less than the 5th percentile, have been reported to be associated with PE; however, the sensitivity was 7.9% with a false-positive rate of 5.2% (positive-predictive value, 3.5%; negative-predictive value, 97.8%). The predictive value for early PE (sensitivity, 39%; specificity, 87%) was generally better than that for late PE (sensitivity, 29%; specificity, 82%)[2] Although low PAPP-A levels are associated with PE, PAPP-A alone is not sufficient to predict PE. PlGF is more predictive of PE than other biomarkers.[7] Soluble fms-like tyrosine kinase1 (sFlt-1) :PlGF ratio of 38 or lower can accurately rule out the likelihood of developing preeclampsia over the next week, with 99.3%, negative predictive value, among women with suspected preeclampsia and less than 37 weeks.[9]

Combined Risk Assessment for PE

Combined risk assessment for PE involves assessing individual risks by using both maternal risk factors (medical history and characteristics) and biomarkers (MAP, Uterine artery PI, and PlGF, with or without PAPP-A). Though there were many studies involved using these combined risk assessment, may concluded that was a better predictor of preterm PE, however, not of term PE.[2] The largest study to date on the development of early onset PE was reported by Tan et al.[10] At a 1 in 100 risk cut off for PE in white women, the positive screening rate was 10% and the detection rates of preterm and full-term PE were 69% and 40%, respectively. The Bayes theorem based approach developed by Fetal Medicine Foundation incorporates Combined screening by maternal factors, MAP, UTPI and PLGF predicts about 90% of early PE (<34 weeks), 75% of preterm PE (<37 weeks) and 45% of term PE (≥37 weeks), at screen positive rate of 10%.

Table :3. Detection rates for PE with various screening tools

Method of Screening	Detection Rate		
	PE < 34 wks.	PE < 37 wks	PE >37 wks
Maternal factors	58%	50%	38%
Maternal factors Plus			
MAP		60%	43%
MAP, UTPI	80%	70%	44%
MAP, PLGF	85%	73%	47%
MAP, UTPI, PLGF		75%	47%

(Adopted from Fetal Medicine Foundation ,UK, Performance of screening for PE)

In resource poor settings in low/middle-income countries, variations of the first-trimester combined test can be considered but the baseline test should be maternal risk factors combined with mean arterial pressure.

Maternal Ophthalmic Artery Doppler Velocimetry

The ratio of the second to first peak velocity in the maternal Ophthalmic artery Doppler at 11-13+6 weeks scan has been postulated for the prediction of early-onset preeclampsia. Unlike the uterine artery, the change in ophthalmic artery Doppler indices cannot be the direct result of trophoblast invasion and is more likely to be related to maternal hemodynamic changes. More studies are needed to include this in routine practise.[11]

Screening for PE in 2nd and 3rd trimester

Screening at later gestations using maternal history, UTPI, MAP, PLGF, sFlt-1 performs better because of its proximity to the event. This allows for increased surveillance and tailored models of care. Late prophylactic intervention have not been proven to reduce the risk of the disease.[12]

Screening in multifetal gestation:

The same first-trimester combined test for PE in singleton pregnancies can be adapted for screening in twin pregnancies but at a higher screen positive rate.[13]

Prevention of preeclampsia

Physical exercise: A systematic review of 3,322 women showed that exercise reduced the risk of PE in 41% of them, without adverse fetal effects.[14] Moderate intensity exercise are recommended for at least 140 minutes per week for significant results.

Induction of labor:

Induction of labour at 39 weeks to 39 weeks and 4 days has shown to reduce the risks of gestational hypertension and PE compared to expectant management[15] but, adopting such a strategy is controversial, given the increased risk for caesarean sections with increase in Induction of labour.

Acetylsalicylic acid (ASA):

There are many robust trials on the use of ASA and prevention of PE. Crandon et al concluded in their trial that patients who took ASA for any reason were less likely to develop PE than patients who did not take ASA.[16] A landmark study, Aspirin for Evidence- Based Preeclampsia Prevention (ASPRE) was randomised, double blinded, placebo controlled trial involving patients at high risk of PE at 11-14 weeks gestation based on FMF combined screening test algorithm.[17] These patients received 150mg ASA daily at bed time while the other group received placebo. There was significant 62% reduction in preterm PE, however no reduction in the incidence of PE at term was noted.[2]

ASA is safe for both the mother and the fetus. There was no increase in risk of congenital malformation or abnormality in fetal development nor any significant risk in neonatal haemorrhage. Mother may have some gastrointestinal symptoms, there was no evidence of any maternal morbidity.

The ASPRE study discontinued ASA use at 36 weeks' gestation, but treatment until delivery is considered safe. There are no studies evaluating if stopping prophylaxis at an earlier gestational age would have similar efficacy.

Calcium supplementation:

Calcium supplementation in the second half of pregnancy, in women with low calcium intake seems to reduce blood pressure directly, but does not prevent the endothelial damage associated with preeclampsia.[18]

Low molecular weight heparin (LMWH):

There is no recommendation for the use of LMWH to prevent PE. The indication of LMWH should be restricted to women with other comorbidities who require anticoagulation during pregnancy, such as antiphospholipid syndrome.

Table 4: Indications for ASA

	ISSHP 2021	ACOG 2018	NICE 2019	WHO 2011
Indication for aspirin	• Prior PE • Chronic hypertension • Chronic renal disease • Pregestational diabetes • BMI > 30kgm2 • APS/SLE • ART • Multiple Pregnancy	• One or more high risk factors • Two or more moderate risk factors	• One or more high risk factors • Two or more moderate risk factors	• Previous PE • Diabetes • Chronic hypertension • Renal disease • Autoimmune disease • Multiple pregnancy
Dose and timing of ASA	• 100-150mg/day (75-162mg/day) • Start before 16 weeks (at least before 20 weeks)	• 81mg/day • Start before 16 weeks (between 12 and 28 weeks) • Continue until delivery	• 75-150mg/day • Start from 12 weeks • Continue until delivery	• 75mg/day • Start before 20 weeks (as early at 12 weeks if possible)

The usage of anti-oxidants, progesterone, diuretics, & metformin are amongst some drugs which was studied to demonstrate significant reduction in PE. Statins esp. Pravastatin is showing promising results. Unfortunately, none had been recommended in the prevention of PE.

Conclusion

Preeclampsia is a condition that results in high maternal and perinatal morbidity and mortality worldwide. The screening of PE, early detection, prevention and treatment will reduce the related morbidity and mortality in both mother and fetus. Low dose aspirin had shown significant results in PE prevention and should be considered in patients at risk.

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Hunter and Howard demonstrated the presence of a pressor substance in placental and decidual extracts as well as in the plasma of the patients with pre-eclampsia: they named this substance “hysterotonin”

Diagnosis and Monitoring of Hypertensive Disorders in Pregnancy

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Dr. S. Tejaswi

Introduction:

Hypertension in pregnancy is the most common medical disorder and it is associated with high morbidity and mortality. Accurate diagnosis helps in management decisions prognosis assessment and plan for management of long term consequences. After diagnosis and classifying the hypertensive disorder, maternal and fetal surveillance is indicated depending on the maternal and fetal condition to optimize the outcome.

Diagnosis:

Chronic Hypertension

1. Clinical Examination which should include general physical evaluation and features which give clue to secondary causes
2. Lab evaluation to have a baseline reference which include
   - Urine microscopy and urinary protein excretion (ideally, by Urine protein creatinine ratio or urine albumin creatinine ratio
   - Full blood count or platelet count
   - Serum creatinine; and
   - Liver enzymes [AST or ALT).

Additional tests like

- S. electrolytes
- LDH and a blood film (for schistocytes) if haemolysis is suspected, or
- 24-hour urine collection (for proteinuria) and serum albumin if nephrotic syndrome is suspected. If resources are limited, prioritise evaluation of urinary protein excretion and serum creatinine.
- If not done within previous one year ECG and 2DECHO

Ongoing Surveillance:

- Antenatal visits every 2-4 weeks depending on BP level, if poorly controlled weekly visit
- In hospital evaluation, if superimposed pre-eclampsia is suspected.

- Screening for FGR with serial ultrasound examinations to monitor fetal growth, starting at 28-32 weeks, or earlier if there is suspicion.
- Twice weekly fetal surveillance at 32 weeks
- If FGR is present management based on umbilical artery Doppler ultrasound

Gestational Hypertension

The main goal when increased readings are documented for the first time after 20 weeks is to differentiate gestational hypertension from preeclampsia.

This includes history, clinical examination and accurate measurement of BP.

Lab investigations which include

- Measuring proteinuria, Urine PCR<0.3
- (False negatives and false positives occur with dipsticks)
- Platelet count
- Creatinine
- ALT&AST

Angiogenic markers (if available) could be performed; The lack of angiogenic imbalance, as assessed by normal PlGF (≥5th centile for gestational age) or normal sFlt/PlGF ratio, suggests that there is no uteroplacental dysfunction.

- Angiogenic imbalance has high negative predictive value in ruling out: development of proteinuric pre-eclampsia within 7 days, adverse maternal outcomes within 14 days, or delivery with Pre-eclampsia within 14 days when suspected pre-eclampsia is primarily related to hypertension (but not when FGR is a prominent reason.
- Fetal ultrasound (where available) should be performed to assess fetal growth, amniotic fluid volume and umbilical artery Doppler. If FGR is detected, local/national fetal surveillance guidance should be followed.

Ongoing Surveillance:

- Antenatal contacts should occur at least once weekly.
- Proteinuria testing should be performed at each subsequent antenatal visit.
- The risk of adverse maternal outcomes increases with earlier gestational age and/or the onset/ worsening of the following features that women should be informed to report between visits, according to the miniPIERS model.
    - Headache/visual disturbances chest pain/ dyspnoea vaginal bleeding with abdominal pain
    - SBP (if self-monitoring)
    - Dipstick proteinuria (if self- monitoring)
    - Pulse oximetry (if self-monitoring).

Fetal ultrasound should be repeated at least monthly to assess fetal growth, amniotic fluid volume and umbilical artery Doppler. If pre-eclampsia is again suspected on clinical grounds, the woman should be re-evaluated for pre-eclampsia

Preeclampsia

Diagnosis

Clinical examination to identify defining features of Preeclampsia

Lab investigations

- Measurement of proteinuria; Urine PCR>.3 Or 24 Hours Proteinuria >300
- Platelet count
- S. creatinine
- AST & ALT

Uteroplacental dysfunction (e.g., placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death).

Monitoring of Women with Pre-eclampsia

Maternal testing should include Twice weekly monitoring of the following components of the fullPIERS model,

- Gestational age
- Symptoms: chest pain/dyspnoea
- Oxygen saturation
- Platelet count
- Serum creatinine
- AST or ALT

These components, identifies women who are at increased risk of adverse maternal outcomes from 48hrs to 7 days before complication arises and there by helps to modify direct patient care. FULLPIERS can be used at any gestational age.

- The PREP-L and PREP-S models are externally validated prognostic models predicting the risk of complications in early-onset pre-eclampsia.
- PREP models can be used to obtain predictions of adverse maternal outcome risk, including early preterm delivery, by 48 hours (PREP-S) and by discharge (PREP-L), in women with early onset pre-eclampsia in the context of current care.
- PREP-S Prediction model Aims to predict the risk time of adverse outcomes in early onset peeclampsia at a number of times from 2 days to 42 days [Survival Analysis Model]

- Can be used in women up to 34+6 WEEKS
- Factors in the model include
  - Maternal age
  - Gestational age at diagnosis
  - Presence or absence of tendon reflexes
  - Presence or absence of pre-existing conditions (hypertension, renal disease, diabetes mellitus, autoimmune disease, previous pre-eclampsia)
  - Systolic blood pressure
  - Oxygen saturations
  - Platelets
  - Urea
  - Creatinine
  - PCR
  - Whether woman receive antihypertensive or MgSo4 at diagnosis or 24hrs

HDP Gestosis Score:

This is a simple risk model devised for effective screening and prediction of preeclampsia. This score considers all the pregnant women's present and emerging risk factors.

- Each clinical factor is given a score of 1,2,3 based on its severity in the development of preeclampsia. A total score is obtained from detailed history and examination of women. When a pregnant woman's total score is equal to or greater than 3, is labelled as, "at risk for eclampsia"
- After 20 weeks of pregnancy, the women were assessed for the development of pre-eclampsia.
- Gestosis score differs from other scoring system in avoiding the use of USG or biomarkers and making the scoring system easy at a very basic level by calculating the maternal history and baseline tests.

Risk factor	Score
Age > 35 years	1
Age < 19 years	1
Maternal anaemia	1
Obesity (BMI > 30)	1
Primigravida	1
Short duration of sperm exposure (cohabitation)	1
Woman born as small for gestational age	1
Family history of cardiovascular disease	1
Polycystic ovary syndrome	1
Inter pregnancy interval more than 7 years	1
Conceived with Assisted Reproductive (IVF/ ICSI) reatment	1
MAP > 85 mm of Hg	1
Chronic vascular disease (Dyslipidemia)	1
Excessive weight gain during pregnancy	1
Maternal hypothyroidism	2

ADVERSE MATERNAL OUTCOME

The adverse maternal outcomes are a composite derived from Delphi consensus reflecting one/more of:

- Maternal death;
- Neurological complications (eclampsia or posterior reversible encephalopathy syndrome; stroke, transient ischaemic attack, or reversible ischaemic neurological deficit; Glasgow coma score <13);
- Cardiorespiratory complications (infusion of a third parenteral antihypertensive drug; pulmonary oedema; positive inotropic support; myocardial ischaemia or infarction; oxygen saturation <90%; ≥50% inspired oxygen for more than one hour; intubation other than for Caesarean);
- Renal complications (acute renal sufficiency [creatinine >150 µmol/ L] with pre-existing renal disease, acute renal failure with pre-existing renal disease [creatinine >200 µmol/L], dialysis;
- Hepatic (liver dysfunction or capsule haematoma or rupture);
- Haematological (platelet count <50 ×109 per L or transfusion of any blood product); placental abruption; other (severe ascites, Bell's palsy).
- Angiogenic markers (if available) could beperformed;ifthereisangiogenicimbalance; the diagnosis of pre- eclampsia would be strengthened if PlGF<5 and increased Sflt/PlGF ratio of >38 by Roche assay.

Placental Growth Factor

- PlGF-based tests measure the amount of PlGF in blood plasma or serum. PlGF is a protein involved in placental angiogenesis • In normal pregnancy, PlGF levels rise and peak at 26–30 weeks, so when PlGF levels do not rise during pregnancy there may be placental dysfunction.
- Fetal ultrasound should be performed to assess fetal growth, amniotic fluid volume and umbilical & uterine artery Doppler. Fetal ultrasound should be performed once every two weeks to assess fetal growth, amniotic fluid volume and umbilical artery Doppler.
- We recommend that at less than 34 weeks GA when there is fetal FGR - Doppler velocimetry of Ductus Venosus be performed to assess risk of adverse perinatal outcome.
- In hypertensive pregnancy, fetal biophysical profile is not needed.

Conclusion:

- Attempt should be made to diagnose HDP correctly to facilitate optimal care during and after pregnancy. Protocol based maternal and fetal monitoring reduce morbidity and mortality.

SURVEILLANCE IN HDP SUMMARISED

	Chronic hypertension	Chronic hypertension with superimposed PE	Gestational hypertension	Pre-eclampsia without severe features	Pre-eclampsia with severe features
1st T	Home BP check daily Baseline maternal laboratory evaluation 4 weekly Antenatal visits Fetal:NT +EFTS	Same as chronic hypertension Fetal:NT+EFTS	Not applicable	Not applicable	Not applicable
2nd T	Home BP monitoring daily Monthly labs*- U.Albumin/ U.PCR Platelets, ALT, LDH, S.Creatinine Fetal: TIFA - 19- 24 WEEKS + uterine artery doppler	Same as chronic HTN If PE with severe features weekly twice ANC and labs same	At diagnosis CBP, LFT, S. creatinine, Serum Electrolytes Urine Albumin/ Urine PCR Home BP check Monthly ANC and labs same	Same as gestational hypertension same	Weekly ANC with labs same
3rd T	Home BP monitoring daily ANC from 28-35 weeks once in 2weeks Weekly from 36 weeks till 37 weeks	Same as chronic HTN If PE with severe features weekly twice ANC and labs and deliver by 34 weeks	Home BP monitoring ANC once in 2 weeks with labs till 36 weeks, Weekly there after until delivery at 37-38 weeks	Same as gestational HTN To watch for PE with severe features	Inpatient monitoring. Twice weekly mini PE (if normal) Delivery SOS if worsening blood pressures, lab parameters, complications
Fetal Mnitoring*	Fetal wellbeing scan at 28, 32, 36 weeks. Weekly NST from 32-34 weeks till delivery	Fetal wellbeing scan at 28, 32, 36 weeks. Weekly NST from 32-34 weeks till de	Fetal wellbeing scan at 28, 32, 36 weeks. Weekly NST from 32-34 weeks till delivery	Fetal wellbeing scan at 28, 32, 36 weeks. Weekly NST from 32-34 weeks till delivery	Dependent on severity of growth restriction, doppler compromise and maternal condition

* Scan frequency and NST monitoring dependent on growth restriction, doppler compromise and maternal condition.

ANC - Antenatal check-up, HTN- Hypertension, CBP - Complete blood picture, LFT - Liver function test

NT- Nuchal Translucency, NST- Non stress test, ALT - Alanine amino transferase, LDH-Lactate dehydrogenase, TIFA -Total imaging fetal Anamoly, BP - Blood pressure

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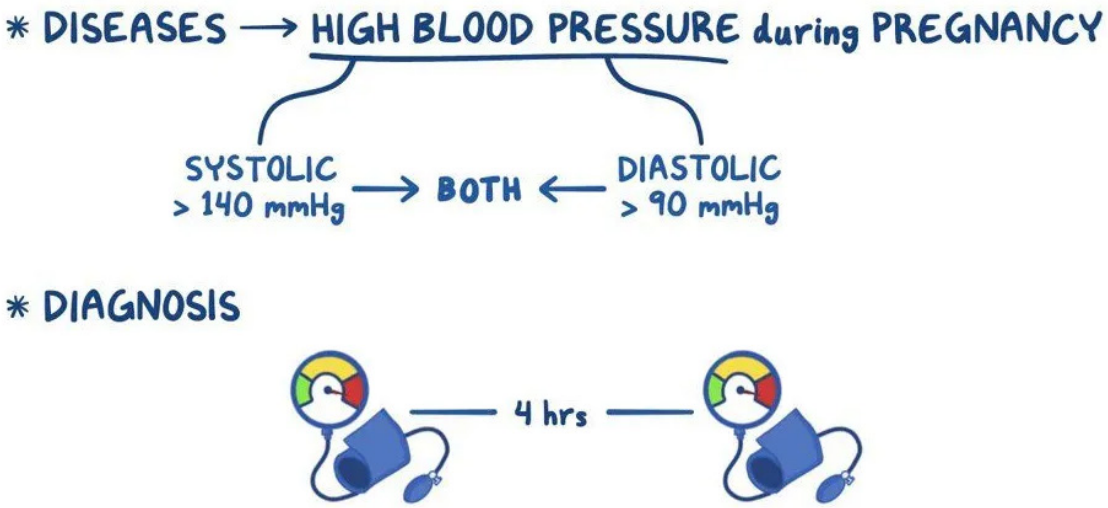
When eclampsia was first described as an entity the only remedies were attempts to bring body " fluids into balance" through altered diet, purging and blood-letting



Management of Hypertensive disorders in Pregnancy Antihypertensive Drugs

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Introduction

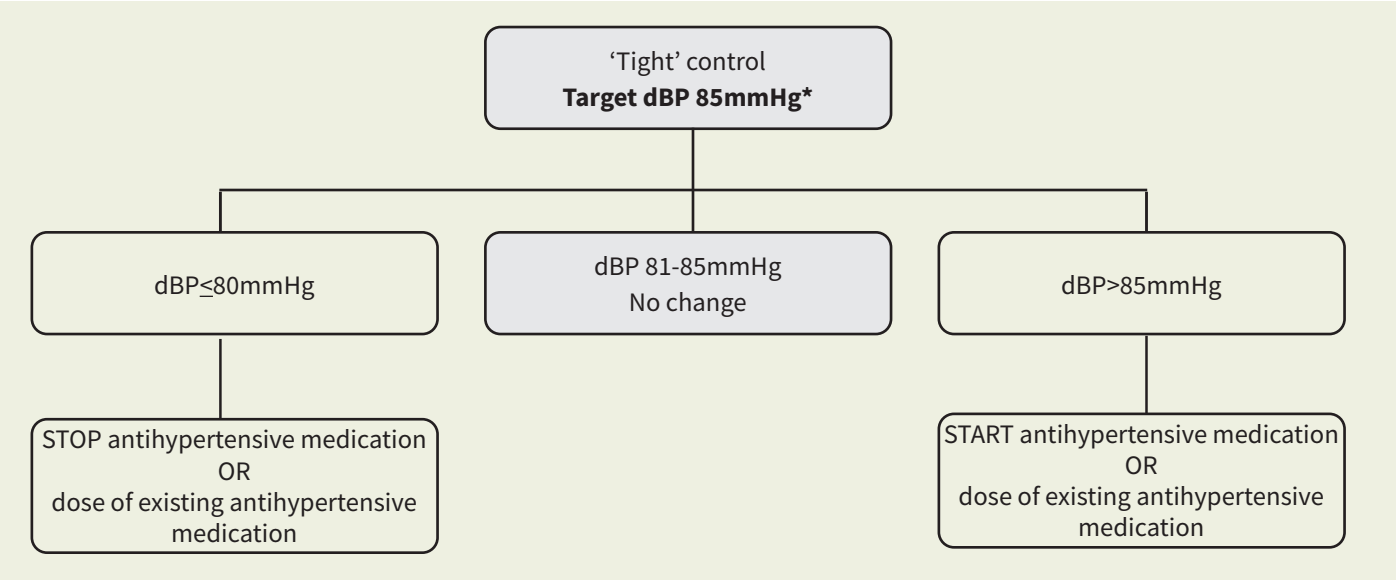
Blood pressure control is important irrespective of the type of HDP because high mean arterial pressure (MAP)exposes the mother to the risk of complications like cerebral bleed. Antihypertensives with established safety profile should be initiated once the diagnosis is confirmed and continued until delivery and also postpartum.

Initiating therapy and target levels:

The management principles include determining threshold for initiating treatment, maintaining target BP with appropriate dose and avoiding drugs with potential adverse fetal effects.

Though it is an ongoing debate whether non severe hypertension should be treated because it does not affect fetal outcome, treatment reduces progression to severe hypertension and hence maternal risk.

Now it is widely accepted that the treatment should be initiated when the Blood Pressure is≥ 140/90mm Hg and the target should be at diastolic BP<85 mm Hg based on the findings of the Control of Hypertension in pregnancy Study (CHIPS)[1] which is also endorsed by ISSHP .The dose should be titrated to maintain target level and it should be continued until delivery and in postpartum. In women with comorbidities also, this is the target. Though the reading recorded on HBPM is lower than hospital reading normally, the recommended target currently is the same for home and hospital BP to minimize risk of hypotension at home.[2]



Algorithm used in CHIPS trial to achieve BP control(from Magee et al Ultrasound Ostet Gynecol 2020;56:7-10)

In the setting of Severe BP which is≥160/110 the mother should be managed in a HDU with medications to reduce the BP urgently.[3,4] It is important to reduce severe BP in 60 minutes to reduce maternal mortality.[4] In women with preeclampsia because of the contracted intravascular volume, short acting drugs cause a precipitous fall in BP. Therefore continuous monitoring is required. Management of severe hypertension is discussed in the chapter on Hypertensive Emergency.

When severe hypertension resolves, oral maintenance dose is to be initiated and continued.

Choice of maintenance drug would depend on whether there are contradictions to a drug, if the woman is able to tolerate it well, her preference and the clinician's experience. Studies have demonstrated hospital variations in antihypertensive use.[5]

Drugs to be avoided: Angiotensin Converting Enzyme Inhibitors, (ACEI) Angiotensin Receptor Blockers,

Betablockers like Atenalol[6] Enalapril, and ACEI can be used in **lactation**[7]

Antihypertensive drugs used in pregnancy

Drug	Dose Starting & Maximum	Pregnancy Category	Adverse effects/Contra indication	Safety in Lactation
Labetalol 1st Line	100mg b.d - 300 qid	C	C/I in Bronchial asthma, HF, HR<60/min or greater than first degree heart block	Safe
Alpha Methyldopa 1st Line	10mg bd- 20mgqid	B	Depression, Sedation, Postural Hypotension Rarely LFT derangement, Hemolytic anemia	Safe (avoided in postpartum)
NifedipineSR 1st Line	10mg bd- 20mgqid	C	Headache, facial Flushing, edema Tachycardia C/I Aortic stenosis	Safe
Hydralazine 2nd Line	25 mgtid- 50 mg tid	C	Reflex tachycardia Headache Not to be used as monotherapy	Safe

Labetalol

It is a peripheral ,selective alpha-1 and non selective beta -1 and 2 receptor adrenergic blocking agent. It is a well tolerated drug .Parenteral Labetalol has an important role in managing severe Hypertension. Beta blockade may mask the the signs of hypoglycemia in insulin treated patients with diabetes. Parentral Labetalol may cause neonatal bradycardia if the woman is in labour and the neonatologist should be informed of the administration.

Alpha Methyldopa

The drug is a centrally acting alpha-2 receptor agonist. Because it is a centrally acting drug it can be associated with sedation but patients become tolerant to the sedative side effect in a week[6] .Though methyldopa can cross the placenta and is secreted in breast milk, no teratogenicity has been reported and it is considered safe for breastfed infants. In view of epidemiological and pharmacological trials suggesting the possibility of the drug as a risk factor for maternal depression, it is is to be avoided in the postpartum period.

Nifedipine

Is a calcium channel blocker.

Because of its rapid onset of action it is useful in treatment of severe Hypertension when used in capsule form. There are three types of Nifedipine preparations, Capsule, immediate -release tablets(retard tablets) and slow-release tablets(LA),with varying half-life and awareness is needed on these different preparations. The rapid acting capsules may cause acute reduction in BP, reflex tachycardia and. may be problematic for placental perfusion and hence close monitoring is required. Overshoot hypotension which occurs with Hydralazine is less frequent with Nifedipine.

Hydralazine

It is a peripheral vasodilator by acting directly on smooth muscles in the arterioles. The drug does not cross placenta in significant amount. Parentally it is

used for acute-onset severe hypertension. It can cause maternal hypotension, headache, palpitations, flushing, anxiety, tremors, vomiting, epigastric pain and fluid retention when used intravenously. Some of these symptoms can be mistaken for symptoms of severe preeclampsia. If the hypotension is severe it can result in maternal oliguria. Uteroplacental flow may also be compromised which causes abruption and fetal distress. Compared to Labetalol, the efficacy to reduce BP was more but adverse effects were also significantly higher in a meta analysis[8]

Diuretics:

Diuretics are usually avoided in pregnancy except when there are indications like left ventricular failure and pulmonary edema.[6]

Maintenance therapy and dose titration in non urgent Hypertension(ISSHP 2021)

		DOSAGE (mg)				
		Low *	If BP not controlled	Medium	If BP not controlled on medium dosage	Hight	Maximum
FIRST-LINE	CAUTION		Proceed to medium dose of same low-dose medication		Consider ADDING another low-dose medication rather than going to a high dose of the same medication(s), for a maximum of 3 medications		
Labetalol	• Contraindicated with poorly-controlled asthma • May cause neonatal bradycardia and hypoglycaemia and warrants newborn screening	100 mg three to four times/day	→	200 mg three to four times/day		300 mg three to four times/day	→ 1200 mg/day
Nifedpine PA or MR	• Contraindicated with aortic stenosis	10 mg two to three times/day	→	20 mg two to three times/day		30 mg two to three times/day	→ 120 mg/day
Nifedipine XL or LA		30 mg once/day	→	30 mg two times/day or 60 mg once/day		30 mg each morning and 60 each evening	→ 120 mg/day
Methyldopa	• May cause maternal depression	250 mg three to four times/day	→	500 mg three to four times/day		750 mg three times/day	→ 2250 mg/day

Conclusion:

Irrespective of underlying cause BP should be managed to prevent severe complications . Decision regarding initiating therapy at appropriate time, with the correct choice of Drug ,dosage and maintaining the target level of BP are important in achieving good maternal and fetal outcome.

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Mauriceau, an eminent French physician who has contributed to literature on Eclampsia wrote in 1694, the mortal danger to mother and fetus is greater when the mother does not recover consciousness in between seizures, primigravida are at far greater risk, convulsions during pregnancy are more dangerous than those after delivery and when the fetus is dead

Management of Hypertensive Emergency

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Dr. Siri Y.

Introduction

Hypertensive emergency in obstetrics is defined as acute-onset, severe hypertension with a blood pressure of more than or equal to 160/110 mm Hg which is persistent over 15 minutes during pregnancy and the postpartum period.[1] It is often associated with end-organ damage which includes the brain, the eyes, the heart, the liver, the kidneys, and central and peripheral arteries[2] Irrespective of the underlying cause, this condition requires immediate intervention and intensive care as markedly elevated blood pressure if not treated promptly can lead to Hypertension-mediated end-organ damage like cerebral hemorrhage, pulmonary edema, myocardial infarction, and eclampsia.[3]

Epidemiology

Hypertensive emergencies affect 1% of women with hypertensive disorders of pregnancy with a significantly higher mortality rate if not treated immediately and women with pre-existing hypertension, cardiovascular and renal diseases are more vulnerable.

Maternal Complications

Women with acute uncontrolled hypertension can present with stroke (25%), pulmonary edema (23%), congestive heart failure (12%), acute kidney injury, and intracranial hemorrhage, aortic dissection, eclampsia, and retinal involvement.[4] Among these, the cerebral injury was found to be the most common cause of maternal death.[5] The various maternal complications which arise due to uncontrolled hypertension is discussed in the chapter on Crisis in Pre eclampsia.

Severe Maternal Morbidity

One of the strategies to reduce maternal mortality is to investigate factors leading to severe maternal morbidity

which precedes death. The grave circumstance that is faced by a woman due to severe morbidity is like those just before death. Hypertensive disorders of pregnancy along with hemorrhage are the common causes of severe maternal morbidity and mortality in both high- and low-income countries. The incidence of severe maternal morbidity in hypertensive emergencies is as high as 10%.[6]

Fetal Complications

The pathophysiology of hypertensive disorders of pregnancy resulting in uteroplacental and fetoplacental insufficiency contributes to fetal growth restriction, preterm delivery and stillbirth, respiratory distress, intensive care unit admission, and neonatal deaths. The risk of fetal growth restriction and stillbirth is one and a half times higher in pregnancies affected with hypertension.[7] The end-organ damage that is caused by an acute rise in blood pressure also involves the placenta leading to abruption, resulting in stillbirth within no time if not intervened immediately.

Diagnosis

Blood Pressure:

Hypertensive emergency in pregnancy is diagnosed when a woman presents with either of the following:

- A systolic blood pressure of 160 mm Hg or more and diastolic blood pressure of 110 mm Hg or more are recorded twice at an interval of 15 minutes.
- A single record of systolic blood pressure more than or equal to 160 mm Hg or more and diastolic blood pressure of 110 mm Hg or more in the presence of symptoms related to end-organ damage.

Signs and Symptoms:

The clinical manifestation depends on the organ involved and triaging immediately based on the symptoms at arrival is an essential step. Around 22% of women present with shortness of breath, 27% with chest pain, and 21% with neurological symptoms like headache, visual disturbances, and altered consciousness which indicate hypertension mediated-end organ damage. The woman should be admitted into a high dependency unit and treated immediately to prevent progression to permanent damage.

Maternal Evaluation

A complete history of drug usage, past medical history, and present medications should be noted. The physical examination directed towards evaluating for end-organ damage should be undertaken. Oxygen saturation of less than 93%, respiratory rate above 24 per minute, and grunting or gurgling sounds on auscultation indicate pulmonary edema.

Laboratory evaluation should include the following:

- Hemogram to look for hemolysis and thrombocytopenia indicating endothelial damage
- Serum creatinine, 24-hour urine protein, or urinary spot protein creatinine ratio to rule out renal involvement
- Liver function tests wherein if the liver enzymes are elevated twice the normal range are considered as significant
- Serum Electrolytes and Lactate Dehydrogenase
- ECG and chest X-ray when suspecting pulmonary edema
- Imaging in the presence of neurological symptoms to rule out intracranial hemorrhage, cerebral thrombosis, posterior reversible encephalopathy syndrome
- Ultrasound abdomen if there is abdominal pain to look for hepatic hematoma and rupture.

Fetal Evaluation:

If the fetus is viable, fetal evaluation should include:

- Fetal heart rate monitoring during maternal stabilization
- Ultrasound to rule out fetal growth restriction amniotic fluid assessment
- Doppler study to look for uteroplacental or fetoplacental insufficiency

Management

The adverse maternal and fetal outcomes in a hypertensive emergency can be prevented by early identification and initiation of the treatment. Maternal Early Warning Trigger tool (MEWT) is one of the clinical tools which is designed to identify women with abnormal physiology and addresses four major causes of maternal morbidity and mortality. The hypertension pathway is one among them and overlaps with the cardiovascular dysfunction pathway.[8] The pathway is activated when the blood pressure is persistently elevated to 160/110 mm Hg and above or in the presence of headache, visual disturbances, vomiting, and abdominal pain. Anti-hypertensive drugs should be administered within one hour, maternal and fetal evaluation to be done and magnesium sulfate infusion to be given if blood pressure remains constantly elevated or in the presence of clinical symptoms despite well-controlled blood pressures. Pulmonary edema is suspected if a woman with severe hypertension presents with a low oxygen saturation of less than 93% or a respiratory rate of more than 24 per minute. In the presence of signs indicating respiratory failure, overlap with the cardiopulmonary pathway to rule out other cardiac causes to be thought out and evaluated accordingly. (Figure 1)

Reducing blood pressure expeditiously is the primary goal in the management of the hypertensive emergency. Antihypertensive treatment should be initiated immediately to reduce systolic blood pressure to less than 160 mm Hg maintaining at 140 to 150 mm Hg and diastolic blood pressure to be maintained at 90 to 100 mm Hg. Sudden fall in blood pressure results in ischemia, infarction, and uteroplacental hypoperfusion leading to adverse maternal and fetal outcomes. Considering the adverse effects of sudden hypotension, the aim of initiating treatment should be to reduce the mean arterial pressure by 15 to 25 %.

Aniti-Hyprtensive Drugs For Hypertensive Emergency in Pregnancy:

The anti-hypertensive therapy for acute hypertension is the same in antepartum and postpartum (up to 6 weeks after delivery) period.

Labetalol and Hydralazine are administered intravenously and immediate release Nifedipine is administered orally. No significant difference was found among these three drugs concerning safety and efficacy and any of these drugs can be used based on the clinical situation.[9] In the absence of intravenous access immediate-release oral Nifedipine is the preferred choice of drug (Table1)[10]

First line antihypertensives are discussed in the chapter on Antihypertensive drugs.(Chapter 5)

The algorithms for drug dosage and escalation according to the response for the first-line antihypertensive drugs are depicted in Figures 2, 3, and 4.

In case of resistant hypertension wherein the first-line drugs have failed to reduce blood pressure, the second-line antihypertensive drugs to be considered are Nicardipine, Esmolol, Nitro-glycerine, Sodium Nitroprusside.

- Nicardipine is a second-line antihypertensive agent which is administered intravenously in a hypertensive emergency. This is another calcium channel blocker belonging to the dihydropyridine class which acts on the smooth muscle of blood vessels reducing peripheral vascular resistance. It has a rapid onset of action within 5 to 15 minutes and a short half-life which allows for easy titration. It brings about general arterial dilatation with selective action on cerebrovascular and coronary arteries and thus is a good option in preventing cerebral and cardiac ischemia. It increases the stroke volume without affecting uteroplacental or fetal circulation.[11] It is given as an infusion of 2.5 to 5 mg/hr up to a maximum of 15 mg/hr until the desired response. Its side effects are headache, flushing, and dizziness and are contraindicated in severe aortic stenosis.
- Nitroglycerine is an anti-hypertensive drug that is administered intravenously and is particularly useful in the presence of pulmonary edema. It is given as an infusion of 1 to 10 mg/hr.
- Esmolol is a short-acting cardioselective beta-1 blocker with an onset of action within 60 seconds which lasts for 15 to 30 minutes. It is given as an intravenous bolus of 500 mcg/Kg, with a maintenance dose of 50 mcg/Kg/min. It is increased by 50 mcg/Kg/min every 4 minutes to a maximum dose of 300 mcg/Kg/min. It is a preferred drug in acute myocardial infarction and aortic dissection and is contraindicated in congestive heart failure, first-degree heart block, bronchospasm, and maternal bradycardia. It can also cross the placenta and cause fetal bradycardia.
- Sodium nitroprusside is a fast-acting drug with a short period of action that acts by releasing nitric oxide. It is given as an intravenous infusion of 0.25 mcg/Kg/min and increased by 0.25 to 0.5 mcg/Kg/min every 2 -3 minutes with the onset of action within 1 minute lasting for 2 to 3 minutes. It is indicated in aortic dissection, left ventricular dysfunction, and pulmonary edema. When given for a prolonged duration or in the presence of renal insufficiency, cyanide toxicity is an important concern and hence should be considered as a last resort when the hypertension is not controlled by other agents.

The choice of the anti-hypertensive drug also depends on the organ involved as shown in Table 2.[12]

Seizure prophylaxis

In addition to immediate control of severe hypertension in women with preeclampsia, simultaneous administration of magnesium sulfate has proven to significantly reduce the incidence of eclampsia halving the rate in both antenatal and postpartum periods.[13]

Fetal assessment

This depends on the gestational age at presentation wherein the fetal monitoring commences after the period of viability and all women with a hypertensive emergency should be delivered after 34 weeks after steroid cover if she is stable and blood pressure is under control.

Conclusion:

Acute and severe hypertension is an emergency that needs a systematic approach to diagnosing and implementing the treatment regime to avoid end-organ-damage. Hence, it is imperative that all the health care workers are aware of the management protocol. Implementation of treatment algorithms has been shown to reduce the time taken for initiating therapy and improve the qulity of care.

Table 1 : First line anti-hypertensive drugs used in a hypertensive emergency

Labetalol		Hydralazine	Nifedipine
Mechanism of action	Selective alpha-1 and beta-blocker	Direct vasodilator	Calcium channel blocker
Onset of action	5 to 10 minutes	10 minutes	5 to 10 minutes
Duration of action	2 to 6 hours	12 hours	2 to 4 hours
Dose	10 to 20 mg IV bolus over 2 minutes repeated every 20 minutes escalating the bolus up to 80 mg maximum of 300 mg	2.5 to 5 mg IV slowly Repeated every 20 to 40 minutes	10 to 20 mg oral repeated every 30 minutes maximumof 50 mg
Contraindications	Asthma, bradycardia, heart block, Congestive heart failure, cardiogenic shock	Mitral valve rheumatic heart disease, coronary artery disease, stroke	Aortic stenosis, coronary artery disease, severe hypotension, acute MI, cardiogenic shock
Pregnancy Category	C	C	C

American College of Obstetricians and Gynaecologists Taskforce on Hypertension in Pregnancy. Hypertension in pregnancy.

Table 2: Hypertensive Emergencies requiring immediate blood pressure control:

Clinical Presentation	Timeline and Target BP	First-Line Treatment
Malignant hypertension with or without TMA or acute renal failure	Several hours, MAP –20% to –25%	Labetalol Nicardipine
Hypertensive encephalopathy	Immediate, MAP–20% to –25%	Labetalol Nicardipine
Acute ischaemic stroke and SBP >220 mm Hg or DBP >120 mm Hg	1 hour, MAP –15%	Labetalol Nicardipine
Acute ischaemic stroke with an indication for thrombolytic therapy and SBP >185 mm Hg or DBP >110 mm Hg	1 hour, MAP –15%	Labetalol Nicardipine
Acute hemorrhagic stroke and SBP >180 mm Hg	Immediate, 130<SBP<180 mm Hg	Labetalol Nicardipine
Acute coronary event Immediate, SBP	Immediate, SBP <140mm Hg	Nitroglycerine Labetalol
Acute cardiogenic pulmonary edema	Immediate, SBP <140mm Hg	Nitroprusside or Nitroglycerine (with loop diuretic)
Acute aortic disease	Immediate, SBP <120 mm Hg and heart rate<60 bpm	Esmolol and Nitroprusside or Nitroglycerine or Nicardipine
Eclampsia and severe preeclampsia/HELLP	Immediate, SBP <160 mm Hg and DBP<105 mm Hg	Labetalol or Nicardipine and Magnesium Sulphate

TMA – Thrombotic Microangiopathy, MAP – Mean Arterial Pressure, SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure.

Figure 1: MEWT Hypertension pathway:

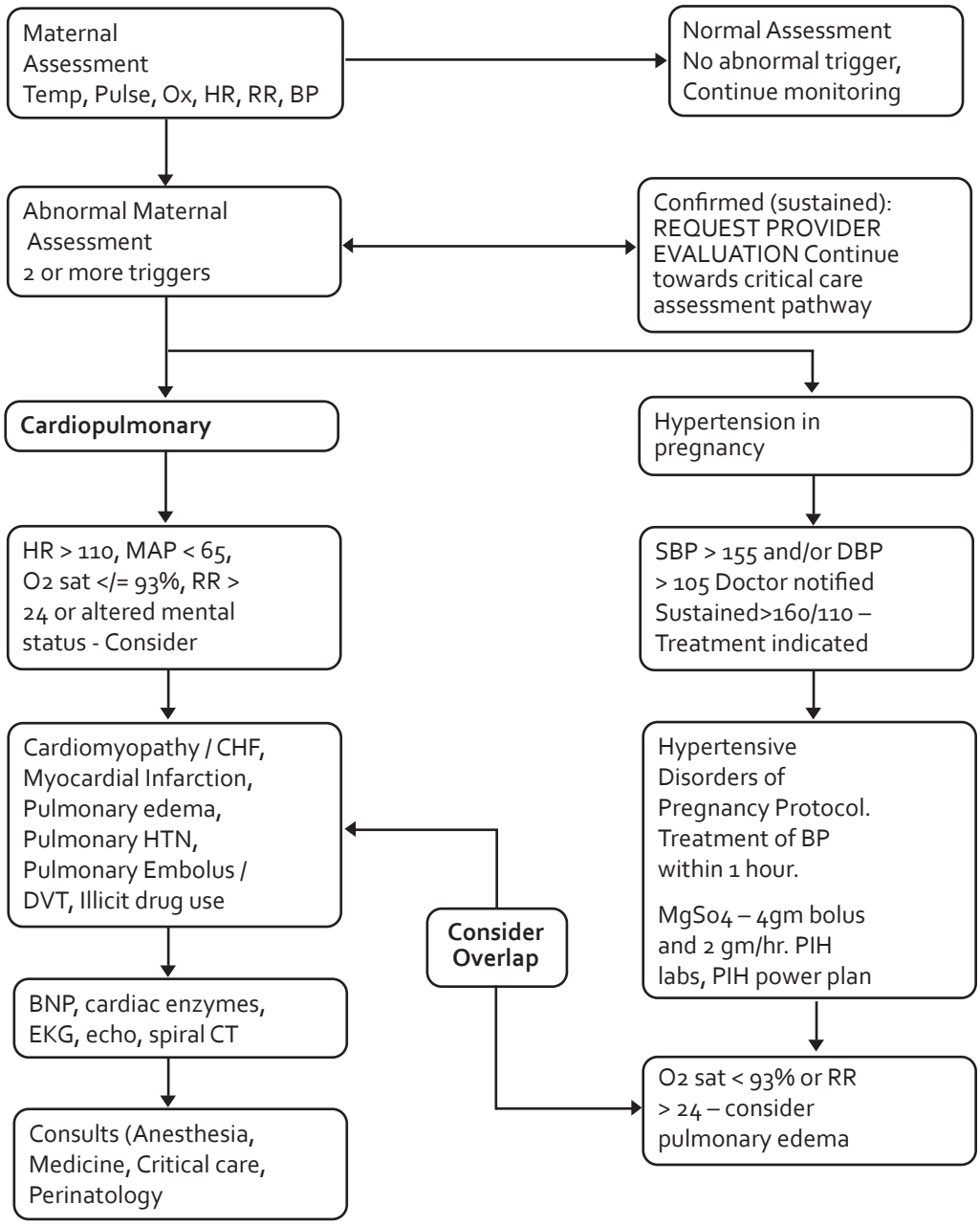


Figure 2: Labetalol Algorithm

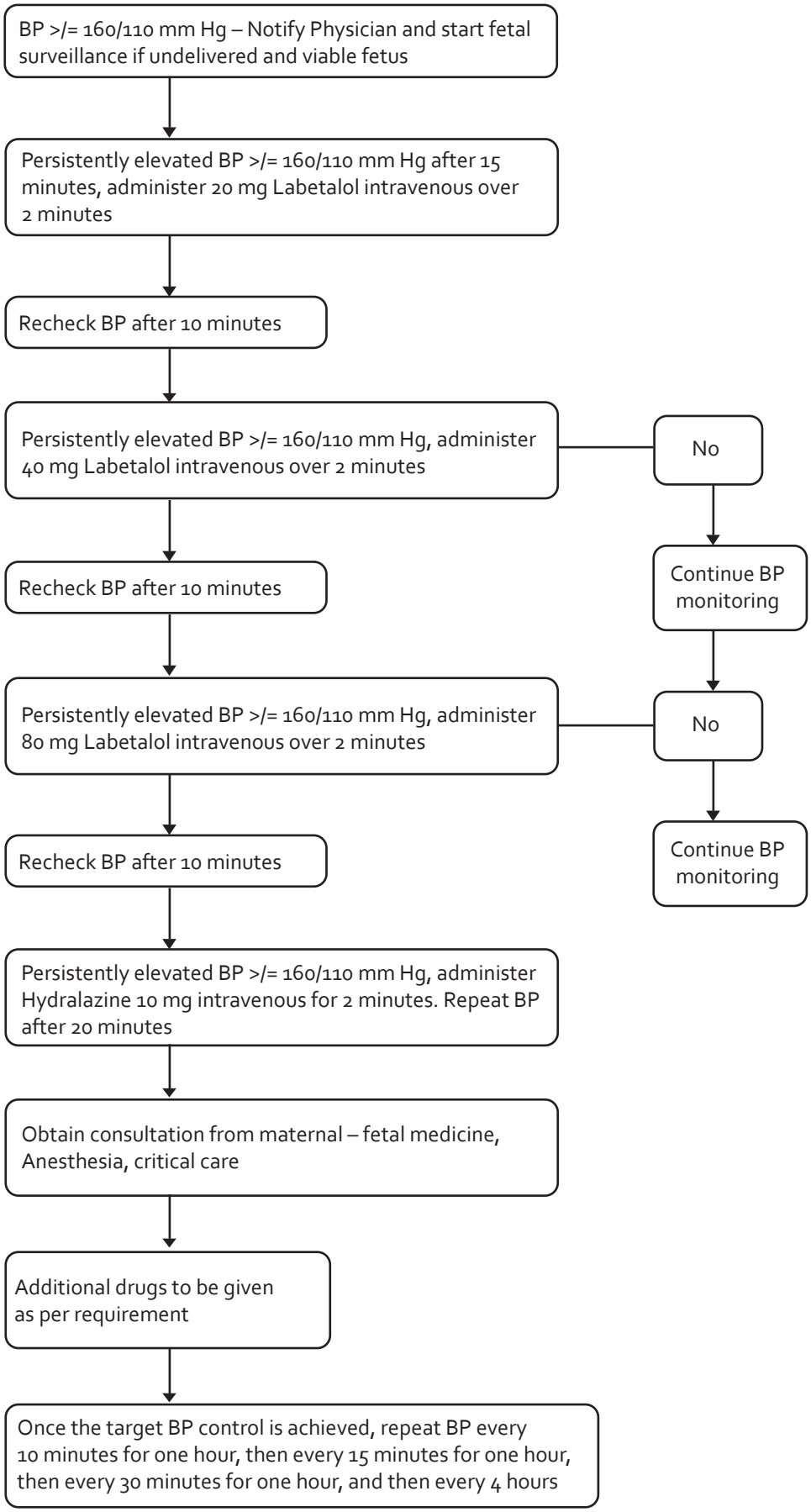


Figure 3: Hydralazine Algorithm

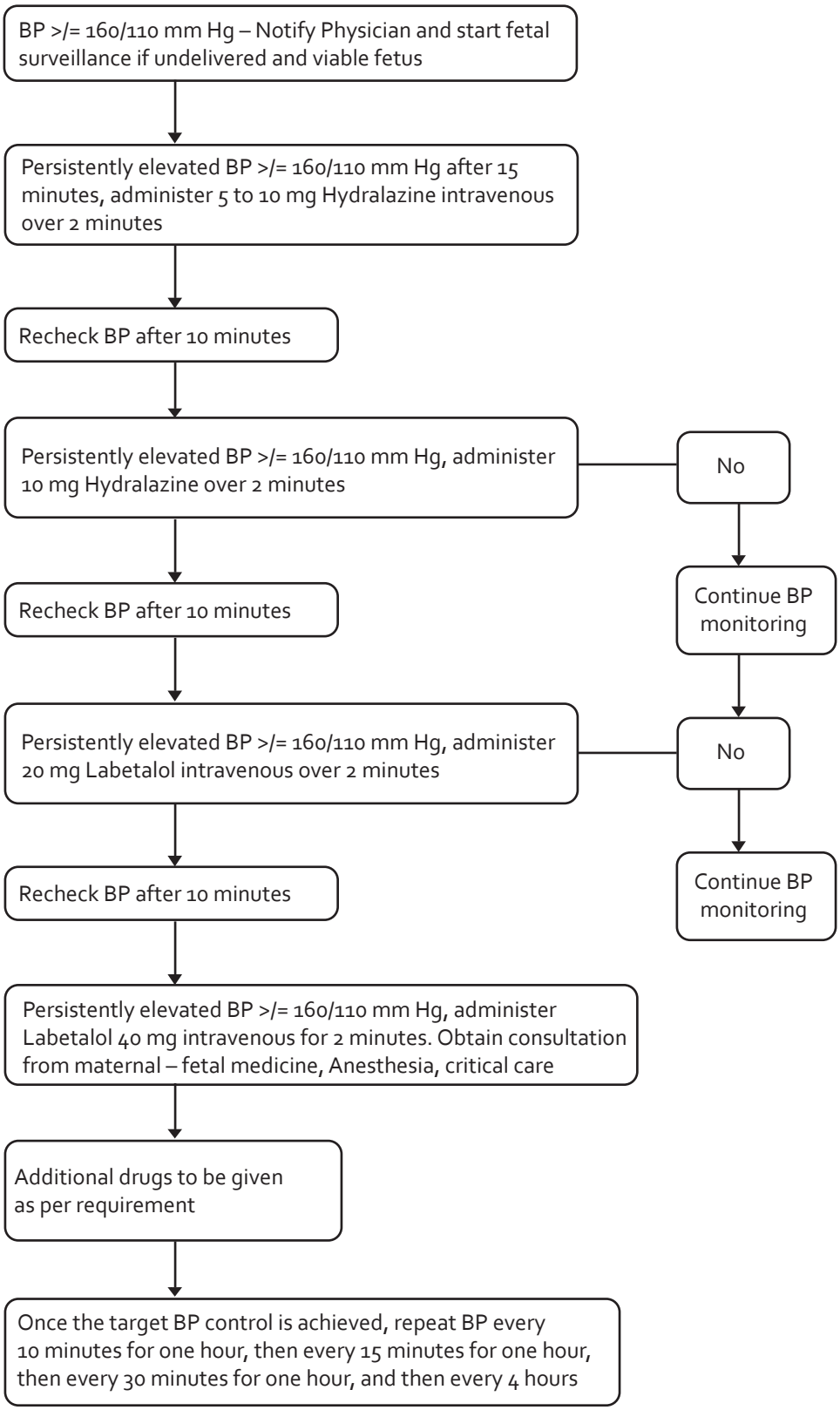


Figure 4: Nifedipine Algorithm

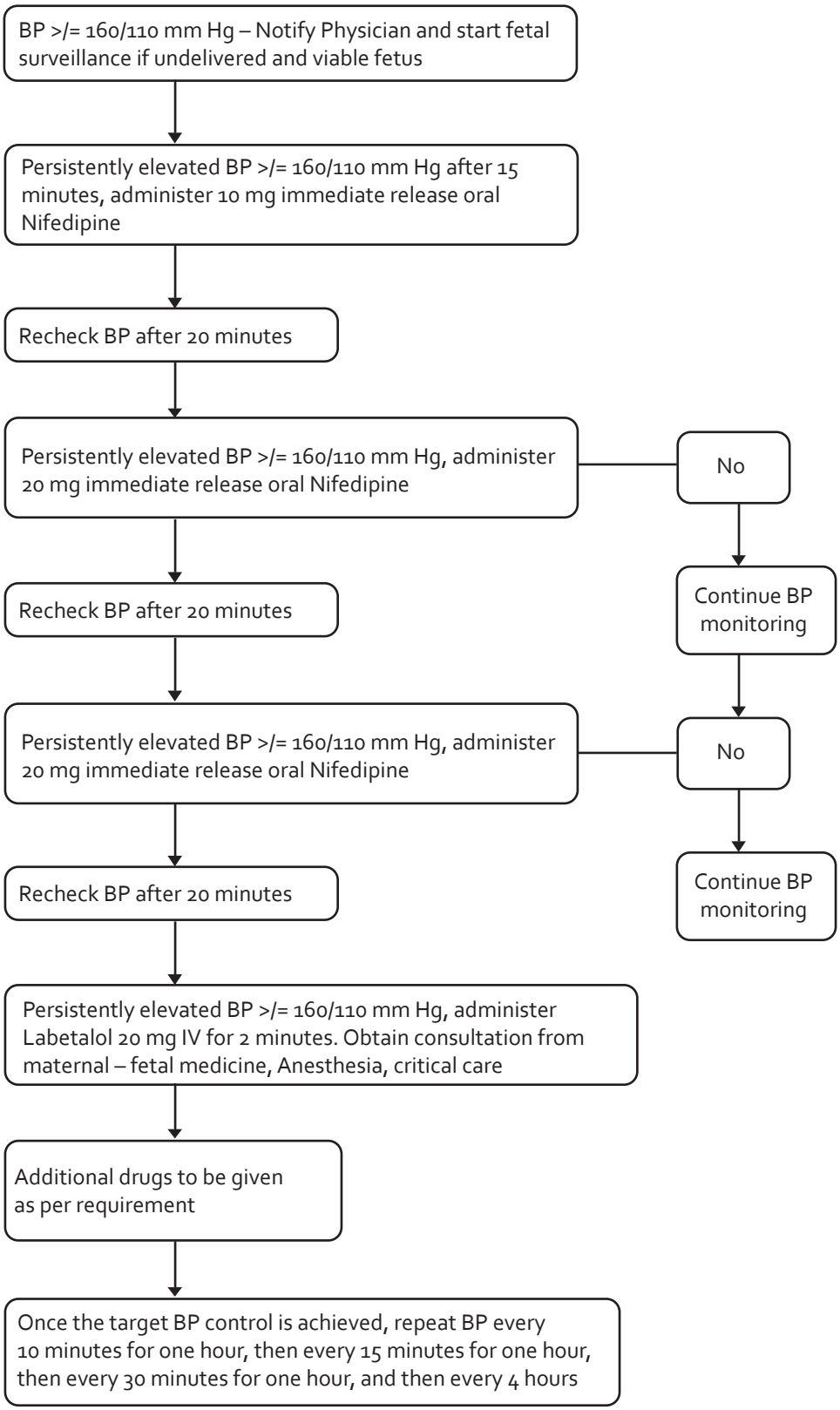
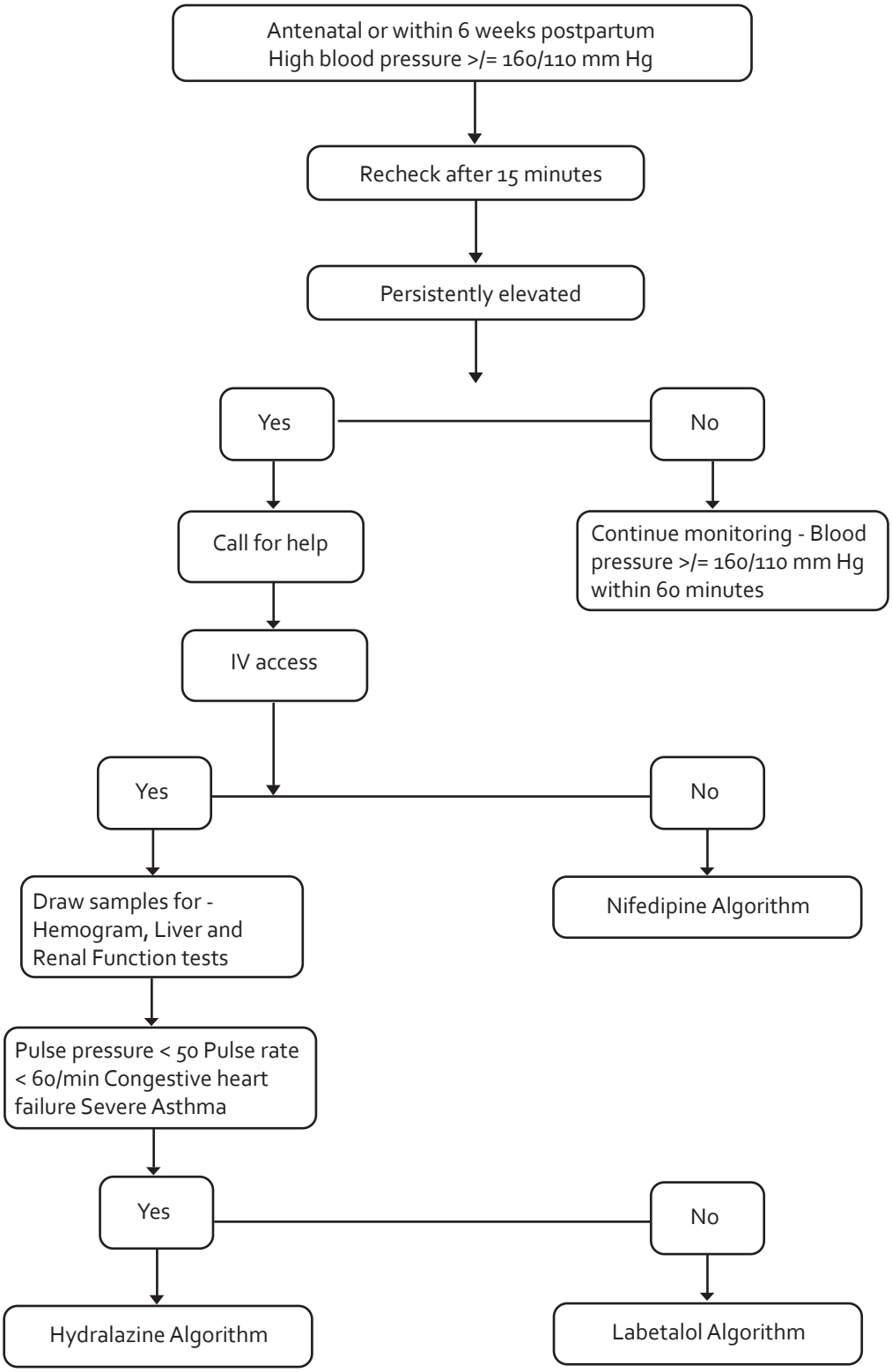


Figure 5: Treatment Algorithm for Hypertesnive Emergency



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Intrathecal injection of Mgso4 was used in tetanus to control seizures which prompted Horn to use it in eclampsia in 1906.Pritchard demonstrated by combined intravenous and intramuscular administration of MgSo4 in 154 consecutive cases of eclampsia there was no maternal death.

Obstetric Management of Hypertensive Disorders in Pregnancy

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Introduction

Management principles of Hypertensives disorders in pregnancy include treating blood pressure with antihypertensives, maternal and fetal surveillance, seizure prophylaxis when indicated and timed birth. The definitive treatment of pre eclampsia is delivery

Antepartum management

Antihypertensives should be initiated as discussed in the chapter on antihypertensive drugs (chapter5) and continued to maintain target BP. Home BP monitoring (HBPM) is suggested and hospital readings are to be obtained during antenatal visits. The frequency of ANC visits should be according to protocol along with lab investigations (Urine Albumin, Platelet count, S. Creatinine, ALT and LDH) and Fetal wellbeing during the visit is monitored. Antenatal corticosteroids are indicated when there is increased risk of delivery before 34 weeks.[1] The mother should be guided about imminent symptoms and instructed to seek medical care if she experiences them. The Maternal Early Warning Tool (MEWT) should be activated appropriately for reducing the incidence of eclampsia.

Place of delivery

Women diagnosed with any form of HDP necessitate delivery at a facility equipped to offer emergency obstetric and neonatal care.

Timing of birth

Recommendations

Indications for delivery with any HDP at any gestational age include[2,3]

- Abnormal neurological features (such as eclampsia, severe intractable headache or repeated visual scotomata);
- Repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents;
- Pulmonary oedema;
- Progressive thrombocytopenia or platelet count <50x109 / L
- Transfusion of any blood product

- Rising S. Creatinine
- Rising liver enzymes
- INR>2 in the absence of DIC or Warfarin ,Hepatic hematoma, Rupture
- Abruption with evidence of maternal or fetal compromise; or
- Non-reassuring fetal status (including death)

Chronic hypertension

If there is no maternal or fetal indication for earlier delivery with BP under control without antihypertensives, delivery is indicated at 37 to 39 completed weeks (ACOG) and if on medications at 37 weeks.[4,5] In women with any of the clinical or lab features mentioned above ,delivery is indicated at 34 weeks. Those women who develop superimposed severe pre eclampsia are also delivered at 34 weeks.[5] In those with superimposed PE without severe features delivery is indicated at 37 weeks.[5]

Gestational Hypertension and PE without severe features

Delivery is indicated at 37 weeks in these women.[1,4] (ACOG, NICE, FIGO, FOGSI)

If delivery is indicated at less than 34 weeks of gestation, administration of corticosteroids for fetal lung maturation is recommended, however, delaying delivery for optimal corticosteroid exposure may not always be advisable. Maternal or fetal deterioration may preclude completion of the course of steroid treatment.(ACOG, NICE)

Fetal and maternal monitoring is indicated until delivery as discussed in the chapter on Diagnosis and Monitoring in Hypertensive Disorders in pregnancy. Severe gestational hypertension should be managed as PE with severe features.

PE with severe features

Delivery is indicated at 34 weeks.[1,4]

Mode of delivery

Mode of delivery depends on standard obstetric indication but labour induction might be difficult at decreasing gestational age in cases of PE with severe features which might necessitates caesarean section.[6]

Intrapartum care in HDP

Intrapartum BP fluctuations should be avoided and euvolemia should be maintained. During labour, mother should be monitored for severe hypertension and symptoms of pre eclampsia because even in women with chronic hypertension and gestational hypertension pre eclampsia can develop intrapartum or postpartum. Along with BP control seizure prophylaxis with Mgso4 in women with PE with severe features is an important aspect of management.[7]

Mg So4 is also indicated as neuroprotective agent in preterm pre eclampsia requiring delivery <32 weeks.

Duration of second stage of labour should be reduced in the presence of imminent symptoms and active management of the third stage of labour, including the administration of oxytocin either intravenously (5 units) or intramuscularly (10 units), is recommended, especially if there are indications of thrombocytopenia or coagulopathy.

Ergometrine maleate should not be administered to women with any hypertensive disorder of pregnancy, particularly pre-eclampsia or gestational hypertension; alternative oxytocics should be considered

Intrapartum management is discussed in the chapter on Anesthetist perspective on management of pre eclampsia.

Complications and crises which arise should be managed asdiscussed in the respective chapters.

Postpartum care

Antihypertensives should be continued, vitals and urine output should be monitored and lab parameters repeated in patients on MgSo4 prophylaxis. MgSo4 infusion is indicated for 24 hours after delivery or following last seizure.

When indicated NSAIDs can be used. Thromboprophylaxis should be administered for 7-10 days. . BP monitoring is continued at regular intervals till discharge

The highest BP values may occur after the women leave the monitored setting, hence caution is required in monitoring these women. They should be treated with antihypertensives and MgSo4 if symptomatic. BP monitoring should be continued at home for 10-14 days as some women develop pre eclampsia for the first time postpartum.

Conclusion:

Initiating antihypertensives at diagnosis, maintaining BP to target, antenatal and maternal fetal surveillance, timed birth and intrapartum and postpartum care in a comprehensive unit with multidisciplinary team result in good outcome in HDP.

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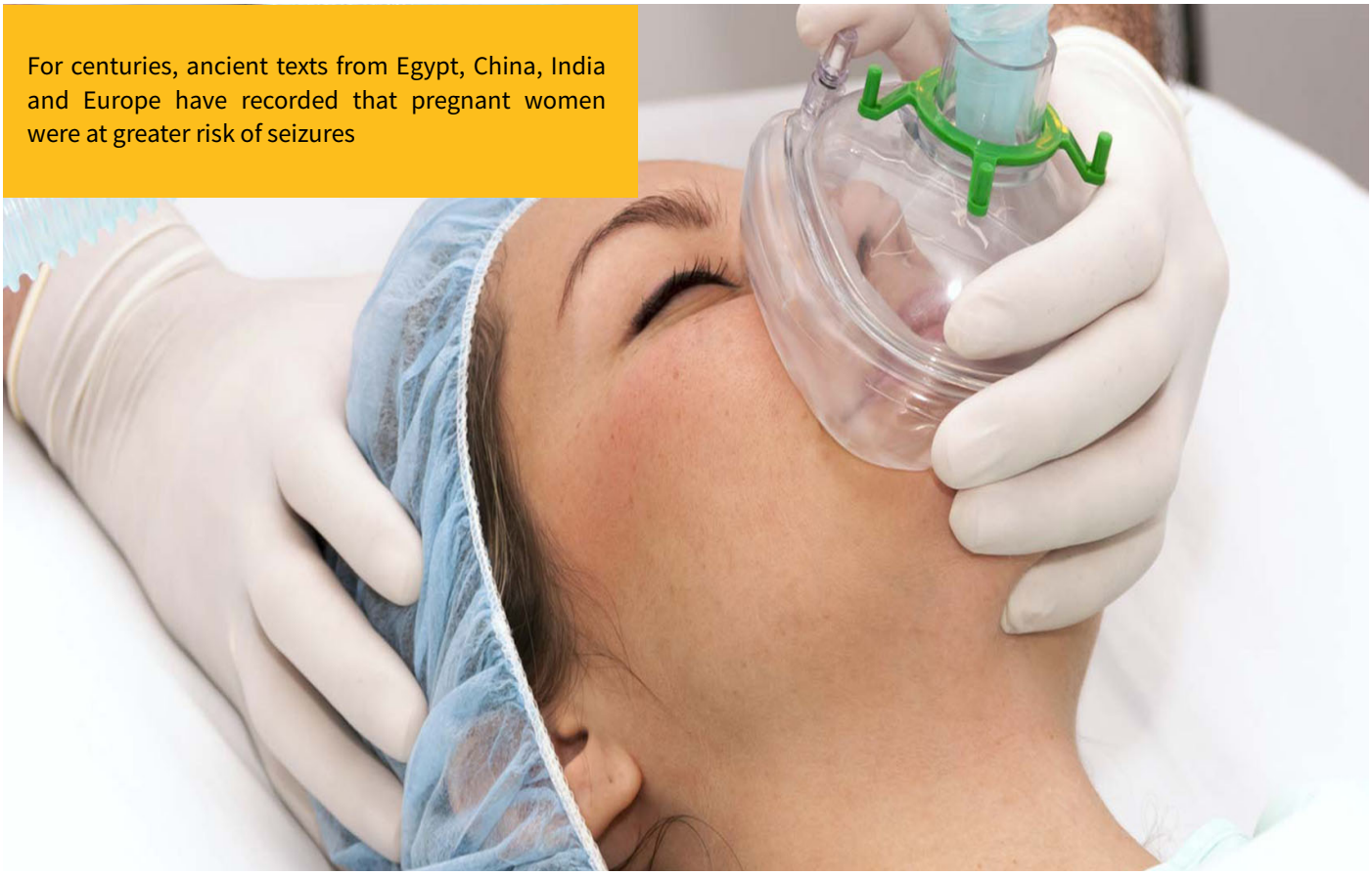
For centuries, ancient texts from Egypt, China, India and Europe have recorded that pregnant women were at greater risk of seizures



Anaesthetist perspective in managing Pre-eclampsia mother

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Hypertensive disorders of pregnancy (HDP) which includes gestational hypertension, chronic hypertension, pre-eclampsia (PE) and eclampsia are one of the most common clinical scenarios we come across in obstetric practice. Globally the average incidence of preeclampsia is 4.6% and eclampsia is 1.4%, but it is much higher in the developing countries.[1] The incidence of HDP increased by 10.92% between 1990 and 2019, while the number of deaths decreased by 30.05% in the same period.[2] Preoperative or pre-labour optimization, planning anaesthesia with a judgement of risk vs benefit for the method chosen and managing complications associated with HDP, are the key areas where the anaesthetist has a vital role to play.

Preoperative optimisation

Anti-hypertensive management: Anti-hypertensive treatment is initiated at the onset of severe PE with persistent systolic blood pressure >160 mm of Hg or diastolic blood pressure > 110 mm of Hg. First line antihypertensive medications are labetalol, nifedipine, and hydralazine. Labetalol and hydralazine can be given as intravenous (IV) initially and transitioned to orals once blood pressure stabilises. Short acting oral nifedipine can be used if IV access is not available or IV medication cannot be administered safely.[3,4]

Seizure prophylaxis: Magnesium sulphate is the drug of choice for seizure prophylaxis in women with severe PE. It is most effective when given to women with signs of cerebral hyperexcitability like severe headache, visual disturbances, hyperreflexia etc,. Expert opinion suggests to start magnesium sulphate at least two hours prior to caesarean section in women with severe preeclampsia and continue during surgery until 24 hours postpartum.[3] Magnesium sulphate is also known

to have vasodilatory effects through its effect on intracellular calcium. It decreases intracellular calcium and in turn de-activates calmodulin dependent myosin light chain kinase activity causing decreased vasospasm and decrease in arterial hypertension. Vasodilatory effects of magnesium are noted both in large vessels like aorta and smaller resistance vessels. This effect is pronounced in the mesenteric arteries particularly during pregnancy.[5] Therefore, magnesium although primarily used for seizure prophylaxis may also have a role in hypertension management especially as an adjuvant to first or second line anti-hypertensives.

Antihypertensive management and protocol for magnesium sulphate seizure prophylaxis are discussed in the topic on Antihypertensive drugs and Eclampsia. (Chapters 5 & 11)

Metabolic assessment and optimization:

Severe PE can lead to a decrease in plasma volume by as much as 40% resulting in contracted blood volume, rise in hematocrit, increased vascular tone and circulating catecholamines. These factors can lead to decreased organ perfusion including placental perfusion and end organ damage. Protein loss, damage to pulmonary endothelial glycocalyx, and systolic dysfunction from hypertension increase the risk of pulmonary edema.[6] Wheeler et al[7] measured blood gases and correlated hemodynamic indices measured through pulmonary artery (PA) catheter in women with severe PE. A negative correlation between base deficit and oxygen delivery index, cardiac index and left ventricular stroke work index was observed. They concluded that base deficit > -8 mEq/L reliably identified foetal acidosis, foetal death and maternal end organ damage.

Severe PE is a major risk factor for pregnancy related acute kidney injury (PR-AKI). Complete recovery can be achieved in the majority of cases through early recognition, timely delivery and renal supportive measures. Avoiding nephrotoxic drugs, adequate control of blood pressure and treating underlying causes are important supportive measures.[8] Balanced crystalloid solutions like ringer lactate and plasmalyte are often the fluid of choice for IV administration. Guarded fluid administration starting with 250 -500 ml to restore and maintain renal perfusion is an essential step to prevent pre-renal AKI from worsening and causing permanent damage. If oliguria persists even after a bolus of 1000ml fluid and hypovolemia is suspected, albumin or whole blood can be administered to correct hypovolemia. Monitoring haematocrit and inferior vena cava collapsibility index through ultrasound may aid in assessment of volume status and optimum fluid administration. Loop diuretics like furosemide can be administered to women if oliguria persists after hypovolemia correction.[9] Care should be taken to avoid overhydration, which can lead to pulmonary edema. Severe AKI not responding to termination of pregnancy and supportive measures, may require dialysis. Acute abruption and delayed management of AKI could lead to bilateral renal cortical necrosis and permanent loss of renal function warranting renal transplant.

In a retrospective audit of PE cases at a tertiary referral centre, 9% of women had hyponatremia as a complication. AKI was associated with 34.1% of these women who had hyponatremia.[10] Advanced maternal age, nulliparity, multifetal gestation increase the risk of hyponatremia secondary to PE.[11] Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and hypervolemic hyponatremia are the proposed mechanisms causing hyponatremia in severe PE.[12] Maternal hyponatremia in severe cases can cause seizures and can be confused with eclamptic seizure. It can also cause foetal hyponatremia, foetal jaundice and foetal seizures. Mild to moderate cases of hyponatremia are treated initially with fluid restriction alone.[12] Oxytocin is known to cause fluid retention, and decrease in urine output.[13] Overall fluid intake should be closely monitored while giving oxytocin for induction and magnesium for seizure prophylaxis. Diluting these drugs to higher concentration concentration preparations and giving through syringe pumps can decrease the total fluid intake while delivering the required dose of the drug. Oral sodium supplements, hypertonic saline infusion and furosemide can be administered in moderate to severe cases with neurological signs and pregnancy should be terminated at the earliest.[12] Fluid restriction should be continued for 48 hours postpartum, by which time most of the women recover.[11,12]

Hematologic evaluation and optimisation:

Thrombocytopenia is frequently associated with severe PE and HELLP syndrome. Other coagulation abnormalities include activation of intravascular coagulation cascade , decreased antithrombin levels, raised D-dimers, raised von Willebrand factor (vWF) and raised thrombomodulin levels in patients with severe PE.[14] Frank coagulopathy is rare when platelets counts are > 1,00,000/^{mm3} . Platelet counts must be checked every 6 hours while on induction for labour to assess trend and prepare for transfusion if required. Platelet levels should be maintained above 50,000/^{mm3} in the peripartum period and level below that may require transfusion if delivery is planned. ABO compatible platelet transfusion is preferable whenever possible as the yields are better. Women with Rh negative group should preferably receive ABO compatible and Rh neg

platelets to prevent development of anti-D antibodies and future risk of RH isoimmunisation. In a rapidly bleeding women platelet transfusion may be initiated at levels of 75,000/^{mm3} to prevent further fall.[6,15]

Pregnancy is a hypercoagulable state with increasing concentration of pro-coagulant factors. Fibrinogen levels increase as pregnancy progresses and often are higher than in non-pregnant states. It has a major role as part of primary haemostasis and is responsible for initial clot formation along with platelets and vWF. Sudden placental abruption is sometimes associated with coagulation failure and massive haemorrhage. Fibrinogen is the first factor to fall after the onset of haemorrhage and if not promptly corrected can affect clot formation. Fibrinogen levels < 2g/l is associated with increased blood loss and increased requirement of blood and blood products. Fibrinogen can be corrected by either cryoprecipitate or pasteurised, lyophilised fibrinogen concentrates available off the shelf. Each unit of cryoprecipitate contains 200 -250 mg of fibrinogen and the initial dose to correct hypofibrinogenemia is usually 8 -10 units. When fibrinogen concentrates are used, 2-3 gm are given IV empirically and further dosage is guided by laboratory test. During haemorrhage the goal is to maintain serum fibrinogen levels above 2g/l.[16,17]

Fresh frozen plasma (FFP) is transfused to replenish clotting factors during massive transfusion. In an ongoing haemorrhage, packed red blood cells (PRBC) transfusion is started first to maintain volume status and haemodynamics. FFP should be started at a dose of 12-15 ml/kg if haemorrhage continues to be severe enough to demand additional transfusions beyond 4 units of PRBCs. The goal of FFP transfusion is to maintain prothrombin time (PT) and activated partial thromboplastin time (aPTT) within 1.5 times normal value. Haemogram, PT, aPTT, and fibrinogen must be sent at regular intervals as per local protocol (hourly or second hourly) and transfusion of blood products must be titrated accordingly. Point of care testing like thromboelastogram (TEG®) and rotational thromboelastometry (ROTEM®) facilitate quick bedside assessment of coagulation and prompt correction through appropriate blood products.[15,16,18] Other important aspects of managing haemorrhage and coagulation failure are to prevent hypothermia, hypocalcemia, acidosis and hyperkalemia. Having an institutional massive transfusion protocol for obstetric haemorrhage will help in early recognition, managing logistics of blood procurement and early transfusion of blood and blood products in adequate quantities.[16]

Anaesthesia in Severe Preeclampsia:

Central Neuraxial block : It is the preferred anaesthesia technique in all women with severe preeclampsia in absence of coagulopathy and platelet counts > 70,000/ ^{mm3} . Traditionally epidural anaesthesia was preferred over spinal anaesthesia for fear of sudden hypotension and hemodynamic collapse. Over the years, there is ample evidence published in the literature to suggest otherwise. Severe PE women are less prone to hypotension from spinal anaesthesia compared to normal women and the resulting hypotension can easily be corrected with small doses of vasopressors. Epidural anaesthesia do not confer any additional benefit over spinal anaesthesia, while having a slightly higher risk of epidural haematoma due to indwelling catheter.[6]

Society of obstetric anaesthesia and perinatology (SOAP) interdisciplinary consensus statement on neuraxial procedures, recommends neuraxial anaesthesia when platelet counts are > 70,000/^{mm3} and coagulation profile is within normal range. For counts between 50,000 - 70,000/ ^{mm3} and in absence of coagulopathy, airway vs neuraxial risk assessment should guide our choice of anaesthesia.[19] Overall the incidence of neuraxial hematoma is extremely low in absence of coagulopathy when compared to difficult airway and airway related morbidity.[6] When caught in a difficult situation wherein platelet counts are between 50,000 - 70,000/^{mm3} with difficult airway, inadequate help, and lack of advanced airway aids, it is wise to check coagulation profile and bedside clotting time. If there is no coagulopathy and clotting time is within normal range, anecdotally it may be prudent to choose spinal anaesthesia over general anaesthesia.

General anaesthesia:

General anaesthesia becomes necessary in situations where there is an underlying coagulopathy, sustained foetal compromise which precludes spinal anaesthesia due to lack of time or in cases of maternal haemodynamic instability. Pregnancy related airway edema further worsens in preeclampsia increasing the risk of difficult intubation over and above that exists in normal pregnant women.[20] Additional senior help during intubation, availability of advanced airway equipment like videolaryngoscope (VLS), and second generation supraglottic airway devices (SAD) are vital while attempting intubation in severe preeclamptic mother. Hypertension from laryngoscopic response should be mitigated by timely administration of beta blockers like labetalol, esmolol or opioids like fentanyl,remifentanil before intubation. Depolarising muscle relaxant like succinylcholine is preferred at the time of intubation. Long acting muscle

relaxants like vecuronium and atracurium should be used cautiously at reduced dosages due to potential prolongation of effect from concurrent use of magnesium sulphate.[6] In presence of AKI and elevated potassium levels, rocuronium or remifentanil for intubation may be a better choice.Sugammadex must be available to reverse rocuronium at the end of surgery.

Postoperative care:

Postoperatively all women with severe PE require thromboprophylaxis, which should be administered as per RCOG Green top guideline No.37a.[21] Pain management after caesarean section, early mobilisation and early oral feeds are other key aspects to consider. SOAP consensus statement and recommendations for enhanced recovery after caesarean section emphasises the need for multimodal analgesia (MMA) for effective pain relief.[22] Low dose long acting neuraxial opioid like morphine at a dose of 100 -150 mcg intrathecally or 1-3 mg epidurally can significantly lower the pain scores, increase the time to first rescue analgesia and decrease total opioid consumption. Regional analgesia techniques like transverse abdominis plane (TAP) block, quadratus lumborum (QLB) block, erector spinae plane block (ESPB) , wound infiltration can be considered when neuraxial morphine is not feasible.[23] Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen along with acetaminophen are very effective and must be included in MMA regime. They should be preferentially used over opioids for postpartum pain relief.[3] NSAIDs were believed to worsen postpartum hypertension and increase the risk of renal injury when given to women with HDP. Recent meta-analysis and systematic reviews did not find any increase in adverse outcomes with postpartum NSAID use for pain relief in women with HDP.[24,25] Use of oral opioids or a combination drug with opioids should be limited to decrease the risk of opioid addiction.

Management of Complications

Eclampsia: While managing an eclamptic mother, the primary focus should always remain on arresting the seizure episode, maintaining patent airway, stabilising the mother and preventing further complications. Foetal delivery can be planned after stabilising the mother. Rushing to intubate unprepared could be catastrophic due to increased airway edema and difficult intubating conditions. Drug of choice for managing eclamptic seizure remains magnesium sulphate and dosage is similar to severe PE ie,. 4-6 gm IV as loading dose over 20 min followed by 1-2 gm IV / hour as maintenance dose for 24 hours post partum. Recurrent eclamptic seizure while on magnesium should prompt additional bolus of 2-4 gm IV over 10 min. Benzodiazepines can be used along with magnesium in cases with excessive neurological irritability to increase seizure threshold.[6] In severe cases where woman continues to remain irritable, propofol or thiopentone can be used with succinylcholine for decreasing cerebral metabolism and for intubating in a controlled environment. Spinal anaesthesia for caesarean section can be safely used if the mother regains consciousness and is responsive. In women who require deep sedation or remain unconscious, general anaesthesia is preferred. These women should be sedated and ventilated postoperatively, until hypertensive encephalopathy subsides.

PRES syndrome:

Headache, altered mental function and visual disturbances are the most common symptoms of PRES syndrome. Severe cases can lead to seizures, encephalopathy and mortality. Treatment primarily entails control of hypertension, seizure prophylaxis and removal of instigating factors which in this case implies termination of pregnancy.

Pulmonary edema:

Common causes of pulmonary edema in preeclampsia are fluid overload in the backdrop of reduced oncotic pressure and acute hypertensive crisis. Initial management involves diuretics, antihypertensives and prompt oxygen supplementation. Thorough physical examination, 2D echocardiography, chest x ray, arterial blood gases, electrocardiography (ECG) help in zeroing on the cause for pulmonary edema. IV infusions of nitroglycerin, morphine and furosemide along with antihypertensives like Labetalol remain first line drugs to manage pulmonary edema. Clonidine, prazosin, hydralazine can be used as second line agents to control hypertension.Airway management may require non-invasive ventilation(NIV) or intubation and mechanical ventilation in severe cases to deliver positive pressure ventilation and improve oxygenation.[26]

Conclusion:

Severe PE and eclampsia are associated with airway changes, thrombocytopenia, end organ dysfunction and foetal compromise. Appropriate antihypertensive management, seizure prophylaxis and timely foetal delivery mitigates worsening of the situation and improves outcomes. Anaesthesia for women with severe PE requires careful assessment of risk vs benefits for administering central neuraxial block (preferred). General anaesthesia remains the choice of anaesthetic if severe PE is complicated with coagulopathy, hemodynamic instability and when there is absolute patient refusal to neuraxial technique.

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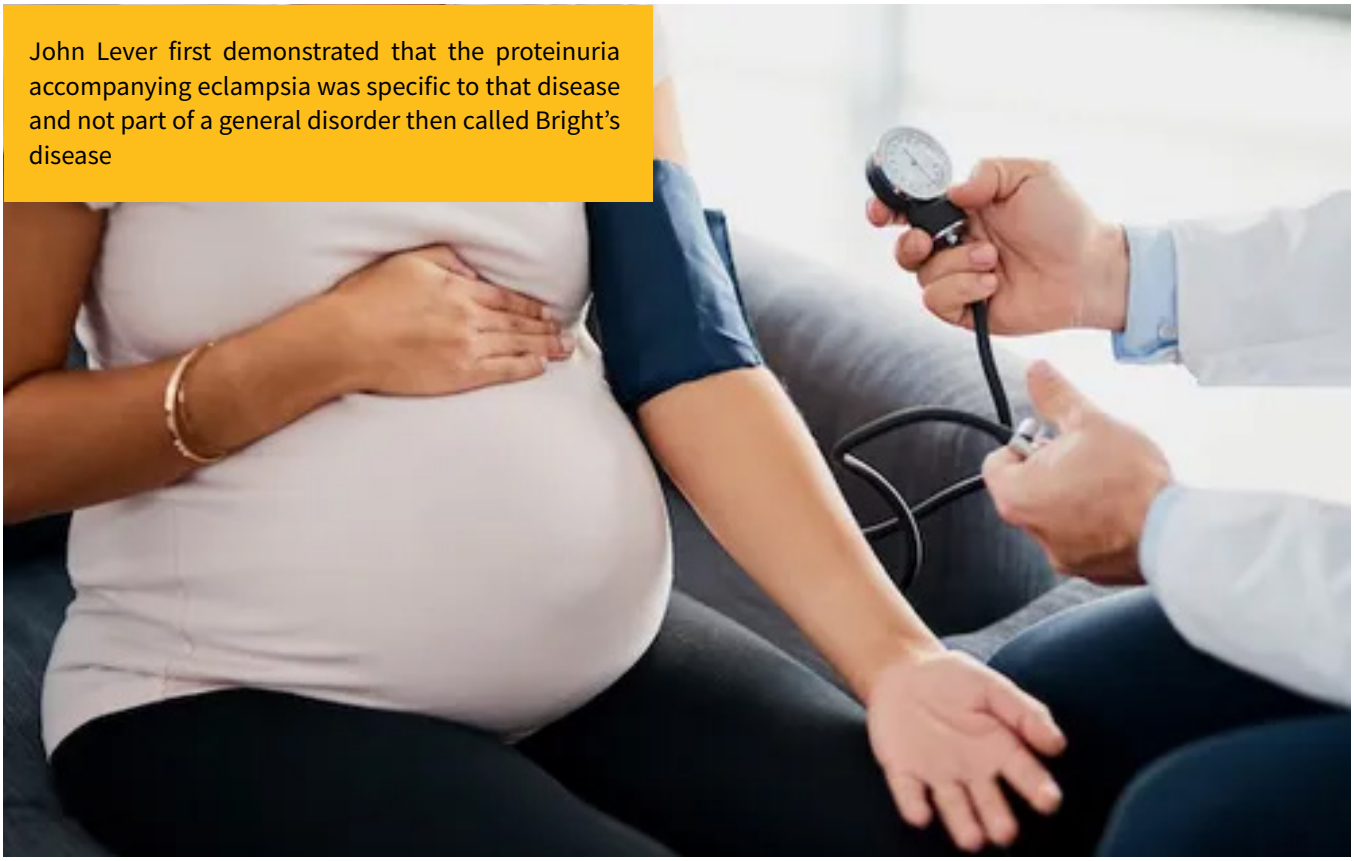
John Lever first demonstrated that the proteinuria accompanying eclampsia was specific to that disease and not part of a general disorder then called Bright's disease



Crises in Pre eclampsia

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Dr. Rashmi Shinde

Introduction:

Pre eclampsia is associated with complications involving multiple organs, some of which could be life threatening. Globally, 76,000 women and 5,00,000 babies die each year from this disorder. A high index of suspicion to identify the complications and immediate intervention is required to reduce mortality and morbidity.

Complications like Acute severe Hypertension, Eclampsia and HELLP are discussed in Chapters 6, 10 & 11 respectively. This chapter discusses other crises states in pre eclampsia (Table1)

Table 1: Crises in pre-eclampsia

- Eclampsia
- HELLP syndrome
- Pulmonary edema
- Placental abruption
- Cerebral hemorrhage
- Cortical blindness
- DIC
- Renal failure
- Hepatic rupture
- Transient left ventricular systolic or diastolic dysfunction

Ophthalmic complications:

Retinal artery and Retinal vein occlusion and ischemic Optic neuropathy have been described in Preeclampsia. Serous Retinal detachment (SRD)[1] is a serious complication and an uncommon cause of sudden visual loss in PE .Treatment is often conservative and vision improves after few weeks as the fluid gets reabsorbed ,however in a subgroup of patients with PSF the visual loss could be permanent. Cortical blindness is a rare and reversible complication.

Neurological complications:

Both hemorrhagic and ischemic stroke can complicate PE, more commonly during peripartum and postpartum period.[2] Risk of stroke is increased by three folds in pregnancy and the risk is further increased in PE. The pathophysiology of Ischemic stroke can be through many mechanisms. Hemorrhagic stroke can be either intracerebral or subarachnoid, can be spontaneous or due to underlying vascular iesions, the former being more common and due to deranged autoregulation and associated coagulopathy. Cerebral venous thrombosis can occur because of systemic inflammation and hyper coagulopathy associated with PE. Posterior Reversible Encephalopathy Syndrome which occurs commonly postpartum, is a radiological diagnosis. It is a syndrome of vasogenic edema which presents with visual disturbance, seizures, head ache and altered mentation. Reversible cerebral vasoconstriction syndrome also occurs commonly during postpartum and is due to transient vasospasm in arteries of the circle of Willis and can be associated with ischemic stroke.

Cardiovascular complications

13% of Women with PE can develop diastolic dysfunction .They have elevated Right ventricular systolic pressure and abnormal cardiac re modelling.[3] There is a two fold increase of heart failure in women with FIBP. 5-10% develop Pulmonary edema.

Respiratory complications:

Pulmonary edema occurs in 5-10% of women and the mechanisms are multifactorial. It is Common in older women and multigravida.Dyspnea,SPO2<93 and chest pain are predictors of poor maternal outcome.[4] Management includes control of BP, Nasal O2 and , i.v Frusemide. Severe pulmonary edema warrants non invasive or mechanical ventilation.

Complications involving Liver:

Subcapsular hematoma is a life threatening complication of PE. It affects .9-1.6% of women with HELLP syndrome.[5] Rupture of the hematoma is a catastrophic complication.

Renal Complications:

Acute kidney injury complicates 15% of admissions with PE and this increases maternal and perinatal mortality. History of HDP in previous pregnancy is a risk factor for development of AKI and worsening severity of AKI.[6]

Coagulopathy:

Disseminated intravascular coagulation in association with Abruption complicates women with PE ,especially in those with HELLP.

Abruptio placenta:

Is a life threatening complication for the mother and the fetus. The incidence is 3% in PE with severe features, some studies report higher incidence. The risk of severe abruption was substantially higher in severe PE.6 PE is one of the most common causes for abruption.[7]

Management:

Crisis warrants control of Blood pressure, stabilizing the mother , and supportive and specific treatment according to the system involved and delivery when it occurs in antepartum.

Conclusions:

Pre eclampsia with severe features is associated with complications involving multiple systems. Early identification, careful monitoring, supportive care, system specific management and delivery improves maternal and perinatal outcome

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Eclampsia and pre eclampsia were originally attributed to toxins or poisons believed to enter the maternal circulation. The search for the toxins responsible for pre eclampsia has lasted for more than a century

HELLP Syndrome

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"It is circumstances and proper timing that give an action its character and make it good or bad"
(Agesilaus 444-400BC) *-Louis Weinstein, MD (2005)*

Dr. Sasirekha R

Introduction:

HELLP syndrome is generally considered as one of the life threatening complications of Preeclampsia (PE) and is characterized by combination of either all or part of these following clinical features.

- Hemolysis: It is characterized by microangiopathy hemolysis in peripheral smear with low haptoglobin and Lactate dehydrogenase of >600U/L
- Elevated liver enzymes: AST/ALT more than twice that of normal
- Low platelet count: Less than 100 X 10^9/L (1 lakh per cumm)

The constellation of clinical symptoms was first described by Pritchard JA in 1954, however the name was coined by Weinstein in 1982 and he described the combination of symptoms in a group of women.

Epidemiology

It complicates almost 0.2-0.8% of all pregnancies, 2-12% of women with hypertensive disorders (HDP) and 10-20% of women with severe PE. HELLP syndrome can present even without high blood pressure (BP) in 10-15% of cases. Despite better understanding in recent times, adverse maternal and perinatal outcome are not uncommon it is diagnosed or treated late. Reported maternal and perinatal mortality in the literature varies with between 3.5-24.2% and 7.7-60% respectively.

Though the peak frequency of HELLP syndrome is after second trimester, 10% can occur before 28 weeks and 20% can occur after 37 weeks. Similarly, 10% of HELLP syndrome can occur after delivery.

Types

Generally, it is classified based on severity of thrombocytopenia (Mississippi classification). It's

also categorized as complete or partial HELLP based on the clinical spectrum. Moreover, HELLP syndrome can be considered atypical when the usual spectrum is associated with normal blood pressure or the presentation mimics postpartum hemolytic uremic syndrome (PHUS) or other thrombotic microangiopathy (TMA).

Table 1: Mississippi three tier classification:

Grades of severity	Platelet count (109/L)	LDH (IU/L)	AST/ALT (IU/L)
Class I	≤50	≥600	≥70
Class II	50-≤100	≥600	≥70
Class III	100-≤150	≥600	≥40

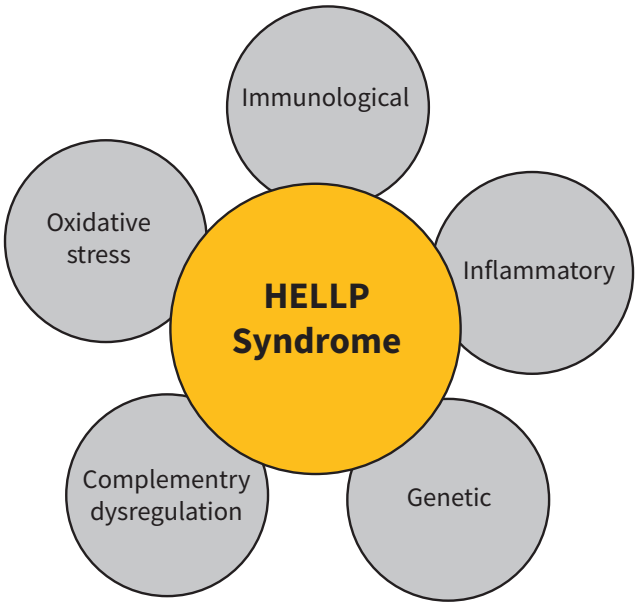
Table 2: Tennessee system of classification:

	Spectrum
Type of HELLP syndrome	• Thrombocytopenia: Platelet ≤100 $X10^9$/L • Elevated liver enzymes: AST ≥70IU/L (twice that of normal) • Hemolysis : Peripheral smear with hemolysis, LDH ≥600IU/L, low serum haptoglobin, serum bilirubin of ≥1.2mg/dl
Complete HELLP syndrome	• All the three features are present
Partial HELLP syndrome	• Any one or two of the above clinical features are present

Pathogenesis & Pathophysiology:

The exact pathophysiology of HELLP syndrome is not clearly known. As it's considered one of the component of PE with severe features (PSF), possibily they could have similar pathophysiology. In a subset of patients, in whom the activation of alternative pathway of complement (APC) is significant ,the presentation mimics atypical hemolytic uremic syndrome (aHUS). Similar to aHUS and PHUS, variants of genes implicated in APC activation has been identified in 30-40% patients with HELLP syndrome. Moreover, positive functional complement assays have been identified in 50% of patients with HELLP syndrome.

Though there are studies describing possibility of conservative management of HELLP syndrome with Eculizumab in the presence of APC activation when they are remote from term, delivery remains the mainstay of treatment for HELLP syndrome currently.



The hemolysis in HELLP syndrome is mechanical which is similar to aHUS. Endothelial cell activation and increased von Willebrand factor explain thrombocytopenia. AST/ALT levels are raised both due to intrinsic liver involvement as well due to red cell lysis. Liver involvement is more common in HELLP syndrome. HELLP syndrome/PE stimulates reticuloendothelium in the liver. It decreases its ability to clear fibrin thrombi from circulation. In addition, microvascular thrombosis and endogenous vascular injury lead on to coagulative necrosis and parenchymal bleeding in the liver which predispose to subscapular hematoma or hepatic rupture.

Studies have shown neutrophil lymphocyte ratio is higher in HELLP syndrome, however the reactive oxygen species levels are reduced which suggest aberrant functionality or completely exhausted neutrophils.

There are studies which consider HELLP syndrome as a separate entity especially in those with the spectrum of complement dysregulation. However, available literature suggests that the varied clinical presentations like atypical, partial and complete HELLP syndrome as a single entity and a component of PE with severe features.

Clinical presentation:

The most common clinical presentation is upper abdominal pain or epigastric pain (~65%) followed by nausea and vomiting (35%). In 10-20% women, neither hypertension nor proteinuria will be present. They could present with imminent symptoms like headache

(30-60%) or blurring of vision (up to 20%). Sometimes, the clinical features of HELLP syndrome mimics acute fatty liver of pregnancy (AFLP). Thorough clinical and laboratory assessment are essential in clinical practise when the presentation is severe and share the common pathophysiology of TMA.

Tabel 3: Clinical features of commonly occuring TMA in pregnancy

	HELLP syndrome	AFLP	TTP	aHUS	Lupus flare
Hypertension	>80%	50%	20-75%	>80%	>80% with APS & nephritis
Proteinuria	90-95%	30-50%	Hematuria	80-90%	100%
Fever	Absent	25-32%	20-50%	-	Common
Jaundice	5-10%	40-90%	Rare	Rare	Absent
Nausea/Vomiting/ Abdominal pain	40-80%	50-80%	Common	Common	With APS
Neurological features	40-60%	30-40%	60-70%	-	50% with APS

HELLP:

Hemolysis, elevated liver enzymes, low platelet count; AFLP: Acute fatty liver of pregnancy; TTP: Thrombotic thrombocytopenic purpura; aHUS: Atypical hemolytic syndrome; APLA: Anti phospholipid antibody syndrome; APS: Anti phospholipid antibody syndrome

Investigations:

Investigations are essential to confirm the diagnosis and to know the severity of HELLP syndrome. Since mimics as well as atypical presentations are not uncommon in clinical wide array of investigations are essential especially when the diagnosis is not clear.

Tabel 4: Extensive list of laboratory investigations in HELLP Syndrome

Investigations	Blood	Urine	Imaging
Routine	Complete blood picture	Protein creatinine ratio	USG abdomen & liver
	Peripheral smear	Routine/Microscopy	Liver imaging – if capsular hematoma/ infarction/rupture is suspected
	Renal function tests		Low threshold for neuroimaging – for PRES/infarction/hemorrhage
	Liver function tests		
	Lactate dehydrogenase		
	Coagulation profile (with clinical picture of coagulopathy/Abruption)		**Fetal assessment**
	Blood glucose		**Growth sean**
	sFlt-1/PlGF ratio in doubtful cases		**Multivessel Doppler**

Special (if the diagnosis is overlap and unclear)	ADAMTS 13		Genetic testing for alternative pathway of complement activation
	Complement levels C3/C5		
	Complement factor F/H		
	ANA/ds DNA		

ANA: Anti-nuclear antibody; **ds DNA:** double stranded DNA; **USG:** Ultrasound; **PRES:** Posterior reversible encephalopathy syndrome

Low levels of ADAMTS 13 (level of <10%) strongly favours TTP rather than HELLP syndrome. In the presence of TMA, a high LDH to AST ratio raises the possibility of TTP more than HELLP syndrome. Often AFLP presents with coagulopathy, however it is not rare with severe HELLP and abruptio placenta. The PsLD (pregnancy specific liver disorders) are often considered as an 'Overlap syndrome' wherein one condition progresses to another in due course. High levels of ammonia and low blood glucose often give a clue towards AFLP. As termination of pregnancy is the rule in both AFLP & HELLP syndrome it is not uncommon the exact diagnosis may not get documented in case files. Serum biomarkers like sFlt-1/PlGF will help to identify PSF and HELLP syndrome, it may not be available routinely in majority of the places. However, if facilities are available, it should be done so that the clinical conundrum can be resolved in severe HELLP.

Though AKI can happen in HELLP syndrome and AFLP, if it is progressive and severe it is essential to make the correct diagnosis of aHUS. Early initiation of Eculizumab protects renal function better.. As recovery is the key after delivery for HELLP syndrome, if the clinical situation gets worsened after 48 hours, it is essential to make the correct diagnosis of TMA.

Other conditions like acute cholecystitis, acute pancreatitis, hypovolemic shock/sepsis and fulminant viral hepatitis are differential diagnosis and appropriate evaluation is required to rule out those conditions. As a rule in our country infectious causes like dengue shock syndrome and Scrub typhus may mimic HELLP syndrome and should not be missed.

Complications:

The frequency of maternal complications are more in HELLP syndrome. Frequently it can be associated with coagulopathy (20%), neurological complications, abruptio placenta (16%), acute kidney injury (7%) and pulmonary edema (6%). The adverse maternal and neonatal outcome are common when the diagnosis is delayed and this is possible when they present with coagulopathy, pulmonary complications and abruption. In such situations, the diagnostic pendulum moves often towards rare causes such as TMA

Table 5: Complications in HELLP syndrome

Maternal	Perinatal
Disseminated intravascular coagulation (15%)	Fetal growth restriction (38-61%)
Pulmonary edema (3-10%), embolism, ARDS	Preterm birth (~70%)
Myocardial ischemia	Neonatal thrombocytopenia (15-50%)
Stroke (<1%), cerebral venous thrombosis and cerebral edema (1-8%)	Perinatal death (7.4-34%)
Eclampsia (4-9%)	
Acute kidney injury (7-36%)	
Sub capsular liver hematoma, rupture (<1%)	
Wound hematoma/Sepsis (7-14%)	
Abruptio placenta (9-20%)	
Maternal death (1-25%)	

Though the maternal and perinatal outcome have improved since the first review by Weinstein on HELLP syndrome, hypertensive disorders of pregnancy remain an important cause of maternal and perinatal mortality across the globe. Early diagnosis is the key and timely delivery along with supportive measures improve the outcome. The adverse outcomes like AKI and pulmonary edema is more if the HELLP syndrome develops for the first time postpartum.

The involvement of liver may be catastrophic in HELLP syndrome. Hepatic hematomas are more common than hepatic infarctions; Hepatic rupture is rare (0.5-2% of HELLP syndrome) and with hepatic hematoma or capsular rupture the maternal and perinatal mortality increases.

Management:

Once the diagnosis of HELLP syndrome is made, the plan is to deliver safely. Woman should be transferred to high dependency unit. Apart from general measures, the goals are antihypertensive management, seizure prevention and obstetric management. Multi-disciplinary management with involvement of anaesthetist/intensivist, neonatologist, hematologist (sometimes) and high risk obstetrician are essential. It is essential to alert the blood bank for blood and blood products either peripartum of before that if the clinical situations warrant.

Prophylactic MgSO4 should be started as IV infusion ,Zuspan regimen is prefered to Dhaka/Prtichard regimen,. Intravenous Labetalol or oral Labetalol/ Nifedipine can be started as first line antihypertensive. Antenatal corticosteroid has to be started for the betterment of neonatal outcome if the gestational age is <34 weeks. As a general rule, it is better to avoid intramuscular injections in the presence of coagulopathy and severe thrombocytopenia.

Caesarean delivery is reserved for obstetric indications. But, in clinical practise when there is HELLP syndrome before 32 weeks and the Bishop score is unfavourable many prefer caesarean delivery to avoid prolonged induction especially in the setting of severe hypertension. Platelet count and coagulopathy guide the possibility of epidural labour analgesia for women in labour.

It is essential to monitor the mother for 48-72 hours after delivery in the hospital. Careful BP monitoring and continuation of antihypertensive medications are essential. Risk assessment for venous thromboembolism is mandatory as there is increased risk for thrombosis. It is generally expected for the platelet count, hemolysis and liver enzymes to improve 48 hours after delivery and if does not happen or worsens postpartum the other spectrum of TMA to be considered.

The need for plasma exchange and renal replacement therapy are limited if the HELLP syndrome is managed timely.

Controversies:

Controversies continue to revolve around the pathogenesis, diagnosis and management over decades. As mentioned earlier, it could be a separate entity from PE and may result from predominant activation of APC. This prompted the evaluation of Eculizumab in the management of HELLP syndrome and while awaiting for fetal maturity. Though there are studies and case reports on this, conservative management is not recommended at present in clinically diagnosed cases of HELLP syndrome whether it is typical or atypical. Though genetic studies suggesting APC activation will be helpful in establishing the diagnosis of aHUS, the mutations are positive in only 40-60% of cases, leaving room for false negative cases which could be labelled as HELLP syndrome or other TMA.

The role of IV Dexamethasone to improve platelet count is a long standing controversy. Dexamethasone administration has resulted in temporary improvement in platelet count and has been tried in selective cases of expectant management. There are randomized controlled trials on high dose of Dexamethasone which showed significant improvement in platelet count with no significant improvement in maternal outcome. It may be a practise to continue Dexamethasone IV after delivery for 48-72 hours, which is the time for recovery for HELLP syndrome otherwise. Similarly, IV Methylprednisolone was tried in some selective cases of expectant management and showed promising effect on neonatal outcome without adverse maternal outcomes and until the results of larger trials are available, these therapeutic options are only investigational.

Though majority accept termination after corticosteroids for lung maturity, expectant management has been explored in the setting of partial/incomplete HELLP. Various authors have tried expectant management with antihypertensives, prophylactic MgSO4, IV corticosteroids and plasma exchange in some situations. Though the intent was to prolong pregnancy for few days to weeks, majority of them in their series had their delivery within a week. Although pregnancy prolongation was possible in few studies with careful monitoring in selective cases of HELLP syndrome without increased adverse maternal outcome, the perinatal outcome was not different from those who delivered within 48 hours after corticosteroids administration. The role of expectant management also remains an area of clinical research.

Long term prognosis:

The long term prognosis is similar to PSF and it is essential to monitor them in the postpartum period for high BP and its complications. Thromboprophylaxis has to be administered for 7-10 days if the for high BP and its complications. Thromboprophylaxis has to be administered for 7-10 days if the platelet count is appropriate. A review at 6-12 weeks postpartum with advice on contraception is essential. If there is early onset PSF, it is essential to rule out secondary causes like APS and lupus. Long term follow-up of these women like PE is a challenge especially in a low resource country but life style modifications as in other women with PE will be helpful for them in long run.

Recurrence:

As such, the risk of HELLP syndrome (~5%) in future pregnancies is rare, but there is high chance for PE and preeclampsia with severe features (20%). The recurrence risk is high if the onset of HELLP syndrome is before 32 weeks. They should be advised to have preconceptional counselling and register early in pregnancy for risk assessment of PE.

Conclusion

HELLP syndrome is a potential crisis state in Pre-eclampsia. Though Hypertension and Proteinuria may not be severe, it may be associated with several complications which increase maternal and perinatal mortality. Early diagnosis and multidisciplinary approach in a high dependency unit results in better outcome.

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"In pregnancy, drowsiness and headache accompanied by heaviness and convulsions is generally bad"
(Thr pre Hippocratic Coan Prognosis/XXXI, 507

Eclampsia

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Introduction:

Eclampsia is a Greek word meaning "to shine forth" or "flash of lightning". Eclampsia is one of the most acute complications of pregnancy, and it carries high morbidity and mortality for both the mother and the fetus. Eclampsia is defined as the occurrence of one or more generalized, tonic-clonic convulsions unrelated to other medical conditions in women with hypertensive disorder of pregnancy. About 10%of pregnancies are complicated by hypertensive disorders, eclampsia accounts for 0.8% of women with hypertensive disorders.[1] Eclamptic seizures can occur antepartum, usually after 20 weeks of gestation, intrapartum or postpartum. Seizures before 20 weeks are rare but can occur in gestational trophoblastic disease[2]. Though the rate of eclampsia and maternal mortality from hypertension in pregnancy have steadily reduced over the years in developing countries, hypertensive disorders still account for up to 14% of all maternal deaths worldwide. The differences in the incidence and complication rates between developed and developing countries is probably due to gaps in access to appropriate and early prenatal care, surveillance and management protocols for timely hospitalization, management and delivery[1].

Pathophysiology

The pathogenesis of eclampsia is not well understood. Several hypotheses and pathologic mechanisms have been proposed, which stem from the initial disease process, preeclampsia. The pathogenesis of preeclampsia is linked to abnormal placentation. In a normal pregnancy, fetal cytotrophoblasts migrate into the maternal uterus and cause remodelling of the endometrial vasculature for the blood supply of the placenta. In preeclampsia, there is an inadequate invasion of the cytotrophoblasts, thus leading to poor remodelling of the spiral arteries, which reduces the blood supply to the placenta[3].

One proposed model for eclampsia is the alteration of autoregulation in the cerebral circulation due to disruption of blood-brain barrier(BBB). Cerebral blood flow autoregulation is mediated and modulated

through myogenic, neurogenic, metabolic or endothelial control. Endothelial control occurs in response to factors released from endothelial cells, such as nitric oxide, which acts as a vasodilator or endothelin-1, a vasoconstrictor. In pre-eclampsia due to poor remodelling of spiral arteries, there are increased levels of vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and oxidized low-density lipopro tein (oxLDL). oxLDL binds to LOX-1 receptor and generates complex signalling cascades leading to the induction of the inflammatory pathway and increases production of superoxide in endothelial cells which further promote vascular dysfunction. Super oxide also binds with nitric oxide to form peroxynitrite, a stable reactive oxygen and nitrogen species that has deleterious effects on endothelial function. BBB permeability may increase due to these circulating factors which may promote formation of vasogenic edema and the neurologic sequelae[1].

Another mechanism suggested for eclampsia is similar to the pathophysiological changes described in hypertensive encephalopathy, failure of autoregulation in acute hypertension, which leads to increased hydrostatic pressure and decreased cerebral vascular resistance, potentially damaging the micro vessels and resulting in increased BBB permeability, micro bleeds, focal cerebral edema, neuroinflammation, and neuronal damage[(1)].

Risk Factors

Several factors have been associated with eclampsia which are similar to that of pre-eclampsia, these include, Maternal age ≤ 20 years and ≥ 35 years, nulliparity, multifetal gestation, h/o preeclampsia or eclampsia in previous pregnancy, autoimmune disorders are few to name.

Maternal and Neonatal Risks

Eclampsia is associated with increased maternal and neonatal morbidity including death few of which are enumerated in Table 1.

Table 1. Maternal and neonatal risks associated with eclampsia

Maternal		Neonatal
Immediate	**Long term Sequelae**	
• HELLP syndrome • Abruptio placentae • Acute renal injury • Disseminated Intravascular Coagulation • Pulmonary edema • Aspiration pneumonia • Cardiopulmonary arrest • Posterior reversible encephalopathy syndrome (PRES) • Maternal death	25% Recurrence of preeclampsia, 2% risk of eclampsia and Cardiovascular morbidity • Myocardial infarction • Cerebrovascular disease • Acute heart failure • Cardiomyopathy • Cardiac arrest • Neuroropsychiatric morbidity • Cognitive failure • Higher risk of anxiety and depression	Fetal growth restriction Complications due to prematurity • Respiratory distress • Necrotising enetrocolitis • Intraventricular haemorrhage Perinatal/neonatal mortality (5.6% - 11.8%)

Clinical Manifestations

Eclampsia can occur in antepartum, intrapartum or postpartum period. Up to 59% to 70% of seizures occur during the antepartum period, around 20% to 30% intrapartum and 20% to 30% in postpartum period, even up to 6 weeks following delivery. Antepartum eclampsia, usually occurs after 28 weeks. Seizures before 20 weeks need an ultrasound examination to rule out molar pregnancy and an extensive medical and neurological evaluation to rule out other causes. When a woman presents with hypertension, proteinuria and convulsions, a diagnosis of eclampsia is made unless proven otherwise. However, hypertension may be absent in 25% cases and proteinuria may be absent in 14% cases.

Several signs and symptoms may precede eclampsia, such as visual disturbances like blurred vision, double vision, scotoma, photopsia, epigastric pain, vomiting and severe persistent occipital or frontal headaches, but none of these symptoms accurately predict eclampsia. The most common symptoms reported in literature are headache (66%), visual disturbance (27%), and right

upper quadrant or epigastric pain (25%). The hallmark physical exam finding for eclampsia is generalized tonic-clonic seizures, which typically last 60 to 90 seconds in duration. A postictal state is often present after seizure activity. The most common finding during the neurologic examination following a seizure is altered mental status and deficits of memory or visual perception.

Differential Diagnosis

In scenarios of normal blood pressure with absent proteinuria, seizures <20 weeks or > 48 hours, alternative diagnosis should be considered. The differential diagnosis to be considered is in mentioned in the Table 2.

Table 2. Differential diagnosis for seizure in pregnancy

Pregnancy related	Pregnancy unrelated
• Eclampsia • Thrombocytopenic thrombocytopenic purpura • Amniotic fluid embolism	Neurovascular • Intracranial haemorrhage • Subarachnoid haemorrhage • Arterial embolism or thrombosis • Cerebral venous thrombosis • Space occupying lesion • Posterior reversible encephalopathy syndrome • Metabolic • Hepatic or renal failure • Hypoglycaemia/ Hyponatremia/ Hypocalcaemia • Hyperosmolar states • Autoimmune • Systemic lupus erythematosus • Antiphospholipid syndrome Infectious encephalitis/ meningitis Psychogenic non epileptic seizures (pseudo seizures) Trauma

Evaluation

Women with eclampsia require urgent evaluation in determining the cause and for management decisions, delaying which may result in complications for the mother and the fetus. The diagnostic evaluation and interventions most of the times must be performed simultaneously.

Evaluation depends on clinical history, clinical signs and symptoms and investigations which are similar to that of preeclampsia and additional investigations depending on clinical condition. Table 3 lists the tests recommended as a part of evaluation. After maternal stabilisation it is important to evaluate the fetal wellbeing with ultrasound imaging to detect any growth restriction and non-stress test.

Table 3 – Laboratory tests for evaluation

Recommended	Tests to be considered If clinically indicated
• Complete blood picture • Liver function tests • Renal function tests • Electrolytes • Urinary protein/ creatinine ratio or 24hour urinary protein	• Coagulation profile – Prothrombin time(PT), activated Partial Thromboplastin Time(aPTT), fibrinogen, fibrin degraded products in case of DIC • Chest X Ray in the presence of pulmonary edema • Neurological imagining in atypical presentations

Prevention and Management for Eclampsia

Prevention of eclampsia starts from preventive interventions for pre-eclampsia which usually is the underlying cause. Primary prevention of preeclampsia by screening and starting Ecosprin 150 mg per day in women who were found to be high risk for pre-eclampsia identified by first trimester combined screening, has shown to reduce preterm preeclampsia by almost 60% as per ASPRE trial[4] and thereby reduce risk of eclampsia.

Secondary prevention includes regular monitoring and appropriate usage of antihypertensive medications and timely delivery in women with gestational hypertension and pre-eclampsia.

Magnesium sulfate(MgSO4) remains mainstay in both prevention and treatment of eclampsia as it exerts its effect by depressing the central nervous system. In women with preeclampsia with severe features, magnesium sulfate has been shown to significantly reduce the rate of eclampsia compared to placebo, phenytoin, nimodipine or diazepam. In the setting of eclampsia, magnesium sulfate has been demonstrated to be superior to diazepam, phenytoin, or lytic cocktails in reducing the risk of recurrent seizures as well as reducing the risk of maternal death[6-9].

Management of eclampsia requires the women to be admitted to high dependency unit or intensive care unit, initial stabilisation and delivery irrespective of period of gestation. For women in remote areas it is

important to refer to a tertiary care center. Before transferring, it is important to stabilize the blood pressure and control convulsions.

Management during or immediately after a seizure includes

- Supportive care to prevent serious maternal injury
- Assessing and establishing airway patency
- Supplemental oxygen administration
- Left lateral decubitus to prevent aspiration
- Magnesium sulfate, as discussed is the drug of choice to prevent subsequent convulsions. A loading dose of 4gm (6gm if BMI>35)[1,3,4] over 15 to 20 minutes is recommended, followed by a maintenance does of 2 grams per hour as a continuous IV solution. In women without an intravenous access, MgSO4 can be administered by intra muscular (IM) injection, 10 grams initially as a loading dose (5 g IM in each buttock), followed by 5 g every 4 hours in alternate buttock.
- About 10% of women with eclampsia may have a second convulsion after receiving MgSO4. Additional bolus of 2 g of MgSO4 can be given intravenously (IV) over 3 to 5 minutes in such case.
- Simultaneously securing IV access, drawing blood for recommended tests and administration of antihypertensive medications to reduce elevated blood pressure is important to prevent further maternal morbidity
- In case of refractory seizures, Lorazepam 4 gm IV over 3-5 mins or Midazolam 1-2 mg IV or Diazepam 5-10 mg Iv or Phenytoin 18 mg/kg at 50 mg/hr IV can be given. Other medications like Sodium thiopental, sodium amobarbital and propofol can be used with assistance from anaesthesiologists[5].

Post Seizure management

It is important to assess fetal wellbeing post convulsive state as maternal hypoxia and hypercarbia can cause fetal heart changes and uterine activity including bradycardia, late decelerations, decreased variability, or compensatory tachycardia. These changes usually resolve after correction of maternal hypoxia, hence it is important not to rush the woman for an emergency caesarean delivery based on these findings.

Women with severe preeclampsia/eclampsia, who are ≥ 34 weeks of gestation or are unstable need delivery as soon as the mother is stabilized. Women ≤ 34 weeks, corticosteroids should be given if mother is stable to aid fetal lung maturation. Delivery should not be delayed for steroid administration if condition worsens. Lab tests are to be repeated every 6 hours for evidence of thrombocytopenia, elevated creatinine levels or evidence of haemolysis.

Mode of delivery depends on gestational age, fetal status and BISHOP's score. If BISHOP score > 5, trial of vaginal birth can be considered with close maternal and continuous electronic fetal monitoring. Epidural analgesia can be given for maternal pain relief during labor and delivery provided platelet count is more than 70000^{mm3}

Magnesium sulfate infusion should be continued for 24 hours post-delivery or last seizure, whichever is latest. It is important to look for features of magnesium toxicity, by monitoring the urine output, eliciting deep tendon reflexes and monitoring respiratory rate. Recommended therapeutic levels of magnesium are 4-7 mEq/l. Deep tendon reflexes are lost at > 7 mEq/L, respiratory depression is seen at > 10 mEq/L and cardiac arrest may occur at > 25mEq/L. In case of magnesium toxicity, Calcium gluconate 1gm IV over 3 minutes is to be administered. In women with a serum creatinine of >1.2 mg/dL or oliguria (<30ml per hour for 4 hours) the maintenance dose should be reduced to 1 gm/hr instead of 2gm /hr. MgSO4 is contraindicated in women with myasthenia gravis and alternative anticonvulsants should be used in them as management of eclampsia[5].

Risk of eclampsia is highest in the first 48 hours after birth, hence blood pressure control is crucial during this time. Systolic blood pressure ≥150 mmHg, and diastolic pressure ≥100 mmHg on two readings at least four hours apart. Or systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg after one hour, treatment should be started[3].

Postpartum Care

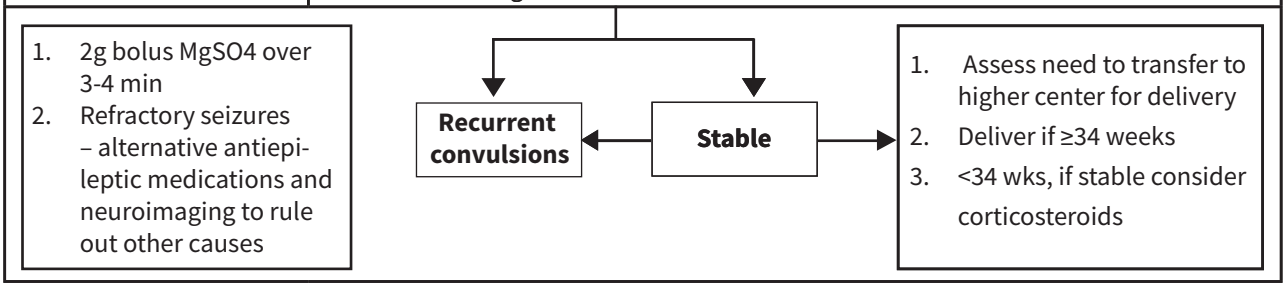
Women should be in hospital at least 72 hrs post-delivery and should be educated about home blood pressure monitoring, need for compliance with antihypertensive medication and when to reach hospital in case of worrying symptoms. Follow up visits should be scheduled at 7-14 days post-delivery, 6 weeks, 3 months, 6 months and then annually. Women should be educated about contraception, recurrence risk of preeclampsia and eclampsia in future pregnancy, increased risk of cardiovascular disorders and appropriate interventions for risk reduction[5]

Conclusion

Eclampsia is a life threatening complication of pregnancy resulting in both maternal and fetal morbidity. Prevention and timely treatment of pre-eclmapsia reduces the risk of eclampsia. Magnesium sulfate is the mainstay for both prevention and treatment of eclampsia. Protocols should be in place for education and implementation of antepartum and postpartum care for women presenting with eclampsia. It is important to have a postpartum follow up plan for

all women with eclampsia not only in view of recurrence risk but also due to increased risk of long term sequelae.

Time	Emergency treatment
05-min	1.Airway: lateral decubitus position, oxygen, suction 2. IV access 3. Avoid maternal injury : elevate and pad bed rails
	Prevent recurrent convulsions 1.Magnessium sulfate loading dose, 4-6g IV over 15-20 min 2.Maintence dose of 2gm per hour as continuous infusion for 24 hrs post delivery or after last seizure
10-15 min	Control of severe hypertension with IV Labetalol or IV Hydralazine or Oral Nifedipine
15-20 min	1.Obtain lab work 2.Fetal monitoring



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Historically the major thrust in therapy has been to avoid and treat eclamptic convulsions.MgSo4 was introduced in the early 1900's . However it wasn't until the 1990's that major controlled studies demonstrated its superiority over other anticonvulsants

Postpartum Hypertension

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Introduction:

Postpartum hypertension refers to hypertension that occurs after delivery until 6 weeks. It affects approximately 2% of pregnancies. The most common cause is persistence of antepartum hypertension (gestational hypertension or pre-eclampsia). The other causes of postpartum hypertension are chronic hypertension and de novo postpartum hypertension occurring in women with normotensive pregnancy and delivery.[1] Research has quoted the estimates to be chronic hypertension: 60%, preeclampsia (PE) with severe features: 33%, PE without severe features: 24%, and gestational hypertension: 16%.[2] Table 1 lists the causes of postpartum hypertension in pregnancy.

Table 1: Causes of Postpartum Hypertension.[1]

CAUSES OF POSTPARTUM HYPERTENSION
Early Postpartum Hypertension (<6 weeks) • Antepartum/intrapartum hypertension, unresolved- gestational hypertension, preeclampsia, chronic hypertension • De novo/ new onset postpartum preeclampsia • Pain- inadequate analgesia • Anxiety- improves with repeat testing • Medications- Non steroidal anti-inflammatory drugs as analgesics, ergot derivatives like ergometrine in cases of postpartum haemorrhage, ephedrine • Fluid overload- intrapartum use of large volume intravenous fluids • Physiological rise in blood pressure- Mild raise in blood pressure; days 3-6; caused by intravascular shift of pregnancy associated extravascular volume; resolves spontaneously

Persistent Hypertension (>6 weeks)

Preceded by antepartum hypertension or de novo hypertension that continues > 6 weeks postpartum-Essential/ Primary hypertension

- Associated with family history, advanced maternal age, obesity. Secondary causes need to be ruled out.

Secondary Hypertension

- Renal disorders: chronic kidney disease, nephrotic syndrome, reflux nephropathy
- Connective tissue disorders: Systemic Lupus Erythematosus, Systemic Sclerosis, Rheumatoid arthritis, Polyarteritis Nodosa
- Vascular disorders: Renovascular Hypertension, Aortic Coarctation
- Endocrine disorders: Diabetes mellitus, Hyperthyroidism, Hypothyroidism, Phaeochromocytoma, Acromegaly, Cushing's syndrome, Primary hyperaldosteronism

The old belief was 'delivery cures hypertension'. However, this is a dangerous assumption as the risks to the mother due to hypertension persist throughout the postpartum period. Hypertension remains the number one reason for postpartum hospital readmission, which in turn, is associated with higher healthcare costs, disruption of early parenting, and increased family burden.[3] Studies in the United Kingdom have shown 32-44% of eclampsia cases occur after delivery.[1] An American study quoted the incidence of stroke among women with hypertensive disorders of pregnancy being 1.6 per 10,000 pregnancy hospitalizations with the majority occurring postpartum.[4] A study from Japan revealed that 26.3% of cases of postpartum intracerebral hemorrhage were due to preeclampsia with a mortality rate of 40%.[5] Substandard care for hypertension continues to be an important cause of maternal mortality as per the Triennial Confidential Enquiry into Maternal Deaths.[1]

In the current practice of early postnatal discharge, continued surveillance is needed as postpartum hypertension not only poses a risk to the mother in the postnatal period, but also has implications on her future health. Referral and management guidelines need to be in place in order to prevent short and long term maternal morbidity and mortality.

Definitions

The definitions of hypertensive disorders of pregnancy (HDP) have rapidly changed in the past few years due to our better understanding of the pathophysiology and clinical course of the disorder where in evidence of organ damage is included.[6]

De novo postpartum hypertension should be distinguished from underlying pre-pregnancy chronic hypertension, because the blood pressure goals and morbidity differ substantially and the management should be more aggressive.[7] Also at present proteinuria no longer differentiates among the subtypes of postpartum hypertension as women without proteinuria are just as likely to experience adverse clinical outcomes as women with substantial proteinuria.[7] The types of hypertensive disorders in pregnancy have been detailed in the previous articles.

Pathophysiology

Blood pressure usually falls immediately after delivery, then tends to rise, reaching a peak 3-6 days postpartum in both normotensive and hypertensive women. This may be secondary to salt and water accumulated during pregnancy moving into the intravascular compartment and restoration of vascular tone. Other reasons for transient hypertension even in uncomplicated pregnancies may be due to pain, anxiety, medications or even excessive use of intravenous fluids.[1]

Whether postpartum PE or eclampsia represents a distinct entity from PE or eclampsia with antepartum onset is still unclear. A prospective study showed significantly higher sFlt-1 levels and a higher sFlt-1-to-PlGF ratio in postpartum women with PE than normotensive women and this pattern was same as that observed in antepartum PE.[8] Women with postpartum PE show elevated levels of natural killer cells along T lymphocytes which is not seen in women with antepartum PE.[9] Placenta, however, shows the same evidence of maternal vascular malperfusion in both these groups.[10]

Risk factors

Demographic risk factors

Advanced maternal age (≥35 years) has been shown to be associated with a 2-fold increased risk of postpartum PE.11 Pre-pregnancy obesity is also a consistent risk factor with up to 7.7-fold increased risk with BMI >40 kg/m^2.[(7)] These risk factors are the same as in antepartum hypertension. However, unlike antepartum PE which is more common in primipara, postpartum PE is shown to develop more commonly among women with a history of a hypertensive disorder in previous pregnancy.[11]

Antenatal and Intrapartum risk factors

Iatrogenic preterm delivery due to maternal hypertension, severe antepartum hypertension and antepartum hypertension with proteinuria have been shown to be associated with a higher risk of persistent

hypertension in the postpartum period.[12] Cesarean delivery increases the risk of postpartum hypertension by 2-to7-fold as compared to vaginal birth.[12] Excessive intravenous (IV) fluid infusion during labor is also increases risk of postpartum PE due to volume overload and raised blood pressures when the fluid is remobilized to the intravascular space post-delivery.[13] Studies overall have however, not shown an increased risk of postpartum PE with use of pharmacological agents such as vasopressors or ergot derivatives in labor.[12]

Risk prediction models

New research has focused on developing risk prediction models for women with HDP that can help to guide care in the postpartum period. These prediction models can be used to plan timing of discharge post-delivery, starting antihypertensive medications, frequency of surveillance and scheduling postnatal visits. The variables used in these models include antepartum hypertension, advanced maternal age, obesity, multiparity, prolonged labor, systolic blood pressure trends and mean diastolic blood pressure after delivery.[14] These models, however, still need to be validated before clinic use. They do offer a good scope for planning appropriate targeted interventions for early diagnosis and management of women at risk.

Clinical presentation

Postpartum hypertension due to persistent antenatal hypertension is easier to diagnose because such women are typically subject to increased surveillance postpartum. Picking up de novo postpartum hypertension is trickier. These women have been shown to have a higher risk of eclampsia, stroke and overall severe morbidity than women with antepartum hypertension.[15] Majority of women with de novo postpartum hypertension will present within 7-10 days after delivery. However, the onset can be even up to 3 months post-delivery.[7] Women present frequently with neurological symptoms, with headache being reported as the most common symptom in approximately 60% to 70% of women across various studies. Eclampsia has been reported as the presenting symptom in up to 10% to 15% of women.[11] Other symptoms reported are associated with volume overload such as shortness of breath, chest pain, and peripheral edema. Isolated elevated blood pressures noted at home monitoring or at follow up visit is the least common presentation reported.[15]

Guidelines, therefore, recommend informing all women at discharge of the possible occurrence of hypertension and the associated symptoms like severe headache not responding to analgesics; visual disturbances like blurred vision, flashing lights, double vision or floating spots; nausea and vomiting; breathlessness; sudden swelling of the face, hands or feet; or seizures.[16]

Investigation

Evaluation of postpartum hypertension involves diagnosis and assessment of severity of the hypertension, tests to rule out complications and to rule out underlying secondary cause as indicated.

Laboratory evaluation should include assessment of electrolytes and renal function, platelet count, liver enzymes, and urine protein assessment. NICE guidance recommends the blood parameters to be checked 48-72 hours after birth and only repeated if still abnormal or clinically indicated as frequent testing is unlikely to change the management especially in absence of clinical triggers.[16]

Further laboratory assessment and imaging studies should be guided by the clinical presentation. Women who present with hypertension with neurological symptoms that persist even after management of the hypertension, should be investigated for intracerebral pathology.[(1)] Other causes of postpartum headache such as postdural puncture headache, subarachnoid hemorrhage, central venous sinus thrombosis, thrombotic thrombocytopenic purpura and migraine, need to be ruled out.[7]

In women presenting with symptoms of volume overload (breathlessness, orthopnea, palpitations), assessment of brain natriuretic peptide (BNP) can confirm the diagnosis of fluid overload and guide management. BNP, secreted predominantly by the left ventricular cardiac myocytes in response to increased wall tension, increases diuresis and decreases vascular tone. High BNP levels have a good correlation with echocardiography findings of fluid overload in pregnancy.[17] These women should also be evaluated for peripartum cardiomyopathy with echocardiogram.[7]

Workup for cause of secondary hypertension such as preexisting renal disease, lupus exacerbation, hyperthyroidism, primary hyperaldosteronism, renal artery stenosis, pheochromocytoma, should also be guided by the clinical presentation.[7]

Management

The mainstay of treatment is antihypertensive medication. An ideal antihypertensive for the postnatal period should reliably control the blood pressure, have minimal maternal adverse effects, be safe in lactation and should be effective in less frequent dosing to ensure compliance.[12] Table 2 describes the antihypertensive medications that are most commonly used in the postpartum period. Methyldopa should be changed to alternative medication due to associated sedation, postural hypertension, and depression.[16]

Table2: Antihypertensive medications

Medication	Dose	Contraindication	Side Effect	Breastfeeding
Beta Blockers				
LABETOLOL	100- 600 mg 2-3 times daily	Asthma, cardiac failure, bradycardia, 2nd or 3rd degree AV block	Postural hypotension, headache, urinary hesitancy, fatigue	Safe. Only small quantities detected in breast milk
ATENOLOL	25-100 mg once daily			
Calcium channel blockers				
NIFEDIPINE SR	10–40 mg 2-3 times daily	Advanced aortic stenosis	Headache, tachycardia, palpitations, flushing	Safe, low levels in breast milk
AMLODEPINE	5-10 mg once daily			
ACE inhibitors				
ENALAPRIL	5–20 mg twice daily	Avoid in Acute Kidney Injury	Hypotension, cough, renal impairment	Safe, excreted into breast milk in low concentrations
Other ACE inhibitors and ARBs- not recommended. Minimal data for use in lactation				
Diuretics: Recommended in indicated cases for short duration. Produce excessive thirst in breastfeeding women. Large doses may suppress lactation				

Acute severe hypertension

Treatment needs to be initiated within 30-60 minutes of onset of severe hypertension (≥160/110 mmHg) to reduce the risk of maternal stroke. First line medications include iv labetolol and hydralazine, or oral nifedipine in situation where iv access is not feasible. Since there are no fetal considerations postpartum, even a lower threshold of 150/100 mmHg may be considered to prevent progression.18 Both NICE and ACOG recommend achieving target goals of 140 to 150/90 to 100 mmHg.[16,19]

Non-Steroidal Anti-inflammatory Drugs (NSAID)

A RCT has shown that NSAID use may be as safe as acetaminophen in hypertensive women.[20] Considering the concerns with use of opioids for pain management, the authors suggest NSAID as the first line analgesic agent for postpartum pain even in hypertensive women at least until discharge from the hospital.[20] However, they are to be used with caution in women with severe hypertension, renal impairment, or in women with additional cardiovascular risk factors.[1]

Magnesium sulphate

Intravenous magnesium is recommended for seizure prophylaxis among patients with antenatal HDP with severe features. The highest risk period for postpartum eclampsia is within 7 days post-delivery, most commonly presenting within 48 hours after delivery.[1] However, the risk of seizures in de novo hypertension is unclear. There is a need to be judicious with use of magnesium sulphate to reduce risks of a potentially harmful medication as it is associated with major toxicity such as respiratory depression and cardiac arrest. It should be reserved for women with severe hypertension with persistent neurological symptoms.[21] In another meta-analysis, a shortened duration (12 hours) of magnesium was found to be equally effective as compared to the 24-hour traditional administration for seizure prophylaxis.[22]

Diuretics

Several studies have demonstrated that diuretics may be useful in postpartum women with HDP with a phenotype of increased intravascular volume or in women with clinical evidence of volume overload. The diuresis can be achieved with iv or oral furosemide with concurrent serum electrolyte monitoring.[7] Trials of postpartum hypertensive women with severe features have shown decreased requirement for additional antihypertensive if a combination of furosemide and nifedipine was used.[7] Another study evaluating patients with gestational hypertension and preeclampsia with and without severe features, demonstrated that patients randomized to furosemide 20 mg daily for the first 5 days postpartum were less likely to have persistent hypertension at postpartum day [7.23] Additional research is still needed before incorporating diuretics in routine use for postpartum hypertension.

Follow-up

Since the first 48 hours post-delivery have the highest risk for eclampsia, the discharge should be delayed till day [3.12]

Raised blood pressures normalize by 3 days in 29-57% cases and in 7 days in 50-85% cases. Women with chronic hypertension, long duration of antihypertensive treatment in pregnancy, higher maximum systolic and diastolic blood pressures, obesity, or occurrence of preterm pre-eclampsia are more likely to have sustained hypertension.[2] Proteinuria resolves in 86-88% of women by six weeks, remaining persistent in fewer than 5% beyond three months. In such cases, nephrology referral is indicated to rule out underlying renal disease.[1]

The 6-week postnatal visit is an opportunity to establish the diagnosis and to discuss implications for future pregnancies. Blood pressure and proteinuria should be checked in all women at this visit regardless of their previous hypertension history.12 Additional visits at 3 months and 6 months postpartum are also recommended in hypertensive women to ensure BP, urinalysis and labs have normalized.[24]

Table 3 summarizes the approach to management of postpartum hypertension.

Table 3: Management of postpartum hypertension.[7,24,25]

Investigations	**Baseline test for hypertension** • Complete blood count • Serum Creatinine • Liver function test • Serum Lactate dehydrogenase. • Urine protein creatinine ratio	**Based on clinical presentation** • Persistent neurological symptoms: Neuroimaging (CT/MRI) • Visual changes: fundoscopy • Volume overload: 2D echo, Brain Natriuretic Peptide • Investigations to rule out secondary hypertension
Acute severe hypertension	**Management considerations** • Short acting antihypertensive • Administered within 30-60 mins • Threshold for treatment: BP of ≥160/110 mm Hg • Goal: <150/100 mmHg	**Medications** **Labetolol:** 20 mg iv over 2 min, followed at 20-min intervals by doses of 40 to 80 mg (max total cumulative dose 300 mg) **Nifedipine:** 10 mg oral, followed at 20-min intervals by doses of 10 to 20 mg (max 4 doses) **Hydralazine:** 5 mg iv over 1-2 min, repeat 5-10 mg bolus after 20 mins
Magnesium sulphate • For seizure prophylaxis • Women with neurological symptoms	**Diuretics** • In women with pulmonary oedema or volume overload	**Long acting antihypertensive** • Maintain BP <140s-150s/90s-100s mmHg • details in table 3
Follow up	• Home BP monitoring • Postpartum review with obstetrician and physician: 2 weeks, 6 weeks, 3 months. • Education on long-term morbidity associated with hypertensive disorders of pregnancy, risk factor identification	
Intervention strategies	**Remote BP monitoring** • Home blood pressure monitoring or 24-hour ambulatory blood pressure monitoring is an effective and low cost intervention. **Telehealth** • Teleconsultation or even texting the blood pressure values can bridge the gap of postnatal visit dropouts, especially in areas with logistical issues for physical follow-up. **Health programs** • National public health campaigns emphasizing the warning signs and risk factors for postpartum hypertension. • se of community health workers to provide health education and coaching, peer support, streamline patient-provider communication and aid in therapeutic optimization.	

Long term implications

Future pregnancy

Women with gestational hypertension have a 16-47% risk of recurrent gestational hypertension in subsequent pregnancy and a 2-7% risk of pre-eclampsia. Women with pre-eclampsia have a 13-53% risk of gestational hypertension and a 16% risk of pre-eclampsia. This rises to 25% if pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome, or eclampsia or led to preterm deliver <34 weeks; rising to 55% if delivery occurred <28 weeks' gestation.[16] Women with early onset PE or severe hypertension should be screened for antiphospholipid antibodies in the interval period.[1] Women who have persistent hypertension beyond the postpartum period should aim for good blood pressure control and to switch to safer antihypertensive prior to pregnancy planning. Baseline laboratory testing should also be done prior to conception.[7]

Women who remain normotensive in the antenatal period in subsequent pregnancy should still be vigilant for development of postpartum hypertension.[7]

Cardiovascular disease

HDP are known risk factors for cardiovascular disease in later life such as chronic hypertension, heart failure and cardiovascular related mortality.[2)] About one in five women with hypertension in pregnancy will end up with chronic hypertension. The risk could be increased by the underlying metabolic abnormalities that predispose to both atherosclerosis as well as HDP, or by the placental disease itself. Predictors of subsequent development of hypertension in women with resolution of postpartum hypertension include obesity, high-normal blood pressure, family history of hypertension, recurrence of a hypertensive disorder in a subsequent pregnancy, and markers of the metabolic syndrome including dyslipidemia and hyperinsulinaemia.[1]
Women who go through a normotensive pregnancy are at a lower risk of developing hypertension as compared to nulliparous women. The reason is unclear but this shows that pregnancy offers a window into the future cardiovascular health of women.[25]

Following a hypertensive pregnancy, all women and their offspring should adopt a healthy lifestyle with healthy diet, exercise, smoking cessation, and aiming for BP < 120/80 mmHg[24]

The understanding of the long term implications of HDP have increased the focus on transitioning women from postpartum care to primary care so as not to miss out on providing these women with the care and treatment they need for long term health.

Conclusion

The postpartum period poses a threat to women with or without antepartum hypertension. The surveillance should continue for timely diagnosis and early intervention of postpartum hypertension thus preventing maternal morbidity and mortality. Understanding the etiology and each postpartum woman's risk of the disease will guide counselling and individualize management strategy. A combined multidisciplinary approach by obstetricians, physicians and educators with focus on continued surveillance even after the designated postpartum period, will ensure long term wellbeing of women with HDP.

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